

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125320

CROSS DISCIPLINE TEAM LEADER
REVIEW

Cross-Discipline Team Leader Review

Date	May 6, 2010
From	Theresa Kehoe, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	BLA 125320
Supplement#	000, resubmission
Applicant	Amgen, Inc
Date of Submission	January 25, 2010
PDUFA Goal Date	July 23, 2010
Proprietary Name / Established (USAN) names	Prolia denosumab
Dosage forms / Strength	60 mg q6 months subcutaneous injection administered by a healthcare provider
Proposed Indication(s)	1. Treatment of postmenopausal osteoporosis
Recommended:	Approval

1. Introduction

Amgen, Inc. has submitted this complete response to the October, 2009, Action Letter issued for the biologic licensing application (BLA) for denosumab, a monoclonal antibody against receptor activator of nuclear factor-kappa B ligand (RANKL). In the original biologic licensing application, Amgen sought four different indications: treatment of postmenopausal osteoporosis, prevention of postmenopausal osteoporosis; treatment and prevention of bone loss associated with hormone ablation therapy for breast cancer; and treatment and prevention of bone loss associated with hormone ablation therapy for prostate cancer.

In this complete response, Amgen is seeking approval of the treatment of postmenopausal osteoporosis indication only. No new efficacy data have been submitted. This review will focus on the data presented in the safety update as well as the postmarketing studies and risk evaluation and mitigation strategy (REMS) components.

2. Background

Osteoporosis is a skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone leading to an increase in fragility and susceptibility to fracture. While osteoporosis can occur in both men and women, studies in postmenopausal women represent the majority of the data defining the disease and its sequelae. Currently, osteoporosis is predominantly diagnosed using bone mineral density (BMD) techniques based on the diagnostic criteria set forth by the World Health Organization (WHO) in 1994. However, it has long been recognized that BMD alone is not sufficient to accurately predict fracture risk. Inclusion of other risk factors, most notably age and prior history of fracture, along with BMD, improves fracture risk prediction.

The Applicant submitted their original biologic licensing application for denosumab on December 20, 2008. Four separate indications were sought: treatment of postmenopausal osteoporosis; prevention of postmenopausal osteoporosis; treatment and prevention of bone loss associated with hormone ablation therapy for breast cancer; and treatment and prevention of bone loss associated with hormone ablation therapy for prostate cancer. The postmenopausal osteoporosis indications were reviewed by the Division of Reproductive and Urologic Products while the bone loss due to hormone ablation in breast and prostate cancer indications were reviewed by the Division of Biologic Oncology Products.

Denosumab is a full-length human monoclonal IgG2 that targets receptor activator of nuclear factor kappa B ligand (RANKL). RANKL exists in both transmembrane and soluble forms, and denosumab is fully capable of binding to either form. The mechanism of action for this antibody involves the antibody binding to RANKL and inhibiting the interaction of RANKL and its receptor (RANK). Inhibition of the RANK-RANKL interaction prevents receptor activation and clustering as well as the downstream signaling from the receptor. RANKL-induced RANK signaling is essential for the formation, function, and survival of mature osteoclasts, which are responsible for bone resorption. The resulting decrease in bone resorption leads to an increase in bone mass.

Denosumab's efficacy was adequately demonstrated in the osteoporosis clinical trials. However, during the initial review cycle, the following adverse events were seen in the osteoporosis trials that raised significant concern: serious infections, including serious skin infection, dermatologic adverse events, and over-suppression of bone turnover. After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, it was determined that a Risk Evaluation and Mitigation Strategy (REMS) would be necessary to ensure that the benefits of denosumab outweigh the risks. In addition, long-term postmarketing studies would be required.

For the postmenopausal osteoporosis indications, a Complete Response Action letter was issued on October 16, 2009. The deficiencies noted in the letter included (*in italics*):

Regarding the proposed indication for treatment of postmenopausal osteoporosis (under BLA 125320):

Clinical Deficiency

- 1. We have reviewed your proposed postmarketing observational study (Protocol 20090522 (Phase B): "Denosumab Global Safety Assessment Among Women With Postmenopausal Osteoporosis (PMO) Using Multiple Observational Databases". Because of the design and methodological challenges noted in your proposal, there is concern that the proposed study will not successfully capture the necessary safety information regarding denosumab use. Therefore, additional assessment of methodology and background adverse event rates as specified under Protocol 20090521 (Phase A) is needed before agreement can be reached on the design of Protocol 20090522 (Phase B).*

Information Needed to Address the Clinical Deficiency

It is necessary for you to complete your methodology and background adverse event rate assessment study (Protocol 20090521 (Phase A): "Denosumab Global Safety Methodology and Background (AE) Rate Assessment Among Women With Postmenopausal Osteoporosis (PMO) Using Multiple Observational Databases") and submit the data for review prior to approval.

Regarding the proposed indication for prevention of postmenopausal osteoporosis (under BLA 125331):

(b) (4)

RISK EVALUATION AND MITIGATION STRATEGIES (REMS) REQUIREMENTS

3. *As described in our letter dated October 2, 2009, in accordance with section 505-1 of the Federal Food, Drug, and Cosmetic Act (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. We have determined that under section 505-1, the REMS for this product must include a Medication Guide, a communication plan, and a timetable for submission of assessments.*

We acknowledge the submission of your proposed REMS on October 8, 2009. Once FDA finds the content of your REMS acceptable and determines that BLA 125320 can be approved, we will append the REMS, Medication Guide, and all relevant REMS materials including educational and communication materials to the approval letter. If and when BLA 125320 is approved, BLA 125331 will be converted to a supplement of BLA 125320.

POSTMARKETING REQUIREMENTS

As described in our letter dated October 2, 2009, FDA has determined that, if BLA 125320 is approved, you will be required to conduct post-marketing studies of ProLia (denosumab) to assess the signal of a serious risk of serious infection, including skin infections, dermatologic adverse events, and over-suppression of bone turnover.

Specifically, we have determined that, if BLA 125320 is approved, you will be required, pursuant to section 505(0)(3) of the FDCA, to conduct the following:

- 1. 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)*
- 2. 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 turnover (Protocol 20090601)*
- 3. A long-term pregnancy exposure registry study in denosumab users who become pregnant on the drug (Protocol 20090589)*

We acknowledge receipt of your amendments dated September 11 and October 12, 2009, containing your proposed postmarketing studies to address these issues.

We will continue discussion of your postmarketing study proposals so that your complete response to this action letter contains adequately designed and acceptable studies. Comments regarding your protocols will be provided separately.

This complete response addresses only the treatment of postmenopausal osteoporosis indication and contains a report summarizing the findings from the feasibility study 20090521, the REMS components, the draft protocols for the required postmarketing studies, a safety update, and product labeling. The Applicant intends to request a meeting to further discuss the prevention of postmenopausal osteoporosis indication.

3. CMC/Device

Please refer to Dr. Sarah Kennett's review and Dr. Chana Fuch's quality team leader executive summary for complete details. The data submitted in the original BLA supported the approval of denosumab. Denosumab is a full-length human monoclonal IgG2 antibody that specifically binds to the D-E loop of human receptor activator of nuclear factor kappa B ligand (RANKL).

Denosumab drug substance is manufactured at two different sites: Amgen, Colorado (ACO) and Boehringer Ingelheim Pharma, Germany (BIP). In the drug substance manufacturing process, (b) (4)

(b) (4) There are differences in the charge variants between ACO and BIP. However, the noted variants have equal *in vitro* potency and are not expected to have a clinical effect. In the denosumab clinical program, two processes (CP1 and CP2) were used for drug substance manufacturing. CP1 material came from the master cell bank and was used in phase 1 trials. CP2 material came from the working cell bank and was used in the phase 2 trials and all pivotal phase 3 clinical trials. There were minor differences (b) (4)

(b) (4) seen during development between these two processes. Nonclinical studies as well as clinical bioequivalence studies were performed to ensure there are not clinically significant changes between the denosumab manufactured through the CP1 and CP2 processes. During

the original review cycle, pre-approval inspections of the BIP and ACO facilities were performed and found acceptable.

Drug product is manufactured at Amgen, Puerto Rico (AML). 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. The only difference in the formulations for these presentations is the addition of 0.01 % (w/v) polysorbate to the formulation used for the prefilled syringe. Facilities inspection of the AML site specifically for the denosumab drug product was not performed based on the compliance history, current GMP status, and previous inspections of manufacturing processes similar to the denosumab manufacturing process. A routine CGMP inspection of the Puerto Rico site (AML) was concluded on 9/11/09. Findings included low level syringe breakage identified on the Enbrel SureClick manufacturing line. While these findings suggested a serious failure of the quality control unit at the drug product manufacturing plant that likely affected all products produced at the plant, after final review the Office of Compliance provided an Acceptable recommendation based on new information **received and the firm's intent** to provide corrective actions.

CMC information in the resubmission package included additional drug product (DP) stability data to support storage and handling information in the product labeling. Amgen was asked to add breakloose and extrusion (BLE) acceptance specifications to release and stability testing of the PFS during the original BLA review. The company committed to providing this information in the first quarter 2010 and the data were submitted on 4/23/2010. As outlined in **Dr. Kennett's review of the drug product stability data** submitted, the drug product should remain stable for 14 days at room temperature, **even if "room temperature" is greater than 25°C**. The Applicant has committed to providing additional data that may support extending the room temperature storage to (b) (4).

The current data support the following labeling language (~~striketrough~~ for deleted text and underline for new text):

Store [TRADENAME] in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze. Prior to administration, [TRADENAME] may be allowed to reach room temperature (up to 25°C/77°F) in the original container. Once removed from the refrigerator, [TRADENAME] must not be exposed to temperatures above 25°C/77°F and must be used within (b) (4) 14 days. If not used within the (b) (4) 14 days, [TRADENAME] should be discarded. Do not use [TRADENAME] after the expiry date printed on the label.

The following postmarketing commitments are recommended by the Division of Monoclonal Antibodies:

Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70.

1. To confirm validation of the updated SE-HPLC method (MET-001208). The method was revised to add column conditioning using material containing the high molecular

- weight species. The protocol and final report will be included in an annual report to be submitted by [*Amgen to provide date for Final Report Submission*].
2. To submit proposed revisions to the breakloose and extrusion release and shelf-life specifications for pre-filled syringe drug product based on an appropriate statistical method after XX commercial manufacturing runs. The proposed revision to the specifications, the corresponding data from the XX commercial manufacturing runs, and the analysis plan used to create the revisions will be provided in a Prior Approval Supplement by September 30, 2010. [*Amgen to provide number of runs*].
 3. To submit proposed revisions to the breakloose and extrusion release and shelf-life specifications for pre-filled syringe drug product based on an appropriate statistical method to reflect increased manufacturing experience. The proposed revision to the specifications, the corresponding data from the commercial manufacturing runs to date and the analysis plan used to create the revisions will be provided in a Prior Approval Supplement by March 31, 2012.

4. Nonclinical Pharmacology/Toxicology

Please see Dr. Kim Hatfield's review and Dr. Lynnda Reid's Pharmacology team leader summary for complete details. Denosumab is a fully human IgG₂ monoclonal antibody that binds to the receptor activator of nuclear factor- κ B (RANK) ligand (RANKL) and inhibits RANKL activity. The antibody is specific to human and non-human primate RANKL. Because the antibody does not bind to rodent RANKL, studies in two animal species were not possible and the cynomolgus monkey was the species mainly used for nonclinical evaluations of denosumab toxicology. Other studies were done using genetically altered mice (human RANKL knock-in mice where human RANKL was expressed instead of murine RANKL). In addition, the Applicant conducted studies in rodents using an osteoprotegerin-Fc fusion molecule. The rationale for this approach was that OPG is an endogenous regulator of RANKL activity and like denosumab, OPG binding to RANKL inhibits RANKL activity.

High levels of protein expression were 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.

The RANK/RANKL signaling pathway interacts with the immune system in several ways including lymphocyte development and lymph node organogenesis, monocyte / dendritic cell maturation, activation and longevity, antigen presentation and CD40 ligand-independent T helper cell activation. 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 by inhibiting mammary gland maturation. A causative role for denosumab in the deaths and oral abscesses observed at the high-dose cannot be ruled out and are potentially secondary to denosumab-induced immunosuppression and an inability to mount an adequate immunologic response.

Two notable issues that had not been adequately addressed in the first review cycle included:

Reproductive and Developmental Toxicity. Only secondary maternal effects on fetal organogenesis were assessed in primates, however, given the primary indication of treatment of osteoporosis in postmenopausal women, DRUP did not consider that additional reproductive and developmental studies were necessary for approval. If denosumab were ever to be evaluated for treatment in a population that included fertile women, further evaluation of the risks on reproduction and development would be necessary. These studies are needed to assess potential adverse effects on skeletal, immune and nervous system development, and would be required to support indications which would include women of child bearing potential in the patient population.

Pediatrics. Preliminary data suggest that denosumab should not be used in patients where the epiphyseal plates are not fully closed. In animals where the epiphyseal plates had not fully closed prior to treatment, growth plates were markedly enlarged with reduced chondroclasis and expanded growth plates associated with cartilage calcification (zone 4) and cartilage erosion and calcification (zone 5).

This BLA resubmission includes two nonclinical studies (study R20090069 and study R20090070) that provide additional data on the effects of denosumab use in the young (pediatric population). Because denosumab does not have the species specificity necessary to conduct preclinical trials, these studies utilized either transgenic rats that over-express osteoprotegerin (OPG-Tg) or rats treated with a surrogate rodent antibody (OPG-Fc fusion protein).

Studies from the literature showed that in transgenic rats that over-express OPG-Tg female rats had narrower midshafts and reductions in peak load and energy to failure of long bones at 12 months. Study R20090069 was conducted to further evaluate the age at which these long bone findings occur and compared the long bone geometry and bone strength of wild type and OPG-Tg rats at one and two months of age. Results indicate that the reductions in biomechanical properties seen at 12 months were not observed in the one and two month old rats. This would suggest the findings of reduction in biomechanical properties of the long bones are likely to develop between 2 and 12 months.

In study R20080340, submitted and reviewed with the original BLA application, young mice (2 weeks of age at initiation of treatment) treated with OPG-Fc for 6 weeks had significant decreases in body weight gain and axial skeletal length. Decreased upper and lower incisor length, and delayed molar eruption proportional to the magnitude of bone resorption suppression were also observed. Study R20090070 evaluated the reversibility of changes induced by 6 weeks of treatment with OPG-Fc or alendronate (ALN) on tooth eruption, tooth root development, bone density/geometry/ histology/strength in neonatal (2-week old) rats after 10 weeks of treatment discontinuation. Results indicate a partial restoration of decreased incisor length and tooth eruption. The 3rd molar eruption was still delayed, with roots of late erupting 2nd and 3rd molars having impaired growth and orientation within the jaw.

Overall, these two studies do not change the concerns regarding use of denosumab in the pediatric population. However, the results regarding reversibility have been included in the

product label by the applicant. Edits recommended by Dr. Hatfield are outlined below (~~strike through~~ for deleted text and underline for new text):

Neonatal RANKIRANKL knockout mice exhibited reduced bone growth and lack of tooth eruption. [REDACTED] (b) (4) ~~A~~ A corroborative study in 2-week-old rats given the RANKL inhibitor OPG-Fc- ~~also showed r~~ Reduced bone growth, altered growth plates and impaired tooth eruption [REDACTED] (b) (4) ~~These changes were partially reversible in this model when dosing of RANKL inhibitors was discontinued. [see Use in Specific Populations (8.1, 8.4)].~~

No postmarketing commitments or requirements are recommended by the pharmacology team at this time. However, if denosumab were ever to be evaluated for treatment in a population that included fertile women, further evaluation of the risks on reproduction and development will be necessary. These studies would need to assess potential adverse effects on skeletal, immune and nervous system development, and would be required to support indications which would include women of child bearing potential in the patient population.

5. Clinical Pharmacology/Biopharmaceutics

Please see Dr. Jee Eun Lee's primary review and Dr. Hae-Young Ahn's secondary review for complete details.

Denosumab is administered as a subcutaneous injection. The mean maximum serum denosumab concentrations (C_{max}) of 6.75 ± 1.89 $\mu\text{g/ml}$ was reached in the median time of 10 days (range: 3 to 21 days) following a 60 mg SC dose. After C_{max} , serum denosumab concentrations decline over a period of 4 to 5 months with a mean half-life of 25.4 ± 8.5 days. 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 are 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 $AUC_{0-\tau}$) 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 $\mu\text{g/ml}$. 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 $\mu\text{g/ml}$ in this case) and becomes saturated as serum denosumab concentration increases.

Because denosumab is a monoclonal antibody and, therefore, a large protein product that is unlikely to interact with cardiac cell ion channels, a thorough QT study was not required or performed. However, during the first review cycle the clinical reviewers were concerned regarding the QT effects noted for denosumab and an IRQT consult was obtained. Despite the lack of a thorough QT study, the clinical development program did include an intensive assessment of the effects of denosumab on electrocardiograms, with particular emphasis on the QTc interval. ECGs were obtained at baseline, around Cmax and at several time points during the follow-up period in most clinical studies. Outliers (patients with absolute post-dose QTcF over 500 ms or over 60 ms change from baseline were noted in several studies although underlying ECG abnormalities were also noted in several of the studies. Notably, 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. The final recommendation from the IRQT team was that the sponsor's ECG evaluations appear adequate and there are no large effects on the QT interval due to denosumab.

No new data regarding the clinical pharmacology of denosumab have been submitted in this complete response. The Applicant has requested reconsideration of the proposed labeling language for the drug interactions section of the product full prescribing information and has submitted their scientific rationale. Specifically, the Applicant does not agree with the inclusion of the following language:

7. DRUG INTERACTIONS

No drug-drug interaction studies have been conducted with [TRADE NAME]. The

(b) (4)

The Applicant believes that this language is not warranted because RANKL has not been demonstrated to have a role in cytochrome P450 (CYP) regulation. In addition, given the lack of expression of its receptor RANK on adult human hepatocytes, a RANKL inhibitor is thus unlikely to directly impact CYP expression or activity. The Applicant also believes that an indirect effect on CYP expression is also unlikely, based on several rodent studies and the lack of effect on C-reactive protein noted in denosumab trials in rheumatoid arthritis patients.

However, no specific drug-drug interaction studies have been conducted for denosumab. As **outlined in Dr. Lee's review, while it is true** that denosumab does not necessarily behave like therapeutic proteins targeting inflammatory cytokines that have demonstrated roles in CYP regulation, it is still uncertain and premature to conclude that a RANKL antagonist will not

impact CYP expression. Based on the current literature, it cannot be definitively concluded that denosumab has no effect on CYP regulation, expression or activity.

Therefore, the Clinical Pharmacology Review Team recommends the sponsor conduct an *in vivo* drug-drug interaction study with CYP3A4 substrate (e.g., midazolam) in postmenopausal female patients with osteoporosis. This trial would “**Assess potential interactions of an approved drug with a frequently concomitantly prescribed medication**”, and, therefore, would qualify as a postmarketing requirement.

6. Clinical Microbiology

Denosumab is not an antimicrobial agent. Clinical microbiology studies are not applicable to this BLA. Drug product sterility and drug product quality microbiology was reviewed by the **Biotech Manufacturing Team. Please see Dr. Obenhuber’s review for complete details.** All processes were found to be satisfactory.

7. Clinical/Statistical- Efficacy

No new clinical efficacy data were included in this resubmission.

The fracture reduction efficacy of denosumab was established with trial 20030216. Trial 20030216 was a multicenter, double-blind, randomized, placebo-controlled, study of denosumab 60mg every 6 months **in women age 60 – 90 years** diagnosed with postmenopausal osteoporosis (PMO). The primary endpoint of the study was incidence of new morphometric (radiographic) vertebral fractures at month 36. The secondary endpoints were time to first nonvertebral fracture and time to first hip fracture. A fixed sequence testing procedure was employed for the primary and secondary endpoints in the order mentioned above (vertebral, nonvertebral, hip) for multiplicity adjustment to maintain the overall significance level at 0.05. There were also 56 tertiary and exploratory efficacy endpoints and no fixed testing procedure or multiplicity adjustment was utilized.

A total of 7868 subjects were enrolled in the trial and 83% completed the three years of the study. The average age of enrollees was approximately **72 years with an age range of 60 – 91** years. Subjects were not required to have a baseline fracture to qualify for study enrollment. Overall 24% of the enrolled population had at least one prevalent vertebral fracture at baseline and 44% of the enrolled population had sustained at least one fracture of any type after age 55 years. The mean lumbar spine BMD T-score was -2.8 standard deviations below the mean bone mass of young healthy adults.

As outlined in the following table, 264/3691(7.2%) subjects in the placebo group and 86/3702 (2.3%) subjects in the denosumab group sustained at least one new morphometric vertebral fracture during the three years of the trial. The absolute risk reduction is 4.8% with a relative risk reduction of 68% ($p < 0.0001$). Subgroup analyses including race, age, geographic location, BMI, baseline lumbar spine BMD T-score, and baseline total hip BMD T-score revealed similar results. Over the three-year treatment period, 531 subjects (293 (7.5%) in the placebo group and 238 (6.1%) in the denosumab group) sustained a nonvertebral fracture. Based on

Kaplan-Meier estimates, the three-year event rates for nonvertebral fracture were 8.0 in the placebo group and 6.5 in the denosumab group, with an absolute risk reduction of 1.5 (95% CI: 0.3, 2.7) and a hazard ratio of 0.80 (95% CI: 0.67, 0.95, $p=0.0106$). Sixty-nine subjects (43 (1.1%) in the placebo group and 26 (0.7%) in the denosumab group) sustained a hip fracture. Based on Kaplan-Meier estimates, the three-year event rates for hip fracture were 1.2 in the placebo group and 0.7 in the denosumab group, with an absolute risk reduction of 0.3% (95% CI: -0.1, 0.7) and a hazard ratio of 0.60 (95% CI: 0.37, 0.97, $p=0.0362$).

Table 1: Trial 20030216: Fracture Endpoints

Trial 20030216: Fracture Endpoints		
Primary Endpoint: New Morphometric Vertebral Fracture, mITT, LOCF		
	Placebo	Denosumab
N, mITT	3691	3702
Crude incidence, n (%)	264 (7.2)	86 (2.3)
Absolute Risk Reduction (95% CI)	4.8 (3.9, 5.8)	
Relative Risk Reduction (95% CI)	68 (59, 74)	
Odds Ratio (95% CI)	0.31 (0.24, 0.39)	
p-value	<0.0001	
Secondary Endpoints: Nonvertebral Fracture and Hip Fracture, ITT		
N, ITT	3906	3902
Nonvertebral Fracture		
Crude incidence, n (%)	293 (7.5)	238 (6.1)
Kaplan-Meier Estimate (%)	8.0	6.5
Absolute Risk Reduction (95% CI)	1.5 (0.3, 2.7)	
Hazard Ratio (95% CI)	0.80 (0.67, 0.95)	
p-value	0.0106	
Hip Fracture		
Crude incidence, n (%)	43 (1.1)	26 (0.7)
Kaplan-Meier Estimate (%)	1.2	0.7
Absolute Risk Reduction (95% CI)	0.3 (-0.1, 0.7)	
Hazard Ratio (95% CI)	0.60 (0.37, 0.97)	
p-value	0.0362	
Source: compiled from CDTL original submission memo		

(b) (4)

Once validated by the key fracture trial, bone mineral density becomes an adequate surrogate marker for subsequent dosage regimens and populations. For this reason, the clinical team believes it is important to include bone mineral density data in the product labeling even though they are tertiary endpoints. Change in bone mineral density was evaluated in the entire study population at months 24 and 36 for the lumbar spine and months 12, 24 and 36 for the hip. No fixed testing procedure or multiplicity adjustments were defined for the BMD

endpoints and the significance level for each analysis was 0.05. The analyses included all subjects who received study drug and had at least one follow-up DXA scan and used an ANCOVA model with LOCF imputation.

As outlined in the table below, significant increases in BMD at the lumbar spine, total hip, femoral neck and trochanter were observed with denosumab treatment compared to placebo at year 3.

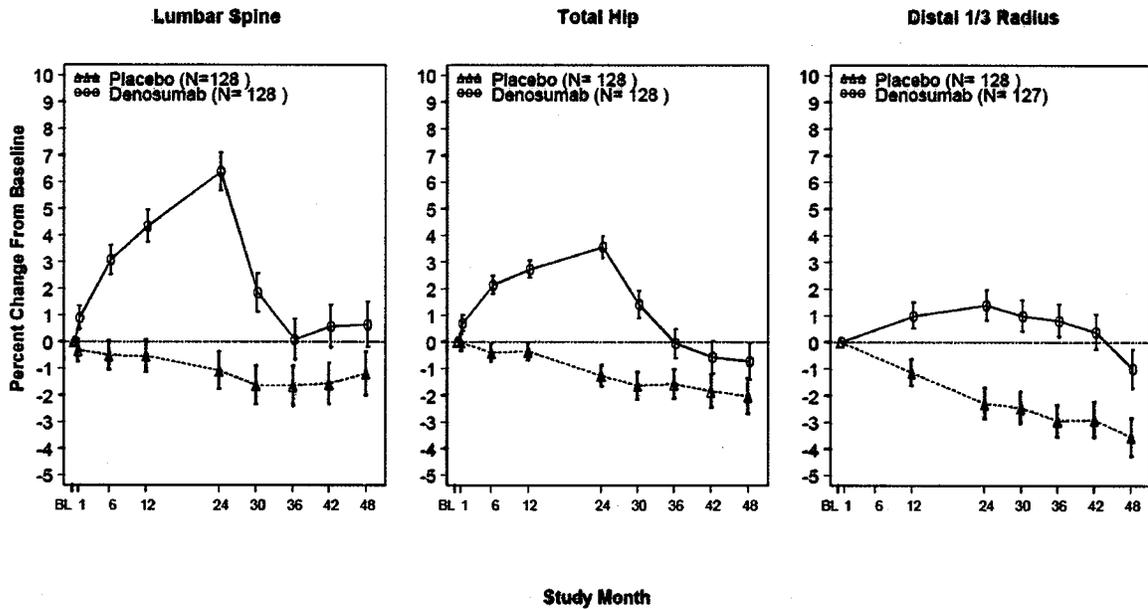
Table 2: Trial 20030216 bone Mineral Density Endpoints

Trial 20030216: Percent Change in BMD at Year 3, mITT, LOCF		
	Placebo	Denosumab
Lumbar Spine, n (mITT)	3160	3203
LS mean percent change	0.6	9.4
LS mean difference (95% CI)	8.8 (9.6, 9.1)	
p-value	<0.0001	
Total Hip, n (mITT)	3608	3624
LS mean percent change	-1.4	5.0
LS mean difference (95% CI)	6.4 (6.2, 6.6)	
p-value	<0.0001	
Femoral Neck, n (mITT)	3608	3624
LS mean percent change	-0.8	4.4
LS mean difference (95% CI)	5.2 (5.0, 5.4)	
p-value	<0.0001	
Trochanter, n (mITT)	3608	3624
LS mean percent change	-1.4	7.0
LS mean difference (95% CI)	8.3 (8.0, 8.6)	
p-value	<0.0001	
Source: compiled by reviewer based on 20030216 study report and statistical review		

The durability of the effect on bone mineral density was assessed in trial 20040132. Trial 20040132 is a randomized, double-blind, placebo- and active-controlled, 4-year, 2-period study trial evaluating the safety and efficacy of denosumab use in the prevention of postmenopausal osteoporosis population. The first 24 months of the study is considered the **“on-treatment” period, where all** subjects received study drug. The second 24 months of the study is the **“off-treatment” period**, where subjects were followed off of study drug. Subjects were randomized to receive either placebo or denosumab 60 mg SC every six months. The primary endpoint of the study was the percent change from baseline in lumbar spine BMD at month 24.

As outlined in Figure 1, the bone density gains achieved with denosumab therapy were rapidly lost in the first year after treatment was discontinued.

Figure 1: Bone Mineral Density by DXA Percent Change From Baseline by Visit, Least Squares Means and 95% CIs From Repeated Measures Model



Source: Figure 10, original primary clinical review, page 70-72.

One safety concern raised in the initial review cycle was whether the degree of bone suppression achieved with denosumab may have unintended consequences over time. During the initial review cycle, it was noted that the 95% confidence interval for the absolute risk reduction at 36 months for hip fracture included zero, so further investigation of hip fracture data at yearly intervals was done. When evaluated by yearly time intervals, the percentage of hip fractures is greater in the placebo group compared to the denosumab group within the year 1 and year 2 time intervals. At year 1, 20/3905 (0.51%) of placebo subjects and 10/3902 (0.26%) of denosumab subjects sustained a hip fracture. In year 2, 14/3672 (0.38%) of placebo subjects and 4/3672 (0.12%) of denosumab subjects had a hip fracture. However, in the year 3 time interval, 9/3430 (0.26%) placebo subjects and 12/3477 (0.34%) denosumab treated subjects sustained a hip fracture. For the denosumab group, the percentage of hip fractures within year 3 is nearly a threefold increase compared to within year 2. The fluctuation in the percentage of hip fractures in the denosumab group appears to be counterintuitive since one would expect the percentage to either decrease or remain the same with an osteoporosis treatment, which is usually what has been observed with other therapies. Also, the percentage within year 3 is greater in the denosumab group compared to the placebo group, suggesting that the percentage of hip fractures in the denosumab group has caught up with that in the placebo group. It is not clear if these findings presage a change in denosumab efficacy with time.

To assess this further, the occurrence of hip fractures, which were reported as adverse events, in the open label extension study 20060289 were evaluated. Of the 2346 subjects who received denosumab in the study 20030219 and continued denosumab in the extension study, 7 (0.30%) hip fractures had occurred. It does not appear that there is a marked difference between the hip

fracture rate in the extension study when compared to year 3 of the original fracture trial (0.34%).

8. Safety

Trial 20030216 provides the majority of the safety database for denosumab use in postmenopausal women with osteoporosis. A complete safety review of this trial was conducted during the first review cycle. Please see the primary clinical review from the first review cycle for complete details.

A total of 7762 subjects (3876 placebo, 3886 denosumab) received at least one dose of study medication in trial 20030216 with 76% of the placebo group and 80% of the denosumab group receiving all six doses of study medication. Of those enrolled, 83% completed the three years of the study.

In this complete response, the Applicant has updated the safety database to include data from 12 ongoing and recently completed clinical studies. These include trial 20060289, which is the open-label extension study for trial 20030216, and trial 20050233, which is the open-label extension phase of the phase 2 trial 20010223. In addition, data from the off-treatment phase of the other 3 main registration trials 20040132 (prevention of osteoporosis), 20040135 (bone loss due to hormone ablation therapy in breast cancer), and 20040138 (bone loss due to hormone ablation therapy in prostate cancer) were submitted.

Of the 6480 subjects (3208 in the placebo group and 3272 in the denosumab group) who completed the three years of trial 20030216, 4550 (2207 from the placebo group and 2343 from the denosumab group) enrolled in the open label extension study 20060289. In this extension study, all subjects receive denosumab 60 mg every 6 months. Therefore, some are new to denosumab (placebo/denosumab group) while others will be on denosumab for an extended period of time (denosumab/denosumab group). The demographic characteristics of those continuing in the study did not differ markedly from the original study population. In the original double-blind study, the mean age of enrollees was 72 years while the mean age was 75 years in the open label extension study.

Deaths: In trial 20030216, 160 subjects (90 in the placebo group a 70 in the denosumab group) died during the study. The system organ class (SOC) classification of deaths was balanced between the two treatment groups. The most common SOC noted for cause of death were neoplasms, cardiac disorders, general disorders and nervous system disorders, which is expected for the general population of the age of the enrolled population.

In the ongoing extension study 20060289, there have been an additional 35 deaths (20 deaths in the placebo/denosumab group, 15 deaths denosumab/denosumab group). The most common SOC noted for cause of death were general disorders, neoplasms, nervous system disorders and cardiac disorders. One subject on continuous denosumab died of infection (pneumonia/sepsis).

Serious Adverse Events: In trial 20030216, nonfatal serious adverse events occurred in 1792 subjects (868 (22%) in the placebo group and 924 (24%) in the denosumab group). The most common SOC for SAEs were cardiac disorders, musculoskeletal disorders, neoplasms, and infections.

Serious adverse events in the first two years of the extension study 20060289 were reported for 610 subjects (14% of prior-placebo subjects and 13% of prior-denosumab subjects). Adjusted for subject-years of exposure, the rate of overall SAEs was 16.8 per 100 subject years in parent trial 20040216 and 18.0 per 100 subject years in the extension study (19.0 in prior-placebo and 17.2 in prior-denosumab subjects). The most common SOC for SAEs were injury, cardiac disorders, neoplasms and infections.

Adverse Events Leading to Study Withdrawal: In trial 20030216, 174 subjects (81 (2%) placebo, 93 (2%) denosumab) discontinued the trial due to an adverse event. Most events occurred in the SOC neoplasms, nervous system disorders, and musculoskeletal disorders. The most commonly reported adverse events leading to study discontinuation were breast cancer, back pain, and constipation.

In study 20050289, 56 (1.2%) subjects withdrew from the study due to an adverse event. Similar to trial 20030216, most events occurred in the SOC neoplasms, nervous system disorders, and musculoskeletal disorders. The most commonly reported adverse events leading to study discontinuation were lung cancer, colon cancer, death, lymphoma and breast cancer.

Adverse Events Leading to Discontinuation of Investigational Product: Subjects had the option of discontinuing study drug and remaining in trial 20030216 for collect further data. Overall, 394 subjects (5% of each treatment group) discontinued study drug. The most common reason for study drug discontinuation was neoplasm in the denosumab group (19 (0.5%) placebo, 40 (1%) denosumab) and fracture in the placebo group (20 (0.5%) placebo, 6 (0.2%) denosumab). Breast cancer was the most common malignancy reported followed by colon cancer, gastric cancer, ovarian cancer and pancreatic cancer.

In the first two years of the extension study 20060289, adverse events leading to study drug discontinuation occurred in 73 (1.6%) subjects. The most common reason for study drug discontinuation was neoplasm (9 (0.4%) placebo/denosumab subjects and 12 (0.5%) denosumab/denosumab subjects).

Adverse Events: Adverse events were reported by 93% of subjects in both treatment groups in trial 20030216. The most commonly reported adverse event SOC were musculoskeletal disorders, infections, and gastrointestinal disorders. The most commonly reported adverse events (>10% in either treatment group) were: back pain, arthralgia, dizziness, hypertension, nasopharyngitis, pain in extremity, and osteoarthritis.

In trial 20060289, 74% of enrolled subjects reported at least one adverse event. The most common SOC for reported AEs are musculoskeletal disorders, infections, gastrointestinal disorders, and nervous system disorders. No specific adverse event preferred term occurred in

greater than 10% of subjects. The most commonly reported adverse events (>5%) were: arthralgia, back pain, hypertension, and nasopharyngitis.

Adverse Events of Special Interest:

Several notable safety issues were identified in the first review cycle. These include hypocalcemia, serious infection, new malignancies, dermatologic adverse events, pancreatitis, and adverse events related to **suppression of bone turnover – osteonecrosis of the jaw**, atypical fractures and fracture healing complications.

Hypocalcemia: Bone is the reservoir for calcium. Inhibition of osteoclasts by anti-resorptive agents such as denosumab impairs **the body's ability to mobilize calcium from** the bone when it is needed. Consequently, hypocalcemia can result from anti-resorptive therapies. The nadir in calcium appears to occur approximately 10 days after denosumab dosing. Laboratory testing in the phase 3 trial 20030216 did not occur during the times of anticipated calcium nadir. The testing a one month post dose likely fails to capture true nadir. However, at month 1, 3 (0.08%) subjects in the placebo group and 33 (0.8%) subjects in the denosumab group were noted to have calcium levels below 8.5 mg/dL.

In the extension study 20060289, five adverse events of hypocalcemia were reported in subjects new to denosumab therapy (previously treated with placebo). Serum calcium was measured at the anticipated calcium nadir 10 ± 5 days. The median decrease in serum calcium at day 10 was greater, -3.1%, in subjects new to denosumab (placebo-to-denosumab group) compared to -2.0% in those that continued on denosumab (denosumab-to-denosumab group). Overall, 3.3% of subjects had a serum calcium < 8.5 mg/dL at day 10.

Hypocalcemia in subjects with renal disease is a particular concern. During the original review cycle, it was noted that in a Phase 1 trial of subjects with all phases of renal function, subjects with baseline creatinine clearance less than 30 mL/min developed significant hypocalcemia (Ca <7.5 mg/dL or symptoms). Subjects in this trial did not receive calcium and vitamin D supplementation, which may have contributed to the extent of the hypocalcemia. The trial was stopped and the protocol was amended to require calcium and vitamin D supplementation. After supplementation was initiated, the calcium nadir ~~is~~ in the severe renal disease group was improved to the levels of the other groups. In trial 20060289, one subject with renal impairment developed a serum calcium of 7.0 mg/dL, associated with nausea.

Hypocalcemia remains a safety concern for all antiresorptive agents. Subjects in both the clinical and extension studies received calcium and vitamin D supplementation. The risk of hypocalcemia will be highest in patients who are not adequately replete or supplemented with calcium and vitamin D. Product labeling will include a contraindication for patients with low calcium levels and a warning and precaution outlining the hypocalcemia risk in patients at risk because of underlying disturbances of mineral metabolism including patients with renal disease.

The following Warning and Precaution language has been agreed upon with the Applicant:

5.1 Hypocalcemia and Mineral Metabolism

Hypocalcemia may be exacerbated by the use of [TRADENAME]. Pre-existing hypocalcemia must be corrected prior to initiating therapy with [TRADENAME]. In patients predisposed to hypocalcemia and disturbances of mineral metabolism (eg, 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 [TRADENAME] 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 (17.1)*].

Cardiovascular Safety. During the development program for denosumab, a concern was raised regarding the potential for denosumab to promote arterial wall calcification and atherosclerosis. Reports in the published literature suggested a possible association between OPG levels and arterial wall calcification, cardiovascular disease and mortality. Inactivation of RANKL by denosumab could result in elevated levels of osteoprotegerin (OPG) as it binds to the same target. A thorough review of cardiovascular events and assessments including aortic calcification scores was conducted in the phase 3 trial 20030216. No clear cardiovascular safety signal was seen. Please see the first cycle primary reviews for complete details.

In the extension study 20060289, five subjects died due to cardiovascular disease (3 in the placebo/denosumab group and 2 in the denosumab/denosumab group). Ischemic cardiovascular serious adverse events were balanced between the two groups. The most common serious adverse events of cardiac disorders were atrial fibrillation (0.3%), angina pectoris (0.3%), and coronary artery disease (0.3%). When evaluated in terms of exposure, in the continuous-denosumab cohort cardiac SAE event rates were 2.6 per 100 subject-years of exposure during trial 20030216 compared to 2.2 per 100 subject-years of exposure in trial 20060289.

With the addition of the resubmission safety update, there remains no clear signal of a cardiac safety concern. For this reason, specific product labeling for cardiovascular safety is not necessary.

Infections. RANKL is expressed on activated T and B lymphocytes, in the lymph nodes, and play a role in dendritic cell (antigen presenting cells) maturation. Therefore, it is

biologically plausible that the RANKL inhibitor denosumab could increase the risk of infection as T and B lymphocytes are responsible for foreign antigen recognition.

As discussed in the first cycle reviews, the finding of three subjects hospitalized for pneumonia after a single dose of denosumab raised concerns. While one subject was older with a history of chronic bronchitis, the other two subjects were healthy males under the age of 35 years. The Applicant believes that these data should not be relied upon because confirmatory records could not be obtained. However, it remains concerning that healthy volunteers appeared to have serious events of pneumonia. Additionally, in the Phase 2 dose-finding study, 20010223, infection serious adverse events occurred in 10 (3.2%) denosumab-treated subjects and no subjects in the placebo or active control groups.

In the phase 3 trial 20030216 opportunistic infections were not increased in the subjects receiving denosumab. When infection serious adverse events were examined in detail, infections related to bacteria and unspecified pathogens occurred at higher incidence in denosumab subjects compared with placebo. Specifically, serious bacterial infections occurred in 15 (0.4%) of placebo subjects and 25 (0.6%) of denosumab subjects and serious infections due to an unspecified pathogen occurred in 115 (2.8%) of placebo subjects and 138 (3.4%) of denosumab subjects. In trial 20030216, denosumab-treated subjects appeared to have a higher incidence of skin, abdominal, ear, and urinary tract infections. Skin infection serious adverse events occurred in 3 (0.1%) placebo subjects and 14 (0.4%) denosumab subjects. Gastrointestinal infection serious adverse events occurred in 22 (0.5%) placebo subjects and 28 (0.7%) denosumab subjects. Serious ear infection adverse events occurred in no placebo subjects and 5 (0.1%) denosumab subjects. The majority of these cases were labyrinthitis. Serious urinary tract infection adverse events occurred in 17 (0.4%) placebo subjects and 28 (0.7%) denosumab subjects. Also of concern is the imbalance in endocarditis serious adverse events, which occurred in no placebo-treated subjects and three denosumab-treated subjects. This occurrence rate is much higher than would be anticipated **based on the published literature = 0.2 – 0.6 cases** pretreatment group based on 11,000 person years of exposure.

In the extension study 20060289, 30% of subjects had an adverse event of infection (29.4% of the placebo/denosumab group and 31% of the denosumab/denosumab group). Serious adverse events of infection were reported in 1.7% of subjects (2.0% of the placebo/denosumab group and 1.5% of the denosumab/denosumab group). Skin infection serious adverse events occurred in 4 subjects (1 placebo-denosumab subjects and 3 denosumab-denosumab subjects). The most common serious adverse events of infection were pneumonia (0.4%) and sepsis, diverticulitis, and bronchitis (0.1% each). An imbalance in the number of sepsis SAEs was noted (1 in the placebo/denosumab group and 4 in the denosumab/denosumab group). There were no imbalances noted in gastrointestinal or urinary tract serious infections, although the numbers are quite small. There were no reports of endocarditis or opportunistic infections.

The findings in the open-label extension study do not change the concern regarding serious infections with denosumab use. Serious infections will be included as a warning and precaution in the product label.

The following Warning and Precaution language has been agreed upon with the Applicant:

5.2 Serious Infections

In a clinical trial of over 7800 women with postmenopausal osteoporosis, serious infections leading to hospitalization were reported more frequently in the [TRADENAME] 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 [TRADENAME]. Endocarditis was also reported more frequently in [TRADENAME]-treated subjects. The incidence of opportunistic infections was balanced between placebo and [TRADENAME] 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 [TRADENAME]. In patients who develop serious infections while on [TRADENAME], prescribers should assess the need for continued [TRADENAME] therapy.

Dermatologic Adverse Events: In trial 20030216, a significant imbalance in dermatologic adverse events (skin infections are not included) was noted in the postmenopausal osteoporosis database. These events did not include skin infections, tended to be generalized and not specific to the drug injection site. This imbalance was mainly due to **imbalances observed in HLGT “Dermal and Epidermal conditions”, driven by dermatitis, eczema, and rashes.** The dermal and epidermal adverse events including toxic skin reactions and bullous conditions occurred at approximately a 10-fold increased incidence in denosumab treated subjects. After further case review, denosumab could not be clearly implicated as the causative agent nor could it be definitively ruled out as the cause.

In the extension trial 20060289, adverse events in the HLGT **“Dermal and Epidermal conditions” occurred in 4% of subjects.** There was no imbalance between the two groups. Adverse events of eczema (including dermatitis, allergic dermatitis, and contact dermatitis) were reported for 0.9% of subjects. When evaluated in terms of exposure, adverse event rates were similar for preferred terms of eczema (0.6 and 0.5 per 100 subject-years, respectively), dermatitis (0.2 and 0.3, respectively), allergic dermatitis (0.4 and 0.1, respectively), and contact dermatitis (< 0.1 and < 0.1, respectively).

The findings in the open-label extension study do not change the concern regarding dermatologic adverse events with denosumab use. A warning and precaution outlining the concern regarding dermatologic adverse events will be included in the product label.

The following Warning and Precaution language has been agreed upon with the Applicant:

5.3 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 [TRADENAME] group compared to the placebo group. Most of these events were not specific to the injection site [see *Adverse Reactions (6.1)*]. Consider discontinuing [TRADENAME] if severe symptoms develop.

New Malignancies: During the first cycle review, concerns arose regarding the incidence of new malignancies in subjects treated with denosumab. In the dose-finding studies, three subjects, all treated with denosumab, died due to neoplasms. ~~and~~ In trial 20030216 breast cancer was a common reason for withdrawal from the trial and cancers (breast cancer followed by colon cancer, gastric cancer, ovarian cancer and pancreatic cancer) ~~was~~ were the most common reason for study drug discontinuation.

In the extension study 20060289, adverse events related to malignant neoplasms were reported in 2.6% of subjects. By preferred term, the most common events were basal cell carcinoma, breast cancer, colon cancer, thyroid neoplasm, and lung neoplasm malignant. Eight subjects died of adverse events in the neoplasms SOC.

As outlined in the first cycle primary clinical review page 204, one case of Schofflers tumor was observed in a subject treated with denosumab in trial 20030216. Schofflers tumor is a rare inflammatory pseudotumour of the abdominal wall with aggressive connective tissue proliferation which frequently infiltrates neighboring abdominal organs. The lesion belongs to the reactive tumor-like fibromatoses. Since RANKL was originally found in dendritic cells of the skin, and this very rare condition occurred in the denosumab group, this one case raises concerns about increased possibility of such events. However, it is not possible to assess the risk of this very rare tumor based on one case.

The higher incidence of several types of malignancies in denosumab subjects is concerning. However, the significance of these findings in studies of moderate duration is unclear due to the long latency for malignancies. Therefore, the information on new malignancies will be presented in the adverse reactions section of the product labeling.

Pancreatitis: In trial 20030216, there was an imbalance in events of pancreatitis in subjects randomized to denosumab. A total of 4 subjects in the placebo group and 8 subjects in the denosumab group reported an event of pancreatitis. When evaluated in terms of severity, one placebo-treated subject had a serious adverse event of pancreatitis while all eight subjects in the denosumab group had pancreatitis events that were serious.

In the extension trial 20060289, one non-serious adverse event of acute pancreatitis was reported in the placebo/denosumab group, with none in the denosumab/denosumab group.

The imbalance in serious events of pancreatitis remains a concern and information on the events of pancreatitis in trial 20030216 will be presented in the adverse reactions section of the product labeling.

Osteonecrosis of the jaw: Osteonecrosis of the jaw (ONJ) has been noted in patients receiving other potent anti-resorptive therapies. For the denosumab development program, the Applicant convened an Osteonecrosis of the Jaw Adjudication Committee to evaluate potential cases of ONJ. Documented cases of ONJ with denosumab use in the advanced

cancer population have been identified and positively adjudicated. These cases were described during the first review cycle.

At the time of the Applicant's initial complete response submission, seven additional cases of possible ONJ had been referred for adjudication and none were confirmed. However, during this review cycle, one case of ONJ from the open label extension study 20060289 has been positively adjudicated and reported.

This is the first case of positively adjudicated ONJ from an osteoporosis clinical trial for any agent. Therefore, osteonecrosis of the jaw will be included in the warnings and precautions section of the product label. This finding heightens the concern regarding bone over-suppression which is thought to be one of the potential etiologies of ONJ.

The following Warning and Precaution language has been agreed upon with the Applicant:

5.4 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 [TRADENAME] treatment. A dental examination with appropriate preventive dentistry should be considered prior to treatment with [TRADENAME] 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 [TRADENAME].

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 [TRADENAME] 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 [TRADENAME] therapy should be considered based on individual benefit-risk assessment.

Ocular Adverse Events: During the first review cycle, adverse events of cataracts were noted with increased frequency in the denosumab-treated subjects in the prostate cancer trial 20030138 (1.2% of the placebo group and 4.7% of the denosumab group). In the PMO trial 20030216, cataracts were reported in 6.3% of the placebo group and 5.7% of the denosumab group. In the extension study 20060289, 8 subjects (3 (0.7%) placebo/denosumab subjects and 5 (1.3%) denosumab-denosumab subjects) reported an adverse event of cataract. No clear safety signal is evident for cataracts in the PMO population.

Suppression of Bone Turnover and Bone Remodeling: Denosumab acts by inhibiting bone resorption. Because bone resorption and bone formation are tightly coupled, both components

(bone resorption and bone formation) become suppressed with denosumab therapy. As noted in the first cycle clinical reviews, biochemical markers of bone turnover were suppressed such **that a 39 – 68% of subjects have serum CTX levels** that were below the limit of quantitation for the assay used. One month after denosumab injection, CTX levels were suppressed as much as 94% from baseline. This level of CTX suppression has not been noted with any other antiresorptive agent.

Bone histomorphometry findings were also reviewed in depth in the first review cycle. When evaluating bone histomorphometry findings, the presence of double tetracycline labeling in a biopsy specimen provides an indication of active bone remodeling and formation. All subjects in the placebo group had double tetracycline label present in their biopsy specimens. However, 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. While a sporadic biopsy specimen with absence of double label is not unusual, the number of patients treated with denosumab who have absence of double labeling is striking. One concern is that absence of double label may suggest over suppression of bone turnover and formation. Trabecular double label is required for full evaluation of dynamic bone formation parameters. Full assessment of dynamic parameters was only possible in 5/26 biopsy specimens from denosumab treated subjects at month 24 and in 2/17 biopsy specimens denosumab treated subjects at month 36, again strikingly low numbers. When bone remodeling parameters were evaluated, remodeling activity was virtually absent at month 36 in the very small number of evaluable biopsies.

While the long-term clinical consequences of this degree of suppression is not clear, the level of suppression of bone turnover markers and the bone histomorphometry findings raise concerns regarding the degree to which denosumab suppresses bone turnover and what impact that may have on adverse events related to bone suppression, especially with prolonged therapy. Specific adverse events of interest potentially related to bone suppression, such as osteonecrosis of the jaw (previously discussed), fracture healing complications, and atypical fractures were reviewed.

Fracture Healing. When bone turnover is significantly suppressed, the potential exists for negative effects on fracture healing, which requires both bone formation and bone resorption. During the development program, specific concerns were raised regarding **denosumab's effect on fracture healing**. Fracture healing complications were reviewed during the first review cycle. A total of 364 subjects in the placebo group and 303 subjects in the denosumab group sustained at least one nonvertebral fracture during the conduct of trial 20030216. For all nonvertebral fractures, data collected on specific case report forms regarding the event included follow-up on fracture complications (eg, delayed healing, malunion, nonunion). The Applicant reported two subjects in each treatment group had delayed fracture healing and one subject in the placebo group had fracture nonunion. However, the Applicant did not report on other fracture healing complications, such as abnormal healing time, chronic pain and the need for further surgical reduction. Upon further review of the data submitted, 25 subjects in the placebo group and 21 subjects in the denosumab group were reported to have a complication related to fracture healing.

The Applicant also conducted a specific fracture-healing substudy in trial 20030216. This substudy was to enroll subjects who experienced a distal radial fracture and were expected to remain in the study for at least 3 more months. A total of 190 distal radial fractures were reported in study 20030216. Of these, only 25 subjects (17 placebo, 8 denosumab) were enrolled in the fracture healing substudy. Two subjects in the placebo group and one subject in the denosumab group had delayed radiographic healing of their distal radius fracture. All 3 of the fractures were radiographically considered healed by the time of the 6 month radiograph.

No adverse events related to fracture healing were reported in the open-label extension study 20060289.

Atypical Subtrochanteric Fractures of the Femur. Recent reports suggest that atypical subtrochanteric fractures of the femur may be a consequence of anti-resorptive therapy. The incidence of subtrochanteric hip or femur fractures with denosumab use was evaluated. In trial 20030216, 79 subjects (48 in the placebo group and 31 in the denosumab group) sustained a hip or femur fracture. The majority were femoral neck (36 subjects: 20 placebo, 16 denosumab) or intertrochanteric fractures (39 subjects: 25 placebo, 14 denosumab). Four placebo-treated subjects had femoral shaft or lower femur fractures reported. One denosumab-treated subject sustained a periprosthetic fracture. There were no fractures reported as subtrochanteric fractures.

In the extension study 20060289, 21 subjects sustained hip or femur fractures (14 in the placebo/denosumab group and 7 in the denosumab/denosumab group). Fifteen of the fractures were of the femoral neck, 6 were intertrochanteric fractures, and one was a subtrochanteric femur fracture (in a denosumab/denosumab subjects).

The degree of bone suppression achieved with denosumab therapy remains a concern, especially given the chronic nature of osteoporosis therapies. While it is reassuring that there is no lasting bone suppression effect after denosumab is discontinued, the clinical consequences of this degree of bone suppression remain unclear. For these reasons, concerns regarding the degree of bone suppression will be included in the Warning and Precautions section of the product label and the following language has been agreed upon with the Applicant:

5.5 Suppression of Bone Turnover

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

9. Advisory Committee Meeting

An Advisory Committee meeting was convened during the first review cycle on August 13, 2009 to discuss the four indications sought for denosumab. Because all four indications were to be discussed, the Committee was comprised of some representative members from the Reproductive Health Advisory Committee and the Oncology Advisory Committee as well as experts in the fields of bone/osteoporosis, infectious diseases, dermatology and epidemiology. The issues that the Committee was asked to consider with regard to the risk/benefit profile for denosumab included the following safety concerns:

- Occurrence of serious infection,
- Development of new malignancies,
- Potential for tumor progression in patients with cancer,
- Bone histomorphometry findings that suggest suppression of bone remodeling which may lead to complications such as delayed fracture healing, ONJ, or atypical fracture with long-term use, and
- Dermatologic adverse events.

Pertinent to the treatment of postmenopausal osteoporosis indication, the committee voted unanimously for approval. Many committee members felt that limiting the treatment population to those at high risk of fracture may be warranted until more information is known about the long-term risks of the therapy. The majority of the panel believed that denosumab should have a Risk Evaluation and Mitigation Strategy (REMS) which included a Medication Guide to inform patients about the risks of the drug and a Communication Plan to educate providers about major safety concerns. In addition, some members also believed that, given the need for providers to administer the drug, a registry was also warranted to better follow patients prospectively.

10. Pediatrics

The Applicant's request to waive the requirement to conduct pediatric studies in all age groups for denosumab was reviewed by the PeRC PREA subcommittee on June 3, 2009, and was granted. A full waiver for pediatric studies was recommended because studies would be impossible or highly impracticable and because the indications for this drug product (postmenopausal osteoporosis) do not occur in the pediatric population.

11. Other Relevant Regulatory Issues

No other outstanding regulatory issues exist for this BLA.

12. Labeling

After thorough review by the clinical team, the Division of Medication Error Prevention and Analysis (DMEPA), and the Division of Drug Marketing, Advertising and Communication (DDMAC), **the Applicant's proposed proprietary name "Prolia" is acceptable.**

Carton and Container labels have been reviewed by DMEPA and the Office of Biotechnology Products. The Applicant has made all requested changes to the carton and container labeling and they are acceptable.

The statement of the indication in the full prescribing information was an area of significant disagreement between the Applicant and the clinical team. The Applicant proposed the **indication language as “treatment of osteoporosis in postmenopausal women at increased risk for fracture”**. **This language reflects the language** of the general osteoporosis indication in the European Union, but would be new label language for osteoporosis therapies in the United States. Currently, there are two indication language scenarios with approved osteoporosis therapies: 1) treatment of osteoporosis in postmenopausal women and 2) treatment of osteoporosis in postmenopausal women at high risk of fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. The distinction between the two indications is based solely on safety, as is the case with Forteo. In the case of Forteo, the osteosarcoma risk was of sufficient concern to warrant limiting the population to one of high risk of fracture. With denosumab, a similar high level of concern exists, and therefore limiting the population to one of high risk of fracture is warranted. While there may be only small differences between **“increased risk of fracture”** and **“high risk of fracture”**, **the clinical team believes it is** important to maintain the two indication approach to osteoporosis therapies and not introduce new terminology that has the potential to add confusion. This is especially true given the term **“increased risk of fracture”** is utilized in the EU as the general osteoporosis indication. After negotiation, the following indication language has been agreed upon with the applicant:

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

[TRADENAME] 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, [TRADENAME] reduces the incidence of vertebral, non-vertebral and hip fractures *[see Clinical Studies (14.1)]*.

The remainder of the language in the full prescribing information has also been agreed upon with the Applicant.

A Medication Guide is required as a component of the REMS, and language has been negotiated and agreed upon with the Applicant.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

This reviewer agrees that denosumab, trade name Prolia, should be **approved** for the indication 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.

- Risk Benefit Assessment

Osteoporosis is a skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone leading to an increase in fragility and susceptibility to fracture. Based on bone mineral density measurements, approximately 8 million women in the United States have osteoporosis. Approximately 45% of women with osteoporosis who are over the age of 55 years will sustain a fracture during their postmenopausal years. Osteoporosis is responsible for more than 1.5 million fractures annually, including approximately 300,000 hip fractures, 700,000 vertebral fractures, 250,000 wrist fractures, and more than 300,000 fractures at other sites based on estimated from the National Institute of Arthritis and Musculoskeletal and Skin Diseases.¹ The goal of treatment for postmenopausal osteoporosis is to reduce the risk of fractures.

In the osteoporosis treatment population, denosumab, 60 mg q 6 months is effective in decreasing the incidence of new morphometric vertebral fractures (absolute reduction 4.8%, relative reduction 68%, p-value <0.0001), nonvertebral fractures (absolute reduction 1.5%, relative reduction 20%, p-value 0.0106), and hip fractures (absolute reduction 0.3%, relative reduction 40%, p-value 0.0362). However, multiple safety issues have been identified, including serious infections, hypocalcemia, dermatologic adverse events, pancreatitis, and events related to over suppression of bone turnover (osteonecrosis of the jaw, delayed fracture healing and the incidence of atypical fractures). These risks can be addressed by restricting the population to patients with osteoporosis at high risk of fracture, appropriate labeling to provide information to both healthcare providers and patients, and by close follow-up in the postmarketing period. A postmarketing Risk Evaluation and Mitigation Strategy will help ensure that the benefits of denosumab therapy outweigh the risks.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

The review division and the Division of Risk Management agree that a REMS is necessary to ensure that the benefits of denosumab therapy outweigh the risks of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover.

The REMS components necessary include a Medication Guide, a communication plan, and a timetable for submission of assessments. The Applicant submitted all REMS components with their complete response. These components have been reviewed by the appropriate teams in the Division of Risk Management. Please see **Dr. Elizabeth Donohue's review for complete details**. Agreement has been reached between the Applicant and FDA for the Medication Guide language. Agreements in principle have been reached regarding the communication plan, which consists of a Dear Healthcare Provider Letter, the REMS-dedicated web page, the REMS document and the REMS supporting document. However, final editorial changes continue to be negotiated at the time of this review.

¹ http://www.niams.nih.gov/Health_Info/Bone/Osteoporosis/default.asp

- Recommendation for other Postmarketing Requirements and Commitments

During the first review cycle, the Applicant proposed a routine pharmacovigilance plan as well as a prospective observational study using large administrative databases to further assess **denosumab's safety in the postmarketing setting**. The proposed prospective observational postmenopausal osteoporosis study uses large administrative databases such as United Healthcare and the Medicare 5% sample, electronic medical records from closed medical systems such as Kaiser Permanente, and the Scandinavian registry database. To assess the feasibility of this proposal, the Applicant proposed to conduct preliminary assessments of background event rates in the relevant patient populations using these databases. These preliminary studies were to assist in identifying appropriate comparator populations to reduce the impact of confounding by indication on event rates. These preliminary assessments would form the basis for the study design and statistical methodologies for the proposed postmarketing observational study. They would also evaluate the strengths and limitations of the proposed databases in the conduct of valid postmarketing pharmacoepidemiology studies.

However, the feasibility of this proposal had not been adequately investigated and the need for adequate assessment of feasibility was believed to be necessary prior to approval of **denosumab**. Please see **Dr. Carolyn McCloskey's initial Division of Epidemiology (DEPI)** review for complete details. For this reason, a complete response letter was issued to the Applicant during the first review cycle. The review division and DEPI continued to work with the Applicant regarding the required elements of the feasibility study. At the time of resubmission, the Applicant did provide all requested data for the feasibility study. Please see **Dr. Carolyn McCloskey's second review for complete details**. Amgen addressed DEPI's comments on their original Feasibility study protocol and completed the Feasibility study prior to denosumab approval as requested by FDA. Overall, the algorithms designed to identify women with postmenopausal osteoporosis (including the use of osteoporosis medication codes) are acceptable. Capturing denosumab exposure appears feasible although concerns remain over the use of temporary codes within the first year of the product launch. The algorithms for identifying the AESIs are consistent across the four data systems but are **tailored for optimal results to each data system's** characteristics, such as review of medical records, radiographic, and laboratory results. The AESI background incidence rates in the literature tended to be lower than those found in the four data systems. Based on the feasibility study, the Observational Databases study should provide valuable information on the safety of denosumab. However, DEPI has the following comments regarding the feasibility study: **The following recommendations for Amgen's Observational Databases study** (protocol 20090522) are because the feasibility study could not address these areas. These comments were conveyed to the Applicant and the Applicant has adequately addressed them:

1. State in the protocol that 100% of the Medicare databases will be used for the study (Section 4.3 still states a 5% random sample, page 25).
2. **The protocol should define "other osteoporosis medications" for the other osteoporosis medications comparison group** (Section 4.4, page 25).
3. Address how missing data will be handled.

4. Validation of denosumab exposures shortly after denosumab marketing because nonspecific or temporary codes for drug use are used by most new drugs.
5. Report the proportion of women ≥ 55 years old with PMO and compare for each of the data systems to the 40% reported in the literature for women ≥ 65 years old.

The Applicant did agree to changes for the long-term observational study (Protocol 200900522) as requested by FDA. In addition to review by DEPI, the Division of Biometrics VII also conducted a statistical review of protocol 20090522. **Please see Dr. Mat Soukup's review for complete details. Using the Applicant's as well as the simulation study using Fisher's Exact test, the planned study appears to be sufficiently powered.** However, concern has been raised that several of the assumptions used in the power calculations may not be precise based upon the available information to date. Therefore, it is recommended that the Applicant consider conducting an analysis of the data base after several years to address the accuracy of their estimates and the potential for the study to be underpowered to detect **AESI's. The following comets were conveyed to the Applicant, and the Applicant agrees to submit a detailed statistical analysis plan by November 1, 2010:**

Accounting for the fact that true market experience of denosumab is unknown at this time, the following comments are based upon the review of Protocol 20090522.

1. The sponsor should submit to the Agency for comment a detailed statistical analysis plan prior to study initiation and include plans for how to make revisions to the SAP based upon information that arises once denosumab has market exposure. The plan should provide details on all statistical analyses outlined in the study protocol, including definitions of exposure, the meta analysis across the data bases, and the various methods discussed for adjustment for confounding when comparing across exposure groups.
2. Based upon the assumptions provided by the sponsor and the simulation study using **Fisher's Exact test, the planned study appears to be sufficiently powered** (power calculations were verified by the reviewer). However, it should be noted that several assumptions are made in the power calculations which may not be precise based upon the lack of information to date about actual use of denosumab. With large deviations from the assumed estimates used in the power calculations, the study may lack **sufficient power to detect AESI's. To protect against the use of inappropriate estimates used in the power calculations, the sponsor should conduct an analysis of the data base after several years to address the accuracy of their estimates and the potential for the study to be underpowered to detect AESI's.**

Because of the difficulty with diagnosis and coding of some of the adverse events of interest, the method of administration of denosumab (by a healthcare provider) provides a unique opportunity to collect data regarding the adverse events of concern in patients being treated with denosumab outside of the controlled clinical trial environment. Therefore, the applicant has agreed to conduct a long-term surveillance study in postmenopausal women administered denosumab to prospectively evaluate the incidence of serious infection including skin infections, dermatologic adverse events, and over-suppression of bone turnover. The Applicant

refers to this study as the Prolia™ Post Marketing Active Safety Surveillance Program for Soliciting Adverse Events of Special Interest in the United States (“**Surveillance Program**”, Protocol 20090601). The Applicant will notify potential providers of the program through mailings, email, sales representatives, and the Prolia website. Enrolled prescribers would then solicit information about adverse events from patients. Any information on appositive adverse event would then be reported to the company either electronically or by mail/phone/fax. Amgen will process the AE report routinely by following-up and reporting to FDA as they would any other AE. These Surveillance Program reports will also be summarized in an annual report to FDA and in the safety update reports submitted. The Surveillance Program will be conducted for 10 years. This study/program will complement the routine pharmacovigilance and observational database approaches also being conducted.

A long-term pregnancy registry was outlined as a postmarketing requirement in the October 2, 2009 letter to the applicant. A revised denosumab pregnancy exposure registry protocol was **submitted in the Applicant’s Complete Response. However, as outlined in Ms. Jeanine Best’s** review, the anticipated small enrollment numbers would mean that any information collected is not likely to be adequate or meaningful. Given that patients appropriate for treatment of postmenopausal osteoporosis would not be able to achieve pregnancy due to their postmenopausal state, the Maternal Health team does not believe that a postmarketing requirement for a pregnancy exposure registry for denosumab would be the appropriate method to collect pregnancy exposure data at this time.

However, the applicant has established a voluntary pregnancy surveillance program that is designed to gather data about pregnancy of women who have had exposure to an Amgen product prior to conception or during pregnancy. While this program is voluntary, it is another method of collecting drug exposure data during pregnancy, especially when a prospective observational pregnancy cohort study is not feasible. The Amgen Pregnancy Surveillance Program would be the appropriate method to use at this time to collect data about women who are exposed to denosumab within six months of conception or during pregnancy. The maternal health team has already reviewed the questionnaires used to collect information during pregnancy and on the infant following delivery. Therefore, the postmarketing requirement for a pregnancy exposure registry for denosumab has been removed from the Postmarketing Requirements and the Amgen Pregnancy Surveillance Program and contact information are included in the product labeling.

(b) (4)

As previously discussed, no specific drug-drug interaction studies have been conducted for denosumab. While it is true that denosumab does not necessarily behave like therapeutic proteins targeting inflammatory cytokines that have demonstrated roles in CYP regulation, it is still uncertain and premature to conclude that a RANKL antagonist will not impact CYP

expression. Therefore, the sponsor should conduct an *in vivo* drug-drug interaction study with CYP3A4 substrate (e.g., midazolam) in postmenopausal female patients with osteoporosis.

In their letter dated May 4, 2010, the Applicant has agreed to the following Postmarketing Requirements and Commitments:

Post-marketing Requirements

1. Conduct a retrospective cohort study using multiple existing observational databases to collect data from a 5-year period prior to the availability of denosumab. The study should identify women with postmenopausal osteoporosis and determine the occurrence of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover in each database in order to assess the background rates of those adverse events. The data obtained in this study will be used to inform the implementation of postmarketing requirement #2. The final protocol for this study was submitted on January 25, 2010.

Study Completion Date: May 2011
Final Report Submission: August 2011

2. Conduct 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.

Final Protocol Submission: November, 2010
Submit Report providing information on denosumab use: June 30, 2013
Study Completion Date: December, 2022
Final Report Submission: June, 2023

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

Final Protocol Submission: August 2010
Study Completion Date: December 2021
Final Report Submission: June 2022

4. Conduct an *in vivo* drug-drug interaction study with CYP3A4 substrate (e.g., midazolam) in postmenopausal female patients with osteoporosis to characterize the potential risk of drug interaction of denosumab with CYP3A4.

Final Protocol Submission: August 2010
Study Completion Date: November 2011
Final Report Submission: March 2012

Post-marketing Commitments

Office of Biotechnology Products:

Post-marketing Studies not subject to reporting requirements of 21 CFR 601.70:

1. To confirm validation of the updated SE-HPLC method (MET-001208). The method was revised to add column conditioning using material containing the high molecular weight species. The protocol and final report will be included in an annual report to be submitted by February 28, 2011.
2. To submit proposed revisions to the breakloose and extrusion release and shelf-life specifications for pre-filled syringe drug product based on an appropriate statistical method after 15 commercial manufacturing runs. The proposed revision to the specifications, the corresponding data from the 15 commercial manufacturing runs, and the analysis plan used to create the revisions will be provided in a Prior Approval Supplement by September 30, 2010.
3. To submit proposed revisions to the breakloose and extrusion release and shelf-life specifications for pre-filled syringe drug product based on an appropriate statistical method to reflect increased manufacturing experience. The proposed revision to the specifications, the corresponding data from the commercial manufacturing runs to date and the analysis plan used to create the revisions will be provided in a Prior Approval Supplement by March 31, 2012.

- Recommended Comments to Applicant

Although not specifically relevant to the postmenopausal osteoporosis population, the Pharmacology review team recommends that (b) (4)

[REDACTED]

If you intend to pursue denosumab for treatment in a population that included fertile women, further evaluation of the risks on reproduction and development would be necessary. These studies are needed to assess potential adverse effects on skeletal, immune and nervous system development, and would be required to support indications which would include women of child bearing potential in the patient population.

Theresa Kehoe

5/27/2010

Theresa Kehoe, MD

Clinical Team Leader, Division of Reproductive and Urologic Products

George Benson

5/28/2010

George Benson, MD

Deputy Director, Division of Reproductive and Urologic Products