

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**125320**

**SUMMARY REVIEW**

**Deputy Division Director Review**

<b>Date</b>	<b>May 28, 2010</b>
<b>From</b>	<b>George S. Benson, MD</b>
<b>Subject</b>	<b>Deputy Division Director Review</b>
<b>NDA/BLA#</b>	<b>BLA # 125320/000</b>
<b>Applicant</b>	<b>Amgen, Inc.</b>
<b>Date of Submission</b>	<b>January 25, 2010</b>
<b>PDUFA Goal Date</b>	<b>July 23, 2010</b>
<b>Proprietary Name/ Established name</b>	<b>Prolia/ denosumab</b>
<b>Dosage forms/Strength</b>	<b>60 mg subcutaneous injection administered every six months</b>
<b>Proposed Indications</b>	<b>Treatment of postmenopausal osteoporosis</b>
<b>Recommendation</b>	<b>Approval</b>

Best Possible Copy

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**DDMAC=Division of Drug Marketing, Advertising and Communication**  
**OSE= Office of Surveillance and Epidemiology**  
**DMEPA=Division of Medication Error Prevention and Analysis**  
**DSI=Division of Scientific Investigations**  
**DDRE= Division of Drug Risk Evaluation**  
**DRISK=Division of Risk Management**  
**CDTL=Cross-Discipline Team Leader**  
**DCRP=Division of Cardioresenal Products**  
**DAIOP=Division of Anti-infectives and Ophthalmology Products**  
**DDDP=Division of Dermatologic and Dental Products**  
**DEPI=Division of Epidemiology**  
**PMHS=Pediatric and Maternal Health Staff**  
**DRUP=Division of Reproductive and Urologic Products**  
**DMPQ=Division of Manufacturing and Product Quality**

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## 1. Introduction

This submission is a Complete Response to the October 16, 2009, action letter issued for the biologic licensing application (BLA) for denosumab (Prolia). Denosumab is a human monoclonal IgG2 antibody that targets receptor activator of nuclear factor kappa B ligand (RANKL).

Amgen, Inc. submitted a biologic licensing application (BLA) on December 19, 2008, for denosumab for four separate indications: 1) treatment of postmenopausal osteoporosis; 2) prevention of postmenopausal osteoporosis; 3) treatment and prevention of bone loss associated with hormone ablation therapy for breast cancer; and 4) treatment and prevention of bone loss associated with hormone ablation therapy for prostate cancer. Each of these four indications was assigned a separate BLA number:

BLA 125320: Treatment of postmenopausal osteoporosis

BLA 125331: Prevention of postmenopausal osteoporosis

BLA 125332: Treatment and prevention of bone loss in patients undergoing hormone ablation for breast cancer

BLA 125333: Treatment and prevention of bone loss in patients undergoing hormone ablation for prostate cancer

The two postmenopausal indications were reviewed by the Division of Reproductive and Urologic Products and the bone loss indications in the two cancer populations were reviewed by the Division of Biologic Oncology Products.

A Complete Response action letter for the two postmenopausal osteoporosis indications was sent to the sponsor on October 16, 2009. This complete response submission is seeking approval of only the "treatment of postmenopausal osteoporosis" indication. No new efficacy data are submitted. Updated safety information as well as information concerning post-marketing studies and risk evaluation and mitigation strategy (REMS) components are reviewed.

## 2. Background

Denosumab is the first monoclonal antibody submitted for the indication of treatment of postmenopausal osteoporosis. Denosumab is a human monoclonal IgG2 antibody that targets receptor activator of nuclear factor kappa B ligand (RANKL). The mechanism of action involves the antibody binding to RANK ligand and inhibiting the interaction of RANKL and its receptor (RANK). Inhibition of the RANK-RANKL interaction prevents receptor activation and 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. RANKL is also involved in the immune system where it is important in B-cell and T-cell differentiation as well as dendritic cell maturation.

The 1994 osteoporosis guidance document entitled "Guidelines for Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis" describes the need for a clinical trial to assess the effects of treatment on the incidence of new vertebral fractures at three years for approval of an osteoporosis indication. In the pivotal fracture trial, bone mineral density is generally a secondary endpoint. Once fracture efficacy has been demonstrated, this provides validation of the bone mineral density (BMD) endpoint, which then can be used as the primary endpoint for other indications such as the prevention of postmenopausal osteoporosis.

The denosumab original IND (IND 9837) was submitted on May 21, 2001. At that time, therapeutic monoclonal antibodies were reviewed in the Center for Biologic Evaluation and Research (CBER). Subsequently, all therapeutic proteins including monoclonal antibodies were transferred to the Center for Drug Evaluation and Research (CDER). There was no special protocol assessment requested for the pivotal fracture trial (Trial 20030216). The BLA was initially submitted on December 19, 2008.

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.

The Complete Response Action letter of October 16, 2009, relating to the treatment of postmenopausal osteoporosis, stated the following:

### 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.*

**A Risk Evaluation and Mitigation Strategies (REMS), consisting of a Medication Guide, a communication plan, and a timetable for submission of assessments was also required. In addition, post-marketing studies of Prolia (denosumab) were required to assess the signal of the risks of serious infection, including skin infections, dermatologic adverse events, and over-suppression of bone turnover.**

**This complete response submission 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.**

- 3. CMC**
- 4. Nonclinical Pharmacology/Toxicology**
- 5. Clinical Pharmacology**

**The CMC, nonclinical pharmacology/toxicology, and clinical pharmacology reviews are well summarized in the cross discipline team leader review and excerpts from these reviews are included in Appendix A of this review. No findings which would preclude approval of denosumab are identified.**

**A GMP inspection of the drug product manufacturing site in Puerto Rico initially revealed deficiencies which were detailed on the 483 form issued to the site. Upon final review, however, the Office of Compliance provided an “acceptable recommendation based on new information received and the firm’s intent to provide corrective actions to adequately address the CGMP deficiencies.”**

**6. Clinical Microbiology**

**The Division of Manufacturing and Product Quality review stated that “the BLA is recommended for approval from a sterility assurance and product quality microbiology perspective.”**

## 7. Efficacy/Statistics

No new efficacy data were submitted in this complete response resubmission.

The primary trial submitted to support the efficacy and safety of denosumab for the treatment of postmenopausal osteoporosis was Trial 20030216 which was submitted during the initial BLA submission. Trial 20030216 was a large (approximately 8000 subjects) trial whose primary endpoint was the incidence of new morphometric (radiographic) vertebral fractures at month 36.

### Trial 20030216

*Study population:* Subjects enrolled in this trial study were age 60 to 90 years, with diagnosed osteoporosis. Enrollees were required to have a bone mineral density T score of at least -2.5 but not lower than -4.0 at the lumbar spine and/or total hip. Radiologic evidence of baseline vertebral fracture was not required. Subjects previously on intravenous bisphosphonate, fluoride, or strontium therapy were excluded from the study. Subjects previously on oral bisphosphonate therapy for less than 3 months could be enrolled in the study. If the cumulative exposure were more than 3 months but less than 3 years, subjects could be enrolled only after a wash-out period of one year. For subjects on other osteoporosis therapies, subjects could be enrolled after a 6 week wash-out period.

*Study treatments:* Eligible subjects were randomized 1:1 to receive denosumab 60 mg or placebo subcutaneous injection, administered by a healthcare professional, every 6 months. All subjects were to receive daily calcium and vitamin D supplementation.

*Efficacy measures:* Trial 20030216 had one primary, two secondary, and fifty-six tertiary/exploratory efficacy endpoints. The primary endpoint was incidence of new morphometric vertebral fracture 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.

Lateral spine x-rays were performed at screening and months 12, 24, and 36 for all subjects. All lateral spine x-rays were assessed at a central reading facility using the Genant semi-quantitative scoring method. Nonvertebral fractures (osteoporotic) were those occurring during the study excluding those of the vertebrae (cervical, thoracic, and lumbar), skull, facial, mandible, metacarpus, finger phalanges, and toe phalanges. Hip fracture included fractures of the femoral neck, femur intertrochanteric region, and femur subtrochanter. All clinical fractures were to be reported as adverse events and were radiographically confirmed by the central reading facility.

Bone density measurements at the lumbar spine, determined by dual x-ray absorptiometry (DXA), were obtained on all patients at baseline, and month 36. Bone density measurements at the hip were obtained at baseline and months 12, 24, and 36. In the DXA substudy, bone density measurements at the spine and hip were obtained at baseline

and months 1, 6, 12, 24, and 36 as well as measurements of the distal radius and total body at baseline and months 12, 24, and 36. All DXA scans were evaluated by a central reading facility (b) (4)

Laboratory measurements of bone turnover markers included bone resorption markers serum c-telopeptides (CTx) and tartrate resistant acid phosphatase 5b (TRAP 5b); and the bone formation markers serum bone specific alkaline phosphatase (BSAP) and procollagen type 1 amino-terminal propeptide (PINP). Bone turnover markers were measured at baseline and months 6, 12, 18, 24, and 30 for subjects enrolled in the bone turnover marker substudy.

**Results:**

A total of 7868 subjects were enrolled into the study. Eighty-three percent of the enrolled population completed the study (3208 in the placebo group and 3272 in the denosumab group). Baseline subject demographics were generally well balanced across the treatment groups. The average age of enrollees was approximately 72 years with an age range of 60 – 91 years. Ninety-five percent of the enrolled population was age 65 years or older and 32% were age 75 years or older. 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 fracture at baseline and 44% had sustained a fracture after age 55 years. The mean lumbar spine BMD T-score was -2.8 standard deviations below the mean bone mass

*Morphometric Vertebral Fracture:* The proportion of subjects with at least one new vertebral fracture over the three years of the trial was the primary endpoint of the study. The modified ITT population (subjects who had received at least one dose of study drug and had at least one follow-up spinal radiograph) was used in the analysis. The results were analyzed using an ANCOVA model adjusting for age with last observation carried forward (LOCF) imputation.

As outlined in Table 1, 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.

**Table 1. Subjects with at Least One New Morphometric Vertebral Fracture**

Trial 20030216: Subjects with At Least One 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	
Source: compiled by medical reviewer based on 20030216 study report and statistical review		

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. The primary endpoint was met and the results statistically significant.

*Nonvertebral fracture:* The time to the first nonvertebral fracture was a secondary endpoint. Fractures were required to be confirmed by radiologic examination or documented in a radiology report, surgical report, or discharge summary. The analyses used the intent to treat population (all subjects that had received at least one dose of study drug) and cumulative incidence was summarized using the Kaplan-Meier estimates.

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 (Table 2).

**Table 2. Subjects with Nonvertebral Fractures**

Trial 20030216: Subjects with Nonvertebral Fracture at Month 36, ITT		
	Placebo	Denosumab
N, ITT	3906	3902
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	
Source: compiled by reviewer based on 20030216 study report and statistical review		

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).

*Hip Fracture:* The time to first hip fracture was the second secondary endpoint of the trial. Hip fracture includes fractures of the femoral neck, femur intertrochanter and femur subtrochanter. The analyses used the intent to treat population (all subjects that had received at least one dose of study drug) and cumulative incidence was summarized using the Kaplan-Meier estimates.

Over the three-year treatment period, 69 subjects [43 (1.1%) in the placebo group and 26 (0.7%) in the denosumab group] sustained a hip fracture (Table 3).

**Table 3. Subjects with Hip Fracture at Month 36**

Trial 20030216: Subjects with Hip Fracture at Month 36, ITT		
	Placebo	Denosumab
N, ITT	3906	3902
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 by reviewer based on 20030216 study report and statistical review		

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).

**Bone Mineral Density:** Change in bone mineral density of the lumbar spine was evaluated in the entire study population at screening and months 24 and 36. Changes in bone mineral density of the hip were evaluated at screening, months 12, 24 and 36. Changes in bone mineral density were tertiary endpoints.

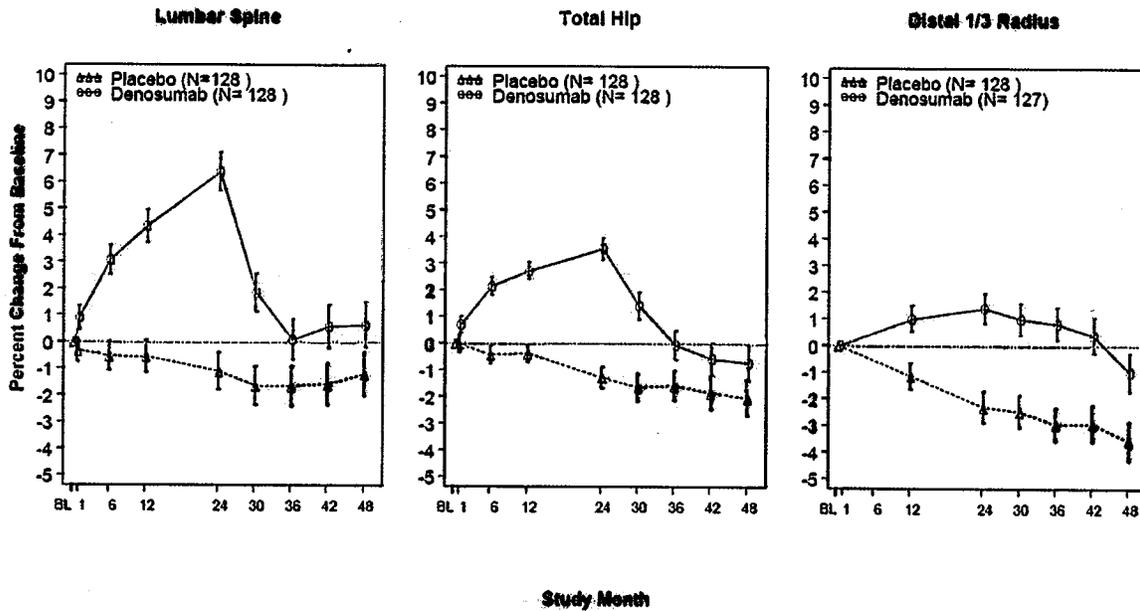
Significant increases in BMD at the lumbar spine, total hip, femoral neck and trochanter were observed with denosumab treatment compared to placebo at year 3 (Table 4).

**Table 4. Percent Change in BMD at 36 Months**

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

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. Figure 1 shows that the bone density gains achieved with denosumab therapy were 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.

A safety concern raised during 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. 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 sustained 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. In addition, the percentage of fractures within year 3 is greater in the denosumab group compared to the placebo group. It is not clear if these findings at year 3 indicate a change in denosumab efficacy with time.

To further assess this observation, 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 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%).

**Biochemical Markers of Bone Turnover:** Biochemical markers of bone turnover were evaluated in the bone marker substudy which enrolled 160 subjects, as well as in all subjects in the pharmacokinetic substudy and the bone biopsy substudy. Treatment with denosumab resulted in levels of suppression of the markers of bone resorption CTX and TRAP5b. The nadir of bone resorption markers appears to occur at 1 – 3 months after administration of the denosumab dose. The level of CTX suppression seen with denosumab has not been noted with other antiresorptive agents and the long-term clinical consequences of this degree of suppression are not clear. Serum CTX increased in the off-treatment period to levels well above baseline.

**Efficacy summary:**

In the three year osteoporosis treatment trial 20030216, denosumab, 60 mg given every six 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). BMD was also assessed and the changes compared to placebo highly statistically significant.

The efficacy of denosumab for the treatment of osteoporosis has been adequately demonstrated in the postmenopausal population.

**8. Safety**

The denosumab clinical development program included data from approximately 14,000 subjects enrolled in 30 clinical trials. The safety database for this application is primarily generated by the large (approximately 8,000 patient), placebo-controlled, three-year fracture trial in postmenopausal women (Trial 20030216).

The safety database for trial 20030216 includes 7762 subjects (3876 placebo, 3886 denosumab) who received at least one dose of study medication. Overall, 75.5% of the placebo group and 79.6% of the denosumab group received all six doses of study medication.

In the complete response submission, the Sponsor 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 6,480 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).

#### Deaths:

In trial 20030216, 160 subjects (90 in the placebo group and 70 in the denosumab group) died during the study. The most common System/Organ/Class (SOC's) for cause of death were neoplasms, cardiac disorders, general disorders and nervous system disorders. These causes of death are not unexpected for the general population of the age of the enrolled subjects.

There were four deaths reported in the phase 2 dose-finding trial 20010223. All subjects received denosumab and three of these subjects died of malignancy (brain tumor in one subject and adenocarcinoma in the other two).

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).

The number of deaths in this three year trial are not higher in the denosumab group compared to the placebo group.

#### Serious Adverse Events (SAE's):

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 SAEs in denosumab treated subjects were infection, pathogen unspecified [112 (2.8%) placebo, 134 (3.3%) denosumab], and coronary artery disorders [69 (1.7%) placebo, 98 (2.4%) denosumab]. Bone and joint injuries which included fracture and joint disorders were more common in the placebo group [108 (2.7%) placebo, 99 (2.4%) denosumab]. The differences in SAE's between treatment groups are small.

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). The most common SOC for SAE's 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. The most commonly reported adverse events leading to study discontinuation were breast cancer, back pain, and constipation.

In extension study 20050289, 56 (1.2%) subjects withdrew from the study due to an adverse event. The most commonly reported adverse events leading to study discontinuation were lung cancer, colon cancer, death, lymphoma and breast cancer.

The study withdrawal rate due to adverse events is similar in the denosumab and placebo groups.

#### Adverse Events:

In trial 20030216, 93% of the enrolled population reported at least one adverse event during the trial. The most commonly reported adverse events System Organ Classes (SOC) were musculoskeletal and connective tissue disorders, infections and infestations, and gastrointestinal disorders.

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 safety issues of special interest were identified by the sponsor and the reviewers during the first denosumab review cycle. These adverse events were discussed at the August 13, 2009, Advisory Committee meeting and include:

- Hypocalcemia,
- Infections, including skin infections
- Dermatologic adverse events
- Adverse events related to suppression of bone turnover (osteonecrosis of the jaw, atypical fractures and fracture healing complications)
- Pancreatitis
- Ocular adverse events
- New malignancies.

#### Hypocalcemia:

Hypocalcemia is a known adverse event seen with anti-resorptive therapies. The nadir in serum calcium appears to occur approximately 10 days after denosumab dosing. Laboratory testing in the phase 3 trial 20030216 was performed at one month post dose and 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. The majority of patients with a serum calcium level below 8.5 mg/dL were asymptomatic.

In a Phase 1 trial of subjects with all degrees 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. The trial was stopped and the protocol was amended to require calcium and vitamin D supplementation. After supplementation was initiated, the calcium nadir in the severe renal disease group was improved to the levels of the other groups.

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  $10 \pm 5$  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 is labeled as a Contraindication and the Warnings and Precaution section states that hypocalcemia must be corrected prior to initiating Prolia and may worsen especially in patients with renal impairment. The Warnings and Precaution section of the label also states that patients receiving Prolia should be adequately supplemented with calcium and vitamin D.

#### Infections, including skin infections:

RANKL is expressed on activated T and B lymphocytes, in lymph nodes, and plays a role in dendritic cell (antigen presenting cells) maturation. Therefore, there is biologic plausibility that the RANKL inhibitor denosumab could increase the risk of infection.

In phase 1 and 2 studies, there was no clear evidence (albeit with small sample sizes) of decreasing lymphocyte cell counts with denosumab therapy.

In phase I studies, three subjects were hospitalized for pneumonia after a single dose of denosumab. While one subject was older and had a history of chronic bronchitis, the other two subjects were healthy males under the age of 35 years. While the Sponsor believes that these data should not be relied upon because confirmatory records could not be obtained, the fact that healthy volunteers appeared to have serious events of pneumonia is concerning. Additionally, in the Phase 2 dose-finding study, 20010223, infection serious adverse events occurred in 10 (3.2%) denosumab-treated subjects and in no subjects in the placebo or active control groups.

In trial 20030216, fatalities due to infection occurred in 6 (0.2%) subjects in each treatment group (denosumab and placebo). Serious adverse events of infection were reported by 292 subjects (133 (3.4%) placebo, 159 (4.1%) denosumab).

Opportunistic infections were not increased in the subjects receiving denosumab.

In trial 20030216, serious adverse events related to infections occurred at a higher incidence in denosumab subjects compared with placebo. Specifically, serious bacterial infections occurred in 15 (0.4%) of placebo subjects and 25 (0.6%) denosumab subjects and serious infections due to an unspecified pathogens 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. An imbalance in endocarditis serious adverse events was also reported. Three denosumab-treated subjects and no placebo-treated patients developed endocarditis.

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 SAE's was noted (1 in the placebo/denosumab group and 4 in the denosumab/denosumab group). There were no reports of endocarditis or opportunistic infections.

During the first review cycle, a Division of Anti-Infective and Ophthalmology Products consultant agreed that patients on denosumab appeared to have infections more frequently, had more severe cellulitis, and more serious abdominal and lower respiratory tract infections. The consultant recommended that the label include information related to the potential risks for infections in the Warnings and Precautions section.

The risk of infection, including skin infections, is included in the Warnings and Precaution section of the label.

#### Dermatologic Adverse Events:

An imbalance in dermatologic adverse events (skin infections are not included) was noted in the postmenopausal osteoporosis database. A total of 501 (12.4%) placebo-treated subjects and 610 (15.1%) denosumab-treated subjects reported an adverse event related to skin and soft tissue disorders. These events did not include skin infections and were generalized, not specific to the drug injection site. This imbalance was mainly due to imbalances observed in HLGTT "Dermal and Epidermal conditions," driven by dermatitis, eczema, and rashes. Of note, dermal and epidermal adverse events including toxic skin reactions and bullous conditions occurred at approximately a 10-fold increased incidence in denosumab treated subjects. The Division of Dermatology and Dental Products was consulted to assist in the evaluation of these cases and their relationship to denosumab

therapy. After review, denosumab could not be clearly implicated as causative 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.

Dermatologic adverse events are included in the Warnings and Precautions section of the label.

**Adverse events related to suppression of bone turnover (osteonecrosis of the jaw, atypical fractures, and fracture healing complications):**

**Bone histomorphometry:**

Parameters of bone resorption are expected to decrease with anti-resorptive agents including denosumab. Iliac crest bone biopsies were performed in a subset of subjects in three studies. Absence of double tetracycline labeling in bone biopsy specimens (suggestive of suppressed bone turnover and formation) was observed in 21% of denosumab-treated subjects at month 12, in 35% of subjects at month 24, and in 38% of subjects at month 36. Absence of labeling was not observed in any placebo-treated subject tested.

Study 20050234 provided bone histomorphometry data for postmenopausal subjects with low BMD (T-scores between -2.0 and -4.0) previously treated with alendronate who either continued alendronate or switched from alendronate to denosumab. In this study, evidence for further suppression of bone remodeling following initiation of denosumab treatment was noted.

In addition to the bone histomorphometry findings, 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.

Over suppression of bone resorption may be related to osteonecrosis of the jaw, atypical fracture, and delayed fracture healing. Although the clinical consequence of these histomorphometry findings is unclear, the possibility of over suppression of bone turnover with chronic denosumab therapy remains an outstanding clinical concern and requires further study. Specific adverse events of interest potentially related to bone suppression, such as osteonecrosis of the jaw, fracture healing complications, and atypical fractures were reviewed.

***Osteonecrosis of the Jaw:*** Osteonecrosis of the jaw (ONJ) has been noted in patients receiving other anti-resorptive therapies and inhibition of bone resorption has been postulated as a possible etiology for ONJ. For the phase 3 program, the Sponsor convened an Osteonecrosis of the Jaw Adjudication Committee. Twenty one cases were identified to go forward with adjudication and no cases of ONJ were identified. It should be noted that documented cases of ONJ associated with denosumab use in the advanced cancer population have been identified and positively adjudicated.

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. This finding heightens the concern regarding bone over-suppression which is thought to be one of the potential etiologies of ONJ.

Osteonecrosis of the jaw is included in the Warnings and Precautions section of the label.

***Atypical Subtrochanteric Fractures of the Femur:*** Recent reports have appeared which suggest that atypical subtrochanteric fractures of the femur may be a consequence of anti-resorptive therapy. The incidence of subtrochanteric hip or femur fractures 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 subject).

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.

***Fracture Healing:*** Because of denosumab's negative effect on bone turnover, 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 Sponsor reported two subjects in each treatment group who had delayed fracture healing and one subject in the placebo group had fracture nonunion. However, the Sponsor 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 Sponsor 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.

The concern about long-term potential consequences of bone turnover suppression as it relates to ONJ, atypical fracture, and delayed fracture healing is included in the Warnings and Precaution section of the label.

#### 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. Regarding the severity of the events, 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. Many of these subjects had underlying risk factors for pancreatitis.

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 is included in the adverse reactions section of the product labeling.

#### Ocular Adverse Events:

Adverse events of cataracts were noted with increased frequency in the denosumab treated subjects in the prostate cancer trial 20030138 [9 (1.2%) of the placebo group and 34 (4.7%) of the denosumab group]. In the PMO database, adverse events related to the eye were reported in 537 (13%) placebo-treated subjects and 513 (12.6%) denosumab

treated subjects. Cataracts were reported in 253 (6.3%) of the placebo group and 229 (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. Based on the available data, there is no clear safety signal for ocular adverse events in the PMO population. The reason(s) for the increased number of cataracts in the men in the prostate cancer trial is not clear.

**New malignancies:** The incidence of new malignancies in subjects treated with denosumab was a review concern for several reasons. No carcinogenicity studies were performed because of the lack of an animal model. In addition, in the dose-finding studies, three subjects, all treated with denosumab, died due to neoplasms. Breast cancer was a common reason for withdrawal from trial 20030216 and cancer (breast cancer followed by colon cancer, gastric cancer, ovarian cancer and pancreatic cancer) was the most common reason for study drug discontinuation. In the combined PMO database (studies 20030216 and 20040132) adverse events related to neoplasms were reported in 285 (7.1%) placebo-treated subjects and 316 (7.8%) denosumab-treated subjects. Malignant and unspecified neoplasms were reported in 162 (4.2%) placebo-treated subjects and 192 (4.7%) denosumab-treated subjects. There were more malignant gastrointestinal, breast, and reproductive malignancies in the denosumab group and more respiratory malignancies in the placebo group.

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.

A higher number of several types of cancers in the denosumab versus the placebo group in this large database is difficult to interpret. No definite safety signal for neoplasms has emerged.

#### **Safety summary:**

Hypocalcemia is a recognized adverse event with all anti-resorptive therapies. Hypocalcemia is labeled as a Contraindication and is included in the Warnings and Precautions section of the label.

In addition to hypocalcemia, the three safety issues of primary concern are serious infections (including skin infections), dermatologic adverse events, and sequelae of over suppression of bone.

The risk of serious infection was not limited to skin infection. While the overall infection rates were similar, denosumab treated subjects appeared to have infections that were more serious. This was most notable in the younger subjects in trial 20040132. There is also biologic plausibility related to infection, given the role of RANK ligand in B cell, T cell and dendritic cell functions.

Dermatologic adverse events of dermatitis and eczema were significantly increased with denosumab use.

Over suppression of bone resorption may be related to ONJ, atypical fracture, and delayed fracture healing. Although the clinical consequences of the histomorphometry and bone turnover marker findings are unclear, the possibility of over suppression of bone turnover with chronic denosumab therapy remains a clinical concern and requires further study. Post-marketing data/studies will be necessary to resolve this issue.

## **9. Advisory Committee Meeting**

An Advisory Committee meeting was held during the first review cycle on August 13, 2009, to discuss the four biologic licensing applications/indications 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 were 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.

The Advisory Committee voted unanimously for approval of denosumab for the indication "treatment of postmenopausal osteoporosis." Many committee members believed that limiting the treatment population to those at high risk of fracture was warranted until more data are available concerning long-term risks of therapy. The majority of the Committee members believed that a Medication Guide to inform patients about the risks of the drug and a Communication Plan to educate providers about major safety concerns were warranted. Some members also suggested that, given the need for providers to administer the drug, a registry was also warranted to better monitor safety outcomes in denosumab users prospectively.

## **10. Pediatrics**

The Pediatric Review Committee (PeRC) reviewed the sponsor's request to waive the requirement to conduct pediatric studies in all age groups for denosumab on June 3, 2009, and the waiver 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**

### **Risk Evaluation and Mitigation Strategies (REMS)**

The Division, in consultation with OSE, determined that a REMS is necessary for Prolia (denosumab) to ensure that the benefits of the drug outweigh the risk of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover. The REMS for this product includes a Medication Guide, a communication plan, and a timetable for submission of assessments.

The Sponsor submitted a REMS and REMS supporting documents and these documents were found to be adequate. The Medication Guide and Dear Health Care Provider letter were also judged to be satisfactory.

### **Postmarketing Requirements**

Based on the signals of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover described above, the Division, in consultation with OSE, determined that the following three studies would be required as post-marketing requirements:

1. 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.
2. A long-term observational study in administrative databases to prospectively evaluate the incidence of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover in postmenopausal women administered Prolia (denosumab).
3. A long-term surveillance study in postmenopausal women administered Prolia (denosumab) to prospectively evaluate the incidence of serious infection including skin infections, dermatologic adverse events, and over-suppression of bone turnover.

In addition, 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 will conduct an *in vivo* drug-drug interaction study with CYP3A4 substrate (e.g., midazolam) in postmenopausal female patients with osteoporosis. This is post-marketing requirement #4.

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

The Office of Biotechnology Products requested that the Sponsor perform the following three post-marketing commitments:

5. 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.
6. 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.
7. 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.

In a letter dated May 4, 2010, the Sponsor agreed to the above seven Postmarketing Requirements and Commitments.

**Financial Disclosure:** The primary medical officers reviewed the financial disclosure information provided by the Sponsor during the first review cycle and do not believe that the disclosures reported compromise the data submitted.

**Division of Medication Errors and Analysis (DMEPA):**

The Sponsor's proposed tradename (Prolia) was found to be acceptable by the Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Drug Marketing, Advertising and Communication (DDMAC).

**Division of Scientific Investigations (DSI):**

The Division of Scientific Investigation conducted four inspections for this application during the first review cycle. Two domestic sites and two international sites were inspected. Although isolated issues were noted at one site, the final assessment was that the data appear acceptable in support of the application.

**Office of Surveillance and Epidemiology/DEPI:**

The Office of Surveillance and Epidemiology, Division of Epidemiology (DEPI) was consulted regarding the proposed observational study protocols. Their recommendation during the first review cycle was that the results from Phase A (protocol 20090521), including the development and validation of the methodology and background adverse event rate assessments, be acceptable before accepting Phase B as adequate and before approving denosumab. The sponsor's complete response was deemed adequate by DEPI.

## 12. Labeling

The wording of the indication in the full prescribing information was initially an area of disagreement between the Sponsor and the clinical team during labeling negotiations. The Sponsor initially proposed the indication language a (b) (4) (b) (4) The final agreed upon indication is:

[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 Sponsor.

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

The Medication Guide language has also been agreed upon.

## 13. Decision/Action/Risk Benefit Assessment

I agree with the cross discipline team leader, primary medical officers, and the CMC, pharmacology/toxicology, clinical pharmacology, statistical, and OSE reviewers that BLA 125320 receive an approval action. The deficiencies noted in the October 16, 2009, complete response letter have been adequately addressed.

### Risk-benefit Analysis:

The primary efficacy data submitted to support the treatment of post-menopausal osteoporosis indication was Trial 20030216. This was a large (approximately 8,000 subjects) trial whose primary endpoint was the incidence of new morphometric (radiographic) vertebral fractures at month 36. In the osteoporosis treatment population, denosumab, 60 mg given every six 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). BMD was also assessed and the changes compared to placebo highly statistically significant. The efficacy of denosumab has been adequately demonstrated in this patient population.

Multiple potential safety issues have been identified, including serious infections (including skin infections), dermatologic adverse events, and the potential for the occurrence of events related to over suppression of bone turnover (osteonecrosis of the jaw, delayed fracture healing, and atypical fractures). Hypocalcemia is a known adverse event associated with antiresorptive therapy. I believe that these risks can be adequately mitigated by restricting the treatment 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 post-marketing period. A post-marketing Risk Evaluation and Mitigation Strategy should also positively impact risk management.

### **REMS**

As discussed in section 11 of this review, a REMS for this product has been deemed necessary and must include a Medication Guide, a communication plan, and a timetable for submission of assessments.

### **Postmarketing Requirements (PMR's):**

The Sponsor has agreed to conduct four PMR's:

1. 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.
2. A long-term observational study in administrative databases to prospectively evaluate the incidence of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover in postmenopausal women administered Prolia (denosumab).
3. A long-term surveillance study in postmenopausal women administered Prolia (denosumab) to prospectively evaluate the incidence of serious infection including skin infections, dermatologic adverse events, and over-suppression of bone turnover.
4. An *in vivo* drug-drug interaction study with a CYP3A4 substrate (e.g., midazolam) in postmenopausal female patients with osteoporosis to characterize the potential risk of drug interaction of Prolia (denosumab) with CYP3A4.

There are no outstanding issues which would preclude approval of this BLA.

## Appendix A

### 3. CMC/Device

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 (small glycosylation changes) 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)

#### 4. Nonclinical Pharmacology/Toxicology

Denosumab is a fully human IgG<sub>2</sub> monoclonal antibody that binds to the receptor activator of nuclear factor- $\kappa$ 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 show 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.

No postmarketing commitments or requirements are recommended by the pharmacology/toxicology 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

Denosumab is administered as a subcutaneous injection. The mean maximum serum denosumab concentrations ( $C_{max}$ ) of  $6.75 \pm 1.89$   $\mu\text{g/ml}$  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  $25.4 \pm 8.5$  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  $\geq 60$  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  $C_{max}$  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 were submitted in this compete response.

The Clinical Pharmacology Review Team recommends the sponsor conduct an *in vivo* post-marketing drug-drug interaction study with CYP3A4 substrate (e.g., midazolam) in postmenopausal female patients with osteoporosis.

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