Background Document for Meeting of Advisory Committee for Reproductive Health Drugs (August 13, 2009)

Denosumab

(Proposed trade name: PROLIA)

Amgen, Inc

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

Dosing regimen

60 mg subcutaneous injection every 6 months administered by a healthcare provider

Prepared by Division of Reproductive and Urologic Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

July 21, 2009
amended August 3, 2009

Table of Contents

TABLE OF TABLES **5**

TABLE OF FIGURES **7**

1 BACKGROUND **8**

1.1 OBJECTIVE OF MEETING AND OVERVIEW OF DEVELOPMENT PROGRAM 8
1.2 ISSUES FOR COMMITTEE CONSIDERATION 8
1.3 INDICATIONS 9
1.3.1 Postmenopausal Osteoporosis *9*
1.3.2 Bone Loss Associated with Hormone Ablation for Prostate Cancer or Breast Cancer *12*
1.4 THE ROLE OF RANK LIGAND 12
1.5 REGULATORY GUIDANCE FOR THE DEVELOPMENT OF PRODUCTS FOR OSTEOPOROSIS TREATMENT 13
1.6 REGULATORY HISTORY OF MONOCLONAL ANTIBODY PRODUCTS 13
1.7 THE FOOD AND DRUG ADMINSTRATION AMENDMENTS ACT OF 2007 14
1.8 SPECIAL CONSIDERATIONS FOR SUPPORTIVE CARE AGENTS IN CANCER PATIENTS 15

2 CLINICAL DEVELOPMENT OF DENOSUMAB **16**

2.1 OVERVIEW FROM THE OFFICE OF BIOTECHNOLOGY PRODUCTS 16
2.2 OVERVIEW OF PHARMACOLOGY AND TOXICOLOGY 17
2.3 OVERVIEW OF CLINICAL PHARMACOLOGY 18
2.3.1 Pharmacokinetics *18*
2.3.2 Pharmacodynamics *19*
2.3.3 Exposure-Response *19*
2.4 OVERVIEW OF CLINICAL STUDIES 20
2.5 DOSE SELECTION FOR PHASE 3 STUDIES 20
2.6 APPLICANT'S PIVOTAL PHASE 3 CLINICAL STUDIES 21
2.6.1 Treatment of Postmenopausal Osteoporosis *22*
2.6.2 Prevention of Postmenopausal Osteoporosis *22*
2.6.3 Treatment and Prevention of Bone Loss with Hormone Ablation for Breast Cancer *22*
2.6.4 Treatment and Prevention of Bone Loss with Hormone Ablation for Prostate Cancer *22*
2.7 APPLICANT'S OTHER PHASE 3 STUDIES 22

3 DESIGN OF THE PIVOTAL PHASE 3 TRIALS **23**

3.1 STUDY 20030216 23
3.2 STUDY 20040132 26
3.3 STUDY 20040135 27
3.4 STUDY 20040138 28

4 EFFICACY FINDINGS FROM THE PIVOTAL PHASE 3 TRIALS **28**

4.1 STUDY 20030216 (PMO FRACTURE STUDY) 28
4.1.1 Subject Enrollment and Disposition *28*
4.1.2 Demographics *29*
4.1.3 Primary efficacy endpoint: *31*
4.1.4 Secondary efficacy endpoint: *31*
4.1.5 Important Tertiary Endpoints *33*
4.2 STUDY 20040132 (PMO PREVENTION STUDY) 35
4.3 STUDY 20040135 (HORMONE ABLATION - BREAST CANCER STUDY) 37
4.4 STUDY 20040138 (HORMONE ABLATION - PROSTATE CANCER STUDY) 39
4.5 SUMMARY OF EFFICACY 43

5 SAFETY FINDINGS **44**

5.1 OVERVIEW OF SAFETY CONCERNS WITH INHIBITORS OF RANKL 44
5.2 OVERVIEW OF THE SAFETY DATABASE FOR DENOSUMAB 44
5.2.1 Postmenopausal Osteoporosis *45*

5.2.2 Cancer-related Trials *46*
5.3 SAFETY FINDINGS FROM THE DENOSUMAB CLINICAL DEVELOPMENT PROGRAM 46
5.3.1 Deaths *46*
5.3.1.1 Postmenopausal Osteoporosis 48
5.3.1.2 Cancer-related Trials 49
5.3.2 Serious Adverse Events *49*
5.3.2.1 Postmenopausal Osteoporosis 49
5.3.2.2 Cancer-related Trials 50
5.3.3 Discontinuations Due to Adverse Events *51*
5.3.3.1 Postmenopausal Osteoporosis 51
5.3.3.2 Cancer-related Trials 53
5.3.4 Common Adverse Events (AEs) *53*
5.3.4.1 Postmenopausal Osteoporosis 53
5.3.4.2 Cancer-related Trials 54
5.3.5 Adverse Events of Interest *55*
5.3.5.1 Infection 55
5.3.5.2 Malignancy 59
5.3.5.3 Dermatologic Adverse Events (excluding infections) 60
5.3.5.4 Pancreatitis 61
5.3.5.5 Cardiovascular Adverse Events 64
5.3.5.6 Hypocalcemia 66
5.3.5.7 Osteonecrosis of the Jaw 69
5.3.5.8 Hypersensitivity and Immunogenicity 70
5.3.6 Bone Histomorphometry *71*
5.3.7 Laboratory Findings *77*
5.3.8 Vital Signs *78*
5.4 SUMMARY OF SAFETY 79

6 APPENDICES 81

APPENDIX 1 82
APPENDIX 2 87

Table of Tables

TABLE 1. APPROVED PRODUCTS FOR OSTEOPOROSIS PREVENTION AND/OR TREATMENT 11
TABLE 2: SUB-STUDIES WITHIN STUDY 20030216 25
TABLE 3: SUBJECT DISPOSITION IN STUDY 20030216 29
TABLE 4: DEMOGRAPHICS AND BASELINE DISEASE CHARACTERISTICS FOR SUBJECTS IN STUDY 20030216 (PMO FRACTURE TRIAL) 30
TABLE 5: SUBJECT INCIDENCE, ABSOLUTE RISK REDUCTION, AND RISK RATIO FOR NEW VERTEBRAL FRACTURE THROUGH MONTH 36 (PRIMARY EFFICACY ANALYSIS SET, LOCF IMPUTATION) 31
TABLE 6: STUDY 20030216: SUBJECT INCIDENCE, ABSOLUTE RISK REDUCTION, AND HAZARD RATIO FOR NONVERTEBRAL AND HIP FRACTURE THROUGH MONTH 36 (FULL ANALYSIS SET) 32
TABLE 7: LUMBAR SPINE AND TOTAL HIP BONE MINERAL DENSITY BY DXA PERCENT CHANGE FROM BASELINE AT MONTH 36 (PRIMARY EFFICACY POPULATION, LOCF) 33
TABLE 8: PERCENT CHANGE FROM BASELINE THROUGH MONTH 36 IN SERUM BONE MARKERS (LOCF) 34
TABLE 9: DEMOGRAPHICS AND BASELINE DISEASE CHARACTERISTICS FOR SUBJECTS IN STUDY 20040132 (PMO PREVENTION TRIAL) 35
TABLE 10. TRIAL 132 PERCENT CHANGE FROM BASELINE TO MONTH 24 IN LUMBAR SPINE BMD BY DXA (ANCOVA MODEL, PRIMARY EFFICACY SUBSET, LOCF) 36
TABLE 11: SUBJECT DISPOSITION FOR STUDY 20040135 (HORMONE ABLATION – BREAST CANCER) 37
TABLE 12: DEMOGRAPHICS AND BASELINE DISEASE CHARACTERISTICS FOR SUBJECTS IN STUDY 20040135 (HORMONE ABLATION – BREAST CANCER) 38
TABLE 13 TRIAL 135 BMD PERCENT CHANGE FROM BASELINE AT MONTH 12 (LOCF) 39
TABLE 14: SUBJECT DISPOSITION FOR STUDY 20040138 (HORMONE ABLATION – PROSTATE CANCER) 40
TABLE 15: DEMOGRAPHICS AND BASELINE DISEASE CHARACTERISTICS FOR SUBJECTS IN STUDY 20040138 (HORMONE ABLATION – PROSTATE CANCER) 41
TABLE 16 TRIAL 138 BMD PERCENT CHANGE FROM BASELINE AT MONTH 24 (LOCF) 42
TABLE 17: EXTENT OF EXPOSURE STUDIES 20030216 AND 20040132 45
TABLE 18. CAUSE OF DEATH BY SYSTEM ORGAN CLASS FOR THE PRIMARY PMO AND HORMONE ABLATION STUDIES 48
TABLE 19. NONFATAL SERIOUS ADVERSE EVENTS BY STUDY FOR THE DENOSUMAB PRIMARY PMO SAFETY POPULATION 49
TABLE 20. NONFATAL SERIOUS ADVERSE EVENTS ORDERED BY SOC AND TREATMENT GROUP FOR THE DENOSUMAB PRIMARY PMO SAFETY POPULATION (POOLED DATA) 50
TABLE 21. REASON FOR ENDING INVESTIGATIONAL PRODUCT IN PRIMARY PMO SAFETY POPULATION (POOLED DATA) 52
TABLE 22. MOST COMMON ADVERSE EVENTS THAT LED TO DISCONTINUATION OF INVESTIGATIONAL PRODUCT IN PRIMARY PMO SAFETY POPULATION (POOLED DATA) 53
TABLE 23 COMMON ADVERSE EVENTS IN PRIMARY PMO SAFETY POPULATION 54
TABLE 24: COMMON ADVERSE EVENTS IN HORMONE ABLATION THERAPY POPULATION (OCCURRING IN >5% OF SUBJECTS IN EITHER GROUP) 55
TABLE 25. ADVERSE EVENTS OF CONCERN IN THE NEOPLASMS SOC IN PRIMARY PMO STUDIES (POOLED DATA) BY HLGT AND SELECT HLT 60
TABLE 26 ADVERSE EVENT HIGH LEVEL TERM IN EPIDERMAL AND DERMAL CONDITIONS 61
TABLE 27. EVENTS OF PANCREATITIS IN PRIMARY PMO STUDIES (POOLED DATA) 62
TABLE 28. LINE LISTING OF PANCREATITIS EVENTS IN SUBJECTS RECEIVING DENOSUMAB IN PRIMARY PMO STUDIES (POOLED DATA) 62
TABLE 29: ADJUDICATED CARDIOVASCULAR-RELATED SERIOUS ADVERSE EVENTS FOR TRIAL 20030216 65
TABLE 30: NUMBER OF SUBJECTS WITH SELECTED SERUM CALCIUM LEVELS AT MONTH 1 IN TRIAL 20030216 AND DAY 10 IN 20060289 68
TABLE 31 LABELING STATUS IN 3 TRIALS WITH BONE BIOPSY SUB STUDY 73
TABLE 32. STUDY 216: QUANTITATIVE HISTOMORPHOMETRY PARAMETERS 75
TABLE 33. STUDY 234: QUANTITATIVE HISTOMORPHOMETRY PARAMETERS 76
TABLE 34. STUDY 216: TRABECULAR LABEL STATUS AND PRESENCE OF DETECTABLE CTX LEVELS AT MONTH 1 77

TABLE 35: SUBJECT INCIDENCE OF MARKED LABORATORY ABNORMALITIES IN STUDY 20030216 AND STUDY 20040132 78
TABLE 36: LISTING OF ALL CLINICAL STUDIES 88

Table of Figures

FIGURE 1. MEAN SERUM DENOSUMAB CONCENTRATION-TIME PROFILES FOLLOWING SC ADMINISTRATION OF 60 MG OR 1 MG/KG TO POSTMENOPAUSAL WOMEN (FROM STUDIES 20010124, 20010223, 20030164, AND 20030180) 18
FIGURE 2. MEAN SERUM DENOSUMAB CONCENTRATION AND MEAN PERCENT CHANGE FROM BASELINE FOR SERUM CTX1 AND LUMBAR SPINE BMD FOLLOWING TWO 60 MG Q6M DOSES OF DENOSUMAB TO POST MENOPAUSAL WOMEN WITH LOW BMD (FROM STUDY 20010223) 19
FIGURE 3. STUDY 223 PERCENT CHANGE IN LUMBAR SPINE BMD FROM BASELINE (CONTINUOUS-TREATMENT DENOSUMAB COHORTS) 21
FIGURE 4: STUDY SCHEMA 24
FIGURE 5: CTX1 % CHANGE FROM BASELINE BY VISIT 34
FIGURE 6: S. CALCIUM % CHANGE FROM BASELINE IN TRIAL 20030216 ROLLING OVER TO 20060289 (N=4550) 68
FIGURE 7. ORGANIZATION OF THE DENOSUMAB CLINICAL STUDIES IN THE INITIAL BLA SUBMISSION 87

1 BACKGROUND

1.1 Objective of Meeting and Overview of Development Program

The purpose of this Advisory Committee meeting is to review and discuss the safety, efficacy, and overall risk/benefit profile of denosumab, a monoclonal antibody against receptor activator of nuclear factor-kappa B ligand (RANKL), for four separate indications:

- treatment of postmenopausal osteoporosis
- prevention of postmenopausal osteoporosis
- treatment and prevention of bone loss associated with hormone ablation therapy for breast cancer
- treatment and prevention of bone loss associated with hormone ablation therapy for prostate cancer

Treatment of postmenopausal osteoporosis (PMO) is considered the primary indication. For this indication, demonstration of fracture efficacy is required. The basis for approval of treatment of PMO is study 20030216, a three-year, randomized, double-blind, placebo-controlled trial in postmenopausal osteoporotic women with the primary endpoint of incidence of morphometric vertebral fracture.

The pivotal trial for the prevention of PMO indication is study 20040132, a four-year, randomized, double-blind, placebo and active-controlled study of postmenopausal women with low bone mass. The primary endpoint of the study was change in lumbar spine bone mineral density (BMD) at month 24.

The pivotal trial supporting the treatment and prevention of bone loss associated with hormone ablation therapy for breast cancer is study 20040135, a four-year, randomized, double-blind, placebo-controlled study in women with nonmetastatic breast cancer undergoing aromatase inhibitor therapy. The primary endpoint was change in lumbar spine BMD at month 12.

The pivotal trial supporting the treatment and prevention of bone loss associated with hormone ablation therapy for prostate cancer is study 20040138, a five-year, randomized, double-blind, placebo-controlled in men with nonmetastatic prostate cancer undergoing androgen-deprivation therapy. The primary endpoint was change in lumbar spine BMD at month 24.

1.2 Issues for Committee Consideration

Committee Members will find statements by the Division entitled "Issues for Consideration" throughout this Background Document. These statements identify issues that the Division

believes to be of particular importance in the Committee's assessment of the safety and overall risk/benefit profile of denosumab for the proposed indications.

The following safety issues associated with denosumab exposure have been identified in clinical trials:

- 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.

Of particular concern, in light of these safety issues, is whether the risk/benefit balance for the osteoporosis prevention indication, both for patients with and without cancer, supports approval. In addition, if denosumab were to be approved, we seek advice from the Committee regarding whether a risk evaluation and mitigation strategy or REMS would be needed to ensure that its benefits outweigh its risks.

1.3 Indications

1.3.1 Postmenopausal Osteoporosis

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, along with BMD improves facture risk prediction. Because of the potential for safety consequences of long-term treatment with many of the available osteoporosis therapies, accurate prediction of fracture risk and, therefore, who would best benefit from treatment, is vital for healthcare providers.

A new risk assessment tool for prediction of osteoporotic fracture (FRAX) was developed by the WHO in 2008. The FRAX algorithms include clinical risk factors that predict an increased risk of fracture (age, sex, prior fragility fracture after age 50 years, history of corticosteroid use [≥ 5mg for more than three months], parental history of hip fracture, rheumatoid arthritis, secondary osteoporosis [e.g., type 1 diabetes, osteogenesis imperfecta in adults, longstanding hyperthyroidism, hypogonadism, premature menopause, chronic malabsorption, and chronic liver disease], current smoker, alcohol use of greater than 2 units daily, and body mass index). Using the FRAX tool fracture risk is reported as the 10 year risk of hip fracture and the 10-year risk of major osteoporotic fracture. Currently, the National Osteoporosis Foundation recommends treatment be considered for patients who have had an osteoporotic fracture, patients with a BMD T-score of <-2.5 (2.5 standard

deviations below the young adult mean), and patients over age 50 years with low bone mass (T-score -1.0 to -2.5) with a risk probability of >3% for hip fracture or >20% for major osteoporotic fracture as obtained using the FRAX algorithm.

Products currently approved in the U.S. for the prevention and/or treatment of postmenopausal osteoporosis are outlined in Table 1.

Table 1. Approved Products for Osteoporosis Prevention and/or Treatment

Class	Drug	Route	Dose	Prevention	Treatment
Bisphosphonate	Fosamax	oral	5 mg daily	XX	
		oral	10 mg daily		XX
		oral	35 mg weekly	XX	
		oral	70 mg weekly		XX
	Fosamax PlusD	oral	70 mg/2800IU weekly		XX
		oral	70 mg/5600IU weekly		XX
	Actonel	oral	5 mg daily	XX	XX
		oral	35 mg weekly	XX	XX
		oral	75 mg 2days/month		XX
		oral	150 mg monthly		XX
	Actonel with Calcium	oral	35 mg once weekly 1250 mg days 2-7	XX	XX
	Boniva	oral	2.5 mg daily	XX	XX
		oral	150 mg monthly	XX	XX
	Boniva	IV	3mg every 3months		XX
	Reclast	IV	5mg yearly		XX
	Reclast	IV	5mg every 2 years	XX	
Estrogen Agonist/Antagonist	Evista	oral	60 mg daily	XX	XX
PTH analog	Forteo	SC	20 mcg daily		XX
Calcitonin	Miacalcin	SC	100 IU every other day	XX*	
	Miacalcin	NS	200 IU daily	XX*	
	Fortical	NS	200 IU daily	XX*	
Estrogen and Estrogen/Progestin combination products	Premarin	oral	0.3 – 1.25 mg daily	XX	
	Premphase	oral	0.625 mg daily D1-14 5mg daily D 15-28	XX	
	Prempro	oral	0.3/1.5 – 0.625/5 mg daily	XX	
	Climara	transderm	0.025 – 0.1 mg/day, applied once weekly	XX	
	Climara Pro	transderm	0.45/0.015 mg/day, applied once weekly	XX	
	Prefest	oral	1 mg estradiol daily for 3 days; alternate with 1/0.09 mg daily for 3 days	XX	
	Femhrt	oral	2.5/0.5 – 5/1 mg daily	XX	
	Activella	oral	0.5/0.1– 1/0.5 daily	XX	
	Vivelle	transderm	0.025 – 0.1 mg/day, applied twice weekly	XX	
	Alora	transderm	0.025 – 0.1 mg/day, applied twice weekly	XX	
	Menostar	transderm	0.014 mg/day, applied once weekly	XX	
	Vivelle Dot	transderm	0.025 – 0.1 mg/day, applied twice weekly	XX	
* Original Approval based on BMD, not fracture efficacy					

Denosumab, the focus of this Advisory Committee meeting, would be, if approved, the first biologic agent available in the United States for the prevention and treatment of postmenopausal osteoporosis.

1.3.2 Bone Loss Associated with Hormone Ablation for Prostate Cancer or Breast Cancer

The most commonly diagnosed cancers among men and women in the United States are prostate and breast cancer. Prostate cancer accounts for approximately 29% of all new cancers reported while breast cancer accounts for approximately 26%. Cancer therapy induced bone loss has been shown with both breast and prostate cancer therapies which are directed at lowering sex steroid levels.

Androgen deprivation is an important therapeutic modality utilized in the treatment of men with prostate cancer. The main effect of these modalities is decrease of testosterone to castrate levels. Multiple studies have shown that androgen deprivation therapy results in decreasing bone mass in men with a concomitant increase in fracture risk.

Aromatase inhibition is used in the treatment of hormone receptor positive breast cancer in postmenopausal women. The main consequence of these agents is the reduction in estrogen levels. It is well recognized that bone loss is associated with estrogen deficiency in postmenopausal women. Postmenopausal bone loss may be accelerated with further reductions in estrogen levels by the aromatase inhibition. Bone loss in postmenopausal women occurs at a rate of approximately 1% per year. In the Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial, treatment with the aromatase inhibitor Arimidex alone resulted in a median percent change in lumbar spine bone mineral density of -2.3% at one year and -4.0% at two years (Eastell R, et.al., J Clin Oncol 2008; 26:1052-1058).

For patients with nonmetastatic prostate or breast cancer, the median survival time is long and may approach a decade or more. For this reason, long term bone health is an issue that should be addressed as part of the treatment paradigm.

Currently, there are no products approved for bone loss associated with hormone ablation for prostate cancer or breast cancer.

1.4 The Role of RANK Ligand

Receptor activator of nuclear factor-kappa B ligand (RANKL) is a tumor necrosis factor superfamily cytokine member (Tnfsf11). RANKL stimulates its specific receptor, RANK, initiating intracellular signaling cascades which promote osteoclast formation, fusion, differentiation, activation, and survival, leading to enhanced bone resorption and bone loss. Another important function of RANKL is in the immune system where RANKL is involved in B-cell and T-cell differentiation as well as dendritic cell maturation. RANKL expression is modulated by various cytokines, glucocorticoids, and PTH and it is produced by osteoblastic lineage cells and activated T cells.

Osteoprotegerin (OPG) is also a member of tumor necrosis factor superfamily of cytokines. OPG's main function is inhibition of osteoclast differentiation. OPG itself is an inhibitor of RANKL.

1.5 Regulatory Guidance for the Development of Products for Osteoporosis Treatment

The FDA osteoporosis guidance document entitled "Guidelines for Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis" was issued in 1994. As outlined in that document, the preclinical requirements include an examination of bone quality in two species to adequately investigate the effectiveness and safety of drugs for the prevention and/or treatment of osteoporosis. The clinical requirements include adequate assessment of treatment on the incidence of new vertebral fractures at three years of treatment. In the pivotal fracture trial, bone mineral density is a secondary endpoint. Once fracture efficacy has been demonstrated, this provides validation of the BMD endpoint, which is then allowed to be the primary endpoint for other indications such as prevention of postmenopausal osteoporosis.

In their development program for denosumab, the Applicant was not able to examine bone quality in two nonclinical species because the monoclonal antibody is species specific. All nonclinical studies were performed in the monkey. The clinical program does include the requisite three-year fracture trial in postmenopausal women. In the pivotal fracture trial, BMD was a tertiary endpoint. In the pivotal trials for the other indications, BMD served as the primary endpoint.

1.6 Regulatory History of Monoclonal Antibody Products

Denosumab represents the first biologic product and the first monoclonal antibody agent seeking approval for the prevention and treatment of postmenopausal osteoporosis as well as for the prevention and treatment of bone loss due to cancer therapies that act to lower sex steroid levels. Appendix 1 lists 27 therapeutic monoclonal antibody products that have been approved since 1992 for treatment of conditions such as organ rejection, cancers, autoimmune disorders, paroxysmal nocturnal hemoglobinuria, and macular degeneration. Some monoclonal antibodies and antibody fusion proteins have had serious safety issues identified prior to approval or in the postmarketing period, including serious infections, opportunistic infections, severe infusion reactions, anaphylaxis, and malignancies. Twenty of the 27 monoclonal antibody products have Black Box Warnings. Some have required MedGuides, FDA Alerts or Risk Evaluation and Mitigation Strategies (REMS), both pre- and post-marketing, to address these safety issues.

1.7 The Food and Drug Adminstration Amendments Act of 2007

The Food and Drug Administration Amendments Act (FDAAA) of 2007 was signed into law on September 27, 2007. Included in the provisions of this new law are amendments to the Federal Food, Drug and Cosmetic Act (FDCA) which provide FDA with enhanced authorities regarding postmarket safety of drugs. Specifically, Title IX of FDAAA which took effect on March 25, 2008, provides FDA with several new authorities including the ability to require applicants to develop and comply with risk evaluation and mitigation strategies (REMS).

A REMS may be required before a new drug application is approved if the determination is made that the REMS is necessary *to ensure that the benefits of the drug outweigh the risks of the drug*. This determination is based on factors including: (1) The estimated size of the population likely to use the drug; (2) The seriousness of the disease or condition that is to be treated with the drug; (3) The expected benefit of the drug with respect to the disease or condition; (4) The expected or actual duration of treatment with the drug; (5) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug; and (6) Whether the drug is a new molecular entity.

A REMS is composed of various elements which are chosen based on the goals of the REMS and the seriousness of the risk(s) being addressed. One element required for all REMS is a timetable for submission of assessments. The timetable provides a framework for periodic submission of assessments to determine the effectiveness of the REMS. At a minimum, assessments are required by 18 months, by 3 years, and in the seventh year after initial REMS approval. Additional elements are included depending on the objective of the REMS. Other potential elements include a Medication Guide, a communication plan, and elements to assure safe use.

The most frequently required element in a REMS is a Medication Guide. During the first year after Title IX took effect (March 25, 2008 – March 25, 2009), 34 REMS were approved of which 28 were Medication Guide only REMS (Medication Guide and timetable for submission of assessments). A Medication Guide is required if FDA determines that one or more of the following circumstances exist: (1) Patient labeling could help prevent serious adverse effects; (2) Drug has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the drug; (3) Patient adherence to directions for use is crucial to the drug's effectiveness. Distribution of the Medication Guide to the patient is required when the drug is initially dispensed and at each refill.

A communication plan for healthcare providers may be required if needed to support implementation of a REMS. The plan may include letters to healthcare providers; communicating the elements of the REMS to encourage implementation or to explain safety protocols, such as monitoring by periodic lab tests; or disseminating information through professional societies about serious risks of the drug.

The most restrictive element that may be required as part of a REMS is an element to assure safe use. Elements to assure safe use include the following: (1) prescriber training or certification; (2) certification of dispensers; (3) drug administration limited to certain health care settings; (4) documentation of safe use prior to dispensing; (5) required monitoring of patients; or (6) enrollment of patients in a registry. Elements to assure safe use are reserved for situations in which a drug is shown to be effective, but is associated with a specific serious risk such that the drug could only be approved with a REMS which includes an element to assure safe use. During the first full year since Title IX became effective, 4 REMS were approved which included an element to assure safe use.

1.8 Special Considerations for Supportive Care Agents in Cancer Patients

Two groups of supportive care agents for palliation of patients receiving cancer treatment have raised concerns regarding the potential to adversely affect tumor outcomes: 1) agents designed to mitigate chemotherapy- or radiotherapy-induced toxicity and 2) agents binding to specific receptors present on some tumors or on cells in the tumor microenvironment. Examples of the former are dexrazoxane and amifostine; examples of the latter are granulocyte-colony stimulating factors, erythryopoietin-stimulating agents, and keratinocyte-growth factors. It has been the practice of the Office of Oncology Drug Products (OODP) and it's predecessors in CDER and CBER to examine *in vitro* and *in vivo* nonclinical proof-of-concept and available clinical data for evidence of adverse effects on tumor outcomes prior to marketing approval, with the requirement for definitive clinical studies to rule out adverse risks to be performed as post-marketing commitments, provided no safety signals were identified prior to marketing approval. In cases where pharmacodynamic or nonclinical data suggested the potential for stimulation of tumor growth, such as the receptor for a growth factor being present on tumor cells, and clinical studies were lacking in specific tumor types, the indication for the product was restricted until such studies were performed (e.g., initial approval for granulocyte colony stimulating factors was limited to patients with non-myeloid malignancy). In addition, there is a growing body of evidence suggesting that promotion of tumor growth may exist for drugs in which there is no demonstrable direct relationship between receptors and tumor proliferation. In these instances, drugs used to palliate cancer treatment-related toxicity may not only bind directly to tumor cells with consequent alterations in known signal transduction pathways, but may also stimulate tumor growth through binding to receptors in non-malignant components of the tumor microenvironment, through off-target binding, or through activation of other signal transduction pathways not directly or intentionally targeted. Many aspects of tumor promotion are still not well understood.

The potential for adverse effects arising from a supportive care product administered to patients with cancer may be best illustrated by the evolving data from studies of erythropoiesis-stimulating agents (ESA). At the time of the initial approval of the first ESA for the treatment of anemia associated with cancer chemotherapy in the early 1990s, FDA noted that ESAs could stimulate malignant tumors, either directly through erythropoietin receptors on tumor cells or indirectly, through effects on tumor vasculature. Because of this concern, post-marketing studies were conducted to rule out detrimental effects of ESA use on response to chemotherapy. Although initial studies in one type of lung cancer did not

demonstrate adverse effects, accumulating data from randomized trials in other common cancers (breast, colon, head and neck cancer) with higher than recommended doses of ESAs demonstrated shorter survival and more rapid time to tumor progression in patients receiving ESAs compared to controls. Despite multiple studies, the mechanism by which ESAs shorten survival and result in more rapid tumor progression remains unknown.

There is now clear evidence that some agents that palliate cancer treatment-toxicity may enhance tumor growth. The Office of Oncology Drug Products currently requires that supportive care drugs which may affect tumor growth directly or indirectly be carefully evaluated in studies designed to identify detrimental effects on cancer outcomes (i.e., time-to-event endpoints such as progression free survival or overall survival); such studies are required at the time of approval if sufficient data are not contained in the marketing application.

2 CLINICAL DEVELOPMENT OF DENOSUMAB

2.1 Overview from the Office of Biotechnology 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 through an epitope in the D-E loop on the receptor binding portion of RANKL. The mechanism of action for this antibody involves a blocking mechanism, where the antibody's binding to RANKL inhibits the interaction of RANKL and its receptor (RANK). Inhibition of the RANK-RANKL interaction prevents receptor activation and clustering 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. As an IgG2, it is expected that denosumab would not have significant antibody dependent cell-mediated cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC) activities (Salfeld, JG, Nature Biotechnology 25:1369, 2007).

The antibody was derived using XenoMouse technology to create a fully human antibody sequence within an IgG2κ framework. Denosumab is expressed in genetically engineered mammalian cells (Chinese hamster ovary). As a mammalian cell-expressed immunoglobulin, denosumab is a glycoprotein. The glycosylation structures have been characterized. Structurally, denosumab exhibits the heterogeneity previously identified for IgG2 antibodies; IgG2 antibodies have been shown to dimerize and to contain heterogeneity due to disulfide bonding variation (Yoo, EM, et al., J. Immunol. 170:3134, 2003, Wypych, J, et al., J. Biol. Chem. 283:16194, 2008). Parameters including product-related species such as these have been assessed for potential impact on antibody binding, efficacy, and pharmacokinetic activities. Production and purification are performed using standard antibody manufacturing techniques. Immunogenicity of the drug product was assessed using ECL bridging assays for detection of binding antibodies, including pre-existing and transient antibodies; less than 1% of the subjects tested positive using these assays. The binding antibodies that were detected were evaluated for neutralizing activity using a cell-based assay

representative of the denosumab mechanism of action; no neutralizing antibodies were detected.

2.2 Overview of Pharmacology and Toxicology

Important issues related to pharmacology/toxicology evaluations were as follows:

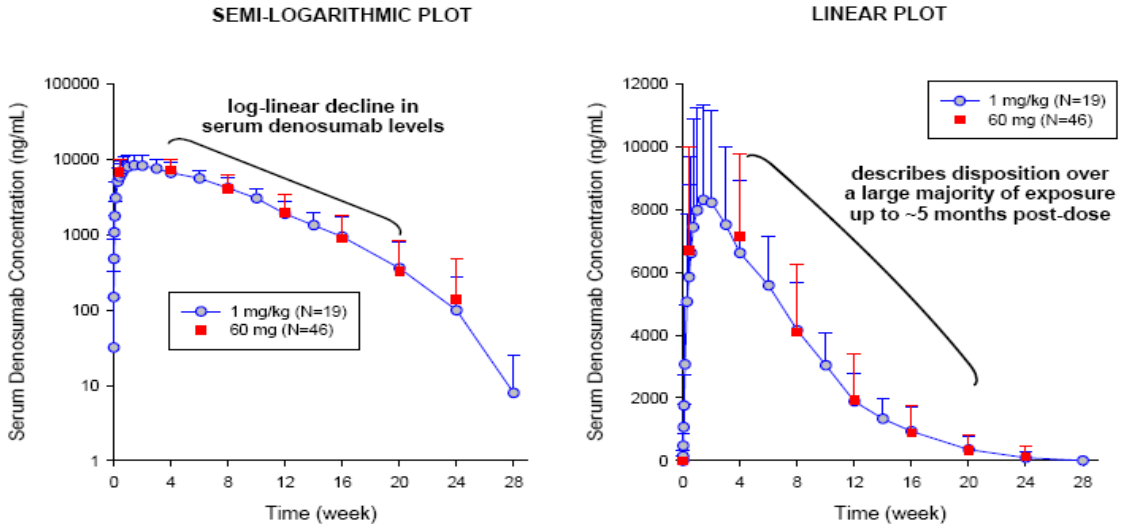
- Denosumab is not pharmacologically active in rodents (mice or rats), the monkey was the only relevant species for animal testing of the effect of denosumab. Safety evaluation programs should normally include two relevant species, however, according to the ICH S6 guidance for preclinical safety evaluation of biotechnology derived products, one relevant species may suffice in certain justified cases.
- Carcinogenicity studies were not conducted with denosumab due to lack of an appropriate test species. While the Applicant does have a surrogate knock-in mouse model with huRANKL that was used primarily for pharmacology studies, it is not an appropriate model for carcinogenicity studies due to adaptive responses during development.
- Embryofetal reproductive toxicity studies may not have optimally assessed fetal toxicity to denosumab. While dosing occurred during the period of primate organogenesis (gestation days 20-50), antibodies do not typically cross the placenta until later in development. Therefore, the study likely only assessed potential secondary effects of denosumab on the fetus resulting from maternal exposure. In addition, only limited organs were evaluated by histopathology, and fetal lymph nodes were not examined. This would have been beneficial since signaling via RANK has been shown to be required for lymph node development in mice. The published literature shows that RANK-RANKL signaling during pregnancy is involved in a crucial step in breast development and lactation. In RANK/RANKL knockout mice, there is impaired lymph node formation, and absence of lactation due to inhibition of mammary gland maturation. As the target population for this study is postmenopausal women, this is not a major concern for this product. This may be an issue for women of reproductive age (hormone ablation population may include young women with breast cancer and hormone ablation therapy).
- Possible signs of immune suppression were noted at denosumab doses ≥ 10mg/kg in a 12-month toxicity study in monkeys, including deaths of 2 high dose males due to protozoal infection, and an increased incidence of abscesses of the teeth and jaws in mid-dose and high dose females. In a 16-month pharmacology (bone quality) study, the total lymphocyte count was slightly and statistically significantly decreased for the high denosumab dose. Absolute counts of CD3+/CD8+ cytotoxic T lymphocytes were also slightly and statistically significantly decreased at the high dose compared to controls.
- Finally, in neonatal rats, inhibition of RANK ligand with a construct of osteoprotegerin bound to Fc (OPG-Fc) at high doses was associated with inhibition of bone growth and tooth eruption. Adolescent primates dosed with denosumab at greater than 27 times (10 mg/kg dose) the clinical exposure had abnormal growth plates.

2.3 Overview of Clinical Pharmacology

2.3.1 Pharmacokinetics

Denosumab showed dose-dependent, nonlinear pharmacokinetic (PK) profile (see Figure 1). However, approximately dose-proportional increases in exposure were observed for doses ≥ 60 mg (in the range of fixed doses of 60 to 210 mg). Following a 60 mg single subcutaneous (SC) dose, maximum serum denosumab concentrations (C_{max}) are typically observed 1 to 4 weeks post-dose; after C_{max}, serum denosumab levels decline over a period of 4 to 5 months with a mean half-life of approximately 25 to 30 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).

Figure 1. Mean Serum Denosumab Concentration-Time Profiles following SC Administration of 60 mg or 1 mg/kg to Postmenopausal Women (From Studies 20010124, 20010223, 20030164, and 20030180)

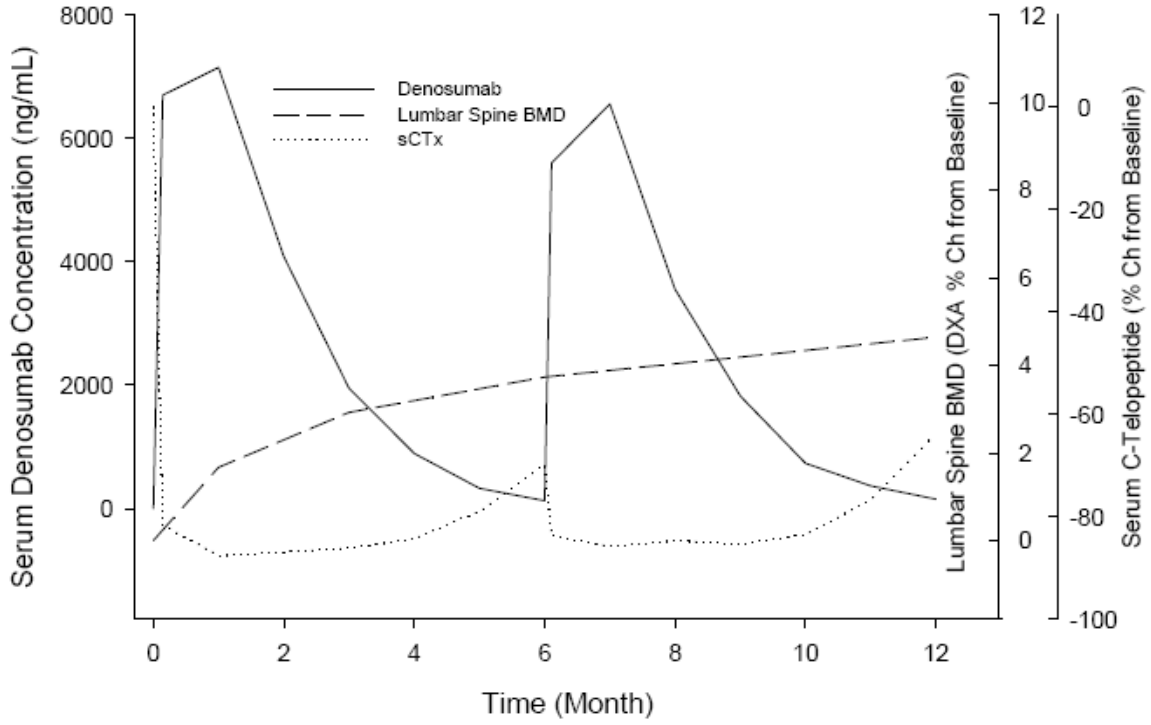


Because denosumab is a monoclonal antibody and is not eliminated via hepatic metabolic mechanisms (e.g., by cytochrome P450 [CYP] enzymes), hepatic impairment and drug interaction studies (e.g., with CYP inhibitors or inducers) were not considered appropriate by the Applicant and have therefore not been conducted. However, a study including transition from a bisphosphonate to denosumab was conducted and allowed indirect evaluation of drug interactions when compared to results from other studies. The PK of denosumab was not altered in subjects who transitioned from bisphosphonates to denosumab. A renal impairment study was conducted in patients with normal, mild, moderate, severe, and end-stage renal disease. No notable relationship was observed between denosumab PK and renal function and it was concluded that no dose adjustment is necessary in patients with renal impairment.

2.3.2 Pharmacodynamics

Denosumab administration resulted in significant inhibition of bone resorption, as assessed by reductions in serum levels of Type 1 C-telopeptide (CTX1). In clinical studies, treatment with 60 mg of denosumab resulted in rapid reduction in the bone resorption marker serum CTX1 within 6 hours of SC administration by approximately 70% (Studies 20030216 and 20040132), with reductions of approximately 85% occurring by 3 days (Study 20010223). Serum CTX1 reductions in bone turnover appeared to be maintained throughout the dosing interval (6 months). At the end of the dosing cycle, some attenuation of bone resorption inhibition was observed (Figure 2), indicating that reduction of bone turnover associated with denosumab administration is reversible when serum concentrations of denosumab diminish. Bone mineral density (BMD) continuously increased during treatment (Figure 2).

Figure 2. Mean Serum Denosumab Concentration and Mean Percent Change from Baseline for Serum CTX1 and Lumbar Spine BMD following Two 60 mg Q6M Doses of Denosumab to Post menopausal Women with Low BMD (From Study 20010223)



2.3.3 Exposure-Response

A population PK analysis showed that age, race and disease status had no significant effect on the denosumab PK parameters. Although body weight was identified as a covariate for clearance, body weight did not appear to affect the incidence of new vertebral fractures and change in the BMD levels. Therefore, a fixed dosing regimen appears to be appropriate for all patients.

2.4 Overview of Clinical Studies

The Applicant has investigated the safety and efficacy of denosumab for the treatment of postmenopausal osteoporosis, prevention of postmenopausal osteoporosis, treatment and prevention of bone loss in patients undergoing hormone ablation for breast cancer and treatment and prevention of bone loss in patients undergoing hormone ablation for prostate cancer. Some studies for other indications have contributed to the overall safety database for denosumab.

Appendix 2 contains a listing of the Applicant's Phase 1, Phase 2 and Phase 3 studies with summary information on overall design, treatment groups, number of subjects, and study duration. In total the Applicant completed 12 Phase 1 studies that include standard pharmacokinetic and pharmacodynamic studies as well as a renal impairment study. The Applicant completed 7 Phase 2 studies, including dose-finding study (20010223). The Applicant completed 11 Phase 3 clinical trials. The primary clinical trials in support of the safety and efficacy of denosumab for each of the proposed indications are as follows:

A) **20030216** - treatment of postmenopausal osteoporosis
B) **20040132** - prevention of postmenopausal osteoporosis
C) **20040135** - treatment and prevention of bone loss in patients undergoing hormone ablation therapy for breast cancer
D) **20040138** - treatment and prevention of bone loss in patients undergoing hormone ablation therapy for prostate cancer

2.5 Dose Selection for Phase 3 Studies

Study 20010223 was a Phase II dose finding study that examined 7 different SC doses of denosumab and 1 cohort each of placebo or weekly oral alendronate in postmenopausal women with low bone mass. The denosumab cohorts were given double-blind study drug as a subcutaneous injection as follows: 6 mg, 14 mg, or 30 mg every 3 months; or 14 mg, 60 mg, 100 mg, or 210 mg every 6 months for the first 24 months of the study. There were approximately 40 subjects per dosing cohort, for a total of 412 subjects (319 denosumab, 46 placebo, 47 alendronate). The study design and objectives were adequate to assess dose response.

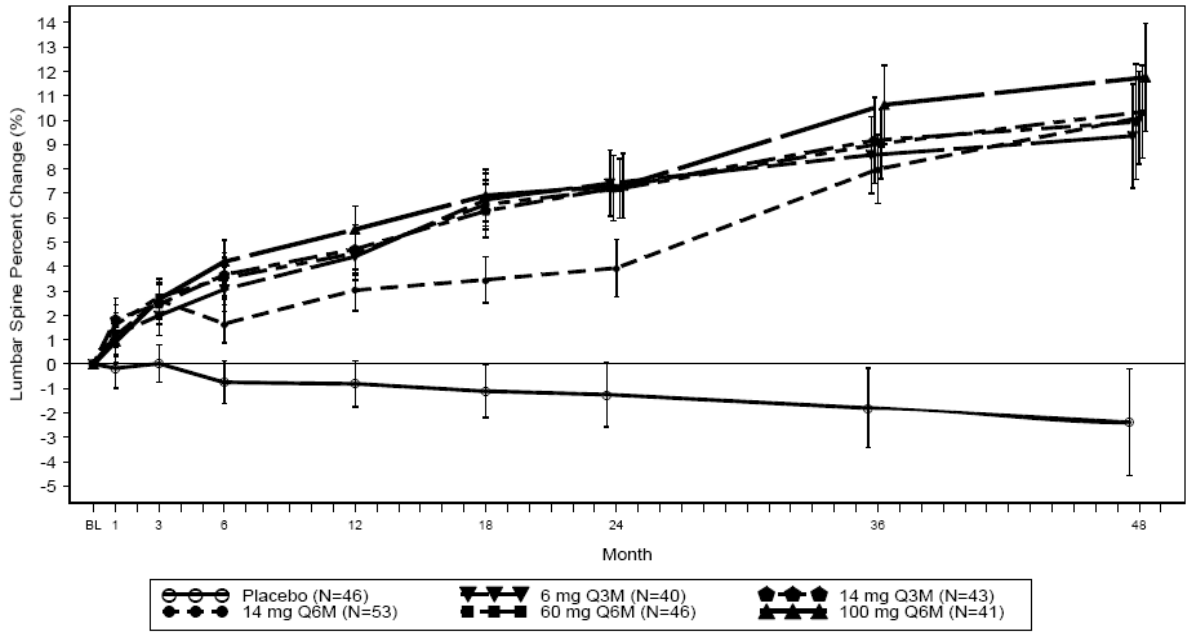
The Applicant selected one dose (60 mg SC Q6months) for the four Phase 3 pivotal trials for treatment of postmenopausal osteoporosis (20030216), prevention of postmenopausal osteoporosis (20040132), bone loss associated with hormone ablation for prostate cancer (20040138), and bone loss associated with hormone ablation for breast cancer (20040135). The Applicant provided the following rationale for the dose selection:

> *"Evaluation of markers of bone resorption (eg, serum CTX1) and BMD data from all anatomic sites indicated that: (1) despite more prolonged reductions in bone resorption markers over a six month dose interval, the doses higher than 60 mg did not result in greater gains in BMD, and (2) doses of 30 mg every 3 months and 60 mg every 6 months displayed, overall, similar PD activity. Furthermore,*

denosumab doses ≥ 60 mg administered every 6 months were at least as effective as 70 mg of alendronate administered once a week. Since denosumab was effective when dosed using either a 3- or a 6-month dosing interval, the 6-month dosing interval was selected because it is more convenient and may increase compliance."

Dose-response relationship data for lumbar spine BMD in the denosumab continuous treatment cohorts are shown in Figure 3. In the first 24 months of the study, subjects received a subcutaneous injection of denosumab as follows: 6 mg, 14 mg, or 30 mg Q3 months; or 14 mg, 60 mg, 100 mg, or 210 mg Q6months. In the remaining 24 months of the study, subjects who had received denosumab 6 mg and 14 mg Q3months or denosumab 14 mg, 60 mg, and 100 mg Q6months then received denosumab 60 mg Q6months for the remainder of the study; this group was classified as the continuous treatment cohort.

Figure 3. Study 223 Percent Change in Lumbar Spine BMD from Baseline (Continuous-Treatment denosumab cohorts)



Population includes all subjects who had at least one baseline and at least one postbaseline measurement
Note: Least squares means and its 95% confidence intervals are from a linear model with percent change from baseline value as the dependent variable and treatment, geographic location and baseline value as independent variables.

Program: /stat/amg162/osteo/20010223/analysis/final_48mon/graphs/program/g_bmdxa_lsm_95ci.sas
Output: g1-01_003_002_bmdxa_lsm_95ci_bmd_spine_cont_dmab_noaln.cgm (Date Generated: 12JUL2007: 7:59:57)
Source Data: adam:abmdxa

Source: Clinical Study Report 20010223, Figure 9-1, page 169 of 9933.

2.6 Applicant's Pivotal Phase 3 Clinical Studies

The applicant conducted 4 pivotal Phase 3 clinical trials that are listed below. Additional information on the Phase 3 osteoporosis studies (overall design, treatment groups, number of subjects, and subject demographics) can be found in Appendix 2. The primary clinical trial

in support of the safety and efficacy of denosumab for the treatment of osteoporosis (Study 20030216) is described in detail in Sections 3 and 4.

2.6.1 Treatment of Postmenopausal Osteoporosis

Study 20030216 - an international, multicenter, randomized, double-blind, placebo controlled study to evaluate denosumab in the treatment of postmenopausal osteoporosis. This 3-year study enrolled 7868 subjects (60 subjects from one site were excluded due to Good Clinical Practice (GCP) violations), randomized to denosumab or placebo.

2.6.2 Prevention of Postmenopausal Osteoporosis

Study 20040132 - a randomized, double-blind study to evaluate denosumab in the prevention of postmenopausal osteoporosis. This 4-year study enrolled 332 women (denosumab – 166, placebo – 166); subjects received therapy for 24 months and were monitored for an additional 24 months.

2.6.3 Treatment and Prevention of Bone Loss with Hormone Ablation for Breast Cancer

Study 20040135 - a randomized, double-blind, placebo-controlled study to evaluate denosumab in the treatment of bone loss in subjects undergoing aromatase inhibitor therapy for nonmetastatic breast cancer. This 4-year study enrolled 252 subjects (denosumab -127, placebo - 125); subjects received therapy for 24 months and were monitored for an additional 24 months.

2.6.4 Treatment and Prevention of Bone Loss with Hormone Ablation for Prostate Cancer

Study 20040138 - a randomized, double-blind, placebo-controlled study to evaluate denosumab in the treatment of bone loss in subjects undergoing androgen-deprivation therapy for nonmetastatic prostate cancer. This 5-year study enrolled 1,468 subjects (denosumab – 734, placebo – 734); subjects received therapy for 36 months and were monitored for an additional 24 months.

2.7 Applicant's Other Phase 3 Studies

Study 20050141: This was a multicenter randomized, double-blind, active controlled, double-dummy, parallel-group study to compare the Efficacy of Treatment with Denosumab versus Alendronate Sodium in Postmenopausal Women with Low Bone Mineral Density. 1189 subjects were enrolled into the study, with 1:1 randomization. Primary endpoint was percent change from baseline in BMD at the total hip as measured by DXA at 12 months in postmenopausal women. At month 12, the mean percent change in total hip BMD was 3.5% in the denosumab and 2.6% in the alendronate group (1-sided $p < 0.0001$). Clinical fractures were reported by the investigators for 18 subjects (3%) in the denosumab group and 13 subjects (2%) in the alendronate group.

Study 20050234: This was a phase 3b multicenter, randomized, double-blind, active-controlled, double-dummy, parallel-group study to evaluate safety and efficacy of transitioning therapy from alendronate to denosumab in postmenopausal women with low bone mineral density. The trial randomized (1:1) 504 women with BMD T score ≤ -2.0 and ≥ -4.0 at the lumbar spine or total hip. The primary objective of this study was to evaluate the effect of denosumab 60 mg Q6M on total hip bone mineral density (BMD) at 12 months in postmenopausal women with low BMD previously treated with alendronate 70 mg every week or equivalent compared to that in subjects continuing on alendronate therapy.
The mean percent change from baseline in total hip BMD at month 12 was 1.90% in the denosumab group and 1.05% in the alendronate group with a difference of 0.85% (95% CI: 0.44, 1.25). Bone biopsy evaluation of labeling status and histomorphometric parameters showed decreased bone turnover in subjects treated with denosumab compared to alendronate.

Study 20060289: This is an ongoing, multinational, multicenter, open-label, single-arm seven-year extension study to evaluate long term safety and sustained efficacy of denosumab in the treatment of postmenopausal osteoporosis; enrolled 4550 subjects who completed Study 20030216. In this study, serum calcium assessments were obtained in all subjects at day 10 ± 5 days to further characterize the timing and magnitude of maximal reductions in serum calcium after denosumab dose.

3 DESIGN OF THE PIVOTAL PHASE 3 TRIALS

3.1 Study 20030216

Study 20030216: This was an international, multicenter, randomized, double-blind placebo-controlled clinical trial.

Objectives:
The primary objective was to determine whether denosumab treatment can reduce the number of postmenopausal osteoporotic women (BMD T-score below –2.5) with new vertebral fractures as compared with control (placebo plus vitamin D and calcium) at 3 years.

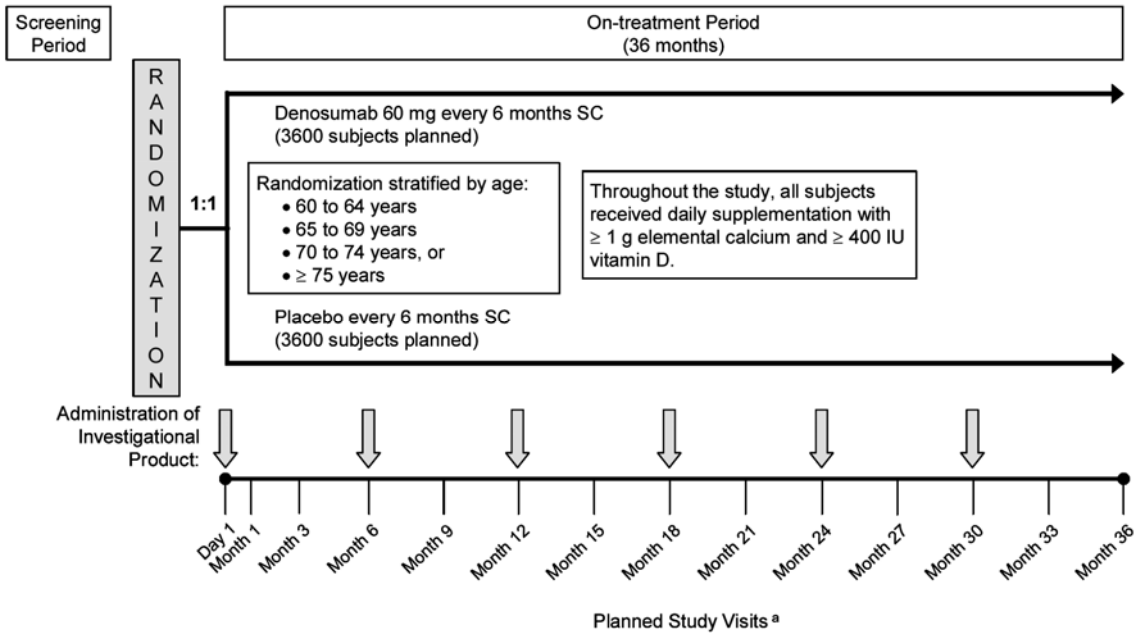
The secondary objectives were to assess the effect of denosumab on 1) time to first non-vertebral fracture, 2) time to first hip fracture, 3) characterization of the safety and tolerability profile in postmenopausal women.

Study design and methods:
Subjects were randomized (1:1) to receive either denosumab (60 mg) or placebo every 6 months (Q6M) subcutaneously (SC) for 3 years. All subjects received daily calcium (≥ 1 g) and vitamin D (≥ 400 IU) supplementation throughout the study. Randomization was stratified by age at study entry: 60 to 64 years, 65 to 69 years, 70 to 74 years, and ≥ 75 years. The following constraints were placed on the proportion of subjects in each age group to ensure that an appropriate age distribution is achieved to evaluate the effect of denosumab on hip fracture incidence:

- A maximum of 5% of subjects 60-64 years of age may be enrolled.
- Either a minimum of 35% of subjects must be 75 years or older, or a minimum of 70% of subjects must be at least 70 years of age.

The general study scheme is presented in Figure 4:

Figure 4: Study Schema



Study visits occurred every 6 months, for a total of seven visits over 3 years. Telephone contacts were conducted every 3 months in between scheduled visits. The last scheduled dose of investigational product was at Month 30; subjects were followed until Month 36.

Study Conduct:
All subjects had lateral spine X-rays taken at Screening, month 12, 24 and 36/early termination. Additionally, a lateral spine x-ray was done at Month 6 if the subject had a suspected fracture based on Vertebral Fracture Analysis (VFA) or if VFA technology was not available at the study center. VFA of the spine by DXA was collected at Baseline/Day 1 before dosing and Month 6 if the VFA by DXA technology were available at the study center.

All subjects had a DXA of the spine at Screening and month 36/early termination. All subjects had a DXA of the proximal femur at Screening and at months 12, 24 and 36/ET. DXA spine was also performed at Month 24 for subjects who discontinued treatment prior to Month 24.

Adverse events, clinical fracture recording, concomitant medications recording and disability back pain questionnaires were assessed at every 3 months. For some of these assessments, telephone contact between clinic visits was utilized.

In addition to the primary study in which all subjects participated, several sub-studies also were conducted within the main study. These substudies evaluated subjects at more frequent visits compared to the whole population. The number of enrolled subjects for these sub-studies is provided in Table 2.

Table 2: Sub-studies within Study 20030216

Substudy	Enrolled N
Bone Biopsy Substudy	103
DXA Substudy	441
Bone Marker Substudy	160
PK Substudy	803
QCT Spine/Hip Substudy	209
QCT Distal Radius Substudy	182
Fracture Healing Substudy	**25**

Eligibility criteria

Inclusion Criteria
The target population was postmenopausal, ambulatory women, between 60 and 90 years old with a BMD T-score between –2.5 and -4.0 at the lumbar spine or total hip.

Exclusion Criteria (Including, but not limited to)

- Any medication affecting bone metabolism:
  - Oral bisphosphonate (use less than 3 months allowed; 3 months – 3 years exposure – 1 year wash-out; 3 or more years exposure – ineligible)
  - Within 5 years: intravenous bisphosphonate, fluoride or strontium
  - Within the last 6 weeks:
    - PTH or PTH derivatives, e.g., teriparatide
    - Anabolic steroids or testosterone
    - Glucocorticosteroids (> 5 mg prednisone equivalent per day for more than 10 days)
    - Systemic hormone replacement therapy, SERMs
    - Tibolone, Calcitonin, Calcitriol

- Conditions affecting bone metabolism
    - Hyper or hypothyroidism; patients on stable thyroid treatment with a normal TSH allowed
    - Hyper- or hypoparathyroidism,
    - Hypocalcemia (albumin adjusted serum calcium 8.5 mg/dL)
    - Vitamin D deficiency (25-hydroxy Vitamin D level < 12 ng/mL). If repeat 12-20 ng/mL after repletion, subject was allowed
    - Rheumatoid arthritis, Paget's disease

- Malignancy (except basal cell carcinoma, cervical or breast ductal carcinoma *in situ*) within the last 5 years
- Any bone disease, e.g., osteomalacia or osteogenesis imperfecta
- Malabsorption syndrome

Study Medication: All subjects received a subcutaneous injection of denosumab or placebo administered by a health care professional every 6 months. Subjects were provided daily supplements of calcium (≥ 1000 mg) and vitamin D (≥ 400 IU if screening level was > 20 ng/mL or ≥ 800 IU if screening level was 12 to 20 ng/mL) throughout the study.

Efficacy Endpoints: The primary efficacy endpoint was the incidence of new vertebral fractures at Month 36. Secondary efficacy endpoints included time to first non-vertebral fracture and time to first hip fracture.

Vertebral fractures: Vertebral fractures were determined from X-rays of the lateral thoracic and lumbar spine (T4-L4). All films were read by two independent radiologists at a Central Reading Facility using the semi-quantitative methodology described by Genant (Genant HK, *J Bone Miner Res*. 1993; 8:1137-1148.). If there were disagreement, a third radiologist adjudicated the films independently. A prevalent vertebral fracture was defined as a fracture (Genant grade ≥ 1) present at baseline. A new vertebral fracture was defined as an increase of ≥ 1 grade in any vertebra from T4 to L4 from the previous grade of 0. A clinical vertebral fracture was defined as a new vertebral fracture associated with any signs and/or symptoms of a fracture.

Nonvertebral fractures: Nonvertebral fractures (osteoporotic) were those occurring on study excluding those of the vertebrae (cervical, thoracic, and lumbar), skull, facial, mandible, metacarpus, finger phalanges, and toe phalanges.

3.2 Study 20040132

Trial 132 was a multinational, multicenter, double-blind, placebo-controlled trial of 332 postmenopausal women with BMD T-scores of -1.0 to -2.5. The primary objective of this study was to determine whether denosumab treatment can prevent lumbar spine bone loss (as measured by percent change from baseline in the lumbar spine BMD [by DXA] at 24 months of treatment) in both early and late postmenopausal women with low bone mass (lumbar spine BMD T-score between –1.0 and –2.5). The secondary objectives were to assess the effect of denosumab on BMD measured by DXA at the hip, distal radius, and total body and to measure trabecular, cortical, and total volumetric BMD by quantitative computerized tomography at the distal radius in both early and late postmenopausal women with low bone mass.

Eligibility Criteria: Subjects were eligible for this study if they were a postmenopausal woman not more than 90 years of age and have signed the written informed consent. Subjects were not eligible for this study if they met any of the following criteria: long-term

or recent bisphosphonate administration; use of IV bisphosphonate, fluoride (for osteoporosis) or strontium within the last 5 years; use of any anabolic agent (e.g. parathyroid hormone, teriparatide, anabolic steroids) within the last 6 weeks; evidence of diseases that would interfere with calcium homeostasis (e.g. hyperthyroidism, hyperparathyroidism, bone diseases, malignancy); enrollment in an investigational device or drug trial(s) within the past 30 days; any other condition which the investigator believes would prevent the subject from completing the study or interfere with the interpretation of the study results.

Study Medication: Subjects were randomized (1:1) to receive either denosumab or placebo; randomization was stratified by time since onset of menopause (≤ 5 years or > 5 years). All subjects received daily supplementation of calcium (at least 1000 mg) and vitamin D (at least 400 IU) through month 48. During the off-treatment period (months 25 to 48), study drug was discontinued and all subjects continued with their calcium and vitamin D supplementation.

Efficacy Endpoints: The primary efficacy endpoint was percentage change in lumbar spine BMD at 24 months of treatment in both early (≤ 5 years since menopause) and late (> 5 years since menopause) postmenopausal women with low bone mass. Key secondary endpoints were percentage change in BMD at the total hip, femoral neck, trochanter, distal 1/3 radius, and total body at 24 months. The incidence of new vertebral fractures at or before month 24 and the incidence and time to first clinical fracture at or before month 24 was among many exploratory endpoints in this study. A 24 month off-treatment follow-up period was ongoing at the time the BLA was submitted.

3.3 Study 20040135

Trial 135 was a multinational, multicenter, double-blind, placebo-controlled trial involving 252 patients with breast cancer receiving adjuvant aromatase inhibitor therapy following definitive local therapy.

Eligibility Criteria: Eligible patients had an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 with no distant metastasis, no evidence of unstable systemic disease, no recent exposure to bisphosphonates or other medications having an influence on bone metabolism, no other concurrent therapy for cancer, no history of fractures after age 25, and lumbar spine, total hip, and/or femoral neck BMD T-score of -1.0 to -2.5 (low bone mass).

Study Medication: Patients were randomized 1:1 to denosumab (127) or placebo (125) once every 6 months for a total of 4 doses during the treatment period of 24 months. Randomization was stratified by the planned duration of aromatase inhibitor therapy (≤ 6 months vs. > 6 months). A 24 month safety follow-up period was ongoing at the time the BLA was submitted.

Efficacy Endpoints: The primary efficacy endpoint was percentage change in lumbar spine bone mineral density (BMD) from baseline to month 12. Key secondary endpoints were percentage change in lumbar spine bone mineral density (BMD) from baseline to month 6, and percentage change in total hip and femoral neck BMD from baseline to months 6 and 12.

There were no neoplastic disease assessments specified as part of the trial and such data were not captured during the conduct of the trial. Survival rate at month 24 was an exploratory endpoint.

3.4 Study 20040138

Trial 138 was a multinational, multicenter, double-blind, placebo-controlled trial involving 1468 patients with prostate cancer following definitive local therapy receiving androgen deprivation therapy (ADT) with gonadotropin-releasing hormone (GnRH) agonists or following orchiectomy. Approximately 10% of the study population underwent orchiectomy.

Eligibility Criteria: Eligible patients were ECOG performance status 0, 1, or 2, with no distant metastasis, no evidence of unstable systemic disease, no recent exposure to bisphosphonates or other medications having an influence on bone metabolism, ≥ 70 years, or < 70 years with a history of osteoporotic fracture or BMD T-score at the lumbar spine, total hip, or femoral neck < -1.0 (using the normative male database), had BMD T-score at the lumbar spine, total hip or femoral neck not < -4.0.

Study Medication: Patients were randomized 1:1 to either denosumab (734) or placebo (734) once every 6 months for a total of 6 doses over a 36-month treatment period. Randomization was stratified by age group (< 70 years vs. ≥ 70 years) and duration of ADT at trial entry (≤ 6 months vs. > 6 months). Upon completion of the 36-month treatment period, patients were continued on trial for 24 months during which no investigational product was administered, or were offered enrollment in a 2-year extension trial.

Efficacy Endpoints: The primary efficacy endpoint was the percent change in lumbar spine BMD from baseline to month 24. Key secondary endpoints were percentage change in femoral neck BMD and total hip BMD from baseline to month 24, percentage change in lumbar spine BMD, femoral neck BMD, and total hip BMD from baseline to month 36, subject incidence of any fracture, and subject incidence of new vertebral fracture over the 36-month treatment period. Neoplastic disease assessments consisted of bone scans at baseline and month 36 and PSA levels every 6 months during the treatment phase of the trial. There were no pre-specified analyses to assess effects on disease-free survival based on bone scan or PSA results. Survival rate at 36 months was an exploratory endpoint.

4 EFFICACY FINDINGS FROM the PIVOTAL PHASE 3 TRIALS

4.1 Study 20030216 (PMO fracture study)

4.1.1 Subject Enrollment and Disposition

This multinational study enrolled 7868 subjects, of which 355(5%) came from United States. 60 subjects from Lithuania site 803 were excluded from all efficacy and safety analysis before unblinding, due to Good Clinical Practice (GCP) violations. Therefore, the ITT population consisted of 7808 subjects (denosumab: 3902 subjects, placebo: 3906 subjects).

Overall, 3206 subjects (84%) in the denosumab group and 3272 subjects (82%) in the placebo group completed the study (Table 3).

Table 3: Subject Disposition in Study 20030216

Subject Disposition	Placebo	Denosumab
	N (%)	N (%)
Randomized	3906 (100%)	3902 (100%)
Discontinued study prior to Month 36	700 (17.9%)	630 (16.1%)
Completed IP[1]	67 (1.7%)	79 (2%)
Completed study	3206 (82.1%)	3272 (83.9%)
Completed IP	2882 (73.8%)	3052 (78.2%)
Discontinued IP	324 (8.3%)	220 (5.6 %)
Analyzed for primary endpoint (ITT)	3906	3902
Analyzed for adverse events (safety population, subjects who received at least one dose of IP)	3876	3886

[1]IP= Investigational product.

4.1.2 Demographics

All participants were females, a majority of whom were Caucasian (approximately 93%). The mean age at randomization was 72 years with 32% being ≥ 75 years old. The mean BMI was 26 kg/m2 and the average number of years since menopause was 24 years. Prevalent morphometric vertebral fractures at baseline in 23.8% of subjects in the denosumab group and 23.4% subjects in placebo group. Baseline mean BMD T-scores at the lumbar spine, total hip, femoral neck, and trochanter were -2.8, -1.9, -2.2, and -1.5, respectively, for both treatment groups. Baseline subject demographics were balanced between the treatment groups (Table 4).

Calculation of fracture risk by FRAX tool:

Before database lock and unblinding, probabilities of 10-year major osteoporotic and hip fracture risk for each subject were generated by an independent statistical service provider (Helena Johansson, Kalserud 124, 460 64 Frändefors, Sweden). The 10-year osteoporosis fracture risk and hip fracture risk by the FRAX tool were approximately 19% and 7%, respectively, in both treatment groups (Table 4).

Table 4: Demographics and baseline disease characteristics for subjects in study 20030216 (PMO fracture trial)

	Placebo (N = 3906)	Denosumab (N = 3902)
Demographics		
Ethnic group / race, n (%)		
White or Caucasian	3629 (92.9)	3609 (92.5)
Black or African American	27 (0.7)	30 (0.8)
Hispanic or Latino	232 (5.9)	241 (6.2)
Asian	8 (0.2)	9 (0.2)
Japanese	4 (0.1)	7 (0.2)
Native Hawaiian or Pacific Islander	2 (<0.1)	0 (0.0)
Other	4 (0.1)	6 (0.2)
Age (years), mean (SD)	72.3 (5.2)	72.3 (5.2)
Age group, n (%)		
60 - 64 years	208 (5.3)	206 (5.3)
≥65 years	3698 (95)	3696 (95)
≥ 75 years	1236 (32)	1235 (32)
BMI, mean (SD)	26 (4.2)	26 (4.1)
Years since menopause, mean (SD)	24.2 (7.5)	24.2 (7.4)
Baseline disease characteristics		
Baseline Fracture History		
Baseline prevalent vertebral fracture	23.4%	23.8%
Nonvertebral fracture	38.6%	39.1%
Baseline BMD		
Mean Lumbar spine BMD T scores	-2.84	-2.82
Mean Total hip BMD T scores	-1.91	-1.89
Mean Femoral neck BMD T-scores	-2.17	-2.15
Fracture risk by FRAX tool		
10-year osteoporotic fracture risk	18.7%	18.5%
10-year hip fracture risk	7.19%	7.24%

Source: This table is from analysis of ASLINFO dataset and combining several tables supplied by the Applicant.

Biomarkers of bone turnover:

Mean (SD) baseline serum concentrations of CTX1 and TRAP 5b, PTH, serum calcium, and phosphorous were similar between the 2 treatment groups. Baseline rate of smoking and alcohol use were similar between the two treatment groups. At baseline, almost all subjects (99.3%) reported using calcium and vitamin D supplementation. A history of osteoporosis medications was low and similar between the two study groups.

4.1.3 Primary efficacy endpoint:

The results of the Applicant's primary efficacy analysis (subject incidence of new vertebral fractures) are shown in Table 5. Based on the analysis, there was a statistically significant reduction in the number of subjects with new vertebral fractures through each of Years 1, 2, and 3.

Table 5: Subject Incidence, Absolute Risk Reduction, and risk Ratio for New Vertebral Fracture through Month 36 (Primary Efficacy Analysis Set, LOCF Imputation)

Number (%) of subjects	Plac. (N= 3906)	Denos. (N=3902)	Absolute risk reduction %, 95% CI	Relative risk reduction %, 95% CI	Risk Ratio (95% CI)	P value
0-1 year	82/3691 (2.2%)	32/3702 (0.9%)	1.4 (0.8,1.9)	61 (42,74)	0.39 (0.26, 0.58)	<0.0001
0-2 years	183/3691 (5.0%)	53/3702 (1.4%)	3.5 (2.7,4.3)	71 (61,79)	0.29 (0.21, 0.39)	<0.0001
0-3 years Primary endpoint	**264/3691 (7.2%)**	**86/3702 (2.3%)**	**4.8 (3.9,5.8)**	**68 (59,74)**	**0.31 (0.24,0.39)**	**<0.0001**

P value is based on Mantel-Haenszel method adjusting for age stratification variable

Subgroup analyses:
In subgroup analyses, denosumab significantly decreased risk of new vertebral fracture at month 36 ($p < 0.0001$) in all subgroups of baseline characteristics examined (subgroups of age ($\geq$75 years, $\geq$ 65 years, < 75 years), geographic region, body weight, BMI, lumbar spine BMD T-score, total hip BMD T-score, fracture risk assessed by FRAX, prior use of medication for osteoporosis and serum CTX1). The results remain significant and consistent when analyzed by prevalent vertebral fracture or non-vertebral fracture at baseline.

4.1.4 Secondary efficacy endpoint:

Secondary efficacy endpoints include the following:

- Time to first non-vertebral fracture, assessed at the time of the 36-month analysis,
- Time to first hip fracture, assessed at the time of the 36-month analysis.

Nonvertebral fractures were those occurring on study excluding those of the vertebrae (cervical, thoracic, and lumbar), skull, facial, mandible, metacarpus, finger phalanges, and toe phalanges. In addition, fractures associated with high trauma severity and pathologic fractures were excluded from this category. Nonvertebral fractures were required to be

confirmed either by radiographs or other diagnostic images such as computerized tomography (CT) or magnetic resonance imaging (MRI), or by documentation in a radiology report, surgical report, or discharge summary.

Denosumab significantly reduced the risk of nonvertebral fracture compared to placebo (p = 0.0106) as shown in Table 6. The incidence of nonvertebral fractures at Month 36 (based on Kaplan-Meier estimates) was 8% in the placebo group and 6.5% in the denosumab group. The relative risk reduction was 20%, with a hazard ratio of 0.80 (95% CI: 0.67, 0.95) at Month 36.

Denosumab significantly reduced the risk of hip fracture compared to placebo. The subject incidence of hip fractures at month 36 (based on Kaplan-Meier estimates) was 1.2% in the placebo group and 0.7% in the denosumab group, resulting in an unadjusted absolute risk reduction of 0.5% (95% CI: 0.0%, 0.9%). The relative risk reduction was 40%, i.e., a hazard ratio of 0.60 (95% CI: 0.37, 0.97) at month 36.

Table 6: Study 20030216: Subject Incidence, Absolute Risk Reduction, and Hazard Ratio for Nonvertebral and Hip Fracture Through Month 36 (Full Analysis Set)

	Number of Events	Crude Incidence %	Kaplan-Meier Estimate of Incidence at Month %			Absolute Risk Reduction[1] at 36 Months % (95% C.I.)	Hazard Ratio[2] (95% C.I.)	p-value
Nonvertebral fracture								
			12	**24**	**36**			
Denosumab (N=3902)	238	6.1	2.6	4.6	6.5	1.5 (0.3, 2.7)	0.80 (0.67, 0.95)	0.0106
Placebo (N=3906)	293	7.5	3.1	5.8	8.0			
Hip fracture								
Denosumab (N=3902)	26	0.7	0.3	0.4	0.7	0.3 (-0.1, 0.7)	0.60 (0.37, 0.97)	0.0362
Placebo (N=3906)	43	1.1	0.6	0.9	1.2			

Source: Table 9-5 and 9-6, page 251, Study 20030216 report and Statistical Reviewer's calculation.
[1] Absolute risk reduction based on inverse variance-weighted method adjusting for age stratification variable.
[2] Hazard ratio and p-value based on Cox proportional hazards model stratified by age stratification variable.

4.1.5 Important Tertiary Endpoints:

Bone Mineral Density

Denosumab treatment increased BMD in the lumbar spine and total hip compared to placebo. Denosumab increased lumbar spine BMD compared with placebo, with a mean difference between the treatment groups in change from baseline to Month 36 of 8.8%. Total hip BMD increased in denosumab group compared to placebo, with a mean difference between the treatment groups in change from baseline to Month 36 of 6.4% (Table 7).

Table 7: Lumbar Spine and Total Hip Bone Mineral Density by DXA Percent Change from Baseline at Month 36 (Primary Efficacy Population, LOCF)

Location	N	Difference from Baseline+%	Difference from Placebo+ % (95% C.I.)	P Value
Lumbar Spine				
Placebo	3160	0.6		
Denosumab	3203	9.4	8.8 (8.6, 9.1)	< 0.0001
Total Hip				
Placebo	3608	-1.4		
Denosumab	3624	5.0	6.4 (6.2, 6.6)	< 0.0001

+ Based on an ANCOVA model that includes treatment, age stratification variable, baseline value, machine type, and baseline value-by-machine type interaction

Subgroup analyses: Increases from baseline to month 36 in lumbar spine BMD in body weight subgroups (< 55; 55 to < 65; 65 to < 75; and ≥ 75 kg) were similar among denosumab-treated subjects within those subgroups (9.3%, 9.7%, 9.2%, and 9.3%, respectively). As expected, and consistent with observations in other studies, subjects treated with placebo who weighed more did not lose BMD as rapidly (-0.3%, 0.4%, 0.8%, and 1.8%, respectively). Thus, the difference between the denosumab and placebo groups decreased with increasing body weight (9.6%, 9.3%, 8.4%, and 7.5%, respectively). A similar trend was noted for the BMI subgroups for lumbar spine, and body weight as well as BMI subgroups for total hip BMD.

Biochemical Markers of Bone Turnover

Denosumab reduced biomarkers of bone turnover at each time point in the Biomarker Sub-study. These markers included bone resorption markers (CTX and TRAP 5b), and bone formation markers (N-terminal Propeptide Type I Procollagen and bone specific alkaline

phosphatase). The percent changes from baseline to Month 36 for these biomarkers are summarized in Table 8.

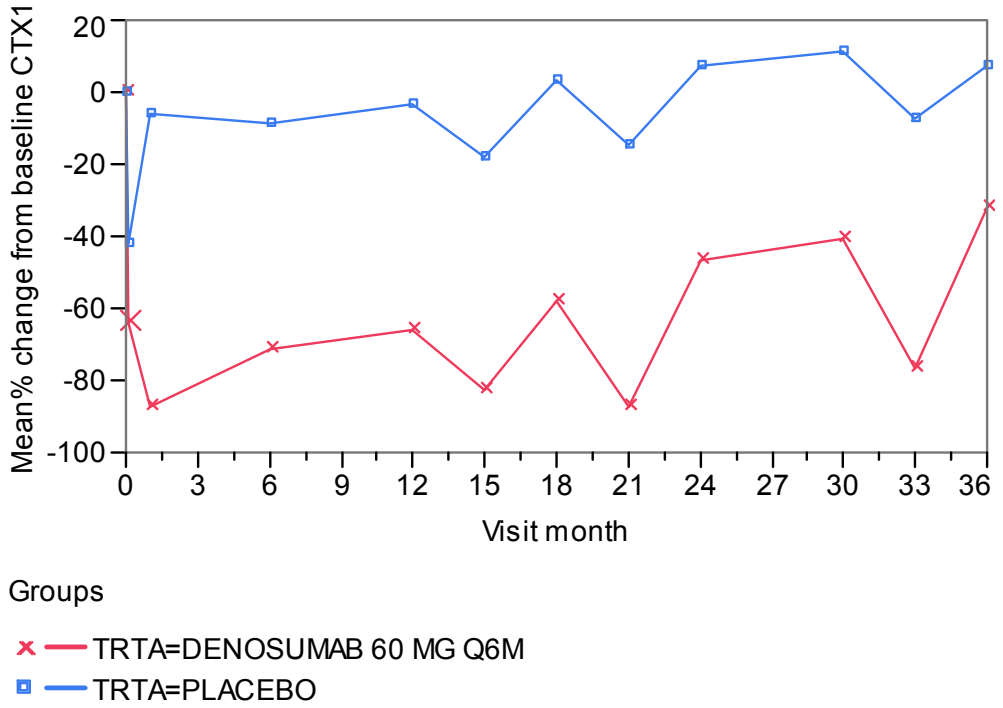
Table 8: Percent Change from Baseline through Month 36 in Serum Bone Markers (LOCF)

LAB Test Name	Placebo mean (SD) %Chg From BL	Denosumab mean (SD) %Chg From BL
Markers of Bone resorption		
Serum C-Telopeptide	-1.9(46)	-53.4(44)
Tartrate-Resistant Acid Phosphatase 5b	5.1(34)	-26.2(30)
Markers of Bone formation		
Bone-Specific Alkaline Phosphatase	0.2(28)	-13.9(21)
N-terminal Propeptide Type I Procollagen	2.5(73)	-40.1(38)

Source: This table is based on analysis from albbnsp dataset including subjects who received ≥1 IP dose.

Treatment with denosumab resulted in reductions in concentrations of serum CTX1, a marker of bone resorption, relative to placebo at each post-baseline assessment ($p < 0.0001$ at all time points) (Figure 5). Similarly, tartrate-resistant acid phosphatase 5b levels were decreased compared to placebo at each post-baseline assessment starting at month 1. Treatment with denosumab reduced concentrations of BALP and PINP relative to placebo at each post-baseline assessment beginning with month 6 through 36.

Figure 5: CTX1 % change from baseline by visit



4.2 Study 20040132 (PMO prevention study)

The primary efficacy endpoint in this study was percentage change in lumbar spine BMD at 24 months of treatment in both early (≤ 5 years since menopause) and late (> 5 years since menopause) postmenopausal women with low bone mass. Key secondary endpoints were percentage change in BMD at the hip, distal radius, and total body at 24 months and percent change in trabecular, cortical, and total volumetric BMD as measured by quantitative computerized tomography (QCT) at the distal radius at 24 months.

Table 9: Demographics and baseline disease characteristics for subjects in study 20040132 (PMO prevention trial)

	Placebo (N = 166)	**Denosumab (N = 166)**
Age (years), mean (SD)	58.9 (7.5)	59.8 (7.4)
Age group, n (%)		
≥ 65 years	33 (20)	39 (23)
≥ 75 years	6 (4)	9 (5)
Ethnic group, n (%)		
White or Caucasian	137 (83)	137 (83)
Black or African American	6 (4)	8 (5)
Hispanic or Latino	13 (8)	10 (6)
Asian or Japanese	8 (5)	9 (5)
Other	2 (1)	2 (1)
BMI, mean (SD)	26.2 (4.8)	26.6 (4.8)
Years since menopause		
≤ 5 years	81 (48.8)	81 (48.8)
> 5 years	85 (51.2)	85 (51.2)
Prevalent vertebral fracture, n (%)	0 (0)	1 (1)
Baseline LS BMD T-score, mean (SD)	-1.66 (0.44)	-1.55 (0.41)

The results of the primary efficacy analyses are shown in Table 10. There was a statistically significant increase in lumbar spine BMD for denosumab compared to placebo at 24 months (denosumab +6.5%, placebo -0.6%) based on the least squares of the mean. This statistically significant increase in lumbar spine BMD with denosumab was observed for all subjects, subjects ≤ 5 years since menopause, and subjects > 5 years since menopause. The overall treatment difference was +7% (95% CI: 6.2, 7.8), with the greatest treatment effect in subjects ≤ 5 years since menopause. Consistent effects on lumbar spine BMD were observed regardless of baseline age, race, weight/BMI, BMD, and menopause stratum.

Table 10. Trial 132 Percent Change From Baseline to Month 24 in Lumbar Spine BMD by DXA (ANCOVA Model, Primary Efficacy Subset, LOCF)

Treatment Arm / Stratum	Difference from Baseline[a]			Difference from Placebo[a]		
	n	Least Squares (LS) Mean	C.I. [b]	LS Mean	C.I. [b]	P-value
Overall						
Placebo (N = 163)	163	-0.6	(-1.2, 0.1)			
Denosumab (N = 163)	163	6.5	(5.8, 7.2)	7	(6.2, 7.8)	<0.0001
≤ 5 years since menopause						
Placebo (N = 80)	80	-1.2	(-2.3, -0.2)			
Denosumab (N = 79)	79	6.2	(5.1, 7.3)	7.4	(6.1, 8.7)	<0.0001
> 5 years since menopause						
Placebo (N = 83)	83	0.1	(-1.0, 1.2)			
Denosumab (N = 84)	84	6.8	(5.6, 7.9)	6.7	(5.4, 8.0)	<0.0001

n = Number of subjects with values at baseline and at ≥ 1 post-baseline visit at or prior to the time point of interest
N = Number of subjects with values at baseline and at least ≥ 1 post-baseline visit
a Based on an ANCOVA model (for each stratum) that adjusts for treatment, baseline value, machine type, and baseline value-by-machine type interaction; the model (for overall assessment) also adjusts for strata.
b 97.5% CI for each stratum and 95% CI for the overall assessment
Source: Clinical Study Report for Study 20040132 (24-month results), Table 9-1, page 133 of 2440.

For key secondary endpoints, the treatment differences from baseline to month 24 in BMD were statistically significant at the total hip with 4.5% (95% CI: 4.0, 5.0), femoral neck with 3.7% (95% CI: 2.9, 4.4), trochanter with 6.0% (95% CI: 5.3, 6.6), distal 1/3 radius with 3.5% (95% CI: 2.8, 4.3), and total body with 3.8% (95% CI: 3.1, 4.5) ($p < 0.0001$ at all sites).

The Applicant determined that there were clinical fractures in 2 subjects (1%) in the denosumab group and 7 subjects (4%) in the placebo group (all fractures confirmed by central imaging vendor). All of the clinical fractures were non-vertebral fractures. Fractures were reported as adverse events for 9 subjects (6%) in the denosumab group and 14 subjects (9%) in the placebo group.

4.3 Study 20040135 (Hormone ablation - breast cancer study)

Disposition: As outlined in Table 11, 252 subjects were enrolled in the trial and 249 subjects received at least one dose of study medication. Ninety-nine subjects (79%) in the placebo group and 106 subjects (83%) in the denosumab group completed the 24-month treatment period. Consent withdrawn was the most common reason for study discontinuation [9 subjects (7%) in the placebo group and 11 subjects (9%) in the denosumab group] (Table 11).

Table 11: Subject Disposition for Study 20040135 (Hormone ablation – Breast cancer)

Subject Disposition	Placebo N (%)	Denosumab N (%)
Randomized	125 (100)	127 (100)
Safety population (at least one dose of IP)	124 (99)	125 (98)
Discontinued study	26 (21)	21 (17)
Death	0 (0)	1 (1)
Disease progression	3 (2)	1 (1)
Adverse event	2 (2)	0 (0)
Consent withdrawn	9 (7)	11 (9)
Noncompliance	4 (3)	2 (2)
Other	8 (6)	6 (5)
Completed study to month 24	99 (79)	106 (83)
Analyzed for primary endpoint (ITT)	122	123

Demographics: The baseline demographic characteristics were balanced between the two treatment groups. The mean age of study participants was 59 years and the mean time since last menses was 13 years. The baseline BMD T-score was -1.06. Participants predominantly had an ECOG status of 0 (Table 12).

Table 12: Demographics and baseline disease characteristics for subjects in Study 20040135 (Hormone ablation – Breast cancer)

	Placebo (N =125)	Denosumab (N = 127)
Age (years), mean (SD)	59.7 (9.7)	59.2 (8.9)
Age group, n (%)		
35 - < 45 years	4 (3)	1 (1)
45 - <55 years	37 (30)	40 (31)
55 - < 65 years	43 (34)	51 (40)
65 - < 75 years	32 (26)	29 (23)
≥ 75 years	9 (7)	6 (5)
Ethnic group, n (%)		
White or Caucasian	119 (95)	116 (91)
Black or African American	1 (1)	1 (1)
Hispanic or Latino	3 (2)	5 (4)
Asian or Japanese	1 (1)	2 (2)
Other	1 (1)	3 (3)
BMI, mean(SD)	28.1 (5.5)	27.5 (5.6)
Years from last menses, mean (SD)	13.1 (10.3)	12.8 (10.8)
Duration of aromatase inhibitor therapy		
≤ 6 months	46 (37)	43 (34)
> 6 months	79 (63)	84 (66)
Baseline LS BMD T-score, mean (SD)	-0.98 (0.93)	-1.13 (0.87)
ECOG status		
0	105 (84)	114 (90)
1	14 (11)	13 (10)
unknown	6 (5)	0 (0)

The primary endpoint was the percentage change in lumbar spine BMD from baseline to month 12. The secondary endpoints were the percentage change in lumbar spine BMD from baseline to month 6 and percentage changes in total hip and femoral neck BMD from baseline to months 6 and 12. The secondary efficacy endpoints analyses were contingent on rejection of the primary null hypothesis at a level of 0.05 (2-sided) and used the Hochberg procedure to adjust for multiplicity at level of 0.05. The primary analysis of the primary endpoint of percentage change from baseline to month 12 in lumbar spine BMD used an analysis of covariance (ANCOVA) model including treatment as the main effect and adjusting for duration of aromatase inhibitor therapy at study entry (≤ 6 months vs. > 6 months), baseline BMD value, machine type (Hologic and GE lunar), and the interaction between baseline BMD and machine type as covariates. The point estimate for the least-squares mean and the 2-sided 95% confidence interval (CI) for the treatment difference (denosumab - placebo) at month 12 were used for primary conclusions for BMD efficacy in the final analysis. Missing 12-month BMD data were imputed using the last-observation-carried-forward (LOCF) method.

The results of the primary efficacy analyses are shown in Table 13. There was a statistically significant increase in lumbar spine BMD for denosumab compared to placebo at 12 months (denosumab + 4.8%, placebo – 0.7%) based on a least square mean estimate. The treatment difference was 5.5% (95% CI: 4.8, 6.3). Consistent effects on lumbar spine BMD were observed regardless of baseline age, duration of aromatase inhibitor therapy, weight/BMI, prior chemotherapy, prior selective estrogen receptor modulator (SERM) use, and time since menopause. The treatment differences in total hip and femoral neck BMDs from baseline to month 12 were also statistically significant (p<0.0001). Trial 135 did not include an evaluation of skeletal related events and relied on the outcome of Trial 216 to demonstrate clinical benefit. The trial was not designed to evaluate oncology treatment endpoints, e.g., progression-free survival (PFS), overall survival OS. All cause mortality included 2 deaths for each treatment group at 24 months.

Table 13 Trial 135 BMD Percent Change from Baseline at Month 12 (LOCF)

	Placebo	**Denos.**	**Treatment difference**		
	estimate	**estimate**	**estimate**	**95% CI**	**p-value**
Lumbar Spine					
n, ITT	122	123			
	- 0.7	4.8	5.5	4.8, 6.3	< 0.0001
Femoral Neck					
n, ITT	122	123			
	- 0.6	1.9	2.5	1.6, 3.3	< 0.0001
Total Hip					
n, ITT	122	123			
	- 0.7	3.1	3.7	3.1, 4.4	< 0.0001

Fracture: No vertebral fractures were reported during the 24-month treatment period. Eight subjects (6%) in the denosumab group and 8 subjects (6%) in the placebo group sustained a nonvertebral fracture during the 24 months of the trial. Kaplan-Meier estimates of the risk of nonvertebral fracture were 3.3% for the denosumab group and 3.5% for the placebo group at month 12 and 7.2% for both treatment groups at month 24.

4.4 Study 20040138 (Hormone ablation - Prostate cancer study)

Disposition: As outlined in Table 14, 1468 subjects were enrolled in the trial and 1456 subjects received at least one dose of study medication. A total of 445 (61%) of subjects in the placebo group and 367 (64%) subjects in the denosumab group completed the 36-month treatment period. Consent withdrawn was the most common reason for discontinuation from study. A number of subjects withdrew consent at month 24 because they were unwilling to reconsent to an additional 12 months of blinded treatment.

Table 14: Subject Disposition for Study 20040138 (Hormone ablation – Prostate cancer)

Subject Disposition	Placebo	Denosumab
	N (%)	N (%)
Randomized	734 (100)	734 (100)
Safety population (at least one dose of IP)	725 (99)	731 (99)
Discontinued study	289 (39)	267 (36)
Death	43 (6)	43 (6)
Disease progression	21 (3)	23 (3)
Adverse event	23 (3)	29 (4)
Consent withdrawn	143 (20)	127 (17)
Lost to follow-up	21 (3)	17 (2)
Other	38 (5)	28 (4)
Completed study to month 36	445 (61)	467 (64)
Analyzed for primary endpoint (ITT)	716	714

Demographics: Baseline demographics were balanced across treatment groups. Most subjects (83%) were white and older than age 65 years (93%). The majority of subjects (63%) (460 denosumab, 460 placebo) were in the stratum of subjects ≥ 70 years of age who had received > 6 months of ADT among 4 groups stratification strata; the other 3 strata had fewer subjects, but were balanced. Most participants qualified for the study based on age alone (> 70 years). The baseline lumbar spine BMD T-score was -0.36, which is in the normal range.

Table 15: Demographics and baseline disease characteristics for subjects in Study 20040138 (Hormone ablation – Prostate cancer)

	Placebo (N = 734)	Denosumab (N = 734)
Age (years), mean (SD)	75.5 (7.1)	75.3 (7.0)
Age group, n (%)		
<60 years	20 (2.7)	24 (3.3)
60 - 69 years	103 (14.0)	100 (13.6)
70 - 79 years	396 (54.0)	405 (55.2)
80 -89 years	205 (27.9)	197 (26.8)
≥ 90 years	10 (1.4)	8 (1.1)
Ethnic group, n (%)		
White or Caucasian	609 (83.0)	615 (83.8)
Black or African American	32 (4.4)	36 (4.9)
Hispanic or Latino	81 (11.0)	77 (10.5)
Asian	7 (0.9)	6 (0.8)
Other	5 (0.7)	0 (0)
ADT duration - months, mean (SD)	30.62 (33.26)	31.70 (33.80)
Prevalent vertebral fracture, n (%)	174 (23.7)	155 (21.1)
Baseline LS BMD T-score, mean (SD)	-0.41	-0.31
ECOG status		
0	538 (73.3)	552 (75.2)
1	174 (23.7)	154 (21.0)
2	21 (2.9)	28 (3.8)
unknown	1 (0.1)	0 (0.0)
Cancer disease history		
time from initial diagnosis, years	4.91 (4.20)	4.97 (4.20)
chemical castration	685 (93.3)	678 (92.4)
surgical castration	61 (8.3)	77 (10.5)

Efficacy: The primary efficacy endpoint in this study was percentage change in lumbar spine BMD from baseline to month 24. The primary analysis of the primary endpoint, the percentage change from baseline to month 24 in lumbar spine BMD, was analyzed using an analysis of covariance (ANCOVA) approach adjusting for baseline BMD value, machine type (GE lunar versus Hologic), the interaction of baseline BMD value and machine type, age group (< 70 years vs. ≥ 70 years), and duration of ADT (≤ 6 months vs. > 6 months) as covariates. Missing 24-month BMD data were imputed using the last-observation carried-forward (LOCF) method. Secondary endpoints included percentage change in femoral neck BMD and total hip BMD from baseline to month 24. The secondary efficacy endpoints analyses were contingent on rejection of the primary null hypothesis at a level of 0.05 and used the Hochberg procedure to adjust for multiplicity at level of 0.05.

The results of the primary efficacy analyses are shown in Table 16. There was a statistically significant increase in lumbar BMD for denosumab compared to placebo at 2 years

(denosumab + 5.6%, placebo -1%) based on a least square mean estimate. The treatment difference was 6.7% (95% CI: 6.2, 7.1). Consistent effects on lumbar spine BMD were observed regardless of baseline age, race, geographical region, weight/BMI, BMD, level of bone turnover, duration of androgen deprivation therapy, and presence of vertebral fracture. The treatment differences from baseline to month 24 in femoral neck BMD were 3.9% (95% CI: 3.5, 4.4, p < 0.0001) and total hip BMD 4.8% (95% CI: 4.4, 5.1. p < 0.0001).

Table 16 Trial 138 BMD Percent Change from Baseline at Month 24 (LOCF)

	Placebo	**Denos**	**Treatment difference**		
	estimate	**estimate**	**estimate**	**95% CI**	**p-value**
Lumbar Spine					
n, ITT	716	714			
	- 1.0	5.6	6.7	6.2, 7.1	< 0.0001
Femoral Neck					
n, ITT	706	701			
	- 1.5	2.4	3.9	3.5, 4.4	< 0.0001
Total Hip					
n, ITT	706	701			
	- 2.0	2.7	4.8	4.4, 5.1	< 0.0001

There was no observed decrease in the incidence of any fracture from baseline to either 24 or 36 months. At month 24, the incidence of any fracture was 45/734 (6.1%) in the placebo group and 32/734 (4.4%) in the denosumab group (p=0.1282). At month 36, the incidence of any fracture was 53/734 (7.2%) in the placebo group and 38/734 (5.2%) in the denosumab group (p=0.1048). Denosumab showed a reduction in incidence of new vertebral fractures of 1.5% as compared to placebo of 3.5% at 3 years (p=0.0125).

It should be noted that the trial was not designed to evaluate oncology treatment endpoints, e.g., progression-free survival (PFS), overall survival. All cause mortality was 5.9% for both treatment groups at 36 months.

<u>Issue for Consideration</u>: The Office of Oncology Drug Products requires that supportive care oncology drug and biologic products administered to patients with cancer that have the potential to either 1) inhibit the anticancer action of drugs used to treat cancer or 2) enhance neoplastic progression by acting as growth factors, be carefully evaluated in studies to identify any detrimental effects on cancer outcomes (Progression free survival (PFS) or Overall Survival (OS)).

Neither trial contained prespecified, defined, rigorous plans to evaluate for potential treatment effects on time-to-disease progression. There were no routine assessments for neoplastic disease status included in the protocol for Trial 135. In Trial 138, the protocol included disease assessments only for metastatic disease to bone (i.e., bone scan at baseline and month 36) and disease specific markers (i.e., PSA at all time points

during the treatment phase of the trial). During the follow-up safety phase of each trial there were no specific instructions contained in either protocol related to the assessment of disease status.

In both trials, overall survival (at 24 months in Trial 135 and 36 months in Trial 138) was a designated exploratory endpoint. However, neither trial was designed to detect a clinically meaningful decrement in overall survival. Case report forms required collection of survival data at various time points during the safety follow up phases for each trial, and each statistical plan included a survival analysis. An analysis of OS was not performed in trial 135 because the small number of deaths (one in each arm) precluded meaningful results. The clinical study report for trial 138 included an analysis of OS. There was no difference in overall survival between denosumab and placebo in this trial. The proportion of subjects who were alive at 36 months, and the Kaplan-Meier estimates of survival were identical (94% and 93%, respectively).

4.5 Summary of Efficacy

Study 20030216: Study 216 demonstrated that treatment with denosumab resulted in a statistically significant improvement in the primary endpoint (reduction of the incidence of new vertebral fracture) and key secondary endpoints compared to placebo at month 36. The decreased risk of new vertebral fractures at month 36 (primary endpoint) by 68% (risk ratio: 0.32 [95% CI: 0.26, 0.41]; $p < 0.0001$) is clinically meaningful. Similar efficacy results were observed in the primary analysis using different populations (ITT, mITT) and different methods of missing data imputation (LOCF, At Visit). Efficacy results of secondary endpoints were supportive of the findings of the primary endpoint.

Study 20040132: The use of denosumab 60 mg Q6months was associated with a statistically significant increase in lumbar spine BMD at Month 24, as compared to placebo, for all subjects, subjects ≤ 5 years since menopause and subjects > 5 years since menopause (p-value <0.0001). The overall treatment difference was +7% (95% CI: 6.2, 7.8), with the greatest treatment effect in subjects ≤ 5 years since menopause. Consistent effects on lumbar spine BMD were observed regardless of baseline age, race, weight/BMI, BMD, and menopause stratum. There were statistically significant increases in BMD at 24 months in the key secondary endpoints, including a treatment difference at total hip of 4.5% (95% CI: 4.0, 5.0), femoral neck of 3.7% (95% CI: 2.9, 4.4), trochanter of 6.0% (95% CI: 5.3, 6.6), distal 1/3 radius of 3.5% (95% CI: 2.8, 4.3), and total body of 3.8% (95% CI: 3.1, 4.5) ($p < 0.0001$ at all sites). There were few clinical fractures during the period of the study, with slightly more fractures in the placebo group.

Study 20040135: In patients with breast cancer undergoing therapy with aromatase inhibitors, treatment with denosumab 60 mg every 6 months resulted in a significant increase in BMD at month 12 when compared to placebo. The overall treatment difference was 5.5% (95% CI: 4.8, 6.3). Consistent effects on lumbar spine BMD were observed regardless of baseline age, duration of aromatase inhibitor therapy, weight/BMI, prior chemotherapy, prior selective estrogen receptor modulator (SERM) use, and time since menopause. There was no

difference between treatment groups in the incidence of vertebral or nonvertebral fractures. The trial was not designed to evaluate oncology treatment endpoints, e.g., progression-free survival (PFS), overall survival. All cause mortality was 1% for both treatment arms.

Study 20040138: In prostate cancer patients undergoing androgen deprivation therapy, treatment with denosumab 60 mg every 6 months resulted in a significant increase in BMD at month 24 when compared to placebo. The overall treatment difference was 6.7% (95% CI: 6.2, 7.1). Consistent effects on lumbar spine BMD were observed regardless of baseline age, race, geographical region, weight/BMI, BMD, level of bone turnover, duration of androgen deprivation therapy, and presence of vertebral fracture. There was no observed decrease in the incidence of any fracture from baseline to either 24 or 36 months. There was a statistically significant reduction in the incidence of new vertebral fractures at month 36. The trial was not designed to evaluate oncology treatment endpoints, e.g., progression-free survival (PFS), overall survival. All cause mortality was 5.9% for both treatment groups at 36 months.

5 SAFETY FINDINGS

5.1 Overview of Safety Concerns with Inhibitors of RANKL

Denosumab is the first therapeutic product whose mechanism of action is via inhibition of RANKL. While the primary function of denosumab appears to be inhibition of osteoclast activation, RANKL also has important functions in the immune system. RANKL plays a pivotal role in dendritic (antigen presenting) cell maturation and also in B-cell and T-cell differentiation. Therefore, denosumab has the potential to affect multiple layers of the immune system.

RANKL is a member of the tumor necrosis factor (TNF) superfamily. These proteins play a role in the regulation of the immune system and hematopoiesis. TNF cytokines play an important role many inflammatory responses. TNF gene mutations have been implicated in common variable immunodeficiency (CVID). As outlined in Appendix 1, multiple monoclonal antibody products that target the TNF superfamily are available. Adverse effects of TNF-blockade include serious infection, early and delayed hypersensitivity reactions, lupus-like syndrome, demyelinating disease and exacerbation of CHF.

With any therapeutic protein product, assessments of hypersensitivity reactions as well as evaluation of immunogenicity and neutralizing antibody formation are important safety evaluations.

These issues were evaluated in the safety review of denosumab.

5.2 Overview of the Safety Database for Denosumab

The denosumab clinical development program included data from approximately 14,000 subjects who participated in 30 denosumab clinical studies and up to 5 years of denosumab exposure. The safety analysis population consisted of all subjects who received at least 1

dose of study drug. Clinical data from the two key Phase 3 studies for the PMO indication (20030216 and 20040132) were integrated and analyzed to assess overall safety in the PMO population. Clinical data from the two key Phase 3 studies for the Hormone Ablation indication (20040135 and 20040138) were integrated and analyzed to assess overall safety in the cancer-related population.

Adverse events in the safety database for denosumab were captured by the study investigators (verbatim adverse event terms). The Applicant then coded these verbatim adverse event terms to preferred terms (PTs) in a medical coding dictionary. The medical coding dictionary used in this application was the Medical Dictionary for Regulatory Activities (MedDRA), version 11.0. MedDRA is a hierarchical medical coding dictionary that is organized as follows:

System Organ Class (SOC)
High Level Group Term (HLGT)
High Level Term (HLT)
Preferred Term (PT)

5.2.1 Postmenopausal Osteoporosis

Key clinical trials to evaluate safety of denosumab 60 mg SC Q6months in postmenopausal osteoporosis (PMO) were as follows:

a) Study 20030216 - an international, multicenter, randomized, double-blind, placebo-controlled study to evaluate denosumab in the treatment of postmenopausal osteoporosis. This 3-year study enrolled 7868 subjects (60 subjects from one site were excluded due to GCP violations), randomized to denosumab or placebo.

b) Study 20040132 - a randomized, double-blind study to evaluate denosumab in the prevention of postmenopausal osteoporosis. This 4-year study enrolled 332 women (denosumab – 166, placebo – 166); subjects received therapy for 24 months and were monitored for an additional 24 months.

Within the Primary PMO studies 20030216 and 20040132, more than 70% of subjects received all 6 doses of investigational product as denosumab 60 mg or placebo SC Q6months. As shown in Table 17 below, fewer subjects in the placebo group completed all 6 doses, with roughly the same incidence of dropouts at each scheduled dose.

Table 17: Extent of exposure Studies 20030216 and 20040132

No. of Doses of Inv Prod Received	Placebo	Denosumab 60 mg Q6M
1	225 (5.6%)	211 (5.2%)
2	202 (5.0%)	176 (4.3%)
3	216 (5.4%)	172 (4.3%)
4	294 (7.3%)	256 (6.3%)
5	218 (5.4%)	142 (3.5%)
6	2886 (71.4%)	3093 (76.4%)
Subjects	4041	4050

5.2.2 Cancer-related Trials

Key clinical trials to evaluate safety of denosumab 60 mg SC Q6months in Hormone Ablation were as follows:

a) Study 20040135 - a randomized, double-blind, placebo-controlled study to evaluate denosumab in the treatment of bone loss in subjects undergoing aromatase inhibitor therapy for nonmetastatic breast cancer. This 4-year study enrolled 252 subjects (denosumab -127, placebo - 125); subjects received therapy for 24 months and were monitored for an additional 24 months.

b) Study 20040138 - a randomized, double-blind, placebo-controlled study to evaluate denosumab in the treatment of bone loss in subjects undergoing androgen-deprivation therapy for nonmetastatic prostate cancer. This 5-year study enrolled 1,468 subjects (denosumab – 734, placebo – 734); subjects received therapy for 36 months and were monitored for an additional 24 months.

The denosumab safety data in the Hormone Ablation trials reflect exposure in 731 men with bone loss receiving androgen deprivation therapy for non-metastatic prostate cancer (Trial 138) and 129 women with bone loss receiving aromatase inhibitor therapy for nonmetastatic breast cancer (Trial 135) who were enrolled in placebo-controlled trials. Denosumab was administered at a dose of 60 mg SC once every six months in both trials. In the prostate cancer trial, the population was aged 48 to 97 years (median 76) and 84% were Caucasian. In the breast cancer trial, the population was aged 35 to 84 years (median 59) and 91% were Caucasian. Exposures were 6 doses during a 36 month treatment period in Trial 138 and 4 doses during a 24 month treatment period in Trial 135.

5.3 Safety Findings from the Denosumab Clinical Development Program

5.3.1 Deaths

The Applicant was asked to provide a listing of all deaths in the denosumab clinical development program, which includes studies in postmenopausal women, men with prostate cancer, women with breast cancer, and patients with rheumatoid arthritis, multiple myeloma or solid tumors. The Applicant listed a total of 354 deaths, including 2 deaths in Phase I studies, 96 in Phase 2 studies and 256 deaths in Phase 3 studies. Of the 354 total subjects who died, 185 subjects had underlying cancer and 169 subjects had osteoporosis or low bone mass as their indication for use of denosumab.

Phase 1 Studies:
The two deaths in subjects in Phase I studies involved an accidental death (a 78-year-old female subject was involved in a head-on collision) and progression of cancer in a 36-year-old breast cancer patient about a month after the initial dose of investigational product.

Phase 2 Studies
A total of 96 subjects died during Phase 2 studies; several Phase 2 studies were conducted in subjects with underlying malignancies (see Appendix 2). It is noteworthy that 4 subjects in the Phase 2 dose-finding study (Study 20010223) died during the study period; all 4 subjects had received denosumab. The cause of death for these subjects is as follows: cerebrovascular

accident (n = 1), “brain tumor” (n = 1), and adenocarcinoma (n = 2); a summary for each of these 5 subjects is provided herein. A 62-year-old female with a history of atrial fibrillation and hypercholesterolemia died of a cerebrovascular accident almost 3 years after initiating denosumab (> 5 months from last dose). There were 3 deaths due to neoplasms (2 subjects with adenocarcinoma, 1 subject with a “brain tumor”), all occurred in the denosumab 100 mg Q6 months cohort. A 75-year-old female with a family history of “brain tumors” was diagnosed with a "brain tumor" in the frontal lobe 15 months after initiating denosumab and died 14 weeks later despite chemotherapy and radiation. Adenocarcinoma (primary site unknown) was diagnosed in a 74-year-old female who had received denosumab for 2 years and was an ex-smoker; lung cancer was listed as the cause of death. Another 78-year-old female with a history of a lumpectomy died of adenocarcinoma (gastric cancer) 18 months after initiating denosumab. In addition, one subject died about 1 year after discontinuation from study, which is not reflected in the total number of fatalities for this study. This 60-year-old subject with a history of alcohol and tobacco use was diagnosed with pancreatic carcinoma 17 days after initiating denosumab. Another female subject subsequently died approximately 6 months after enrolling in the extension phase of the dose-finding study. The subject was 80 years old when she died; family members did not provide a cause of death.

Phase 3 Studies

Fatal events that occurred in Studies 20040138 and 20040216 were adjudicated by an independent cardiovascular adjudication committee that determined whether the death was caused by a cardiovascular event. The cause of death for all other events was determined by the investigator. The cause of death for the two key Phase 3 studies for the PMO indication (20030216 and 20040132) and the two key Phase 3 studies for the Hormone Ablation indication (20040135 and 20040138) are summarized below in Table 18. There were no deaths in Study 20040132, the osteoporosis prevention study. There were 2 deaths in Study 20040135; one subject in each treatment group died due to neoplasm. The denosumab group did not have a higher incidence of fatality in either of the key PMO or Hormone Ablation trials.

Table 18. Cause of Death by System Organ Class for the Primary PMO and Hormone Ablation Studies

	Study 20030216 & Study 20040132 (PMO Treatment) [§]		Study 20040135 & Study 20040138 (Hormone Ablation)	
	Placebo N = 4041	**Denos. N = 4050**	**Placebo N = 845**	**Denos. N = 860**
Total No. of Fatalities	**90 (2.2)**	**70 (1.7)**	**47 (5.6)**	**45 (5.2)**
System Organ Class	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Cardiac	23 (0.6)	18 (0.4)	12 (1.4)	15 (1.7)
Endocrine	0	1 (< 0.1)	0	0
Gastrointestinal	2 (< 0.1)	4 (0.1)	1 (0.1)	1 (0.1)
General disorders & admin. site conditions	6 (0.1)	4 (0.1)	7 (0.8)	3 (0.3)
Hepatobiliary	1 (< 0.1)	1 (< 0.1)	0	1 (0.1)
Infections & infestations	6 (0.1)	6 (0.1)	6 (0.7)	0
Injury, poisoning & proc. complications	3 (0.1)	1 (< 0.1)	2 (0.2)	0
Metabolism & nutrition	1 (< 0.1)	0	0	2 (0.2)
Neoplasms benign, malignant & unspec	26 (0.6)	20 (0.5)	10 (1.2)	7 (0.8)
Nervous system	11 (0.3)	6 (0.1)	3 (0.4)	8 (0.9)
Renal and urinary	0	1 (< 0.1)	1 (0.1)	0
Respiratory, thoracic & mediastinal	11 (0.3)	6 (0.1)	4 (0.5)	8 (0.9)
Social circumstances	0	1 (< 0.1)	0	0
Vascular disorders	0	3 (0.1)	1 (0.1)	0

[§] There were no deaths in Study 20040132

In the denosumab primary PMO studies, there were more deaths in the placebo group compared with denosumab; no noteworthy trends were observed in the cause of death in this population. In the key Hormone Ablation studies, there were more deaths as a result of events in the Nervous and Respiratory systems compared with placebo. The placebo group in the key Hormone Ablation studies had more deaths in the General Disorders (e.g. sudden death, death due to unknown cause), Infections and Infestations, and Neoplasm categories compared with denosumab.

5.3.1.1 Postmenopausal Osteoporosis

Because some of the subjects in the clinical program had an underlying malignancy, the cause of death in the Primary PMO Safety Analysis Set (the safety population in Studies 20030216 and 20040132) was reviewed separately. There were no deaths in Study 20040132 (N=329) during the 24 months of treatment and the first 12 months off-treatment. Thus, all the deaths listed in Table 18 occurred in Study 20030216. Fewer subjects in the denosumab

group had fatal events as compared to the placebo group, specifically 70 subjects (1.7%) vs. 90 subjects (2.2%), respectively.

The largest categories for cause of death were the Cardiac Disorders, Neoplasms, General Disorders and Nervous Systems SOCs. The majority of cardiac deaths were due to acute myocardial infarction, heart failure, and cardiogenic shock. The majority of deaths in the Neoplasms SOC were due to lung cancer and pancreatic cancer. The majority of deaths in the General Disorders SOC were due to accidental deaths, death due to unknown cause or sudden deaths. The Nervous System fatalities were mainly due to cerebrovascular accidents and cerebral hemorrhages. These common causes of death in this analysis are not unusual in postmenopausal women aged 60-90 years; the mean (SD) age of enrolled subjects was 72.3 year (5.2 years) in Study 20030216, the only Primary PMO study with fatalities.

5.3.1.2 Cancer-related Trials

In patients with breast cancer (trial 135), fatal events were reported for deaths occurring at any time during the 24 month treatment period regardless of temporal association to the investigational product. Only 2 (1%) deaths were reported during the 24 month treatment period, one for each treatment arm.

In patients with prostate cancer (trial 138), the numbers of fatal events were balanced between treatment arms, 46 patients (6.3%) treated on the placebo arm and 44 patients (6.0%) treated on the denosumab arm. In general, causes of death were representative of the patient population being studied where the median age for both treatment arms was 76 years and 93% of men enrolled were ≥ 65 years.

5.3.2 Serious Adverse Events

5.3.2.1 Postmenopausal Osteoporosis

In the primary PMO Safety Population, a total of 4,041 subjects received placebo and 4,050 subjects received denosumab in the key PMO studies. The total number of nonfatal serious adverse events for the Primary PMO Studies is summarized below in Table 19:

Table 19. Nonfatal Serious Adverse Events by Study for the Denosumab Primary PMO Safety Population

Study Identifier	Placebo n (%)	Denos. n (%)
20030216	939 (24.2%)	973 (25.0%)
20040132	9 (5.5%)	19 (11.6%)

These nonfatal serious adverse events in the Primary PMO Studies (pooled data) were reviewed by System Organ Class (Table 20). The majority of nonfatal serious adverse events were in the Cardiac Disorders, Injury, Musculoskeletal, Neoplasms, Nervous System and Gastrointestinal Disorders SOCs. Nonfatal serious adverse events were generally balanced

across treatment groups, except that the denosumab group had more non-fatal serious cardiac events, infections and gastrointestinal events, primarily due to more coronary artery disorders, cellulitis and diverticulitis. These events are summarized in the following section 5.3.5.

Table 20. Nonfatal Serious Adverse Events Ordered by SOC and Treatment Group for the Denosumab Primary PMO Safety Population (pooled data)

	Primary PMO Safety Population	
System Organ Class	**Placebo N=4041 n (%)**	**Denos. N=4050 n (%)**
Blood and lymphatic system disorders	22 (0.5%)	20 (0.5%)
Cardiac disorders	141 (3.5%)	181 (4.5%)
Congenital, familial and genetic disorders	1 (0.02%)	0 (0%)
Ear and labyrinth disorders	15 (0.4%)	24 (0.6%)
Endocrine disorders	6 (0.1%)	5 (0.1%)
Eye disorders	45 (1.1%)	39 (1.0%)
Gastrointestinal disorders	101 (2.5%)	143 (3.5%)
General disorders & administration site conditions	30 (0.7%)	34 (0.8%)
Hepatobiliary disorders	33 (0.8%)	29 (0.7%)
Immune system disorders	1 (0.02%)	1 (0.02%)
Infections and infestations	129 (3.2%)	162 (4.0%)
Injury, poisoning and procedural complications	191 (4.7%)	126 (3.1%)
Investigations	9 (0.2%)	5 (0.1%)
Metabolism and nutrition disorders	14 (0.3%)	20 (0.5%)
Musculoskeletal and connective tissue disorders	150 (3.7%)	168 (4.2%)
Neoplasms benign, malignant and unspec	121 (3.0%)	150 (3.7%)
Nervous system disorders	120 (3.0%)	125 (3.1%)
Pregnancy, puerperium and perinatal conditions	0 (0%)	0 (0%)
Psychiatric disorders	14 (0.3%)	20 (0.5%)
Renal and urinary disorders	19 (0.5%)	20 (0.5%)
Reproductive system and breast disorders	38 (0.9%)	32 (0.8%)
Respiratory, thoracic and mediastinal disorders	76 (1.9%)	80 (2.0%)
Skin and subcutaneous tissue disorders	7 (0.2%)	10 (0.2%)
Social circumstances	0 (0%)	0 (0%)
Surgical and medical procedures	0 (0%)	1 (0.02%)
Vascular disorders	71 (1.8%)	71 (1.8%)

5.3.2.2 Cancer-related Trials

For breast cancer patients (trial 135), serious adverse events (SAE) occurred in 30/249 (12%) patients, 19/129 (14.7%) patients who received denosumab and 11/120 (9.2%) patients who received placebo.

For prostate cancer patients (trial 138), SAEs occurred in 475/1456 (32.6%) patients, 253/731 (34.6%) treated with denosumab and 222/725 (30.6%) treated with placebo.

5.3.3 Discontinuations Due to Adverse Events

In the pooled data from the key PMO and Hormone Ablation indication studies, the number of subjects discontinuing investigational product was slightly higher in subjects receiving placebo, with only 74% of placebo subjects and 79% of denosumab subjects completing all scheduled doses of investigational product. The reasons for ending investigational product were balanced across treatment groups as well, except that slightly more subjects in the placebo group withdrew consent, had disease progression or required alternative therapy.

5.3.3.1 Postmenopausal Osteoporosis

In the pooled data from the key PMO indication studies, the incidence of subjects discontinuing investigational product was slightly higher in subjects receiving placebo (Table 21). About 81% of subjects receiving denosumab and 76% of subjects receiving placebo completed all scheduled doses of investigational product. The most common reasons for ending investigational product were consent withdrawn (8.3% placebo, 7.0% denosumab), adverse events (5.2% placebo, 4.9% denosumab) and subject request (2.2% placebo, 2.2% denosumab).

Slightly more subjects in the placebo group withdrew consent, had disease progression or required alternative therapy. These 2 key studies were also reviewed individually to determine whether Study 20040132 differed from Study 20030216 due to differences in the patient population studied. The only notable difference was that 1 placebo subject (0.6%) and 7 denosumab subjects (4.3%) in Study 20040132 ended investigational product due to “subject request,” which may represent adverse events in these subjects.

Table 21. Reason for Ending Investigational Product in Primary PMO Safety Population (pooled data)

	Placebo N=4041 n (%)	Denos. N=4050 n (%)
Randomized	4072	4068
Did not receive IP	24	25
Actual treatment received*	4041	4050
Completed	3084 (76.3%)	3276 (80.9%)
Reason for Ending Invest. Product		
• Administrative decision	5 (0.1%)	9 (0.2%)
• Adverse event	209 (5.2%)	197 (4.9%)
• Consent withdrawn	335 (8.3%)	282 (7.0%)
• Death	58 (1.4%)	38 (0.9%)
• Disease progression	64 (1.6%)	10 (0.2%)
• Ineligibility determined	9 (0.2%)	8 (0.2%)
• Lost to follow-up	40 (1.0%)	39 (1.0%)
• Noncompliance	17 (0.4%)	15 (0.4%)
• Other	37 (0.9%)	33 (0.8%)
• Protocol deviation	27 (0.7%)	22 (0.5%)
• Requirement for alternative therapy	69 (1.7%)	30 (0.7%)
• Subject request	87 (2.2%)	91 (2.2%)

*Seven placebo subjects received denosumab
Numbers for completing IP and ending IP are calculated based on actual treatment received

The most common adverse events occurring at a rate of at least 0.13% in any treatment group and leading to discontinuation of investigational product are listed in Table 22. The most common reason for discontinuing denosumab was breast cancer, with twice as many subjects reporting this event (20 vs. 10 in denosumab vs. placebo). Nausea, headache, constipation and back pain were also frequently cited in the denosumab group. Whereas the placebo group reported more events related to osteoporosis, such as lumbar vertebral fracture, back pain, and thoracic vertebral fractures; breast cancer was also a frequent reason for discontinuation of investigational product in the placebo group. .

Table 22. Most Common Adverse Events that Led to Discontinuation of Investigational Product in Primary PMO Safety Population (pooled data)

	Placebo N=4041 n (%)	Denos. N=4050 n (%)
Total Subjects	209 (5.2%)	197 (4.9%)
Breast cancer	10 (0.2%)	20 (0.5%)
Nausea	1 (0.03%)	6 (0.1%)
Headache	4 (0.1%)	6 (0.1%)
Constipation	6 (0.1%)	6 (0.1%)
Back pain	10 (0.2%)	6 (0.1%)
Gastric cancer	1 (0.03%)	5 (0.1%)
Fatigue	2 (< 0.1%)	5 (0.1%)
Cerebrovascular accident	3 (0.1%)	5 (0.1%)
Colon cancer	4 (0.1%)	5 (0.1%)
Diarrhoea	4 (0.1%)	5 (0.1%)
Femur fracture	5 (0.1%)	2 (< 0.1%)
Lumbar vertebral fracture	12 (0.3%)	2 (< 0.1%)
Thoracic vertebral fracture	8 (0.2%)	1 (0.03%)
Resorption bone increased	5 (0.1%)	0 (0%)

5.3.3.2 Cancer-related Trials

In patients with breast cancer (trial 135), at the end of treatment, there were 2 (2%) patients on the denosumab treatment arm who withdrew from the trial for an adverse event, while there were 5 (4%) patients on the placebo arm.

In patients with prostate cancer (trial 138), at the end of treatment for patients treated with denosumab, 49 (6.5%) withdrew from the trial for AEs while in the placebo arm 47 (6.7) withdrew from the trial.

5.3.4 Common Adverse Events (AEs)

5.3.4.1 Postmenopausal Osteoporosis

The overall incidence of AEs in the PMO population was comparable across the treatment groups and across studies 20030216 (93% in both groups) and 20040132 (95% in both groups). The most commonly reported adverse events were in the Musculoskeletal, Infections, and Gastrointestinal Disorders System Organ Class (SOC), with events reported for each SOC as follows (placebo, denosumab): Musculoskeletal Disorders (64.4%, 64.5%), Infections (54.7%, 53.2%), and Gastrointestinal Disorders (36.7%, 37.6%). There were no apparent dose-related differences in the nature or frequency of these AEs when the entire ISS population was reviewed.

Table 23 Common adverse events in Primary PMO Safety population

	Placebo N=4041		Denosumab N=4050	
	n	%	n	%
Number of subjects reporting any AE	**3765**	**(93.2)**	**3761**	**(92.9)**
Preferred Term				
Back pain	1374	(34.0)	1380	(34.1)
Arthralgia	824	(20.4)	826	(20.4)
Hypertension	650	(16.1)	621	(15.3)
Nasopharyngitis	632	(15.6)	599	(14.8)
Pain in extremity	451	(11.2)	477	(11.8)
Osteoarthritis	447	(11.1)	439	(10.8)
Constipation	369	(9.1)	374	(9.2)
Influenza	355	(8.8)	346	(8.5)
Bronchitis	309	(7.6)	307	(7.6)
Musculoskeletal pain	301	(7.4)	315	(7.8)
Headache	277	(6.9)	263	(6.5)
Urinary tract infection	270	(6.7)	263	(6.5)
Hypercholesterolemia	240	(5.9)	285	(7.0)
Diarrhea	244	(6.0)	242	(6.0)
Cataract	253	(6.3)	232	(5.7)
Cough	243	(6.0)	235	(5.8)
Fall	256	(6.3)	206	(5.1)
Cystitis	228	(5.6)	232	(5.7)
Depression	228	(5.6)	223	(5.5)
Dizziness	227	(5.6)	224	(5.5)
Dyspepsia	222	(5.5)	188	(4.6)
Upper respiratory tract infection	189	(4.7)	211	(5.2)
Nausea	205	(5.1)	194	(4.8)

5.3.4.2 Cancer-related Trials

A total of 860 patients with breast and prostate cancer received denosumab 60 mg SC q 6 months in the key efficacy trials. Exposures were 4 doses for patients with breast cancer and 6 doses for patients with prostate cancer. Table 24 below represents adverse events occurring in greater than 5% of patients on either treatment arm.

Table 24: Common adverse events in hormone ablation therapy population (occurring in >5% of subjects in either group)

Preferred Terms	Placebo		Denosumab	
	n	%	n	%
Arthralgia	110	13.0	123	14.3
Back pain	89	10.5	99	11.5
Constipation	86	10.2	88	10.2
Pain in extremity	65	7.7	85	9.9
Fatigue	62	7.3	61	7.1
Hypertension	58	6.9	59	6.9
Oedema peripheral	53	6.3	61	7.1
Nasopharyngitis	49	5.8	51	5.9
Diarrhoea	48	5.7	45	5.2
Hot flush	40	4.7	45	5.2
Musculoskeletal pain	32	3.8	52	6.0
Dizziness	35	4.1	46	5.3
Urinary tract infection	37	4.4	44	5.1
Cough	32	3.8	46	5.3

Source: This table includes data from trial 135 and 138, AAE dataset.

5.3.5 Adverse Events of Interest

5.3.5.1 Infection

Reason for concern:
The target population for osteoporosis treatment or prevention is postmenopausal women who might use this therapy for many years, including subjects who may have an impaired immune system function due to age, comorbid conditions, or concomitant medications. It is biologically plausible that the RANKL inhibitor denosumab could increase the risk of infection as RANKL is expressed on activated T and B lymphocytes and in the lymph nodes and T and B lymphocytes are responsible for foreign antigen recognition.

Pharmacology/toxicology studies have raised some questions about immune suppression. However, Study 20010124 (Phase 1) and Study 20010223 (Phase 2) examined T & B cell counts and natural killer cells, white blood cell and lymphocyte counts. These studies did not identify any clinically significant changes in these parameters. This section will summarize the overall risk of infection and highlight particular infections of concern.

The overall incidence of serious adverse events (SAEs) of infection in the Primary PMO studies was higher in denosumab than placebo subjects with 4.1% of denosumab and 3.3% of placebo subjects developing a serious infection during the Primary PMO trials. There was no difference in the number of overall infections (serious + non-serious adverse events). Opportunistic infections were not more common in the denosumab group.

When 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 0.7% of denosumab subjects as compared to 0.4% of placebo subjects and serious infections due to an unspecified pathogen occurred in 3.4% of denosumab subjects and 2.8% of placebo subjects. Denosumab subjects appeared to have a higher incidence of bacterial, cellulitis/erysipelas, abdominal, ear, and urinary tract infections. These serious adverse events were reviewed across the key PMO studies. The subjects in Study 20040132 were younger than subjects in Study 20030216.

As denosumab may be used in an elderly population with a waning immune system, events of infection were reviewed by age groups of ≥ 75 years and ≥ 80 years. A review of AEs and SAEs of infection in older subjects did not identify any unusual trends in regards to infection.

Infections of particular concern are summarized below.

5.3.5.1.1 Pneumonia Cases in Phase I Studies

In two Phase I studies, three subjects were hospitalized for pneumonia; all the subjects were from the United States. In Study 20030148, a 75-year-old male subject (SID 8001091) developed pneumonia on Study Day 242 after receiving a single dose of denosumab 3.0 mg/kg SC. The subject had a 20-year smoking history (2 packs per day) and a history of chronic bronchitis. Sixteen days later the subject was diagnosed with small cell lung cancer. In Study 20050146, 2 subjects developed pneumonia after a single 60 mg SC dose of denosumab. Subject 6001122 was a 33 year-old male who developed pneumonia on Study Day 73 and was hospitalized for 13 days. Subject 6001208 was a 34-year-old male who developed pneumonia on Study Day 12 (elsewhere reported as Study Day 74) and was hospitalized for 4 days. Hospital records were unavailable for both subjects in Study 20050146.

Although two of the three cases are not well documented, these three cases of pneumonia in Phase I studies occurred following a single dose of denosumab. One subject was a smoker with bronchitis who was subsequently diagnosed with lung cancer. The other 2 subjects were young, healthy volunteers and did not appear to have risk factors for the development of pneumonia.

5.3.5.1.2 Endocarditis

A total of four denosumab subjects developed endocarditis during the denosumab development program. In addition, there was one 77-year-old man from Canada receiving placebo in Study 20040138 who developed endocarditis; this subject had prostate cancer. There was one 66-year-old female subject from Poland receiving alendronate in Study 20050234 who developed endocarditis. The four denosumab cases are summarized below. The Applicant was unable to obtain the causative pathogen.

SID 20030216-762526: The subject was a 75-year-old female from Estonia who experienced a serious AE of endocarditis on (b) (6). She had a history of hypertension, ischemic heart disease, arrhythmia, chronic pyelonephritits, duodenal ulcer, and anemia. The subject presented with a two-week history of fever up to 39°C approximately 19 weeks after

initial exposure to denosumab. At the time of hospitalization transesophageal echocardiography confirmed the diagnosis of "septical endocarditis." The patient received cefuroxime and gentamicin with resolution of the endocarditis on (b) (6). No causative organism was identified.

SID 20030216-430063: The subject was an 82-year-old female from Brazil who experienced a serious AE of endocarditis on (b) (6) The subject had a history of hypertension, back and leg pain, leg arthrosis, and urinary incontinence. The subject died approximately nineteen months post initiation of denosumab with multiple organ failure. According to the Applicant's narrative, "…the subject was diagnosed with urinary tract infection and treatment included an initiation of antibiotics [cephalexin for 5 days]." On (b) (6) the subject sustained a fall and was hospitalized, however, the Applicant was not able to obtain the details of the treatment. The subject's health progressively declined resulting in transfer to the ICU. She died on (b) (6) while still in the hospital. An autopsy was not performed. No causative organism was identified.

SID 20030216-631230: The subject was a 75 year old female from Denmark who experienced the "nonserious" AE of endocarditis on (b) (6) (149 days post last dose of denosumab and 534 days into the study). The subject had a history of herpes virus infection, arrhythmia, and spinal column stenosis. The patient was reportedly hospitalized on (b) (6) due to nausea and vomiting and was found to "…have endocarditis caused by an unspecified pathogen on 06 May 2006." The investigator reported that an echocardiogram was performed; however no results were available. The event did not resolve and was ongoing.

SID 20050233- 307082: This subject in the extension study was an 83-year-old female from the United States who had received denosumab 100 mg SC Q6months in Study 20010223 and then denosumab 60 mg SC Q6 months in Study 20050233. About 7 months after entering Study 20050233, the subject was hospitalized for *Staphyloccocus aureus* bacteremia for which she received ceftriaxone 2 g IV daily. About 1 month later, the subject developed heart failure and was diagnosed with endocarditis and ultimately required mitral valve replacement and the event resolved.

5.3.5.1.3 Serious Skin Infections

There was an imbalance in serious skin infections during clinical trials in women with postmenopausal osteoporosis. Serious streptococcal infections (also reported as erysipelas) occurred in 7 denosumab (0.2%) and 1 placebo (0.02%) subjects in Primary PMO studies. The non-specific term "bacterial infections" also occurred at a higher incidence for denosumab, with 12 denosumab (0.3%) and 4 placebo (0.1%) subjects developing serious bacterial infections.

When specific adverse event terms were examined, there were 7 denosumab (0.2%) and no placebo subjects who had serious events of erysipelas. There were 7 denosumab (0.2%) and 1 placebo (0.02%) subjects who had serious events of cellulitis. In addition, 2 denosumab (0.05%) and no placebo subjects developed serious events of skin bacterial infection. When all adverse events were examined (serious + non-serious), there was an imbalance in infected

skin ulcers with 4 denosumab (0.1%) and 1 placebo (0.02%) subjects developing an event of infected skin ulcer.

The Applicant has proposed the following Warning and Precaution:

> "In clinical trials in women with postmenopausal osteoporosis, skin infections leading to hospitalization were reported more frequently in the [TRADENAME] (0.4%) versus the placebo (0.1%) groups. These cases were predominantly cellulitis. The overall incidence of skin infections was similar between the placebo and [TRADENAME] groups. Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis."

There is an increased risk of serious skin infections with denosumab that is important to the overall benefit risk assessment for denosumab, particularly for the PMO prevention indication.

5.3.5.1.4 Gastrointestinal Infections

Serious abdominal and gastrointestinal infections occurred in 31 denosumab (0.8%) and 23 placebo (0.6%) subjects in Primary PMO studies. There were 10 denosumab (0.3%) and 7 placebo (0.2%) subjects who had a serious event of diverticulitis. Two denosumab subjects reported serious adverse events with the preferred term of abdominal abscess and one subject each in the denosumab group reported serious adverse events with the preferred term of liver abscess, anal abscess, biliary tract infection fungal, and gastric infection. In the placebo group, one subject each reported serious adverse events with the preferred terms of abscess intestinal, peridiverticular abscess, appendiceal abscess, peritoneal abscess, and gastrointestinal infection.

5.3.5.1.5 Urinary Tract Infections

Serious urinary tract infections occurred in 29 denosumab (0.7%) and 17 placebo (0.4%) subjects in Primary PMO studies. There were 6 denosumab (0.2%) subjects who each developed serious events of cystitis and pyelonephritis, with 2 placebo (0.05%) subjects each developing these serious events.

5.3.5.1.6 Infective Arthritis

Infective arthritis was reported in 8 denosumab subjects (0.2%) and no placebo subjects in the Primary PMO studies. All 8 cases were categorized as non-serious. The causative organism was not reported for these cases.

5.3.5.1.7 Ear Infections

Serious ear infections occurred in 5 denosumab (0.1%) and no placebo subjects in Primary PMO studies, including 4 denosumab (0.1%) subjects who developed serious events of labrynthitis, while no placebo subjects developed this serious event of labrynthitis.

Issue for consideration:
Overall, subjects in the denosumab group had a slightly increased incidence of serious infections. There were more serious infections of the skin, ear, abdominal system and urinary tract. Also, endocarditis, infected arthritis and skin ulcers occurred more commonly in denosumab subjects. There were 3 denosumab subjects in Phase I studies who developed pneumonia requiring hospitalization following a single dose of denosumab. There did not appear to be an increase in opportunistic infections in denosumab subjects.

5.3.5.2 Malignancy

No carcinogenicity studies were performed due to lack of an appropriate animal model because denosumab is not pharmacologically active in rodent species. While the Applicant does have a surrogate model of huRANKL knock-in (KI) mice, this model would not serve as an appropriate model for carcinogenicity studies due to adaptive responses that occur during development.

When individual studies of subjects with osteoporosis and low bone mass were reviewed, an imbalance in the number of denosumab subjects developing a new malignancy was noted. In particular, 3 subjects from the dose-finding Study 20010223 in the denosumab 100 mg Q6 months cohort died of a new malignancy.

In the MedDRA hierarchy, the Neoplasms SOC contains both benign and malignant conditions. Although benign and malignant conditions are summarized, malignancies are the focus of this summary. As shown below, the incidence of malignant female reproductive neoplasms in denosumab subjects was 2-fold higher than placebo (21 vs. 9 subjects). Malignant gastrointestinal neoplasms were also reported more frequently in denosumab subjects (35 vs. 24). Malignant breast neoplasms were slightly more frequent in denosumab subjects (35 vs. 30). Although not commonly reported, malignant endocrine neoplasms were reported for denosumab at a rate that was > 3-fold higher than placebo (7 vs. 2). There were 3 denosumab subjects who developed haematopoietic neoplasms, while none occurred in the placebo group. The only malignancy that occurred more often in the placebo group (by incidence difference of >0.2%) was malignant respiratory neoplasms, at a rate of 15 denosumab and 24 placebo subjects.

Table 25. Adverse Events of Concern in the Neoplasms SOC in Primary PMO studies (pooled data) by HLGT and Select HLT

High Level Group Term ***- High Level Term***	**Placebo N=4041 n (%)**	**Denos. N=4050 n (%)**
Any event in the Neoplasms SOC	**285 (7.1%)**	**316 (7.8%)**
Any event of malignancy or unspecified neoplasm	**168 (4.2%)**	**192 (4.7%)**
Breast neoplasms benign (incl nipple)	14 (0.3%)	16 (0.4%)
- Breast neoplasms benign	*14 (0.3%)*	*16 (0.4%)*
Breast neoplasms malignant and unspecified (incl nipple)	29 (0.7%)	35 (0.9%)
- Breast neoplasms malignant	29 (0.7%)	35 (0.9%)
Endocrine neoplasms malignant and unspecified	2 (<0.1%)	7 (0.2%)
Gastrointestinal neoplasms malignant and unspecified	24 (0.6%)	35 (0.9%)
- Colonic neoplasms malignant	*8 (0.2%)*	*12 (0.3%)*
- Gastric neoplasms malignant	*3 (0.1%)*	*7 (0.2%)*
- Pancreatic neoplasms malign. (excl islet cell & carcinoid)	*3 (0.1%)*	*8 (0.2%)*
Reproductive neoplasms female malignant & unspec.	9 (0.2%)	21 (0.5%)
- Ovarian neoplasms malignant (excl germ cell)	*5 (0.1%)*	*10 (0.2%)*
- Uterine neoplasms malignant NEC	*1 (<0.1%)*	*4 (0.1%)*

In summary, several malignancies occur at a higher incidence in denosumab subjects. No carcinogenicity studies were performed due to the lack of an appropriate animal model This finding of an increased incidence of certain gastrointestinal, reproductive and endocrine malignancies is important to the benefit-risk assessment for this product, particularly for the osteoporosis prevention indication.

Issue for consideration:
No carcinogenicity studies were performed due to lack of an appropriate animal model because denosumab is not pharmacologically active in rodent species. Three subjects receiving a high dose of denosumab in the dose-finding study (Study 20010223) died of a new malignancy; all subjects received denosumab 100 mg Q6 months. Overall, subjects in the denosumab group in the Primary PMO safety population had a slightly increased incidence of breast cancer, pancreatic cancer, gastrointestinal cancer and reproductive cancers. Breast cancer was the most common adverse event that led to discontinuation of investigational product in the Primary PMO safety population, with 20 denosumab (0.5%) and 10 placebo (0.3%) subjects discontinuing due to breast cancer.

5.3.5.3 Dermatologic Adverse Events (excluding infections)

Analysis for skin and soft tissue disorder includes data from 2 pivotal studies (20030216 and 20040132) for postmenopausal women. Subjects with malignancy on hormone ablative therapies may have different background skin conditions. Therefore, this analysis does not include the hormone ablation therapy population.

There were a total of 8091 subjects (4041 in placebo and 4050 in denosumab) in the combined safety population of subjects who received ≥ 1 dose of an investigational product. There were more subjects in the denosumab group (610, 15.1%) with adverse events related to skin and soft tissue disorders compared to placebo (500, 12.4%) This imbalance was mainly due to imbalance observed in "Dermal and Epidermal conditions" (447 vs. 340 events in placebo vs. denosumab).

Table 26 shows number of subjects in adverse events high level terms (MedDRA) in placebo vs. denosumab group. These events are not specific to injection site.

Table 26 Adverse Event High Level Term in Epidermal and dermal conditions

Adverse Event High Level Term	Placebo N=4041	Denosumab N-=4050
Total Subjects with Epidermal and dermal conditions*	340	447
Bullous conditions	3	9
Dermal and epidermal conditions NEC	56	70
Dermatitis and eczema	81	147
Dermatitis ascribed to specific agent	1	6
Photosensitivity conditions	1	6
Pruritus NEC	97	110
Rashes, eruptions and exanthems NEC	89	116

*All subjects with any epidermal and dermal conditions AE are included in this total
Source: This table is generated using ISS AAE dataset, including studies 20030216 and 20040132, and contains the terms with marked imbalances between groups.
NEC= not elsewhere classified.

Overall, this difference was statistically significant [Epidermal and dermal conditions high level group term (HLGT) [p-value < 0.001, relative risk 1.8 (95% CI (1.342,2.356)) and risk difference of 0.014 (95% CI (0.007,0.021)]. Rashes, eruptions and exanthems were also found to be statistically significantly different.

Issue for consideration:
Overall, subjects in the denosumab group were more likely to develop skin and soft tissue related adverse events. There were more bullous conditions, photosensitivity conditions, pruritic conditions, skin rashes, dermatitis and eczema related adverse events in the denosumab group compared to placebo.

5.3.5.4 Pancreatitis

In study 20030216, there was an imbalance in events of acute pancreatitis in subjects randomized to denosumab. As such, all Preferred Terms in the Standardized MedDRA Query (SMQ) for Acute Pancreatitis (v.11.0, narrow) were reviewed for the ISS pooled data to evaluate this event. A search of the ISS pooled data using the narrow SMQ for acute pancreatitis yielded 9 events in 8 subjects receiving denosumab and 4 events in 4 subjects receiving placebo, as listed in Table 27. As shown below, there were more serious events of

pancreatitis in the denosumab group. There were two denosumab subjects who developed pancreatitis that resulted in death. One placebo subject discontinued investigational product due to pancreatitis. All nine events of pancreatitis were serious in the denosumab group while only one was serious in the placebo group.

Table 27. Events of Pancreatitis in Primary PMO Studies (pooled data)

Preferred Term	Placebo n (%)		Denos. n (%)	
No. of Unique Subjects	4		8	
	Non-serious	Serious	Non-serious	Serious
Pancreatitis	1 (0.03%)	0 (0%)	0 (0%))	2 (0.05%)
Pancreatitis acute	1 (0.03%)	0 (0%)	0 (0%)	5 (0.13%)
Pancreatitis chronic	1 (0.03%)	0 (0%)	0 (0%)	1 (0.03%)
Pancreatic pseudocyst	0 (0%)	1 (0.03%)	0 (0%)	1 (0.03%)
Total	**3**	**1**	**0**	**9**

Each of these events was reviewed in detail for risk factors for pancreatitis and a brief summary and commentary is provided below. The 8 denosumab subjects who developed pancreatitis in the Primary PMO studies were reviewed in detail. There was one case that was concerning for a potential causal relationship – a subject with no known risk factors developed pancreatitis < 3 weeks after receiving a dose of denosumab. This subject had been receiving denosumab for more than 2 years. Some of the remaining cases were confounded (prior history of pancreatitis – 3 subjects, hypercholesterolemia (unknown triglyceride levels) – 1 subject). In one case, the subject died about 4 months after receipt of the initial dose of study drug, but the family refused to provide information.

Table 28. Line Listing of Pancreatitis Events in Subjects Receiving Denosumab in Primary PMO Studies (pooled data)

Study / SID	Inv Prod	Study Day (last dose)	Preferred Term	Medical History & Risk Factors	Reviewer Comments
20030216 6136012	Denos	293 (99)	pancreatitis acute	h/o cholelithiasis & bilary pancreatitis	Subject had prior biliary pancreatitis & gall stones
20030216 6412535	Denos	377 (195) 849 (667)	pancreatitis acute pancreatic psuedocyst	2 prior episodes of acute pancreatitis	Subject had 2 prior episodes of pancreatitis
20030216 6413051	Denos	128 (128)	pancreatitis acute	Subject seen in clinic at Month 3. Family said subject died 1 month later. No more information.	Unable to assess due to limited information

Study / SID	Inv Prod	Study Day (last dose)	Preferred Term	Medical History & Risk Factors	Reviewer Comments
20030216 6430212	Denos	751 (17)	pancreatitis	h/o HTN, ex-smoker, thin pt, did not drink alcohol. Conmeds: atenolol, ASA, diclofenac	Event occurred < 3 weeks after last dose (> 2 years since initial dose). Amylase was 1,936 on admission. No obvious risk factors.
20030216 6436050	Denos	1095 (157)	pancreatitis	h/o hypercholesterolemia (triglyceride levels UNK), hypertension	Event occurred ~ 5 months after last dose (~ 3 years from 1st dose). Subject diagnosed with biliary acute pancreatitis.
20030216 6664007	Denos	130 (130)	pancreatitis acute	h/o hypertension, goiter	Subject diagnosed with perforated duodenal diverticulum w/ peritonitis & acute pancreatitis ~4.5 months after 1st dose of i.p.
20030216 6754032	Denos	1095 (104)	pancreatitis acute	h/o HTN, DM (req. insulin), diverticular disease of sigmoid colon, cholecystectomy, cerebral atherosclerosis, GERD.	~3 months after last dose (~ 3years from 1st dose) subject diagnosed w/ acute pancreatitis (hemorrhagic, necrotic) – unk etiology. CT scan: liver steatosis & diverticular dis (sigmoid colon).
20030216 6835096	Denos	87 (87) 95 (95) 572 (26) 584 (38)	pancreatitis chronic (4 episodes)	h/o acute pancreatitis & chronic pancreatitis.	Diagnosed w/ exacerbation of chronic pancreatitis, initial episode ~87 days after 1st dose in subject with h/o acute & chronic pancreatitis. U/S: cyst on head of pancreas. CT scan: pancreatic calcifications & dilated biliary tracts. Event recurred. Subject continued to receive study drug.

The temporal relationship between use of denosumab and the start date for these events is highly variable. In addition, all of the cases except one reviewed herein were confounded by prior episodes of pancreatitis or risk factors for the development of pancreatitis.

5.3.5.5 Cardiovascular Adverse Events

Reason for concern:
The target population for osteoporosis treatment is postmenopausal women who might use this therapy (if approved) for many years. This is a high risk population in terms of cardiovascular disease. During denosumab's development program, a concern was raised for the potential for denosumab to cause atherosclerosis. This was based on reports in the published literature regarding a possible association between OPG levels and arterial (aortic) wall calcification, cardiovascular disease and mortality (Kiechl et al, Circulation, 2004) and the possibility that inactivation of RANKL by denosumab could result in elevated levels of osteoprotegerin (OPG) via an unopposed feedback mechanism. To address these concerns, the Applicant established a committee to adjudicate possible cardiovascular events in two phase 3 trials, one in postmenopausal women (Protocol 20030216) and one in men (Protocol 20040138). In addition, an analysis of changes in abdominal aortic calcification (as assessed using lateral lumbar spine radiographs) was also conducted in a subset of study subjects in trial 20030216.

Key attributes of the adjudication process for potential cardiovascular events:

- Committee members were Cardiologists not otherwise associated with the study.
- Identification of potential cardiovascular-related SAEs and deaths: All deaths were reviewed. Serious adverse events (SAEs) were identified for adjudication using MedDRA preferred terms
- Task of committee was to categorize serious adverse events into one of the following categories,
    - Acute coronary syndrome/revascularization
    - Congestive heart failure
    - Stroke/transient ischemic attacks
    - Cardiac arrhythmias
    - And other vascular disorders/revascularization
- Categorize deaths as cardiovascular or non-cardiovascular;

Baseline cardiovascular risk factors:
Baseline cardiovascular risk factors such as myocardial infarction, percutaneous coronary intervention, coronary artery bypass surgery, diabetes, smoking, hypertension, and high cholesterol were similar in both treatment groups in adjudicated trials 20030216 and 20040138.

Unadjudicated Adverse Event analysis:
Unadjudicated event analysis was done for data from 20 clinical studies in phase 2 and 3 trials, total safety population of 10,638 subjects (4738 placebo and 6329 denosumab) who received > 1 investigational product dose. Overall, 632 (13%) subjects in the placebo group and 723 (11%) in the denosumab group had a cardiovascular-related adverse event. The most common adverse events (placebo vs. denosumab) were angina pectoris (2.1% vs. 1.9%), atrial fibrillation (2.0%, 1.7%), palpitations (1.5%, 1.3%), coronary artery disease (1% vs. 0.9%), and arrhythmia (both groups 1%, 0.8%). The subject incidence of cardiovascular SAEs was 4.6% in the denosumab group and 5% in the placebo group. Subgroup analysis by

age >75 years old did not show any concerning trends. There was no significant dose-related increase in the cardiovascular adverse events.

Cardiovascular serious event adjudication results:
Adjudication of cardiovascular serious adverse events was done in trial 20030216 and trial 20040138. The number of events submitted for adjudication was 526 in the placebo and 572 in the denosumab group for trial 20030216. The number of events adjudicated as CV related was 233(44.3%) in the placebo and 247(43.2%) in the denosumab group. Similarly, in trial 20040138, the number of events adjudicated as CV related was 105 (52% of 203) in placebo and 118 (50% of 236) in the denosumab group.

The point estimate for the hazard ratio for cardiovascular death was 0.7 (0.4, 1.2) for trial 20030216 and 0.97 (0.7, 1.3) for trial 20040138. Any adjudicated event hazard ratio was approximately 1 for both trials. Time to first any adjudicated cardiovascular event analysis does not suggest worsening CV outcomes over time in both low cardiovascular risk and high cardiovascular risk subjects. The incidence of any adjudicated CV serious adverse event (SAE), CV death, acute coronary syndrome, stroke/transient ischemic attack, congestive heart failure and other vascular disorder was similar in the 2 treatment arms (see Table 29).

Table 29: Adjudicated cardiovascular-related serious adverse events for trial 20030216

	20030216			**20040138**		
Incidence at 36 Months	**Placebo (N = 3876)**	**Denosumab (N = 3886)**	**Hazard ratio (95%CI)**	**Placebo (N = 725)**	**Denosumab (N = 731)**	**Hazard ratio (95%CI)**
	n (%)	n (%)		n (%)	n (%)	
Any adjudicated positive CV SAE	178 (4.6)	186 (4.8)	**1.02** (0.8,1.2)	80 (11)	80 (10.9)	**0.97** (0.7,1.3)
CV death	31 (0.8)	23 (0.6)	**0.72** (0.4,1.2)	21 (2.9)	19 (2.6)	**0.9** (0.5,1.6)
Stroke / transient ischemic attack	54 (1.4)	56 (1.4)	**1.17** (0.8,1.8)	17 (2.3)	21 (2.9)	**1.2** (0.6,2.3)
Acute coronary syndrome	39 (1.0)	47 (1.2)	**1.02** (0.7,1.5)	27 (3.7)	18 (2.5)	**0.67** (0.4,1.2)
Congestive heart failure	22 (0.6)	27 (0.7)	**1.19** (0.7,2.1)	11 (1.5)	8 (1.1)	**0.7** (0.2,1.7)
Other vascular event	30 (0.8)	31 (0.8)	**1** (0.6,1.6)	12 (1.7)	18 (2.5)	**1.44** (0.6,2.9)
Arrhythmia	45 (1.2)	52 (1.3)	**1.13** (0.8,1.7)	15 (2.1)	19 (2.6)	**1.23** (0.6,2.4)

This table is Applicant generated from table 11-8, clinical study report 20030216, page 343 and Clinical Study Report 20040138, page 196.

Findings pertaining to osteoprotegerin levels

To address denosumab's effect on osteoprotegerin, osteoprotegerin levels were measured at screening, day 1 and months 1, 6, 12, 24 and 36 in a subset of subjects enrolled in a bone marker sub study of trial 20030216 (N=64 placebo and N=96 denosumab).There was no clear increase in osteoprotegerin levels in denosumab compared to placebo-treated subjects.

Aortic calcification:
Subjects were assessed for aortic calcification score if they were considered high risk (total of ≥4 points). Subjects were assigned points based on the following baseline risk factors.
4 points: Prior myocardial infarction, percutaneous coronary intervention, or CABG
3 points: Diabetes (fasting blood glucose >140 mg/dL or taking diabetes medication)
2 points: Age >70 years
1 point: Age 65-69 years, Current smoker, hypertension or hyperlipidemia

The 2363 subjects assessed for aortic calcification score were similar to the overall study population with regard to subject disposition, baseline body composition and baseline BMD T-scores. The distribution of baseline scores was similar in the two treatment arms and most patients had low baseline aortic calcification scores (7.2 in placebo and 6.8 in denosumab). The mean change from baseline in aortic calcification score was minimal in both treatment groups (0.1 at one year, 0.2 at 2 years and 0.4 at 3 years in the denosumab and placebo groups.)

When the entire ISS population was evaluated, cardiovascular AEs were similarly distributed between the placebo and denosumab groups. The cardiovascular adjudication process was comprehensive. Adjudicated serious cardiovascular events were similar between the two treatment groups in trials 20030216 and 20040135. No differences were found in aortic calcification scores at 3 years between treatment arms. However, lateral lumbar spine x-rays may not be a sensitive method to find small differences.

5.3.5.6 Hypocalcemia

Reason for concern: Denosumab decreases bone resorption. Bone resorption plays an important role in calcium homeostasis. It is physiologically plausible that denosumab administration and associated suppressed bone remodeling may lead to with a higher incidence of hypocalcemia. The Applicant evaluated hypocalcaemia in several clinical trials.

A Phase I, single dose, open label trial (study 20040245) to assess pharmacokinetics, safety and tolerability in patients with both normal and abnormal renal function showed:

1) Nadir of serum calcium occurred at approximately day 8-11.
2) Subjects in the end stage renal disease group were more likely to develop hypocalcemia.

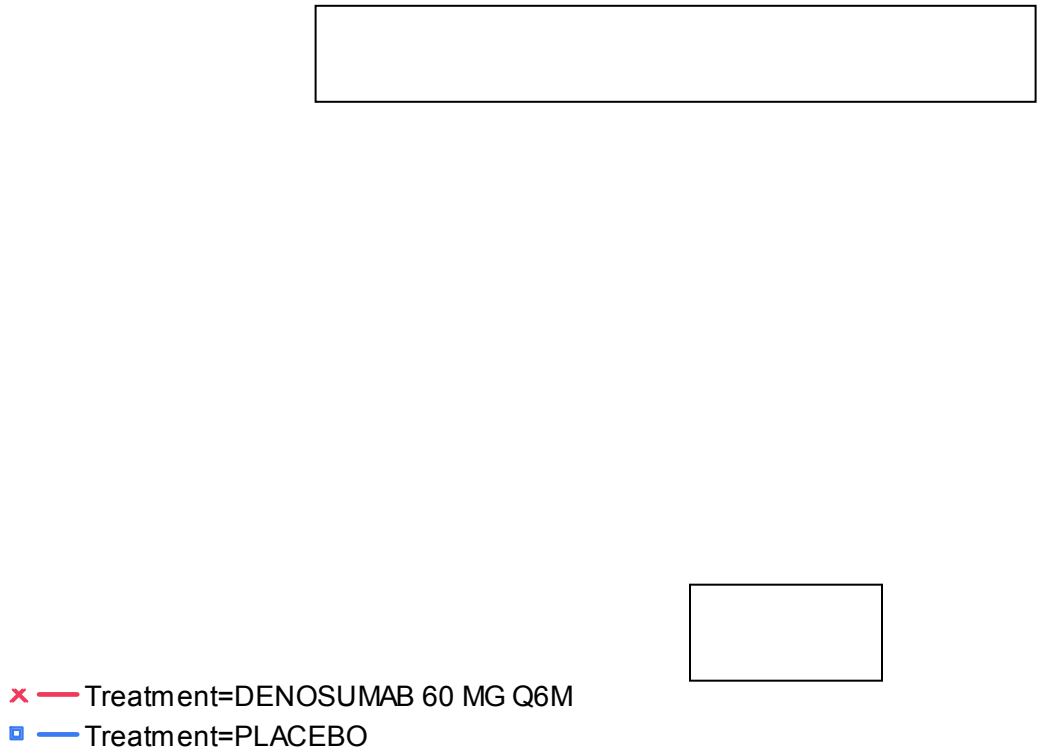
Phase 3 Trials:

In trial 20030216, serum calcium levels were measured at screening, study day 1 and study months 1, 6, 12, 18, 24, 30 and 36. Mean serum calcium levels were similar between the treatment groups at each visit. The between-group differences in mean change from baseline in calcium levels appeared to be greatest at Month 1 but these differences became less pronounced with time and eventually no real differences were seen by Month 24. Similar results were observed in trial 20030132.

Since study 20040245 showed that nadir in serum calcium levels occurs in the first two weeks (day 8-11) after administration, trial 20060289 measured serum calcium levels at day 10 +/- 5 days after denosumab administration to further characterize the timing and magnitude of maximal reductions in serum calcium after denosumab dose. Trial 20060289 is an open label, single arm, extension study of trial 20030216. Figure 6 shows that there was 3-5% decrease in serum calcium levels at day 10 in both treatment groups (groups previously treated with placebo and denosumab). In subjects who received placebo in trial 216 (de novo group), and started receiving denosumab in trial 289, this decrease was observed in more subjects and was slightly more pronounced.

Serum calcium level in these subjects with hypocalcaemia at each visit and their reported adverse events were examined. These reductions in serum calcium were transient and not associated with adverse events (hypoesthesia, oral hypoesthesia, paresthesia, oral paresthesia, and tetany) related to hypocalcemia.

Figure 6: Serum Calcium % change from baseline in Trial 20030216 rolling over to 20060289



There were 100 subjects in the de novo denosumab group who developed hypocalcemia (serum calcium ≤ 8.4) compared to 48 subjects who continued on the denosumab at the day 10 visit. The number of subjects with serum calcium ≤ 8 and ≤ 7.5 mg/dl was small (Table 30). This table also demonstrates that day 10 is more sensitive to measure changes in serum calcium compared to month 1, as seen in study 20030216.

Table 30: Number of subjects with selected serum calcium levels at month 1 in trial 20030216 and day 10 in 20060289

	20030216 Month 1		20060289 Day 10	
	Placebo N=3876	Denos. N=3886	placebo to denos. N=2343	Denos. N=2206
Serum calcium ≤8.4	2	33	100	48
Serum calcium ≤8.0	2	0	7	5
Serum calcium ≤7.5	2	0	2	1

In study 289 there were 2 subjects in the de novo denosumab group who developed serum calcium level of <7.5 mg/dl at day 10. SID 20030126-744099 had a serum calcium level of 7 mg/dl at day 10. This subject had a history of renal impairment, cough, back pain, gout, and "heart valve incompetence." The only associated AE was nausea. Another subject (SID

20030126-744078) had a serum calcium level of 7.3 mg/dl and experienced no adverse events.

Issues for consideration:
Hypocalcaemia is a known class effect of antiresorptive drugs. Denosumab induced hypocalcemia appears to be transient (in first month after dosing, nadir at day 8-11) with spontaneous resolution without any serious sequelae observed in this study. In this clinical trial, hypocalcemia was an exclusion criterion and subjects were given 1 gm calcium as a concomitant medication.

5.3.5.7 Osteonecrosis of the Jaw

Reason for concern: Osteonecrosis, or avascular necrosis of the jaw (ONJ) is a pathological process associated with pain, swelling, exposed bone, local infection, and pathologic fracture of the jaw. Postmarketing experience with bisphosphonates has raised concerns about the potential for bone remodeling inhibition and osteonecrosis of the jaw. Risk factors for bisphosphonate associated ONJ include long-term use (>3 years), patients with malignancy, poor oral hygiene, dental procedures, concomitant therapies (radiation, chemotherapy, corticosteroids), and IV use of bisphosphonates (Ruggiero et al, Annu.Rev Med 2008) The mechanism by which osteonecrosis develops in relationship to treatment with bisphosphonates is not well understood.

ONJ presents as exposed necrotic bone typically involving the maxilla or mandible and an infection. It is especially common in patients with malignancies being treated with intravenous bisphosphonates. It is not known whether ONJ is the primary process that becomes secondarily infected, if ONJ represents primary osteomyelitis, exacerbated by the use of bisphosphonates, or if it is the consequence of a combination of events, including the use of bisphosphonates, poor dental hygiene, and/or a dental procedure or condition. It is also uncertain if the presence of actinomyces, noted commonly in ONJ lesions, is actively contributing to the development or progression of ONJ, or is simply related to the presence of necrotic bone in an anaerobic environment.

The true incidence and risk of ONJ related to treatment with denosumab is unknown; however, based on its antiresorptive effects, there is a recognized risk that patients treated with denosumab have the potential to develop ONJ. As a result, the applicant included in their development a plan to specifically evaluate patients participating in the clinical trials for ONJ signs and symptoms. This was accomplished through formation of an adjudication committee, the Osteonecrosis of the Jaw Adjudication Committee (ONJAC), setting up MedDRA terms which would trigger cases of potential ONJ to be reviewed by the committee. A review of the ONJAC and its processes, procedures, and findings was undertaken.

Definition of ONJ used by the Applicant: "Area of exposed alveolar or palatal bone where gingival or alveolar mucosa is normally found associated with non-healing after appropriate care by 8 weeks in a patient without prior history of radiation to the head, face or mouth.

Although a triggering traumatic event is usually involved, ONJ can be asymptomatic." This definition is accurate and consistent with the current medical literature. The applicant's search identified 21 potential cases of ONJ. The ONJAC reviewed all 21 of the cases and concluded that none that were positive for meeting the criteria. The applicant submitted a listing of the cases, but not a rationale for eliminating them from an ONJ diagnosis.

The Applicant's list of preferred terms did not capture potential surgical procedures and more vague terms (e.g. bone lesion) that could possibly indicate ONJ. A review of MedDRA PTs was also performed which determined that there were a number of potential terms that could be associated with ONJ that were not included in the applicant's list of search terms. It was concluded, however, that a more detailed search utilizing these terms would not likely yield new cases for adjudication. A search of the adverse events database was performed utilizing the expanded search criteria. A list of 21 subjects was compiled who met the expanded criteria, and case report forms were reviewed. On April 29, 2009, the applicant was asked to send further information about the involved patients. The applicant submitted additional information which included case narratives, follow-up documentation from the treating dentists, and photographs. These materials were reviewed by agency experts, who concluded that none of the events in the expanded list met the requirements for the diagnosis of ONJ.

It should be noted that while no cases of ONJ have been confirmed in the PMO and Hormone Ablation trials under review, at least one confirmed case of ONJ has been reported in other trials conducted by the Applicant in patients with multiple myeloma and metastatic cancer.

5.3.5.8 Hypersensitivity and Immunogenicity

To evaluate hypersensitivity, the safety database was queried for conditions (MedDRA preferred terms) hypersensitivity, drug hypersensitivity, angioedema, anaphylactic reaction, and severe cutaneous adverse reactions. Significant differences between the treatment groups were found only in Skin and subcutaneous tissue disorders SOC (system organ class) with p-value 0.001, relative risk 1.515 (95% CI (1.19, 1.93)) and risk difference of 0.0135 (95% CI (0.006, 0.021)). These differences are described in detail in Section 5.3.5.3. Across the Primary PMO and Hormone Ablation Safety Analysis Sets, the incidences of the individual terms hypersensitivity and drug hypersensitivity were 0.7% and 0.4%, respectively, in the denosumab group and 0.6% and 0.3%, respectively, in the placebo group in the Primary PMO and Primary Hormone Ablation Safety Analysis Sets. The incidence of adverse events for "angioedema", "anaphylactic reaction", and "severe cutaneous adverse reaction" was 1.3% in both treatment groups and balanced by organ system.

For immunogenicity, the Applicant conducted two antibody tests. The first was a test for binding antibodies. The second test was a follow-up on the first to confirm if the binding antibodies were neutralizing. A cell-based bioassay was used to test positive binding antibody samples for neutralizing activity against denosumab.

Screening and confirmatory immunoassays were used to detect binding antibodies in >8000 subjects who received at least one dose of denosumab. Based on the data submitted by the Applicant, 5 of 12 studies with antibody tests had positive results: 20030216 (25/3886 or

0.6%), 20010223 (2/314 or 0.6%), 20040132 (2/164 or 1.2%), 20040135 (2/129 or 1.6%), and 20040138 (1/731 or 0.1%).

In study 20030216, 19 subjects tested positive once only, 5 were positive twice and 1 was positive three times (total 25). There was no correlation observed between subjects with positive binding antibody tests and their adverse event profiles. None of the subjects who were positive for binding antibodies were positive for neutralizing antibodies. These results were similar for both PMO and hormone ablation populations. In conclusion, denosumab does not appear to be immunogenic.

.

5.3.6 Bone Histomorphometry

Iliac crest bone biopsy specimens were obtained from subjects enrolled in three different trials:

- Study 20030216 was the randomized, double-blind, placebo-controlled pivotal fracture trial in postmenopausal women. Bone biopsies were obtained from 68 subjects (37 placebo, 31 denosumab) at month 24 and 47 subjects (25 placebo, 22 denosumab) at month 36. Twenty-three (17 placebo, 6 denosumab) of the subjects listed underwent sequential bone biopsy at both month 24 and month 36. The mean age of enrollees in this bone biopsy substudy was 71 years. It should be noted that one subject in the month 36 denosumab group was excluded from the Agency's analysis because the patient had discontinued study drug after month 12.
- Study 20010223 was the randomized, placebo and active-controlled, dose-finding study in postmenopausal women with low bone mineral density. Baseline bone biopsies were obtained from 39 subjects, of which 37 were evaluable (5 placebo, 1 alendronate, 31 denosumab). At month 12 biopsies were obtained from 51 subjects, of which 49 were evaluable (4 placebo, 4 alendronate, 41 denosumab). Twenty-eight of the subjects (3 placebo, 1 alendronate and 24 denosumab) listed had paired baseline and month 12 biopsies performed. Three subjects in the paired biopsy group had specimens that were not evaluable (all denosumab). The mean age of enrollees in the bone biopsy substudy was 60 years.
- Study 20050234 was a double-blind, double-dummy, active-controlled, parallel-group study in postmenopausal women with low BMD (T-score between -2.0 and -4.0) who had received alendronate (70 mg weekly or equivalent) for at least 6 months preceding study entry. At study entry, subjects were randomized to either continue on alendronate 70 mg once weekly or switch to denosumab 60 mg q 6 months. Bone biopsies were obtained from 36 subjects (21 alendronate, 15 denosumab) at month 12. The mean age of enrollees in the bone biopsy substudy was 67 years.

<u>Qualitative Bone Histology</u>

In general, there was evidence of normal lamellar bone and normal mineralization in all treatment groups. In addition, there was no evidence of osteomalacia or woven bone in these studies. However, the following histologic abnormalities were noted:

- In study 20030216, five subjects in the denosumab-treated group at month 24 did not have osteoid that could be visualized. This could be due to suppressed bone turn over.
- In study 20030216, one subject who received all scheduled doses of denosumab, was determined to have normal histology at month 24 and cortical trabecularization at month 36. Cortical-endosteal resorption ("trabecularization" of the cortical bone) is one of the major determinants of reduced bone strength.
- In study 20050234, one subject treated with alendronate had evidence of marrow fibrosis on biopsy.

Quantitative Bone Histomorphometry

Evaluation of bone biopsy specimens using histomorphometry techniques allows for tissue-level assessment of bone turnover, formation and mineralization. In order to assess ongoing bone activity, subjects participating in the bone biopsy substudies were treated with two time-spaced courses of either demeclocycline or tetracycline. Tetracycline is incorporated into mineralized bone and fluoresces under ultraviolet light. Therefore, in active bone, the time-spaced lines of tetracycline can be used for calculation of new bone formation and mineralization rates.

The presence of double tetracycline labeling in a biopsy specimen provides an indication of active bone remodeling and formation. Trabecular bone, the most active site of bone remodeling, is the usual site of evaluation of tetracycline labeling. If trabecular double label is not found, an extended search procedure including cortical bone can be conducted. As outlined in Table 31, all subjects in the placebo group had double label present. 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. One subject treated with alendronate had no label present at month 12 biopsy. While a sporadic biopsy specimen with absence of double label is not unusual, the number of patients treated with denosumab who have absence of double labeling is striking. The clinical consequences of these findings are unclear. One concern is that absence of double label may suggest over suppression of bone turnover 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 2/17 biopsy specimens denosumab treated subjects at month 36.

Table 31 Labeling status in 3 trials with bone biopsy sub study

Study	**223**			**223**			**234**		**216**		**216**	
Time	**baseline**			**month 12**			**month 12**		**month 24**		**month 36**	
	plac	**aln**	**deno**	**plac**	**aln**	**deno**	**aln**	**deno**	**plac**	**deno**	**plac**	**deno***
biopsies, n	5	1	33	4	4	43	21	15	37	31	25	21
evaluable, n	5	1	31	4	4	41	21	13	32	26	22	17
No label	0	0	0	0	**1**	**9**	0	**3**	0	**11**	0	**8**
Single label	0	0	0	0	1	9	0	3	0	9	0	4
Double label	5	1	30	4	2	18	21	9	37	11	25	9
Any label	5	1	31	4	3	32	21	12	37	20	25	21
dynamic, n				4		13	21	6	31	5	22	2

*subject with only 12 months of treatment excluded

It is expected that parameters of bone resorption would decrease with denosumab therapy or any other anti-resorptive agent such as alendronate. Because each study offers a different perspective on denosumab's effect on bone, the quantitative histomorphometry data are presented separately for each study.

In study 20030216, the number of biopsy specimens obtained that were acceptable for analysis of all histomorphometry parameters at month 24 was 31 placebo, 5 denosumab; and at month 36 was 22 placebo and 2 denosumab (after exclusion of one subject who only received denosumab for 1 year). Results are listed in Table 32.

Activation frequency (AcF): Activation frequency represents the probability that a new remodeling cycle will be initiated at any point on the trabecular bone surface. It is a direct and sensitive measure of bone remodeling activity. Treatment with denosumab significantly decreased the activation frequency at both month 24 and 36. In fact, remodeling activity was virtually absent at month 36 in the very small number of evaluable biopsies at month 36.

Bone formation rate per bone surface (BFR/BS): Bone formation rate per bone surface represents the volume of bone formed per unit of trabecular surface. It would be expected that bone formation rate would decrease with anti-resorptive therapy such as denosumab.

Eroded surface/Bone surface (ES/BS): Eroded surface represents the percent of trabecular bone surface occupied by Howship's lacunae where osteoclasts have eroded or are eroding bone. Because denosumab functions by inhibiting osteoclast recruitment, one would expect that treatment with denosumab would result in decreased number of osteoclast sites, as is demonstrated.

Osteoid surface / Bone surface (OS/BS): The osteoid surface/bone surface ratio reflects bone remodeling. A clear decrease in OS/BS, again, would be expected if there is a decreased rate of bone turnover in the absence of any impairment of bone mineralization. Treatment with denosumab resulted in a clear decrease in OS/BS at both month 24 and 36.

Mineral apposition rate (MAR): Mineral Apposition Rate (MAR) is an important parameter assessing mineralized bone accrual at remodeling sites. Treatment with denosumab decreased MAR. No change or small increases in MAR during treatment with study medication would suggest that the mineralization of newly formed bone is not affected by the therapy. Decreases in MAR can be seen with a reduction in bone turnover.

Mineralization Lag Time (MLT, days): Mineralization lag time is a sensitive measure of mineralization abnormalities and represents the time interval between deposition of osteoid and its mineralization, averaged over the life of the osteoid seam. The increase in MLT in denosumab treated patients at month 24 is driven by 3 subjects with MLT greater than 100 days. In each of these subjects, AcF and other dynamic parameters were very low. These elevations in MLT could represent artifact due to the calculation which is based on other parameters.

Osteoid thickness (OTh): Osteoid thickness can be used a marker of bone formation. Increases in osteoid thickness would be expected in the setting of a mineralization defect. Treatment with denosumab did not result in increased osteoid thickness.

Osteoid volume/ Bone volume (OV/BV): Osteoid volume represents the percentage of bone volume that is non-mineralized osteoid. A clear increase in OV/BV would support the hypothesis of impaired mineralization. Treatment with denosumab did not result in increased osteoid volume.

Table 32. Study 216: Quantitative Histomorphometry Parameters

	Month 24		Month 36	
Parameter [median]	**plac**	**denos**	**plac**	**denos**
AcF, n	31	5	22	2
per yr	0.270	0.001	0.200	0.003
BFR/BS, n $um^3/um^2/yr$	31 11.89	5 0.13	22 9.80	2 0.29
ES/BS, n %	32 1.65	26 0.23	22 0.81	17 0.14
OS/BS, n %	32 7.68	26 0.70	22 6.54	17 0.26
MAR, n um/day,	31 0.730	5 0.300	22 0.755	2 0.400
MLT, n days,	31 20	4 167	22 24	2 49
OTh, n µm	32 9.09	26 5.435	22 8.715	17 5.410
OV/BV, n %	32 1.16	26 0.08	22 0.72	17 0.03

Paired bone biopsy evaluation can offer insight into the effect of treatment. In study 20010223, three subjects in the placebo group, one subject in the alendronate group and three subjects in the denosumab 60mg q 6 month group had both baseline and month 12 bone biopsies performed. However, while all three paired samples were evaluable for dynamic parameters in the placebo group, only one paired biopsy sample from the denosumab group was evaluable at month 12 because of lack of double trabecular label in the other biopsy samples. A formal analysis was not performed.

Study 20050234 provides bone histomorphometry data in patients previously treated with alendronate who either continued alendronate therapy or were switched to denosumab. This study offers important safety information for patient who may be switched from bisphosphonate to denosumab. It also offers a direct comparison of histomorphometry data between alendronate and denosumab. Results are listed in Table 33.

Activation frequency was further suppressed with initiation of denosumab treatment, compared to continued alendronate therapy. Bone formation rate increased with denosumab therapy when compared to continued alendronate therapy. Eroded surfaces decreased substantially with denosumab therapy. This likely represents differences in the mechanisms of action of these two drugs. Alendronate acts by inhibition of osteoclast function, but does not impact osteoclast recruitment. Denosumab acts by inhibiting osteoclast recruitment. Osteoid surfaces were further decreased with denosumab therapy, suggesting decreased remodeling. Mineralization lag time and osteoid thickness were not appreciably increased with denosumab therapy, as compared to alendronate. Osteoid volume was further decreased

with denosumab therapy, again suggesting bone remodeling is further decreased with denosumab therapy.

Table 33. Study 234: Quantitative Histomorphometry Parameters

	Month 12	
Parameter [median]	**alendronate**	**denosumab**
AcF, n	21	6
per yr	0.040	0.015
BFR/BS, n	21	6
$um^3/um^2/yr$	1.97	2.77
ES/BS, n	21	13
%	1.9	0.3
OS/BS, n	21	13
%	2.93	1.07
MAR, n	21	6
um/day,	0.550	0.300
MLT, n	21	6
days	53.6	37.8
OTh, n	21	13
µm	6.82	5.54
OV/BV, n	21	13
%	0.320	0.080

In summary, quantitative histomorphometry parameters demonstrate that treatment with denosumab significantly reduces bone remodeling. However, the number of biopsy specimens that lacked any tetracycline label or sufficient label to allow appropriate dynamic analyses is of concern. While it is common to have a small number of biopsy specimens that lack tetracycline labeling, the numbers seen in these denosumab trials have not been encountered before.

The Applicant believes that the lack of label in the post baseline bone biopsy specimens is not concerning because bone turnover markers are not similarly suppressed at month 24 and month 36. However, as previously outlined in Figure 5, months 24 and 36 represent a nadir of denosumab effect, a time when bone turnover markers are trending upward toward baseline. Month 1 would better represent bone turnover markers at peak denosumab effect. In study 216, an evaluation of bone turnover markers at month 1 in subjects based on trabecular label status was performed. There was no apparent correlation between the mean percent change in month 1 serum CTX levels and presence of double label. The mean percent change in month 1 serum CTX levels was -87 to -90% in all denosumab groups regardless of whether double label was present or not.

However, it should be noted that in the reporting of CTX values, the Applicant rounded values originally listed as below the limit of quantitation (<0.049 ng/mL) up to read as a

value of 0.049. Table 34 details the trabecular label status in terms of the original CTX value reported (below 0.049 or above 0.049). When evaluated in this manner, it is clear that in subjects treated with denosumab, the lack of tetracycline label occurred predominantly in those who had CTX levels below the limit of quantitation.

Table 34. Study 216: Trabecular label Status and Presence of Detectable CTX levels at Month 1

n (%)	**Month 24**		**Month 36**	
	plac	**denos**	**plac**	**denos**
n, biopsies	36*	31	25	21*
Double Label Present, n	**33**	**3**	**24**	**6**
CTX < 0.049	0 (0)	1 (33)	0 (0)	2 (33)
CTX > 0.049	33 (100)	2 (67)	24 (100)	4 (67)
Single Label Present, n	**2**	**5**	**1**	**3**
CTX < 0.049	0 (0)	4 (80)	0 (0)	2 (66)
CTX > 0.049	2	1 (20)	1 (100)	1 (33)
No Label Present, n	**1**	**23**	**0**	**12**
CTX < 0.049	0 (0)	20 (87)	0 (0)	9 (75)
CTX > 0.049	1 (100)	3 (13)	0 (0)	3 (25)

* two subjects did not have bone turnover markers available for analysis, one from the month 24 placebo group and one from the month 36 denosumab group

Overall, there is significant concern regarding over suppression of bone turnover. However, the clinical consequences of these bone histomorphometry findings are not clear. The Applicant believes that because reductions in bone remodeling, as reflected by the small number of tetracycline labels in the bone biopsy samples, did not translate into an increase in fracture risk in these subjects, there is not cause for concern. However, the long-term risks of adverse effects related to severely suppressed bone turnover may not be fully recognized.

Issue for consideration:

The bone histomorphometry results raise concerns regarding the degree of apparent bone turnover suppression and the potential for long-term safety consequences.

5.3.7 Laboratory Findings

Clinical Laboratory evaluations among subjects with PMO:
When the central tendency of laboratory values was analyzed, the majority of patients had laboratory values for all parameters that remained in the normal range during the phase 3 trials. Laboratory toxicities of grade 3 or 4 severity were infrequent, and the incidences were balanced between treatment groups as shown in Table 35.

Table 35: Subject incidence of marked laboratory abnormalities in Study 20030216 and Study 20040132

Laboratory Parameters	Relationship to Normal		Placebo (N = 4041) n (%)	Denosumab (N = 4050) n (%)
Sodium	Above	>155 mEq/L	1 (<0.1)	0 (0.0)
	Below	<130 mEq/L	42 (1.0)	38 (0.9)
		<120 mEq/L	2 (<0.1)	0 (0.0)
Potassium	Above	>6 mEq/L	10 (0.2)	4 (<0.1)
		>7 mEq/L	0 (0.0)	3 (<0.1)
	Below	<3 mEq/L	6 (0.1)	5 (0.1)
Magnesium	Above	>3mg/dl	5 (0.1)	2 (<0.1)
	Below	<0.7 mg/dl	1 (<0.1)	0 (0.0)
Creatinine	Above	>6xULN	0 (0.0)	1 (<0.1)
Glucose	Above	>250mg/dl	41 (1.0)	40 (1.0)
	Below	<40 mg/dl	1 (<0.1)	1 (<0.1)
Glucose	Below	<30 mg/dl	0 (0.0)	1 (<0.1)
Hemoglobin	Below	<8 mmol/l	7 (0.2)	9 (0.2)
		<6.4 mmol/l	0 (0.0)	1 (<0.1)
Platelets	Below	<50,000	4 (<0.1)	1 (<0.1)
		<25,000	2 (<0.1)	4 (<0.1)
White Blood Cells	Below	<2000	9 (0.2)	5 (0.1)
		<1000	0 (0.0)	1 (<0.1)
Aspartate Amino Transferase	Grade 3	>5xULN	5 (0.1)	7 (0.2)
	Grade 4	>20xULN	1 (<0.1)	0 (0.0)
Alanine Amino Transferase	Grade 3	>5xULN	6 (0.1)	7 (0.2)
Alkaline Phosphatase	Grade 3	>5xULN	0 (0.0)	2 (<0.1)
Total Bilirubin	Grade 3	>3xULN	0 (0.0)	5 (0.1)

Source: This table includes data from study 20030216 and 20040132 and generated from Applicant table 42, summary of clinical safety. ULN=upper limit of normal

Liver Function Tests: Analysis of central tendency showed no difference in mean and SD of SGOT [22 (10) vs. 21.9(10)], SGPT [18.9(12) in both groups] and total bilirubin [0.6(0.3) in both groups] in placebo vs. denosumab. In evaluating outliers, subjects were balanced with respect to the incidence of grade 3 or 4 transaminase elevations. Five denosumab-treated subjects (0.1%) and 0 placebo subjects had >5X upper limit of normal elevations in bilirubin. Four of these five subjects had a comorbidity that explained the elevation. One subject had pancreatic cancer, one had hepatic neoplasm and two other subjects had cholelithiasis.

5.3.8 Vital Signs

Vital signs including systolic and diastolic blood pressures, pulse rate, body temperature, body weight, and BMI were assessed at each visit and recorded in all phase 3 clinical trials.

In study 20030216 and 20040132, denosumab did not have an effect on mean absolute values, mean changes from baseline values, or overall outlier incidences of systolic and diastolic blood pressures, pulse rate, body temperature, weight, or BMI. Adverse event analysis showed no difference in the incidences of associated clinical events (e.g., hypotension, hypertension, tachycardia, bradycardia, and pyrexia) between the denosumab and placebo groups.

5.4 Summary of Safety

- Deaths: There were a total of 354 deaths in the denosumab clinical development program; 169 in subjects with low bone mass or osteoporosis and 185 in subjects with underlying cancer. The number of subjects who died during the PMO fracture trial 20030216 was not higher in denosumab (70) compared to placebo (90) groups. There were no deaths in the PMO prevention trial 20040132. Serious adverse events were slightly higher in the denosumab group compared to placebo. Likewise, the number of subjects who died during the key Hormone Ablation studies was not higher in denosumab (45) compared to placebo (47) groups.
- Infections: Overall, subjects in the denosumab group had a slightly increased incidence of serious infections. There were more serious infections of the skin, ear, abdominal system and urinary tract. Also, endocarditis, infected arthritis and skin ulcers occurred more commonly in denosumab subjects. There were 4 cases of endocarditis in the denosumab group (including 3 cases in Study 20030216). One case in the placebo group occurred during Study 20040138. "Streptococcal infections" occurred more frequently among denosumab subjects. There were 3 denosumab subjects in Phase I studies who developed pneumonia requiring hospitalization following a single dose of denosumab. There did not appear to be an increase in opportunistic infections in denosumab subjects.
- Malignancy: No carcinogenicity studies were performed due to lack of an appropriate animal model because denosumab is not pharmacologically active in rodent species. Three relatively healthy subjects receiving a high dose of denosumab in the dose-finding study (Study 20010223) died of a new malignancy; all subjects received denosumab 100 mg Q6 months. Overall, subjects in the denosumab group in the Primary PMO safety population had a slightly increased incidence of breast cancer, pancreatic cancer, gastrointestinal cancer and reproductive cancers. Breast cancer was the most common adverse event that led to discontinuation of investigational product in the Primary PMO safety population, with 20 denosumab (0.5%) and 10 placebo (0.3%) subjects discontinuing due to breast cancer.
- Skin and soft tissue disorder: Overall, subjects in the denosumab group were more likely to develop skin and soft tissue related adverse events, which were statistically significant. There were more bullous conditions, pruritic conditions, skin rashes, dermatitis and eczema related adverse events in the denosumab group compared to placebo.
- Bone biopsy histomorphometry: Bone histomorphometry results raise concerns about the degree of bone remodeling suppression. The denosumab group had markedly

suppressed osteoclast and osteoblast counts compared to placebo and alendronate. Dynamic bone formation parameters such as activation frequency, bone formation rate and mineralizing surface were also markedly suppressed. This raises a concern that with long term use, suppression of bone remodeling may lead to complications such as delayed fracture healing, ONJ, or atypical fracture.

- Hypocalcemia: Hypocalcemia is a known class effect of antiresorptive drugs. Denosumab-induced hypocalcemia appears to be transient (nadir at day 8-11) with spontaneous resolution without any serious sequelae observed in this study. Outside of the controlled clinical trial environment, more patients may experience hypocalcemia. The Applicant has proposed hypocalcemia being a contraindication and in the Warnings and Precautions section of the label.
- ONJ: No cases of ONJ have been positively adjuducated in the PMO and Hormone Ablation trials under review. However, at least one confirmed case of ONJ has been reported in other trials conducted by the Applicant in patients with multiple myeloma and metastatic cancer.
- Cardiovascular: In the entire ISS population, cardiovascular AEs were similarly distributed between the two groups. Adjudicated serious cardiovascular events were similar between the two treatment groups in trials 20030216 and 20040135. No differences were found in aortic calcification scores at 3 years between treatment arms.
- Clinical laboratory evaluation: There were no clinically relevant changes seen in the laboratory safety parameters. There was no indication that treatment with denosumab 60mg Q6M SC led to decreases in renal or hepatic function.

6 APPENDICES

Appendix 1

Approval History of Monoclonal Antibodies and Antibody Fusion Proteins

Product	Description	Indication	Date Appr	Safety Actions (Boxed Warnings)
Therapeutic agents				
Simponi golimumab	IgG1 mAb to tumor necrosis factor alpha (TNFα)	treatment of: severely active rheumatoid arthritis; active psoriatic arthritis; active ankylosing spondylitis	2009	BW = risk of serious infections
Arcalyst rilonacept	fusion protein of IgG1 Fc and ligand binding domains of interleukin-1 receptor component and interleukin-1 receptor accessory protein	treatment of cryopyrin-associated periodic syndromes (CAPS), including familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS)	2008	
Cimzia certolizumab pegol	FAb' fragment to tumor necrosis factor alpha (TNFα) conjugated to polyethylene glycol	treatment of moderate to severely active Crohn's disease treatment of moderate to severely active rheumatoid arthritis	2008	BW = risk of serious infection, tuberculosis, invasive fungal and other opportunistic infections 2008: FDA Alert: histoplasmosis and other invasive fungal diseases
Soliris eculizuman	IgG2/4 mAb to complement protein C5	treatment of paroxysmal nocturnal hemoglobinuria to reduce hemolysis	2007	BW = serious meningococcal infections (medguide)
Lucentis ranibizumab	IgG1 mAb fragment to human vascular endothelial growth factor A (VEGF-A)	treatment of neovascular (wet) age-related macular degeneration [intravitreal injection]	2006	
Vectibix panitumumab	human IgG2 mAb to human epidermal growth factor receptor	treatment of EGFR-expressing metastatic colorectal Ca	2006	BW = dermatologic toxicity; severe infusion reactions
Orencia abatacept	fusion protein of IgG1 Fc and human T-lymphocute associated antigen 4 (CTLA-4)	treatment of moderate to severely active rheumatoid arthritis; juvenile idiopathic arthritis	2005	
Avastin bevacizumab	IgG1 to vascular endothelial growth factor	treatment of metastatic Ca of colon or rectum; non-squamous small cell lung Ca; metastatic breast Ca; glioblastoma	2004	BW = GI perforations; wound healing complications; hemorrhage

Product	Description	Indication	Date Appr	Safety Actions (Boxed Warnings)
Erbitux cetuximab	chimeric human/murine mAb to epidermal growth factor receptor	treatment of EGFR expressing metastatic colorectal cancer; advanced squamous cell carcinoma of the head and neck	2004	BW = severe infusion reactions 3/2006 new BW = cardiopulmonary arrest/sudden death
Tysabri natalizumab	IgG4 against α4 family of integrins on all leukocytes except neutrophils	treatment of relapsing forms of multiple sclerosis; treatment of Crohn's disease	2004	2006: new BW = progressive multifocal leukoencephalopathy
Amevive alefacept	fusion protein of IgG1 Fc and CD2 binding portion of human leukocyte function antigen 3 (LFA-3)	treatment of moderate to severe plaque psoriasis	2003	
Bexxar tositumomab	murine mAb to CD20 covalently linked to Iodine-131	radioinmmunotherapeutic agent for patients with CD20 positive follicular non-Hodgkins lymphoma	2003	BW = hypersensitivity reaction including anaphylaxis; prolonged and severe cytopenia
Raptiva efalizumab	IgG1 mAb to CD11a (leukocyte function antigen-1)	treatment of chronic moderate to severe plaque psoriasis	2003	2008: new BW = risk of serious infections; REMS 2009: new BW = progressive multifocal leukoencephalopathy 2009: Withdrawn from the market
Xolair omalizumab	IgG1 mAB to IgE	for patients with moderate to severe persistent asthma who have positive skin test or reactivity to a perennial aeroallergen	2003	2/2007: new BW = anaphylaxis
Humira adalimumab	IgG1 mAb to tumor necrosis factor alpha (TNFα)	treatment of moderate to severely active rheumatoid arthritis; juvenile idiopathic arthritis; psoriatic arthritis; ankylosing spondylitis; Crohn's disease; plaque psoriasis	2002	BW = risk of infections, tuberculosis 2008: FDA Alert: histoplasmosis and other invasive fungal diseases
Zevalin ibritumomab	IgG1 mAB to CD20, covalently bound to linker-chelator tiuxetan	for treatment of relapsed or refractory B-cell non-Hodgkin's lymphoma	2002	BW = fatal infusion reactions; prolonged and severe cytopenia

Product	Description	Indication	Date Appr	Safety Actions (Boxed Warnings)
Campath alemtuzumab	Ab to CD52 (cell surface antigen), expressed on B and T lymphocytes, NK cells, monocytes, macrophages and male reproductive tissue	treatment of B-cell CLL	2001	BW = hematologic toxicity; infusion reactions; opportunistic infections
Mylotarg gemtuzumab ozogamicin	IgG4 to CD33 (adhesion protein on cell surface of leukemic blasts and immature myelomonocytic cells) conjugated with cytotoxic antibiotic calicheamicin	treatment of CD33 positive acute myeloid leukemia	2000	BW = myelosuppression; 2001: new BW = hypersensitivity reactions including anaphylaxis, pulmonary events 2001: new BW = hepatotoxicity
Enbrel etanercept	fusion protein of IgG1 Fc and ligand-binding domain of tumor necrosis factor receptor (TNFR)	treatment of moderate to severely active rheumatoid arthritis	1998	2008: conversion to medguide 2008: FDA Alert: histoplasmosis and other invasive fungal diseases
Herceptin trastuzumab	IgG1 mAb to human epidermal growth factor receptor2 (HER2)	metastatic breast Ca overexpressing HER2	1998	BW = cardiomyopathy 2002 new BW = infusion reactions, anaphylaxis, pulmonary toxicity
Remicade infliximab	IgG1 mAb to tumor necrosis factor alpha (TNFα)	treatment of moderate to severely active, or fistualizing Crohn's disease	1998	2002: new BW = risk of serious infection - tuberculosis, invasive fungal infections or other opportunistic infections 2006: new BW = hepatosplenic T-cell lymphoma 2008: FDA Alert: histoplasmosis and other invasive fungal diseases

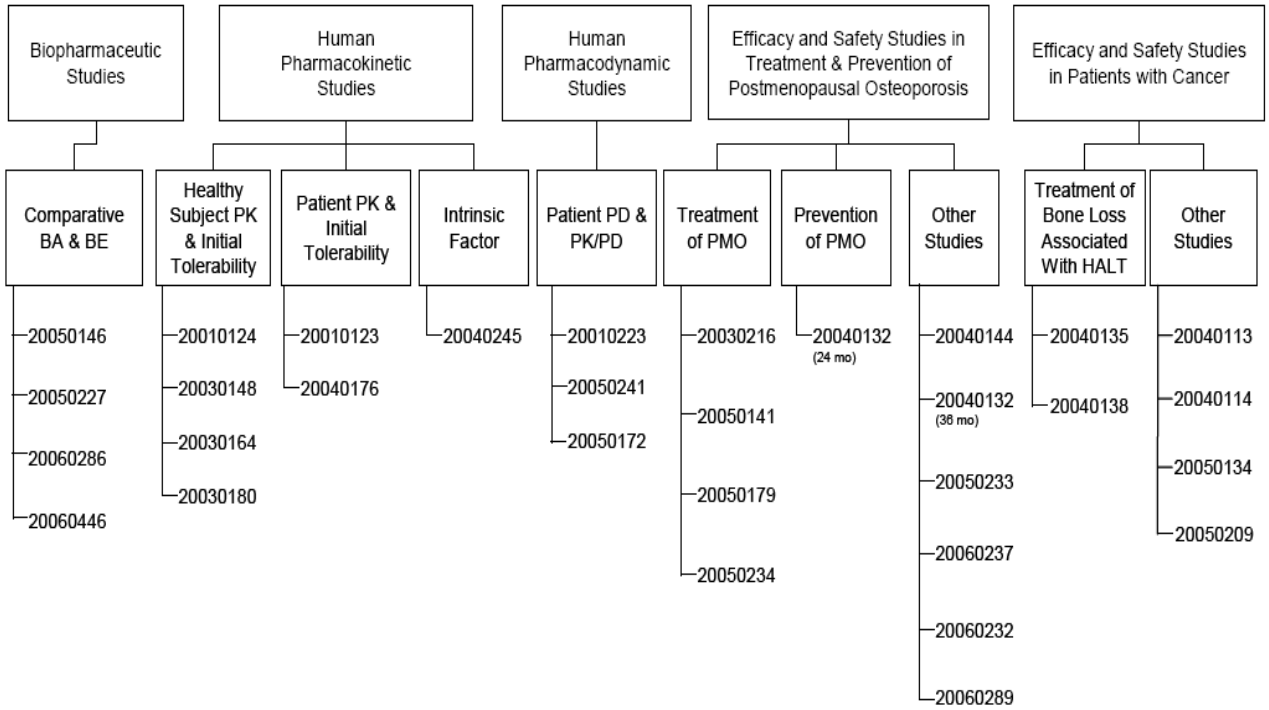
Product	Description	Indication	Date Appr	Safety Actions (Boxed Warnings)
Simulect basiliximab	IgG1 mAb to IL-2Ra (CD25)	for prophylaxis of acute organ rejection in renal transplant recipients	1998	BW = immunosuppressive therapy
Synagis palivizumab	IgG1 mAb to respiratory syncytial virus	prevention of serious lower respiratory tract disease caused by RSV	1998	
Rituxan rituximab	chimeric human/murine mAb to CD20 Ag on B lymphocytes	for treatment of relapsed or refractory CD20 positive B-cell non-Hodgkin's lymphoma	1997	2002: new BW = fatal infusion reactions; tumor lysis syndrome; and severe mucocutaneous reactions with fatal outcome
Reopro abciximab	Fab fragment of chimeric human/murine mAb 7E3 inhibiting platelet aggregation	as adjunct to PTCA intervention for the prevention of cardiac ischemic complications	1993	
Orthoclone OKT3 muromonab-CD3	murine mAb to CD3 (surface Ag on T-lymphocytes)	treatment of renal, steroid resistant cardiac or hepatic allograft rejection	1992	
Zenapax daclizumab	IgG1 mAb to alpha subunit of IL-2 receptor on T cells	for prophylaxis of acute organ rejection in renal transplant recipients	1997	BW = immunosuppressive therapy
Imaging Agents				
Neutrospec	murine mAb to CD15 in kit for technetium (99m Tc) fanolesomab neutrospec	diagnostic imaging agent in patients with signs and symptoms of appendicitis	2004	
Myoscint imciromab pentetate	FAb to myosin bound to diethyletriaminepentaacetic acid (DTPA) and conjugated with Indium In111	diagnostic imaging agent to detect presence of myocardial injury	1996	
Prostascint capromab pendetide	murine mAb to prostate specific membrane antigen, conjugated to glycyl-tyrosyl-(N-diethyletriaminepentaacetic acid)-lysine hydrochloride (GYK-DTPA-HCL) and Indium In111	diagnostic imaging agent for prostate cancer at high risk of lymph node metastases	1996	

Product	Description	Indication	Date Appr	Safety Actions (Boxed Warnings)
Verluma nofetumomab	Fab fragment of murine monoclonal antibody NR-LU-10 in kit for technetium (99m Tc) nofetumomab merpentan	diagnostic imaging agent – for detection of extensive stage small cell lung Ca	1996	

Appendix 2

Overview of Denosumab Clinical Studies

Figure 7. Organization of the Denosumab Clinical Studies in the Initial BLA Submission



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

Note: Prevention of PMO is not a proposed indication for the EU; thus, Study 20040132 is included as a supportive efficacy and safety study only for the EU.

Source: Section 2.5 Clinical Overview, Figure 2, page 27 of 111.

A brief summary of each of these clinical studies is provided below in Table 36.

Table 36: Listing of All Clinical Studies

Study Protocol number	Study Design	Treatment (dose)	Number of subjects/population	Study Duration
Comparative Bioavailability and Bioequivalence Studies				
20050146	Phase 1, rand, open-label, single-dose	denosumab 60 mg SC	**N=148** Healthy volunteers	4 months
20050227	Phase 1, rand, open-label, single-dose	denosumab 1 mg/kg SC	**N=122** Healthy volunteers	4 months
20060286	Phase 1, rand, open-label, single-dose	denosumab 60 mg SC	**N=116** Healthy volunteers	4 months
20060446	Phase 1, rand, open-label, single-dose	denosumab 120 mg SC	**N=116** Healthy volunteers	4.5 months
Healthy Subject PK and Initial Tolerability Studies				
20010124	Phase 1, rand, DB, PC, single- and multiple-dose	Single dose: denosumab (0.01, 0.03, 0.1, 0.3, 1.0, 3 mg/kg, placebo PLA] SC) Multiple dose: (0.1 mg/kg, placebo, SC)	**N=105** Healthy PMP women age 40-70 y	6-8 months
20030148	Phase 1, rand, blinded, PC, single-dose	denosumab (0.1, 0.3, 1.0, 3 mg/kg, PLA, SC)	**N=51** Healthy men, age≥ 50 years	4-9 months
20030164	Phase 1, rand, DB, PC, single-dose	denosumab (0.03, 0.1, 0.3, 1.0, 3 mg/kg, PLA SC)	**N=45** PMP Japanese women 40-64 yr	4-9 months
20030180	Phase 1, rand, blinded, PC, single-dose	denosumab (0.03, 0.1, 0.3, 1.0, 3 mg/kg, PLA SC)	**N=46** Healthy PMP women	4-9 months
Patient PK and Initial Tolerability Studies				
20010123	Phase 1, rand, DB, active-controlled, double-dummy (DD), single-dose	denosumab (0.1, 0.3, 1.0, 3 mg/kg SC, plus PLA IV pamidronate) or pamidronate 90 mg IV plus PLA for denos. SC	**N=54** Men/women with multiple myeloma or breast CA	3 months
20040176	Phase 1, open-label, dose ascending, single- and multiple-dose	Single dose: denosumab 60 or 180 mg SC Multiple dose: 180 mg denosumab Q4W SC	**N=19** Japanese women w/ breast cancer w/bone mets, ECOG ≤ 2	3-5 months
Intrinsic Factor PK Study				
20040245	Phase 1, open-label, single-dose	denosumab 60 mg SC	**N=55** Men/women with normal and impaired renal function	4 months
Patient PD and PK/PD Studies				
20010223	Phase 2, rand, DB, placebo and active-controlled dose-finding	DB: denosumab SC (q3M [6, 14, or 30 mg] or Q6M [14, 60, 100, or 210 mg] or PLA Active control: alendronate (ALN) 70 mg QW po	**N=412** PMP with low BMD (-4.0 ≤ T-score ≤ -1.8 LS or -3.5 ≤ T-score ≤ -1.8 TH or FN)	48 months
20050241	Phase 1, rand, open-label, single-dose	denosumab 15 or 60 mg SC or ALN 70 mg po	**N=20** PMP who have received ALN (70 mg QW or equiv) for ≥ 1 year, -4 ≤ T-score ≤ -1 LS or TH	6 months
20050172	Phase 2, rand, DB,	denosumab 14, 60, or 100	**N=226**	12 months

Study Protocol number	Study Design	Treatment (dose)	Number of subjects/population	Study Duration
	PC, dose response	mg or PLA SC, Q6M x 2 doses	Japenese women with PMO (-4.0 ≤ T-score ≤ -2.5 LS or -3.5 ≤ T-score ≤ -2.5 TH or FN)	
Postmenopausal Osteoporosis: Treatment				
20030216	Phase 3, rand, DB, placebo- controlled	denosumab 60 mg or PLA SC, Q6M x 6 doses	**N= 7868** PMP (-4.0 ≤ T-score < -2.5 LS, TH or both) 60 subjects excluded due to GCP noncompliance (3886 D, 3876 PLA)	36 months
20050141	Phase 3, rand, DB, active- controlled, DD, parallel group	denosumab 60 mg SC Q6M (x 2 doses) plus PLA ALN po QW Or ALN 70 mg po QW plus PLA for denosumab SC Q6M (x 2 doses)	**N=1189** PMP with low BMD (T-score ≤ -2.0 LS or TH)	12 months
20050179	Phase 2, rand, DB, DD, placebo and active- controlled	denosumab 60 mg SC Q6M (x 2 doses) plus PLA ALN po QW Or ALN 70 mg po Qweek plus placebo for denosumab SC Q6M (x 2 doses) Or PLA denosumab SC Q6M (2 doses) plus PLA ALN Qweek	**N=247** PMP with low BMD (-3.0 ≤ T-score ≤ -2.0 LS or TH	12 months
20050234	Phase 3b, rand, DB, active-controlled, DD, parallel group	denosumab 60 mg SC Q6M (x 2 doses) plus PLA ALN po QW Or ALN 70 mg po QW plus placebo for denosumab SC Q6M (x 2 doses)	**N=504** Women with PMO (-4.0 ≤ T-score ≤ 2.0 LS or TH) who received ALN 70 mg QW or equiv for ≥ 6 mo before screening	12 months
Postmenopausal Osteoporosis: Prevention				
20040132	Phase 3, rand, DB, placebo-controlled	denosumab 60 mg or PLA SC, Q6M x 4 doses	**N=332** PMP with low BMD (-2.5 < T-score < -1.0 at LS)	24 month treatment period + 24 mos F/U (off-therapy)
Postmenopausal Osteoporosis: Other Studies				
20040144	Phase 2, rand, DB, PC	denosumab 60 or 180 mg SC Q6M (2 doses)	**N= 227** Men/women with RA on MTX	24 months
20040132	Phase 3, rand, DB, PC	No treatment (follow-up safety study after drug discontinuation)	**N= 256** PMP with low BMD (-2.5 < T-score < -1.0 at LS)	24 mos tx period + 24 mos off-tx extension (ongoing)
20050233	Phase 3, open-label single-arm extension study	denosumab 60 mg SC Q6M (8 doses)	**N=200** PMP w/ low BMD who completed study 20010223	48 months (ongoing)
20060237	Phase 3b, rand, open-label	denosamab 60 mg SC Q6M (2 doses) from either PFS or a vial	**N=311** PMP with low BMD who completed study 20050141	12 months (ongoing)
20060232	Phase 3b, rand, crossover, open-label	denosumab 60 mg SC (12 months [2 doses]) followed by ALN 70 mg QW (12 months) or ALN followed by	**N=250** PMP w/ low BMD (-4.0 ≤ T-score ≤ -2.0 at LS, TH, or FN)	24 months (ongoing)

Study Protocol number	Study Design	Treatment (dose)	Number of subjects/population	Study Duration
		denosumab		
20060289	Phase 3, open-label, single-arm extension	denosumab 60 mg SC Q6M (4 doses)	**N= 4900 to 5600** Women with PMO who completed 20030216	24 months (ongoing)
Cancer Studies: Treatment of Bone Loss Associated with Hormone Ablation				
20040135	Phase 3, rand, DB, PC	denosumab 60 mg or PLA SC Q6M (4 doses)	**N=252** Women with non-metastatic breast CA on aromatase inhibitor with low BMD (-2.5 ≤ T-score ≤ -1.0 at LS, FN or TH	24 months tx period + 24 month f/u
20040138	Phase 3, rand, DB, PC	denosumab 60 mg or PLA SC Q6M (6 doses)	**N=1468** Men with nonmetastatic prostate CA on androgen-deprivation tx excluding subjects w/ T score < -4.0 at LS, TH, FN For those < 70 yrs (but not those ≥ 70 yrs), history of osteoporotic fracture or BMD T-score < -1.0 at LS, TH, FN.	36 months tx period + 24 month safety follow-up or 2-year ext study
Cancer Studies: Other Studies				
20040113	Phase 2, rand, partially blinded, active control, parallel group	denosumab (30, 120, or 180 mg Q4W; or 60 or 180 mg Q12W SC) or Commercially available bisphosphonate Q4W IV	**N=255** Women with advanced Breast CA w/ bone mets without prior IV bisphosphonate tx	13 months
20040114	Phase 2, rand, open-label, active control	denosumab (180 mg Q4W or Q12W SC) or Commercially available bisphosphonate Q4W IV	**N=111** Men/women w/ solid tumors (except lung) or multiple myeloma receiving IV bisphosphon. for bone mets	6 month tx period + 24 month tx extension + 8 mos FU
20050134	Phase 2, open-label	denosumab 120 mg SC on days 1, 8, and 15 of cycle 1 and Day 1 of every 28-day cycle thereafter	**N=96** Men/Women with relapsed or plateau-phase multiple myeloma	Until withdrawal or progression (ongoing)
20050209	Phase 3, rand, DB, PC	denosumab 60 mg or PLA SC Q6M (min of 2 doses)	**N=2800** PMP women with nonmetastatic breast CA on aromatase inh bitor therapy	Until planned # of fractures observed (ongoing)

PLA = placebo; ALN = alendronate; DB = double-blind; PC = placebo-controlled; PMP = postmenopausal; CA = cancer, FU = follow-up; LS = lumbar spine; TH = total hip; FN = femoral neck; RA = rheumatoid arthritis; MTX = methotrexate.
Source: Initial BLA Submission, Section 2.5, Table 5.2 - Tabular Listing of All Clinical Studies, p. 1-12.