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Subject: Review of Denosumab Post-Marketing Study Information
from Amgen's Complete Response, 1/25/2010:

- Complete Response to Action Letter of 16 Oct 2009 and Related Communications, Denosumab (AMG 162)
- Feasibility Assessment for Denosumab Global Postmarketing Safety Observational Study 20090522 (Findings of Feasibility Study; and Protocol 20090521, "Feasibility Study" or "Phase A")
- Denosumab Global Safety Assessment Among Women With Postmenopausal Osteoporosis (PMO) Using Multiple Observational Databases, Amgen Protocol 20090522 ("Phase B")
- Prolia™ Post Marketing Active Safety Surveillance Program for Soliciting Adverse Events of Special Interest in the United States, Amgen Protocol 20090601 ("Healthcare Provider Survey")
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Drug Name(s): Denosumab (Prolia™) (AMG 162)

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EXECUTIVE SUMMARY

Denosumab/ Prolia™, a monoclonal antibody, inhibits osteoclasts. Its proposed indication is for treatment and prevention of osteoporosis in postmenopausal women. It has a post-marketing requirements in postmenopausal women for a safety study, 20090521 (feasibility) and 20090521 (Observational Databases study) and a healthcare professional survey (20090601).

The sources for the safety study data are four observational databases (US Medicare, United HealthCare, Kaiser Permanente in all of California, and the Nordic national health registries (Denmark, Finland, Sweden, and Norway).

The adverse events of special interest (AESI) for observation in these databases are:

- Osteonecrosis of the jaw (ONJ)
- Atypical fracture
- Fracture healing complications
- Hypocalcemia leading to hospitalization or emergency room (ER) visit
- Infections leading to hospitalization or ER visit or parenteral anti-infective administration
- Dermatologic AEs leading to hospitalization or ER visit
- Acute pancreatitis leading to hospitalization
- Hypersensitivity reactions leading to hospitalization or ER visit
- New primary malignancy

Amgen responded positively to FDA's requests for changes to their PMR; however, there are several estimates in the sample size calculations for the Observational Databases Study (20090522). Biostatistics is reviewing these issues. Biostatistics' comments should be reviewed.

DEPI recommendations for the Observational Databases study (20090522):

1. Validation of denosumab exposures shortly after denosumab marketing because nonspecific or temporary codes for drug use are used by most new drugs.
2. Report the proportion of women ≥ 55 years old with PMO and compare for each of the data systems to the 40% reported in the literature for women ≥ 65 years old.
3. Review the comments from Biostatistics regarding the sample size and power calculations.
 - a. The AESI incidence rates for the data systems are much higher than those found in the literature.
 - b. The estimates of the denosumab-exposed population as a proportion of women ≥ 65 years old are lower (13.8 – 30.9%) than the 40% reported in the literature. This might be due to not including osteoporosis medication codes for identifying osteoporosis patients in the Feasibility study. Osteoporosis medication codes will be used in the algorithm for the Observational Databases Study (20090522).
 - c. Since this is an observational study in claims and registry databases, the total number of denosumab exposures cannot be influenced.
 - d. Pulling cases and controls from the same population will reduce bias.
4. State in the protocol that 100% of the Medicare databases will be used for the study (Section 4.3 still states a 5% random sample, page 25).
5. Define the "other osteoporosis medications" for the comparison group (Section 4.4, page 25).
6. Address how missing data will be handled.

One minor recommendation for the ONJ questionnaire of the Surveillance Program: add diabetes to the list of ONJ risk factors on the questionnaire about ONJ.

1 BACKGROUND/HISTORY

Denosumab/ Prolia™, is a monoclonal antibody that inhibits osteoclasts. The proposed indication is for treatment of postmenopausal women with osteoporosis at high risk for fracture.

DEPI provided comments dated November 25, 2009 on two of Amgen's post-marketing requirements: a long-term observational study in administrative databases (Feasibility Protocol 20090521 & Study Protocol 20090522) and a long-term surveillance study (20090601) in postmenopausal women on safety issues including infections and over-suppression of bone turnover.

This memorandum is a review of Amgen's findings from the Feasibility study and their revisions of the safety study in observational databases (20090521 and 20090522) and their safety surveillance study (20090601).

2 REVIEW METHODS AND MATERIALS

Review of Denosumab Post-Marketing Study Information (materials) from Amgen's Complete Response, 1/25/2010:

- Complete Response to Action Letter of 16 Oct 2009 and Related Communications, Denosumab (AMG 162) – Reviewed in Section 3.1
- Feasibility Assessment for Denosumab Global Postmarketing Safety Observational Study 20090522 (Findings of Feasibility Study; and Protocol 20090521, "Feasibility Study" or "Phase A")
- Denosumab Global Safety Assessment Among Women With Postmenopausal Osteoporosis (PMO) Using Multiple Observational Databases, Amgen Protocol 20090522 ("Phase B")
- Prolia™ Post Marketing Active Safety Surveillance Program for Soliciting Adverse Events of Special Interest in the United States, Amgen Protocol 20090601 ("Healthcare Provider Survey")

2.1 SUMMARY OF AMGEN'S RESPONSE TO PRIOR DEPI RECOMMENDATIONS

In the "Complete Response to Action Letter of 16 Oct 2009 and Related Communications, Denosumab (AMG 162)", Amgen agreed to all of FDA's requests or explained their approach regarding the two post-marketing safety requirements (Observational Databases Safety Study (20090522) and the Surveillance Program (20090601)) in the Complete Response Letter, October 16, 2009. :

Amgen completed a feasibility study (20090521) for the Observational Databases Safety Study (20090522) which is reviewed in section 3 below. Highlights are:

1. Methods for assessment of exposure to denosumab are described.
2. Pancreatitis was added as an adverse event of special interest (AESI).
3. Infection AESIs leading to hospitalizations or emergency room visits were added.
4. Feasibility study (20090521) was completed before the databases study (20090522).
5. Information on deaths, drop-out rates, and missing data was provided.

Amgen agreed to the following regarding the observational databases safety study (20090522):

1. Pancreatitis was added as an AESI.
2. The study duration was extended to 10 years.
3. Specific objectives for each database were identified:
 - a. Determine incidence rates of AESIs in three groups of women with postmenopausal osteoporosis (PMO):
 - i. exposed to denosumab,
 - ii. exposed to other osteoporosis medications, and
 - iii. not exposed to osteoporosis medications.
 - b. Describe the characteristics, clinical features, and AESI risk factors for each exposure groups of PMO women (denosumab, other osteoporosis medications, not exposed to osteoporosis medications).
 - c. Compare incidence of the AESIs in the three exposure groups of PMO women (denosumab, other osteoporosis medications, not exposed to osteoporosis medications).
 - d. Describe incidence rates of AESIs in PMO women.
 - e. Describe the denosumab utilization patterns for PMO.
 - f. Describe the denosumab utilization patterns for unapproved indications.

Amgen agreed to the following regarding the FDA proposed healthcare provider survey, renamed to the "Prolia™ Post marketing Active Safety Surveillance Program for Soliciting Adverse Events of Special Interest in the United States", referred to as the "Active Safety Surveillance Program" (20090601):

1. Regarding the minimum effective response rate in capturing AESIs, Amgen proposed their "Active Safety Surveillance Program". Amgen will notify providers, provide questionnaires, collect the clinical data, and promote the program for 10 years. Amgen did not set a minimum effective response rate because the AEs have a broad range of frequencies and the acceptance and use of denosumab/Prolia is unknown; therefore, Amgen will adapt the program annually based on information from their proposed annual survey of providers. This program is reviewed in section 4.
2. In addition to a web-based provider survey of denosumab use, Amgen will provide a paper-based option. The labeling will include information on the surveillance program and the providers will be reminded quarterly to solicit AESI information from their Prolia™ patients. The survey questionnaire will not be attached to the product as suggested by the review division.
3. Instead of survey reminders to providers every 6 months, Amgen will remind providers every 3 months to solicit AESI information from their Prolia™ patients.
4. Complete AESI information will be solicited by the questionnaires similar to the MedWatch reports. Providers will not need to submit a MedWatch report since Amgen will provide FDA with the information.
5. As requested, Amgen will include additional AESIs on suppression of bone turnover in the survey (atypical fractures, delayed fracture healing, and osteonecrosis of the jaw (ONJ)).
6. Follow-up questionnaires designed for each AESI will be included in the Active Safety Surveillance Program
7. The Active Safety Surveillance Program was extended to 10 years.

Amgen agreed to the following November 25, 2009 DEPI recommendations (listed in the Appendix):

1. The Feasibility study (20090521) reported an analysis for pegfilgrastim (Neulasta) which demonstrated the feasibility of capturing denosumab exposures.
2. The Feasibility study (20090521) provided an algorithm for mapping ICD-9 to ICD-10 codes.
3. Drop-out rates, missing values, and codes for death were described.
4. Timeliness and completeness of medical chart reviews are described in the Feasibility study (20090521).
5. A pilot study of 100% of the Medicare database resulted in 1) utilizing 100% of the Medicare database for the safety study (20090522), 2) an algorithm for identifying all women with PMO (a diagnosis of osteoporosis, or fracture at a site associated with osteoporotic fractures (vertebrae, hip, or radius/ulna), or an osteoporosis medication), and 3) validation of medical chart review (supported by three published studies)
6. All AESIs requested by FDA are included in the observational databases study and the Surveillance study.
7. The Feasibility study and the Observational Databases Study were expanded to include all postmenopausal women (≥ 55 years). The background incidence rates for the AESIs were reported for postmenopausal women (≥ 65 years) and PMO women (≥ 65 years); the ≥ 65 years of age were used to be consistent with the Medicare data for the feasibility study.
8. Power calculations are reported in the Feasibility study.
9. The completed Feasibility study report accompanied the revised protocol for the Observational Databases Safety Study.
10. The Observational Databases Safety Study was revised to include all patients exposed to denosumab during the study period.
11. Paper questionnaires will be provided to providers as noted in the paragraph above on the Surveillance Study (20090601).
12. Amgen will follow-up on the surveillance data collected to collect missing data, additional medical data, and outcome.
13. The follow-up periods for both the Observational Databases Safety Study and the Surveillance Study were extended to 10 years.
14. Amgen clarified:
 - a. The differences between the numbers of PMO women and estimated denosumab users were explained as a change in assumptions: First, the Medicare sample of 5% was increased to 100%. Second, the osteoporosis prevalence rates of 7-10% was increased to 40-50% to reflect the prevalence in women ≥ 65 years, and third, the denosumab market uptake of 10% was revised down to 5% based on discussions with FDA.
 - b. "Significant risk" was described as three levels and levels 1 and 2 will be reported to FDA: 1. a new critical safety issue of high patient health risk, 2. a new or worsening serious safety issue of moderate health risk.
 - c. Timeframe for reporting risks to FDA: level 1 is reported within one month, level 2 is reported within 3 months.
 - d. Index dates for PMO-naïve patients were initially random and were revised to the date denosumab becomes available for PMO diagnosed prior to its availability or the date of PMO diagnosis for those diagnosed after denosumab availability.
 - e. Specific objectives for each database are described above in paragraph on the observational databases safety study (20090522).
 - f. The terms "aggregated report" and "appropriate context" were clarified. An aggregated report of US AESIs will be sent annually and will be sent along with global AESI data in the PSUR report according to the PSUR reporting schedule. A final report will be submitted 6 months after the completion of the surveillance

study. The Surveillance Study will generate safety signals which will be interpreted in the context of denosumab clinical studies, epidemiological studies (the observational databases safety study), background incidence rates, and other literature to address the limitations associated with spontaneous reporting systems (under reporting, lack of specificity of cases, reporting biases, lack of denominators, lack of comparison groups, etc).

3 RESULTS OF FEASIBILITY STUDY (PROTOCOL 20090521)

The Feasibility Study (20090521) protocol was reviewed in the November 25, 2009 DEPI memorandum and is summarized in Table 1 of the Appendices

The following sections summarize and comment on the feasibility study results. Detailed tables are presented in the appendix.

3.1 AESI INCIDENCE RATES

Background AESI incidence rates from published literature were summarized (Table 4-1, page 25 of the Feasibility Assessment):

Table 4-1. Summary of Background Incidence Rates for the Adverse Events of Special Interest (page 25 of the Feasibility report)

Adverse Event of Special Interest	Source	Background Incidence Rate (per 100,000 Person-years)
ONJ	Sambrook et al, 2006	1
Atypical fracture	N/A	Unknown
Fracture healing complications	Amgen analysis of data from Kaiser Permanente data system among all women with PMO \geq 65 years old	95.5
Hypocalcemia leading to Hospitalization	Amgen analysis of clinical trial data in placebo control group (see Section 4.4)	9
Serious infection	Smitten et al, 2008	1249.7
Serious dermatologic adverse events	Chan et al, 1990	0.4
Pancreatitis	Fagenholz et al, 2007a	130
Serious hypersensitivity	Peng and Jick, 2004	8.4
New primary malignancy	Horner et al, 2009	1668

Fracture healing complications were reported as low as 7.8 per 100,000 person-years but cortical thickening could not be assessed. The proportion of patients with cortical thickening was thought to be very small.

3.2 DATA SYSTEMS

The data systems for the observational safety study (20090522) are the US Medicare, United HealthCare, California Kaiser Permanente (northern and southern) and the Nordic national health registries (Denmark, Finland, Sweden, and Norway). Summaries of information sought by DEPI

~~Table 5-1 (page 44)~~ and **Table 5-2** (pages 42-43) of the Feasibility report and are copied in the Appendix.

Amgen reported that all of the data systems were suitable for assessment of each of the AESIs. However, subtrochanteric and diaphyseal fractures for the atypical fracture AESI are best assessed in the Kaiser data system and the Nordic countries which have electronic radiographic reports.

For the characteristics of the data systems, the representativeness, number of women ≥ 65 years old enrolled, and the estimated exposure to denosumab are in the partial Table 5-2 from the Feasibility report below (and the Appendix). For the other characteristics, Amgen reported that each of the data systems have:

1. access to medical charts,
2. access to hospital records,
3. access to outpatient/clinic records (partially in the Nordic countries),
4. access to prescription data (only to Part B in Medicare which is pending),
5. reason for data collection (Medicare and UHC are for reimbursement whereas Kaiser and Nordic countries are for health care),
6. average length of follow-up (shortest follow-up is 2-3 years in UHC),
7. annual drop-out rate (highest is 15-20% in UHC),
8. data quality (clinical information is electronic in Kaiser and the Nordic countries but only billable transactions are available in Medicare and UHC), and
9. lag time for data availability (the longest is 14-18 months for Medicare).

Table 5-2. Characteristics of the 4 Data Systems to Be Used in Study 20090522, in part (page 42 of the Feasibility report, see complete table in Appendix)

Assessment Items	US Medicare	Kaiser Permanente	United HealthCare	Nordic National Registries
Representativeness	Population-based capture of US patients ≥ 65 years old	Members are part of the largest US integrated group-model nonprofit health care system; those who enroll in Medicare Advantage or Medicare supplemental programs are captured	Members are predominantly from employer-based groups but Medicaid and Medicare populations represented	Population-based capture of all residents
Number of women enrolled ≥ 65 years old	20.6 million	450,000	207,000	2.4 million
Estimated exposure (person-years) to denosumab in the first 5 years post denosumab launch (person-years)	927,000	20,250	9,315	108,000

3.3 ALGORITHMS DEVELOPED FOR THE OBSERVATIONAL STUDY (20090522)

3.3.1 Identification of Postmenopausal Women with Osteoporosis

Algorithms were developed to identify women with postmenopausal osteoporosis based on IC-9 for the US data systems or ICD-10 for the Nordic countries. The algorithms included any of the following criteria:

1. Diagnostic codes for osteoporosis: one inpatient code or two outpatient codes at least 30 days apart
2. Any osteoporosis medication code including bisphosphonates except those women who have a diagnostic code for a bone metastasis
3. Diagnostic codes for a fracture associated with osteoporosis (hip, spine, or radius/ulna): one inpatient code or one outpatient code with a surgical repair code or an outpatient claim for a closed spine fracture with a physician evaluation and management HCPCS code in the same claim (HCPCS = Healthcare Common Procedure Coding System)

3.3.2 Denosumab Exposure

Denosumab will be administered subcutaneously for PMO every 6 months by a healthcare professional, usually as an outpatient. Denosumab exposure will be assessed independent of the AESIs. The Medicare and UHC data systems will use CPT/HCPCS "J codes" to identify denosumab in the outpatient files where denosumab will most likely be found but also in the inpatient files. For the time immediately after denosumab launch, when non-specific or temporary HCPCS codes are used for newly approved drugs, Medicare will use other information on cost, indication, and diagnosis codes to identify denosumab exposure whereas UHC will use temporary HCPCS "C codes" in combination with National Drug Code (NDC) codes. Kaiser will use physician orders in the electronic medical record (EMR) and the Nordic countries will use their prescription databases which have data on the trade name, pharmaceutical form, strength, package size, number of packages and Anatomical Therapeutic Chemical classification (ATC) code.

Since denosumab is not yet on the market, the methodology of ascertaining exposure to Neulasta (pegfilgrastim) was tested in Medicare. Pegfilgrastim, a biologic G-CSF, is administered subcutaneously once per chemotherapy cycle, usually by a healthcare professional, to reduce infections associated with febrile neutropenia during chemotherapy with myelosuppressive drugs. The Feasibility Study in Medicare was successful in identifying pegfilgrastim including during the time after launch when temporary (J2505, C9119, and Q4053) HCPCS codes and non-specific (J3490 and J3590) medication codes were used for reimbursement.

3.3.3 Identifying Adverse Events of Special Interest (AESI)

Algorithms for AESI identification in observational databases were based on literature and Amgen-sponsored research. See Appendix B (pages 103-130) in Amgen's Feasibility report for the algorithms to identify the AESIs using ICD-9 and ICD-10 diagnostic codes. The cross-mappings of ICD-9 to ICD-10 codes are summarized in Appendix C (pages 132-143) of the Feasibility report. Sensitivity, specificity, and PPV test results of these AESI algorithms are summarized in Appendix E (pages 154-161), Tables E-1 through E-9. Biostatistics will review the statistical aspects.

For osteonecrosis of the jaw (ONJ), it is estimated that 90% of the "probable" cases of ONJ (classified as probable, possible or not ONJ) will be captured for those cases diagnosed prior to

the use of the ONJ specific ICD-9 code in late 2007. The PPV was 33% to 67% for the “probable” cases.

For atypical fractures, the Kaiser data system and certain regions of Denmark will include review of radiologic reports. Subtrochanteric and diaphyseal fractures will be identified from the diagnostic codes in Medicare and UHC systems however it will not be possible to identify the subgroup of atypical, non-traumatic fractures since these data systems do not have radiographic findings available electronically.

For fracture healing complications, which vary with the site of the fracture, patient demographics, comorbidities, and treatment or intervention type, the ICD-9 code for nonunion will be used in the algorithm.

Hypocalcemia codes will be used for hypocalcemia associated with hospitalization or ER visit. Secondary diagnoses of hypocalcemia, such as symptoms of hypocalcemia, and injections of calcium will be excluded from the algorithm for hypocalcemia since these more often reflect electrolyte abnormalities associated with underlying diseases..

Infections leading to hospitalization, ER visit, or the administration of parenteral anti-infective medication will be identified by using codes for the primary diagnosis of infection. Identifying a parenteral anti-infective will require a primary diagnosis of infection plus administration of a parenteral anti-infective in the same outpatient claim or record.

Dermatologic AEs leading to hospitalization or ER visit will be identified by using ICD codes of the primary diagnosis. AESI's will include bullous dermatoses, serious erythematous events, and other less severe dermatologic events. Erythema multiforme (EM), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN) have been validated in the literature.

Acute pancreatitis leading to hospitalization will be identified by using the primary diagnosis code which has been validated in the literature.

Hypersensitivity leading to hospitalization or ER visit will be identified by using the primary diagnosis code. Anaphylactic hypersensitivity has been validated in the literature and will be analyzed separately.

New primary malignancy will be identified using the primary diagnosis code. Non-melanoma skin cancer and those with a malignancy code reported in the 12 months previous to the AESI malignancy code will be excluded.

3.4 AESI CASE ASCERTAINMENT AND RESULTS

3.4.1 Background Rates

Incidence rates for each AESI were calculated for each data system. The number of cases, person years of follow-up, and the crude and age standardized incidence rates are presented in the Appendix in Tables 9-2 through 9-10.

~~3.4.2 By Proposed Data Resource~~

For this feasibility study the populations were women ≥ 65 years and the PMO subgroup in the women ≥ 65 years to be consistent with Medicare. The US databases (Medicare, Kaiser, and UHC) did not use osteoporosis medication as a criteria for inclusion in the osteoporosis cohort, also for consistency with Medicare since Part D pharmacy data was not available. As a result, the osteoporosis cohorts for the feasibility study are less than the 40% estimation based on bone mineral density screening reported in the literature. For the Nordic countries, only data from the Danish National Registries was used. Hypocalcemia data from northern Denmark was used because that area had laboratory data.

For the postmarketing denosumab study (20090522), the population will be in women ≥ 55 years (≥ 65 for Medicare). Women will be included in the osteoporosis cohort if they used an osteoporosis medication. The Nordic countries are expected to have access to laboratory data for confirmation of hypocalcemia.

AESI incidence rates were calculated for 5-year incremental age groups: 65-69, 70-74, 75-79, 80-84, and ≥ 85 years and they were age adjusted with the 2000 US female census data (0.25 for 65-69, 0.24 for 70-74, 0.21 for 75-79, 0.15 for 80-84, and 0.15 for ≥ 85 years). The tables for each AESI include the crude and age-standardized incidence rates.

Table 9-1 (proportion of women ≥ 65 years and women ≥ 65 years with PMO in each data system) and Tables 9-2 through 9-10 (AESI incidence rates for each data system) are included in the Appendix.

For ONJ, the age-adjusted incidence rates were higher in the PMO subgroup than in all the women ≥ 65 years (Table 9-2 in the Appendix). The algorithm is not highly specific for ONJ (PPV range 33-67%) so the incidence of ONJ is overestimated in these populations. Medical charts for ONJ cases will be reviewed for the Observational Database study (20090522).

For atypical fractures (non-traumatic subtrochanteric and diaphyseal femoral fractures), the age-adjusted incidence rates were higher in the PMO subgroup than in all the women ≥ 65 years (Table 9-3 in the Appendix). The algorithm is sensitive to but not specific to atypical fracture (few subtrochanteric or diaphyseal fractures are atypical hip fractures) so the incidence of these non-traumatic fractures is probably overestimated in these populations. Electronic radiologic reports will be reviewed for Kaiser and Denmark study participants.

For healing fracture complications (nonunion), the age-adjusted incidence rates were higher in the PMO subgroup than in all the women ≥ 65 years (Table 9-4 in the Appendix).

For hypocalcemia leading to hospitalization or ER visit, the age-adjusted incidence rates were generally higher in the PMO subgroup than in all the women ≥ 65 (Table 9-5 in the Appendix).

For infection leading to hospitalization, ER visit, or administration of parenteral anti-infective medication, the age-adjusted incidence rates of overall infections and skin infections were higher in the PMO subgroup than in all the women ≥ 65 years (Table 9-6 in the Appendix).

For dermatologic adverse events leading to hospitalization or ER visit, the age-adjusted incidence rates for overall dermatologic events were higher in the PMO subgroup than in all the women ≥ 65 years (Table 9-4 in the Appendix). For the bullous dermatoses and erythematous dermatoses (including SJS and TEN), the age-adjusted incidence rates were slightly higher in the PMO subgroup than in all the women ≥ 65 years (Table 9-7 in the Appendix).

For acute **pancreatitis** leading to hospitalization, the age-adjusted incidence rates were similar to or higher in the PMO subgroup than in all the women ≥ 65 years (Table 9-8 in the Appendix).

For hypersensitivity leading to hospitalization or ER visit, the age-adjusted incidence rates were higher, except in the Danish registry, in the PMO subgroup than in all the women ≥ 65 years (Table 9-9 in the Appendix). For anaphylaxis, the age-adjusted incidence rates were higher, except in Denmark, in the PMO subgroup than in all the women ≥ 65 years (Table 9-9 in the Appendix).

For new primary malignancy, the age-adjusted incidence rates were generally higher in the PMO subgroup than in all the women ≥ 65 years (Table 9-9 in the Appendix).

Summary table for incidence rates in proposed data resources (detail tables are 9-2 through 9-10 of the Appendix):

AESI		US Medicare	United HealthCare	Kaiser Perma- nente	Danish National Registry
ONJ	Women ≥65 years	18.5	36.0	12.1	11.6
	Women ≥65 years With PMO	30.1	45.2	18.5	26.2
Atypical Fractures	Women ≥65 years	95.4	451.4	150.2	204.6
	Women ≥65 years With PMO	187.8	2,325.0	402.9	506.9
Fracture Healing Complications	Women ≥65 years	68.4	134.7	45.2	12.8
	Women ≥65 years With PMO	316.0	489.8	95.5	21.0
Hypocalcemia	Women ≥65 years	6.3	20.5	4.3	0.7
	Women ≥65 years With PMO	11.9	36.8	4.2	0.0
Infections Leading to Hospitalization					
Overall	Women ≥65 years	5,222.8	10,185.2	4,020.7	3,079.9
	Women ≥65 years With PMO	8,471.4	13,431.3	4,714.0	3,617.4
Skin Infections	Women ≥65 years	718.3	1,259.9	709.8	314.6
	Women ≥65 years With PMO	984.0	1,610.8	771.0	326.7
Dermatologic AEs					
Overall	Women ≥65 years	200.9	208.0	107.4	27.5
	Women ≥65 years With PMO	249.0	248.3	120.9	26.1
Bullous Dermatoses	Women ≥65 years	3.9	4.7	1.8	8.0
	Women ≥65 years With PMO	4.0	2.9	2.0	10.4
SJS, TEN, Exfoliation conditions	Women ≥65 years	0.0	0.5	0.7	1.5
	Women ≥65 years With PMO	0.0	1.5	0.5	3.2
Acute Pancreatitis	Women ≥65 years	148.9	174.5	38.7	47.2
	Women ≥65 years With PMO	248.1	191.4	42.3	46.4
Hypersensitivity Leading to Hospitalization	Women ≥65 years	211.5	154.6	124.2	46.9
	Women ≥65 years With PMO	283.2	162.5	141.8	23.8
New Malignancy	Women ≥65 years	1,695.0	2,082.6	1,767.1	1,594.4
	Women ≥65 years With PMO	1,848.3	2,664.8	1,897.1	1,533.9

Amgen mentioned several factors that might impact the AESI incidence rates which are based on ICD codes. Since the exposed and comparator groups will be from the same data sources, these issues affecting coding should not bias comparisons within data systems. Factors possibly affecting AESI incidence rates:

- General factors affecting AESI rates:
 - Varying medical and coding practices influence the ICD codes such as possible more frequent use of codes which generate greater reimbursement in the Medicare and UHC systems compared to the Kaiser and Denmark systems which do not use the codes for reimbursement
 - Diagnoses based on ICD codes may vary between the data systems depending on the nature and purpose for data collection
 - Managed healthcare plans such as Kaiser may see patients in their clinics rather than in an ER and may manage patients as outpatients rather than hospitalize them
 - Differences in medical and coding practices between the Nordic countries and the US may affect coding of diagnoses and hospitalizations or ER visits
- Data resource-specific factors that may affect AESI rates:
 - Kaiser excluded cancer patients from their ONJ ascertainment (ONJ incidence is higher in cancer patients receiving IV bisphosphonates) which might have affected the lower ONJ incidence rate relative to the other data systems. Cancer patients will be excluded in the ONJ algorithm for all data systems in the Observational Databases study.
 - The exclusion of trauma in assessing the incidence of nontraumatic subtrochanteric and diaphyseal femoral fractures, the Medicare time frame for exclusion of trauma was more exclusive than the other data systems. This time period will be standardized for the algorithm in the Observational Databases study.
 - Hypocalcemia was verified by laboratory results in Denmark but not in the US data sources which might explain the lower incidence of hypocalcemia in Denmark.
 - Infusion or injection data were not available for the Danish cases of infection possibly leading to a lower incidence compared to the US data systems. Electronic medical records and pharmacy prescription databases will be used for parenteral anti-infective data for the Observational Databases study.
 - The lower incidence rate of dermatologic adverse events in Denmark and Kaiser may be due to less severe AEs being managed in the outpatient setting.
 - The lower hypersensitivity incidence rate in Denmark might be because two ICD-10 codes for hypersensitivity were not included in the algorithm. These codes will be used in the Observational Databases study.

3.5 SAMPLE SIZE

Sample size calculations were based on the incidence rates for women ≥ 65 years with PMO and on the assumption that

- 40% of women ≥ 65 years have osteoporosis (Cheng 2009¹, Dawson-Hughes 2010²),
- 50% of women with osteoporosis are receiving osteoporosis medication (Vik 2007³, Majumdar 2007⁴, Haussler 2007⁵, Krappweis 1999⁶, Bailey 2002⁷, Andrade 2003⁸, Feldstein 2003a⁹, Feldstein 2003b¹⁰), and

- ~~5% of women with PMO on osteoporosis medication~~ will be administered denosumab (based on discussions with the Agency review division)
- Conclusion:
 - 1% of women ≥ 65 years treated for PMO will receive denosumab, and,
 - During the first year after denosumab launch, 2.5% of women treated for PMO will receive denosumab or 0.5% of women ≥ 65 years old.
 - The final numbers of denosumab exposure will depend on the rate of acceptance of treating with denosumab in each data source population.

The estimated person-years of denosumab exposure are summarized in Table 10-1 (Feasibility report, page 86).

Table 10-1. Estimated Exposure to Denosumab Through 10 Years Post Approval of Denosumab by Data System

Data System	Overall Number of Women ≥ 65 Years Old in the 4 Data Systems (Prevalent Patients)	Estimated Exposure to Denosumab (Person-years)		
		First 2 Years Post Denosumab Approval (Person-years)	First 5 Years Post Denosumab Approval (Person-years)	First 10 Years Post Denosumab Approval (Person-years)
US Medicare	20,600,000	309,000	927,000	1,957,000
Nordic National Registries	2,400,000	36,000	108,000	228,000
Kaiser Permanente	450,000	6,750	20,250	42,750
United HealthCare	207,000	3,105	9,315	19,665
Combined	23,657,000	354,855	1,064,565	2,247,415

The power calculations, using Fisher's 2-sided exact test, $\alpha = 0.5$ and 10:1 match of controls to denosumab-exposed PY, were based on the AESI incidence rates from Table 4-1 and, for women ≥ 65 years old. Amgen calculates that the Observational Databases study will have 100% power to detect a relative risk of 1.5 or higher for hypersensitivity, hypocalcemia, fracture healing complications, serious infection, acute pancreatitis, and new primary all sites malignancy (incidence > 4 cases per 100,000 PY). The study will have 90% power to detect a relative risk ≥ 2.5 for serious dermatologic AEs and a relative risk ≥ 2.0 for ONJ. Power calculations were not done for atypical fracture AEs because the background incidence rate is unknown. Power calculations for each of the AESIs at 2, 5, and 10 years of denosumab exposure are in Tables D-1 through D-4 (Feasibility report, pages 145-152) in the Appendix.

3.6 AMGEN'S CONCLUSIONS ON FEASIBILITY REPORT, 20090521

Amgen concluded that the Observational Databases study is feasible and will have the data to evaluate the long-term safety of denosumab in the postmarketing setting.

4 DEPI COMMENTS ON FEASIBILITY REPORT, 20090521

Amgen addressed DEPI's comments on their original Feasibility study protocol and completed the Feasibility study prior to denosumab approval as requested by FDA. Overall, the algorithms

designed to identify women with PMO (including the use of osteoporosis medication codes) are acceptable. Of note, the AESI background incidence rates in the literature tended to be lower than those found in the four data systems.

Capturing denosumab exposures appears to be feasible. A product with a similar administration route and schedule, Neulasta (pegfilgrastim), was successfully identified in the Medicare databases using the proposed algorithm. Amgen proposed to use nonspecific or temporary codes to identify denosumab use within the 1st year of launch (until permanent codes are in place). Since these codes may be used for other new drugs at the same time as denosumab, a separate validation effort for the temporary codes should be done shortly after denosumab is marketed.

The algorithms for identifying the AESIs are consistent across the four data systems but are tailored for optimal results to each data system's characteristics, such as review of medical records, radiographic, and laboratory results. DEPI agrees that identifying some of the AESIs will be challenging, but the algorithms for each AESI should identify the cases given the limitations of each of the four data systems.

For women ≥ 65 years old, the proportion of women with PMO was less (13.8 – 30.9%) than the 40% used in calculating the estimated number of women with PMO to be exposed to denosumab in each data system. Amgen states that the lower percentages are most likely due to not including the osteoporosis medication codes in the algorithm for osteoporosis to be consistent with the Medicaid data which did not include Part D pharmacy data. The Observational Databases study (20090522) will include codes for osteoporosis medications in the algorithm for women with PMO plus it will include women ≥ 55 years old. These two inclusions should increase the sample size from that found in the Feasibility study. However, since Amgen did not use the osteoporosis medication codes in the Feasibility study for the identification of women with PMO and they did not identify women aged 55-64 in the non-Medicare data systems, the number of women with PMO remains a somewhat looser estimate than could have been demonstrated with actual numbers.

The estimation of osteoporosis medication use of 50% was from the literature but not validated in the Feasibility study for the data systems. This could affect the analyses if the sample size is smaller than estimated.

Based on labeling discussions with FDA (Amgen's Complete Response, page 27), the estimated denosumab use was decreased to 2.5% for the first year of denosumab marketing and 5% thereafter. This is a more conservative estimate and decreased the estimated sample size.

Multiple estimations were used to arrive at the estimated denosumab exposures for the Observational Databases study. As an observational study in claims and registry databases, the total number of denosumab exposures will be captured however, prior to denosumab launch, the number of exposed remains an estimate.

The incidence rates for each AESI in each data system were calculated for women ≥ 65 with and without PMO. Amgen adequately explained the differences of these AESI incidence rates among the data systems. Most of these incidence rates are higher than those found in the literature.

For the statistical calculations, Amgen appropriately used the lower, more conservative, incidence rates from the literature to calculate the sample size and power which resulted in a smaller sample size than if they used the higher incidence rates found in the Feasibility study. The lowest incidence rate, 0.4 cases of serious dermatologic AEs per 100,000 PY, will have an estimated

90% power to detect a relative risk ≥ 2.5 . FDA's Division of Biostatistics will comment on the statistical aspects of the feasibility study separately.

In conclusion, the feasibility study supports the proposed algorithms for identifying women with PMO, denosumab exposures, and AESIs. The number of women with PMO could have been more accurately identified in each data system but given the relative rarity of some of the AESIs and the complexity of identifying these AESIs, the Observational Databases study should provide valuable information on the safety of denosumab although it may not provide statistically significant differences for the rarer AESIs.

The following recommendations for Amgen's Observational Databases study (protocol 20090522) are because the feasibility study could not address these areas:

1. Validation of denosumab exposures shortly after denosumab marketing because nonspecific or temporary codes for drug use are used by most new drugs.
2. Report the proportion of women ≥ 55 years old with PMO and compare for each of the data systems to the 40% reported in the literature for women ≥ 65 years old.
3. Review the comments from Biostatistics regarding the sample size and power calculations when they are available.

5 OBSERVATIONAL DATABASE SAFETY STUDY (PROTOCOL 20090522)

The feasibility study (20090521) addressed the questions from the observational databases study (20090522) review; hence, these issues are not covered again in detail. The Denosumab Observational Databases Safety Study is summarized in Table 1 of the Appendix. It is a 10 year prospective cohort study on the long-term safety of denosumab exposure and comparing the AESIs in four large observational data systems (US Medicare, Kaiser Permanente of Northern and Southern California, United HealthCare, and the Nordic National Health Registry Databases (Denmark, Finland, Sweden, and Norway)).

5.1 SUMMARY OF AMGEN'S RESPONSE TO PRIOR DEPI RECOMMENDATIONS

Amgen made the following changes to Protocol 200900522 as requested by FDA:

1. Methods for assessment of exposure to denosumab are described.
2. Pancreatitis was added as an AESI.
3. Infection AESIs leading to hospitalizations or emergency room visits were added. (All AESIs requested by FDA are included in the Observational Databases study.)
4. The study duration was extended to 10 years.
5. AESI incidence rates will be calculated for women with PMO.
6. AESI incidence rates comparisons will include women with PMO who are:
 - a. Not exposed to osteoporosis medications, in addition to those who are:
 - b. Exposed to denosumab, and
 - c. Exposed to other osteoporosis medications.
7. For each exposure group of PMO women (denosumab, other osteoporosis medications, not exposed to osteoporosis medications) a description of the characteristics, clinical features, and AESI risk factors will be reported (age, geographic location (eg. country, state), fracture history, concurrent medication (eg. bisphosphonates; for medication use, duration, and dosage), history of osteoporosis treatment, comorbidities (eg. infections, diabetes, and disease or conditions that may increase risk of AESI), and year of PMO diagnosis.
8. ALL denosumab exposures will be included.

9. The denosumab utilization ~~patterns~~ will be described for women with PMO and for unapproved indications.
10. 100% of the Medicare database was to be used for the study; however, the revised protocol still states that only 5% of Medicare as a random sample will be used to provide the data for this study (Observational Databases Safety Study, page 24).

5.2 DEPI COMMENTS ON THE OBSERVATIONAL DATABASES STUDY

The following issues in the revised protocol for the Observational Database Safety Study were noted.

Missing data is addressed as a potential selection bias but it is not addressed as part of the analytical plan on how missing data would be handled in the study.

The section on comparing the study outcomes with external comparators was deleted since the focus of the study is older women with PMO and the PMO subgroup is compared to all women ≥ 65 years.

Some of the potential confounding factors were removed (family history, behavior variables, BMI) because these are not available in the electronic databases.

For the Observational Databases Study, DEPI recommends that Amgen:

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

As noted in Section 3.2.3, DEPI Comments on the Feasibility Report, 20090521 include recommendations for Amgen's Observational Databases study, protocol 20090522:

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

6 DENOSUMAB "SURVEILLANCE PROGRAM" PROTOCOL 20090601

The Prolia™ Post Marketing Active Safety Surveillance Program for Soliciting Adverse Events of Special Interest in the United States ("Surveillance Program", Protocol 20090601), was revised based on recommendations from FDA. Amgen will notify potential providers of the program through mailings, email, sales representatives, and the Prolia website with reminders every 3 months. After the prescribers register and receive answers to the questionnaire from their patient(s), they can report AESIs on the web or by paper. Amgen will process the AE report routinely by following-up and reporting to FDA as they would any other AE but these Surveillance Program reports will be summarized in an annual report to FDA and also in their PSUR. Amgen extended the Surveillance Program to 10 years at FDA's request.

6.1 CHANGES TO AMGEN'S SURVEILLANCE PROGRAM

Amgen made the following changes to their Surveillance Program, Protocol 20090601, as requested by FDA:

1. The Surveillance Program has the ~~same~~ 9 AEsIs as the other postmarketing studies: added pancreatitis, infections leading to hospitalizations, ER visits, or parenteral anti-infective medication, and AEsIs on suppression of bone turnover (atypical fractures, delayed fracture healing, and osteonecrosis of the jaw (ONJ)).
2. The study duration was extended to 10 years.
3. The minimum effective response rate in capturing AEsIs is unknown for Amgen's Surveillance Program. To encourage reporting, Amgen will notify providers every 3 months, provide questionnaires, collect the clinical data, and will adapt the program annually based on their proposed annual survey of providers.
4. Amgen will provide a paper-based provider survey of AEsIs associated with denosumab use in addition to a web-based option although the paper survey will not be provided at the time of denosumab administration. The questionnaires will be similar to the MedWatch reports. Providers will not need to report the AEsIs since Amgen will provide FDA with the information. Follow-up questionnaires for each AEsI will be included in the Surveillance Program.
5. Aggregated reports of US AEsIs will be sent to FDA annually and will be in the PSUR report. A final report will be submitted 6 months after the completion of the surveillance study.
6. The surveillance study will generate safety signals interpreted in the context of denosumab clinical studies, epidemiological studies (the observational databases safety study), background incidence rates, and other literature to address the limitations associated with spontaneous reporting systems (under reporting, lack of specificity of cases, reporting biases, lack of denominators, lack of comparison groups, etc).

6.1.1 Division of Epidemiology (DEPI) Comments

Amgen has met all of FDA's requests except to have the questionnaire delivered to the provider during the visit for denosumab. The alternatives provided by Amgen (mailed, delivered by sales representative, online questionnaires) require the provider to take the initiative and remember to either bring a questionnaire or ask the questions and transcribe them later; neither is optimal for recall or completing the questionnaire. If it really is so difficult, as Amgen says, to deliver the questionnaire during the visit, then Amgen has proposed acceptable alternatives.

One minor recommendation for the ONJ questionnaire is to add diabetes to the list of ONJ risk factors.

In conclusion, Amgen's revised protocol for the Surveillance Program is acceptable.

7 RECOMMENDATIONS

A summary of the current DEPI recommendations for the the Observational Databases study (20090522), and the Surveillance Program (20090601):

DEPI recommendations for the Observational Databases study (20090522):

1. Validation of denosumab exposures shortly after denosumab marketing because nonspecific or temporary codes for drug use are used by most new drugs.

2. Report the proportion of women ≥ 55 years old with PMO and compare for each of the data systems to the 40% reported in the literature for women ≥ 65 years old.
3. Review the comments from Biostatistics regarding the sample size and power calculations when they are available.
 - a. The AESI incidence rates for the data systems are much higher than those found in the literature.
 - b. The estimates of the denosumab-exposed population as a proportion of women ≥ 65 years old are lower (13.8 – 30.9%) than the 40% reported in the literature. This might be due to not including osteoporosis medication codes for identifying osteoporosis patients in the Feasibility study. Osteoporosis medication codes will be used in the algorithm for the Observational Databases Study (20090522).
 - c. Since this is an observational study in claims and registry databases, the total number of denosumab exposures cannot be influenced.
 - d. Pulling cases and controls from the same population will reduce bias.
4. State in the protocol that 100% of the Medicare databases will be used for the study (Section 4.3 still states a 5% random sample, page 25).
5. Define the “other osteoporosis medications” for the comparison group (Section 4.4, page 25).
6. Address how missing data will be handled.

One minor recommendation for the ONJ questionnaire of the Surveillance Program: add diabetes to the list of ONJ risk factors on the questionnaire about ONJ.

APPENDIXES

ABBREVIATIONS

CPT	Common Procedural Terminology
ACT	Anatomical Therapeutic Chemical
AE	Adverse event
AESI	Adverse event of special interest
CPT	Common Procedural Terminology
EM	Erythema multiforme
EMR	Electronic medical record
ER	Emergency room
G-CSF	Granulocyte colony-stimulating factor
HCPCS	Healthcare Common Procedure Coding System
NDC	National Drug Code
ONJ	Osteonecrosis of the jaw
PY	Person-years
SJS	Stevens Johnson Syndrome
TEN	Toxic epidermal necrolysis
UHC	United HealthCare

RECOMMENDATIONS FROM DEPI, NOVEMBER 25, 2009

DEPI recommends the following for the data systems studies (Phases A and B) and the survey (loosely ordered by Phase A, Phase B, survey, and clarification requests):

1. Since capture of denosumab use may be challenging in administrative databases, Phase A should examine the ability of capturing a drug product administered in a similar fashion to denosumab in each data system.
2. Uniform case-ascertainment algorithms are important to compare findings across the data systems; therefore, the mapping of ICD-9 to ICD-10 codes should be done in Phase A (this was mentioned in the Phase B protocol, page 27).
3. Drop-out rates, missing values, and codes for deaths and malignancies should be assessed for each database during Phase A.
4. Document the timeliness and completeness of medical chart reviews in each data system, especially in those databases which will utilize paper chart review.
5. Consider a pilot study of the proposed use of 100% of the Medicare database as the sampling domain for the selection of the PMO base cohort and the validation of cases by medical chart review.
6. Include all the AESIs that DRUP requested in each of the data systems for Phases A and B and for the survey (hypocalcemia, ONJ, infections, hypersensitivity, dermatologic events, atypical fracture, and fracture wound healing and new primary malignancies).
7. Include all postmenopausal women (not just PMO women) in Phases A and B (protocol numbers 20090521 and -522). Analyze background AE incidence rates in both postmenopausal and PMO women.
8. Perform power calculations in each data system for detection of an increase in the incidence rates for the AESIs based on the estimated sample sizes for postmenopausal women and for PMO women.
9. Phase A, revised to include all postmenopausal women, should be completed and reviewed by FDA prior to FDA approval of denosumab.
10. Phase B should identify and follow any denosumab exposure.
11. Consider the ease of collection of the survey data and data entry. A paper survey attached to the denosumab product and data entry by office staff may help to increase the reporting rate and provide timely survey reports.
12. Follow-up of survey patients is recommended. This should include information on drug exposure, AESIs, potential confounders, and supporting data (x-ray, lab, and physician consult data).
13. Extend the follow-up of both the data system study (Phases A and B) and the survey to at least 10 years to capture those AEs with long latencies such as ONJ and malignancies.
14. Please have Amgen clarify:
 - a. The differences in numbers of PMO women and estimated denosumab users as reported in Phase A protocol and the Information Package.
 - b. "Significant risk" noted in the annual assessment that would prompt reporting to FDA.
 - c. Timeframe for reporting "significant risk" information to FDA.

- d. ~~The rationale for using random~~ index dates for PMO-naïve patients (Phase B protocol, page 26).
- e. Specific objectives assigned to each selected database (Phase B protocol, page 17).
- f. An “aggregated report” and the “appropriate context” mentioned in the survey protocol (page 5).

TABLES IN APPENDIX

Table 1 – Design Summary of the Feasibility Study (20090521), the Observational Databases Safety Study (20090522), and the Healthcare Provider Survey (“Active Surveillance Safety Study”, 20090601):

Objectives/Aims	Denosumab Feasibility Study for the Observational Databases Safety Study 20090521	Denosumab Observational Databases Safety Study 20090522	Denosumab Active Surveillance A Safety Study 20090601
<p>Advantages & Limitations of each Database</p> <p>Establish algorithms to ascertain PMO women</p> <p>Establish algorithms to ascertain AESIS</p> <p>Estimate background AESI incidence rates</p> <p>Establish feasibility of capturing denosumab-type exposure</p> <p>Characterize PMO populations</p> <p>Identify potential confounding factors and selection biases</p>	<p>Determine incidence rates for AESIs:</p> <ul style="list-style-type: none"> • Osteonecrosis of the jaw (ONJ) • Atypical fracture • Fracture healing complications • Hypocalcemia leading to hospitalization or emergency room (ER) visit • Infections leading to hospitalization or ER visit or parenteral anti-infective administration • Dermatologic AEs leading to hospitalization or ER visit • Acute pancreatitis leading to hospitalization • Hypersensitivity reactions leading to hospitalization or ER visit • New primary malignancy <p>Describe AESI risk factors</p> <p>Compare AESI incidence in denosumab exposed, other osteoporosis medications exposed and not exposed groups</p> <p>Describe AESI incidence rates in women ≥ 55 years</p> <p>Describe denosumab utilization patterns for PMO women and for unapproved indications</p>	<p>Monitor long-term safety of Prolia/denosumab</p> <p>Improve quality of data collection by proactively soliciting reporting of AESIs</p>	

	Denosumab Feasibility Study for the Observational Databases Safety Study 20090521	Denosumab Observational Databases Safety Study 20090522	Denosumab Active Surveillance A Safety Study 20090601
Design	Retrospective cohort feasibility study	Prospective observational databases study	Prospective cross-sectional, active surveillance study
Type	Retrospective cohort study	Prospective cohort study	Prospective interview cohort study – Active, solicited surveillance, interview-type study with notification of providers quarterly
Data Source	US Medicare Kaiser Permanente, Northern & Southern California United HealthCare Nordic Country national health registries (Denmark, Finland, Sweden, and Norway)	US Medicare Kaiser Permanente, Northern & Southern California United HealthCare Nordic Country national health registries (Denmark, Finland, Sweden, and Norway)	Providers of denosumab
Time Period	Retrospective 5 years (2005-2009) - Completed	10 years after denosumab launch	10 years after denosumab launch
Criterion Standards	≥65 year old postmenopausal women and subgroup with osteoporosis (age ≥65 year old used to provide consistency with Medicare data)	≥55 year old postmenopausal women and subgroup with osteoporosis	All recipients of denosumab Providers register in surveillance program
PHI (???)			
Setting	Observational Databases	Observational Databases	Provider administration office or clinic
Exposure/Intervention	Denosumab exposure Other osteoporosis medications exposure	Denosumab exposure Other osteoporosis medications exposure	Denosumab exposure

	Denosumab Feasibility Study for the Observational Databases Safety Study 20090521	Denosumab Observational Databases Safety Study 20090522	Denosumab Active Surveillance Safety Study 20090601
	Not exposed	Not exposed	
Main Outcome	AESIs	AESIs	AESIs for signal generation
Covariates	Demographic data Medication use Common comorbidities	Characteristics for the 3 groups: PMO women on denosumab, or other osteoporosis medications, or not exposed Other osteoporosis medications	Demographic data Concomitant medications including other osteoporosis medications
Sample Size	Total number of women ≥ 65 year old Subgroup with osteoporosis	354,855, 1,064,565, and 2,247,415 person years at 2, 5, and 10 years post approval based on 1. 40% women ≥ 65 years old with osteoporosis, 2. 50% women with osteoporosis on osteoporosis medication, and 3. 5% of PMO women on osteoporosis medication will be on denosumab BUT 2.5% PMO women treated with denosumab in the first year after denosumab launch i.e., 1% women ≥ 65 years old when the market for denosumab has stabilized	All reports of denosumab administration
Statistical Analyses	Number of women ≥ 65 year old & with osteoporosis Person-year data for exposure groups Incidence rates Descriptive statistics	Analyses for each database and combined using meta-analytic methods: Descriptive statistics: characteristics, AESIs, incidence rates of AESIs, denosumab utilization patterns in the 3 groups of PMO women on denosumab, or other osteoporosis medications, or not exposed, and in patients with unapproved	Descriptive statistics

	<p>Denosumab Feasibility Study for the Observational Databases Safety Study</p> <p>20090521</p>	<p>Denosumab Observational Databases Safety Study</p> <p>20090522</p>	<p>Denosumab Active Surveillance A Safety Study</p> <p>20090601</p>
		<p>indicaitons)</p> <p>Kaplan Meier survival curves to estimate time to first event</p> <p>Poisson regression models to assess rates of recurrent events</p> <p>Time-to-event analysis methods: Cox proportional hazards regression models, Anderson-Gill models for time-dependent covariates including denosumab exposure</p> <p>Propensity score method to control for confounding</p>	

Table 1. Characteristics of the Four Data Systems to Be Used in Study 20090522

Assessment Items	US Medicare	Kaiser Permanente	United HealthCare	Nordic National Registries
Longitudinal follow-up (average follow-up time)	Yes (65 years of age to death)	Yes (~5 years)	Yes (~2-3 years)	Yes (lifetime)
Annual drop-out rate (turnover rate)	< 2%	< 5% among older population	~15 to 20%	< 1%
Data quality (missing data)	All billable transactions captured. Chart information not needed for reimbursement is not reliably captured.	Clinical information from each patient encounter with the program entered electronically. Ongoing quality initiatives help assure high data quality.	All billable transactions captured. Chart information not needed for reimbursement is not reliably captured.	Comprehensive high quality data in numerous inter-linked administrative and medical databases. Government incentives help assure high level of completeness and accuracy.
Estimated lag time before data availability	14 to 18 months	~1 month	6 to 9 months	9 to 12 months

Table 2. Suitability of Each Data System for the Assessment of Risk of Specific Adverse Events of Special Interest

Adverse Event of Special Interest	Data System Suitable for Assessment of Risk of Specific Adverse Event of Special Interest			
	US Medicare	Kaiser Permanente	United HealthCare	Nordic National Registries
Osteonecrosis of the jaw	Yes	Yes	Yes	Yes
Atypical fracture	Risk of femoral fracture assessable, but atypical fracture not assessable initially.	Yes	Risk of femoral fracture assessable, but atypical fracture not assessable initially.	Yes
Fracture healing complications (non-union)	Yes	Yes	Yes	Yes
Hypocalcemia leading to hospitalization or emergency room (ER) visit	Yes	Yes	Yes	Yes
Infections leading to hospitalization, ER visit, or administration of parenteral anti-infective medication	Yes	Yes	Yes	Yes
Dermatologic adverse events leading to hospitalization or ER visit	Yes	Yes	Yes	Yes
Acute pancreatitis leading to hospitalization	Yes	Yes	Yes	Yes
Hypersensitivity leading to hospitalization or an ER visit	Yes	Yes	Yes	Yes
New primary malignancy	Yes	Yes	Yes	Yes

From the Feasibility Assessment for Denosumab Global Postmarketing Safety Observational Study 20090522, Amgen 1/25/2010:

Table 5-1. Suitability of Each Data System for the Assessment of Risk of Specific Adverse Events of Special Interest Associated With Denosumab Therapy (page 41 of Feasibility report)

Data System Suitable for Assessment of Risk of Specific Adverse Event of Special Interest

Adverse Event of Special Interest	US Medicare	Kaiser Permanente	United HealthCare	Nordic National Registries
Osteonecrosis of the jaw	Yes	Yes	Yes	Yes
Atypical fracture	Subtrochanteric and diaphyseal fracture	Yes	Subtrochanteric and diaphyseal fracture	Yes
Fracture healing complications (non-union)	Yes	Yes	Yes	Yes
Hypocalcemia leading to hospitalization or emergency room (ER) visit	Yes	Yes	Yes	Yes
Infections leading to hospitalization, ER visit, , or administration of parenteral anti-infective medication	Yes	Yes	Yes	Yes
Dermatologic adverse events leading to hospitalization or ER visit	Yes	Yes	Yes	Yes
Acute pancreatitis leading to hospitalization	Yes	Yes	Yes	Yes
Hypersensitivity leading to hospitalization or ER visit	Yes	Yes	Yes	Yes
primary malignancy	Yes	Yes	Yes	Yes

From the Feasibility Assessment for Denosumab Global Postmarketing Safety Observational Study 20090522, Amgen 1/25/2010:

Table 5-2. Characteristics of the 4 Data Systems to Be Used in Study 20090522 (pages 42-43 of the Feasibility report)

Assessment Items	US Medicare	Kaiser Permanente	United HealthCare	Nordic National Registries
Representativeness	Population-based capture of US patients ≥ 65 years old	Members are part of the largest US integrated group-model nonprofit health care system; those who enroll in Medicare Advantage or Medicare supplemental programs are captured	Members are predominantly from employer-based groups but Medicaid and Medicare populations represented	Population-based capture of all residents
Number of women enrolled ≥ 65 years old	20.6 million	450,000	207,000	2.4 million
Estimated exposure (person-years) to denosumab in the first 5 years post denosumab launch (person-years)	927,000	20,250	9,315	108,000
Access to medical charts	Yes (paper only)	Yes (paper + EMR)	Yes (paper only)	Yes (paper in all regions, EMR in selected regions)
Additional data elements and sources				
Hospital records	Yes	Yes	Yes	Yes
Outpatient/clinic records	Yes	Yes	Yes	Partially
Pharmacy/prescription data	Part B (Part D oral medications) pending	Yes	Yes	Yes
Laboratory results/imaging	No	Yes	$\leq 20\%$	Yes
Primary reason for data collection	Billing/reimbursement	Provision of health care	Billing/reimbursement	Administrative/provision of health care
Longitudinal follow-up (average follow-up time)	Yes (65 years of age to death)	Yes (~5 years)	Yes (~2-3 years)	Yes (lifetime)
Annual drop-out rate (turnover rate)	, 2%	< 5% among older population	~ 15 to 20%	< 1%
Data quality (missing data)	All billable transactions captured. Chart information not needed for reimbursement is not reliably captured.	Clinical information from each patient encounter with the program entered electronically. Ongoing quality initiatives help assure high data quality.	All billable transactions captured. Chart information not needed for reimbursement is not reliably captured.	Comprehensive high quality data in numerous inter-linked administrative and medical databases. Government incentives help assure high level of completeness and accuracy.
Estimated lag time before availability	14 to 18 months	~ 1 month	6 to 9 months	9 to 12 months

Table 9-1. Proportion of Women Identified as Having PMO in the 4 Data Systems (page 70)

Data System	Number of Women ≥ 65 Years Old	Number of Women ≥ 65 Years Old Identified as Having PMO	Percent of women ≥ 65 Years Old Identified as Having PMO	Medications Included in the PMO Algorithm
Medicare	1,029,447	222,841	21.6%	IV bisphosphonates only
United HealthCare	342,354	47,096	13.8%	IV bisphosphonates only
Kaiser Permanente	1,965,558	465,666	23.7%	IV bisphosphonates only
Denmark				
All	462,726	143,1139	30.9%	In-hospital bisphosphonate administration
Northern only	137,071	49,686	36.2%	Any bisphosphonate prescription

Table 9-2. Crude and Age-Adjusted Incidence Rates of Potential ONJ for Women ≥ 65 Years Old From 4 Data Systems: US Medicare, United HealthCare, Kaiser Permanente, and Danish National Registry

Population Data System	Number of Cases	Personyears of Follow-up	Crude Incidence (per 100,000 Person-years)	Agestandardized Incidence ^a (per 100,000 Person-years)
Women ≥ 65 years old				
US Medicare	926	4,930,047	18.8	18.5
United HealthCare	239	637,492	37.5	36.0
Kaiser Permanente	209	1,743,403	12.0	12.1
Danish national registry	277	2,371,533	11.7	11.6
Women with PMO ≥ 65 years old				
US Medicare	190	651,498	29.2	30.1
United HealthCare	31	66,211	46.8	45.2
Kaiser Permanente	75	405,497	18.5	18.5
Danish national registry	36	150,269	24.0	26.2

^a Age-adjusted to Year 2000 US census data (age group weights: 65 to ≤ 70 years: 0.25; 70 to ≤ 75 years: 0.24; 75 to ≤ 80: 0.21; 80 to ≤ 85: 0.15; ≥85 years: 0.15)

Table 9-3. Crude and Age-Adjusted Incidence Rates of Fractures at Sites Where Atypical Fractures Occur for Women ≥ 65 Years Old From 4 Data Systems: US Medicare, United HealthCare, Kaiser Permanente, and Danish National Registry

Population Data System	Number of Cases	Personyears of Followup	Crude Incidence (per 100,000 personyears)	Agestandardized Incidence^a (per 100,000 personyears)
Women ≥ 65 years old				
US Medicare	5,090	4,854,644	104.9	95.4
United HealthCare	2108	636,044	331.4	451.4
Kaiser Permanente	2,700	1,964,263	137.5	150.2
Danish national registry	4,834	2,362,537	204.6	204.6
Women with PMO ≥ 65 years old				
US Medicare	1,236	514,325	240.3	187.8
United HealthCare	1,574	64,798	2,429.1	2,325.0
Kaiser Permanente	2,049	464,689	440.9	402.9
Danish national registry	907	148,443	611.0	506.9

^a Age-adjusted to Year 2000 US census data (age group weights: 65 to ≤ 70 years: 0.25; 70 to ≤ 75 years: 0.24; 75 to ≤ 80: 0.21; 80 to ≤ 85: 0.15; ≥85 years: 0.15)

Table 9-4. Crude and Age-Adjusted Incidence Rates of Fracture Healing Complications for Women ≥ 65 Years Old From 4 Data Systems: US Medicare, United HealthCare, Kaiser Permanente, and Danish National Registry

Population Data System	Number of Cases	Personyears of Followup	Crude Incidence (per 100,000 personyears)	Agestandardized Incidence ^a (per 100,000 personyears)
Women ≥ 65 years old				
US Medicare	3,477	4,922,686	70.6	68.4
United HealthCare	856	637,330	134.3	134.7
Kaiser Permanente	882	1,965,027	44.9	45.2
Danish national registry	302	2,351,913	12.8	12.8
Women with PMO ≥ 65 years old				
US Medicare	1,881	646,363	291.0	316.0
United HealthCare	319	65,978	483.5	489.8
Kaiser Permanente	443	465,396	95.2	95.5
Danish national registry	32	146,600	21.8	21.0

^a Age-adjusted to Year 2000 US census data (age group weights: 65 to ≤ 70 years: 0.25; 70 to ≤ 75 years: 0.24; 75 to ≤ 80 : 0.21; 80 to ≤ 85 : 0.15; ≥ 85 years: 0.15)

Table 9-5. Crude and Age-Adjusted Incidence Rates of Hypocalcemia Leading to Hospitalization or ER Visit for Women ≥ 65 Years Old From 4 Data Systems: US Medicare, United HealthCare, Kaiser Permanente, and Danish National Registry

Population Data System	Number of Cases	Personyears of Follow-up	Crude Incidence (per 100,000 personyears)	Agestandardized Incidence^a (per 100,000 Personyears)
Women ≥ 65 years old				
US Medicare	315	4,928,034	6.4	6.3
United HealthCare	119	637,847	18.7	20.5
Kaiser Permanente	87	1,965,558	4.4	4.3
Danish national registry ^b	3	460,848	0.7	0.7
Women with PMO ≥ 65 years old				
US Medicare	77	650,329	11.8	11.9
United HealthCare	24	66,242	36.2	36.8
Kaiser Permanente	20	465,666	4.3	4.2
Danish national registry ^b	0	88,484	0.0	0.0

^a Age-adjusted to Year 2000 US census data (age group weights: 65 to ≤ 70 years: 0.25; 70 to ≤ 75 years: 0.24; 75 to ≤ 80 : 0.21; 80 to ≤ 85 : 0.15; ≥ 85 years: 0.15)

^b Results for Denmark are based on selected regions of the country for which laboratory results were available.

Table 9-6. Crude and Age-Adjusted Incidence Rates of Infection Leading to Hospitalization, ER Visit, or Administration of Parenteral Anti-infective Medication for Women ≥ 65 Years Old From 4 Data Systems: US Medicare, United HealthCare, Kaiser Permanente, and Danish National Registry

Population Data System	Number of Cases	Personyears of Follow-up	Crude Incidence (per 100,000 Person-years)	Agestandardized Incidence^a (per 100,000 Person-years)
<i>Infection Overall</i>				
Women ≥ 65 years old				
US Medicare	151,251	2,867,985	5,273.8	5,222.8
United HealthCare	54,645	612,061	8,928.0	10,185.2
Kaiser Permanente	75,337	1,976,908	3,810.9	4,020.7
Danish national registry	71,954	2,344,826	3,068.6	3,079.9
Women with PMO ≥ 65 years old				
US Medicare	27,969	286,560	9,760.3	8,471.4
United HealthCare	8,393	60,588	13,852.6	13,431.3
Kaiser Permanente	23,876	470,592	5,073.6	4,714.0
Danish national registry	5,936	147,787	4,016.6	3,617.4
<i>Skin Infection</i>				
Women ≥ 65 years old				
US Medicare	23,407	3,188,881	734.0	718.3
United HealthCare	6,993	612,061	1,142.5	1,259.9
Kaiser Permanente	13,587	1,976,908	687.3	709.8
Danish national registry	7,363	2,344,826	314.0	314.6
Women with PMO ≥ 65 years old				
US Medicare	3,729	330,988	1,126.6	984.0
United HealthCare	993	60,588	1,638.9	1,610.8
Kaiser Permanente	3,824	470,592	812.6	771.0
Danish national registry	513	147,787	347.1	326.7

^a Age-adjusted to Year 2000 US census data (age group weights: 65 to ≤ 70 years: 0.25; 70 to ≤ 75 years: 0.24; 75 to ≤ 80 : 0.21; 80 to ≤ 85 : 0.15; ≥ 85 years: 0.15)

Table 9-7. Crude and Age-Adjusted Incidence Rates of Dermatologic Adverse Events Leading to Hospitalization or ER Visit for Women ≥ 65 Years Old From 4 Data Systems: US Medicare, United HealthCare, Kaiser Permanente, and Danish National Registry

Population Data System	Number of Cases	Person-years of Follow-up	Crude Incidence (per 100,000 person-years)	Age-standardized Incidence ^a (per 100,000 person-years)
<i>Dermatologic Adverse Events Overall</i>				
Women ≥ 65 years old				
US Medicare	9,584	4,814,428	199.1	200.9
United HealthCare	1,284	637,076	201.5	208.0
Kaiser Permanente	2,109	1,963,862	107.4	107.4
Danish national registry	651	2,371,578	27.5	27.5
Women with PMO ≥ 65 years old				
US Medicare	1,401	632,744	221.4	249.0
United HealthCare	163	66,108	246.6	248.3
Kaiser Permanente	560	465,235	120.4	120.9
Danish national registry	40	150,311	26.6	26.1
<i>Bullous Dermatoses</i>				
Women ≥ 65 years old				
US Medicare	204	4,841,884	4.2	3.9
United HealthCare	27	637,076	4.2	4.7
Kaiser Permanente	33	1,963,862	1.7	1.8
Danish national registry	188	2,371,578	7.9	8.0
Women with PMO ≥ 65 years old				
US Medicare	38	635,865	6.0	4.0
United HealthCare	2	66,108	3.0	2.9
Kaiser Permanente	11	465,235	2.4	2.0
Danish national registry	18	150,311	12.0	10.4

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^a Age-adjusted to Year 2000 US census data (age group weights: 65 to ≤ 70 years: 0.25; 70 to ≤ 75 years: 0.24; 75 to ≤ 80 : 0.21; 80 to ≤ 85 : 0.15; ≥ 85 years: 0.15)

Table 9-7. Crude and Age-Adjusted Incidence Rates of Dermatologic Adverse Events Leading to Hospitalization or ER Visit for Women ≥ 65 Years Old From 4 Data Systems: US Medicare, United HealthCare, Kaiser Permanente, and Danish National Registry

Population Data System	Number of Cases	Person-years of Follow-up	Crude Incidence (per 100,000 person-years)	Age-standardized Incidence ^a (per 100,000 person-years)
Select Erythematous Dermatoses (SJS, TEN, exfoliation due to conditions)				
Women ≥ 65 years old				
US Medicare	0	4,842,272	0.0	0.0
United HealthCare	3	637,076	0.5	0.5
Kaiser Permanente	12	1,963,862	0.6	0.7
Danish national registry	34	2,371,578	1.4	1.5
Women with PMO ≥ 65 years old				
US Medicare	0	635,865	0.0	0.0
United HealthCare	1	66,108	1.5	1.5
Kaiser Permanente	2	465,235	0.4	0.5
Danish national registry	4	150,311	2.7	3.2

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^a Age-adjusted to Year 2000 US census data (age group weights: 65 to ≤ 70 years: 0.25; 70 to ≤ 75 years: 0.24; 75 to ≤ 80 : 0.21; 80 to ≤ 85 : 0.15; ≥ 85 years: 0.15)

Table 9-8. Crude and Age-Adjusted Incidence Rates of Acute Pancreatitis Leading to Hospitalization for Women ≥ 65 Years Old From 4 Data Systems: US Medicare, United HealthCare, Kaiser Permanente, and Danish National Registry

Population Data System	Number of Cases	Person- years of Follow- up	Crude Incidence (per 100,000 person- years)	Age- standardized Incidence ^a (per 100,000 person- years)
Women ≥ 65 years old				
US Medicare	7,569	4,900,182	154.5	148.9
United HealthCare	1,027	636,601	161.3	174.5
Kaiser Permanente	749	1,972,100	38.0	38.7
Danish national registry	1,119	2,368,893	47.2	47.2
Women with PMO ≥ 65 years old				
US Medicare	1,671	644,644	259.2	248.1
United HealthCare	131	65,975	198.6	191.4
Kaiser Permanente	203	468,391	43.3	42.3
Danish national registry	76	150,120	50.6	46.4

^a Age-adjusted to Year 2000 US census data (age group weights: 65 to ≤ 70 years: 0.25; 70 to ≤ 75 years: 0.24; 75 to ≤ 80 : 0.21; 80 to ≤ 85 : 0.15; ≥ 85 years: 0.15)

Table 9-9. Crude and Age-Adjusted Incidence Rates of Hypersensitivity Leading to Hospitalization or ER Visit for Women ≥ 65 Years Old From 4 Data Systems: US Medicare, United HealthCare, Kaiser Permanente, and Danish National Registry

Population Data System	Number of Cases	Person-years of Follow-up	Crude Incidence (per 100,000 person-years)	Age-standardized Incidence ^a (per 100,000 person-years)
<i>Hypersensitivity Overall</i>				
Women ≥ 65 years old				
US Medicare	10,222	4,897,544	208.7	211.5
United HealthCare	991	637,350	155.5	154.6
Kaiser Permanente	2,429	1,961,826	123.8	124.2
Danish national registry	1,111	2,370,945	46.9	46.9
Women with PMO ≥ 65 years old				
US Medicare	1,692	646,844	261.6	283.2
United HealthCare	106	66,182	160.2	162.5
Kaiser Permanente	662	464,569	142.5	141.8
Danish national registry	34	150,264	22.6	23.8
<i>Anaphylaxis Only</i>				
Women ≥ 65 years old				
US Medicare	385	4,926,568	7.8	8.1
United HealthCare	50	637,350	7.8	8.4
Kaiser Permanente	46	1,961,826	2.3	2.4
Danish national registry	48	2,370,945	2.0	2.0
Women with PMO ≥ 65 years old				
US Medicare	62	650,503	9.5	10.6
United HealthCare	8	66,182	12.1	13.1
Kaiser Permanente	15	464,569	3.2	3.3
Danish national registry	1	150,407	0.7	0.9

^a Age-adjusted to Year 2000 US census data (age group weights: 65 to ≤ 70 years: 0.25; 70 to ≤ 75 years: 0.24; 75 to ≤ 80 : 0.21; 80 to ≤ 85 : 0.15; ≥ 85 years: 0.15)

Table 9-10. Crude and Age-Adjusted Incidence Rates of New Primary Malignancy for Women ≥ 65 Years Old From 4 Data Systems: US Medicare, United HealthCare, Kaiser Permanente, and Danish National Registry

Population Data System	Number of Cases	Person-years of Follow-up	Crude Incidence (per 100,000 person-years)	Age-standardized Incidence ^a (per 100,000 person-years)
Women ≥ 65 years old				
US Medicare	82,500	4,771,925	1,728.9	1,695.0
United HealthCare	16,286	594,070	2,741.4	2,802.6
Kaiser Permanente	33,301	1,890,482	1,761.5	1,767.1
Danish national registry	36,322	2,285,559	1,589.2	1,594.4
Women with PMO ≥ 65 years old				
US Medicare	11,919	635,816	1,874.6	1,848.3
United HealthCare	1,610	59,917	2,687.1	2,664.8
Kaiser Permanente	8,407	444,985	1,889.3	1,897.1
Danish national registry	2,016	131,295	1,535.5	1,533.9

^a Age-adjusted to Year 2000 US census data (age group weights: 65 to ≤ 70 years: 0.25; 70 to ≤ 75 years: 0.24; 75 to ≤ 80 : 0.21; 80 to ≤ 85 : 0.15; ≥ 85 years: 0.15)

Table D-1. Power to Detect Relative Risk for the Adverse Events of Special Interest, US Medicare^a

Outcomes	Background Incidence Rate (per 100,000 Person-years)	Relative Risk								
		1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	10.0
2 Years Post Launch										
ONJ	1.0	12%	32%	52%	72%	85%	93%	98%	100%	100%
Fracture healing complications	95.5	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious hypocalcemia	9.0	63%	99%	100%	100%	100%	100%	100%	100%	100%
Serious infection	1249	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious dermatologic adverse events	0.4	8%	16%	27%	38%	51%	60%	78%	89%	100%
Pancreatitis	130	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious hypersensitivity	8.4	62%	98%	100%	100%	100%	100%	100%	100%	100%
Malignancy	1668	100%	100%	100%	100%	100%	100%	100%	100%	100%
5 Years Post Launch										
ONJ	1.0	27%	68%	92%	99%	100%	100%	100%	100%	100%
Fracture healing complications	95.5	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious hypocalcemia	9.0	97%	100%	100%	100%	100%	100%	100%	100%	100%

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^a Power calculated using the Fisher's 2-sided exact test with $\alpha = 0.05$ (Agresti, 1990) based on a group ratio of 10:1 between denosumab- and comparator-exposed person-years.

Table D-1. Power to Detect Relative Risk for the Adverse Events of Special Interest, US Medicare³

Outcomes	Background Incidence Rate (per 100,000 Person-years)	Relative Risk								
		1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	10.0
5 Years Post Launch (continued)										
Serious infection	1249	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious dermatologic adverse events	0.4	13%	36%	60%	79%	89%	96%	99%	100%	100%
Pancreatitis	130	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious hypersensitivity	8.4	97%	100%	100%	100%	100%	100%	100%	100%	100%
Malignancy	1668	100%	100%	100%	100%	100%	100%	100%	100%	100%
10 Years Post Launch										
ONJ	1.0	51%	94%	100%	100%	100%	100%	100%	100%	100%
Fracture healing complications	95.5	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious hypocalcemia	9.0	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious infection	1249	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious dermatologic adverse events	0.4	24%	62%	87%	97%	100%	100%	100%	100%	100%
Pancreatitis	130	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious hypersensitivity	8.4	100%	100%	100%	100%	100%	100%	100%	100%	100%
Malignancy	1668	100%	100%	100%	100%	100%	100%	100%	100%	100%

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³ Power calculated using the Fisher's 2-sided exact test with $\alpha = 0.05$ (Agresti, 1990) based on a group ratio of 10:1 between denosumab- and comparator-exposed person-years.

Table D-2. Power to Detect Relative Risk for the Adverse Events of Special Interest, Kaiser Permanente^a

Outcomes	Background Incidence Rate (per 100,000 Person-years)	Relative Risk								
		1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	10.0
2 Years Post Launch										
ONJ	1	1%	1%	1%	2%	2%	3%	4%	6%	14%
Fracture healing complications	95.5	21%	55%	82%	95%	99%	100%	100%	100%	100%
Serious hypocalcemia	9.0	5%	10%	17%	23%	29%	37%	50%	64%	90%
Serious infection	1249	98%	100%	100%	100%	100%	100%	100%	100%	100%
Serious dermatologic adverse events	0.4	0%	0%	0%	0%	0%	0%	1%	1%	3%
Pancreatitis	130	27%	66%	91%	99%	100%	100%	100%	100%	100%
Serious hypersensitivity	8.4	5%	10%	15%	22%	28%	35%	48%	60%	89%
Malignancy	1668	100%	100%	100%	100%	100%	100%	100%	100%	100%
5 Years Post Launch										
ONJ	1.0	2%	4%	7%	10%	13%	14%	20%	27%	51%
Fracture healing complications	95.5	49%	94%	100%	100%	100%	100%	100%	100%	95.5
Serious hypocalcemia	9.0	10%	22%	38%	53%	66%	78%	91%	97%	100%

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^a Power calculated using the Fisher's 2-sided exact test with $\alpha = 0.05$ (Agresti, 1990) based on a group ratio of 10:1 between denosumab- and comparator-exposed person-years.

Table D-2. Power to Detect Relative Risk for the Adverse Events of Special Interest, Kaiser Permanente¹

Outcomes	Background Incidence Rate (per 100,000 Person-years)	Relative Risk								
		1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	10.0
5 Years Post Launch (continued)										
Serious infection	1249	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious dermatologic adverse events	0.4	1%	1%	2%	2%	3%	4%	6%	8%	19%
Pancreatitis	130	60%	98%	100%	100%	100%	100%	100%	100%	100%
Serious hypersensitivity	8.4	9%	20%	35%	50%	64%	75%	89%	96%	100%
Malignancy	1668	100%	100%	100%	100%	100%	100%	100%	100%	100%
10 Years Post Launch										
ONJ	1.0	4%	8%	13%	17%	22%	28%	39%	47%	80%
Fracture healing complications	95.5	79%	100%	100%	100%	100%	100%	100%	100%	100%
Serious hypocalcemia	9.0	15%	37%	61%	80%	91%	96%	100%	100%	100%
Serious infection	1249	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious dermatologic adverse events	0.4	2%	3%	5%	7%	10%	12%	16%	24%	44%
Pancreatitis	130	89%	100%	100%	100%	100%	100%	100%	100%	100%
Serious hypersensitivity	8.4	14%	35%	60%	77%	89%	95%	99%	100%	100%
Malignancy	1668	100%	100%	100%	100%	100%	100%	100%	100%	100%

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¹ Power calculated using the Fisher's 2-sided exact test with $\alpha = 0.05$ (Agresti, 1990) based on a group ratio of 10:1 between denosumab- and comparator-exposed person-years.

Table D-3. Power to Detect Relative Risk for the Adverse Events of Special Interest, United HealthCare^a

Outcomes	Background Incidence Rate (per 100,000 Person-years)	Relative Risk								
		1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	10.0
2 Years Post Launch										
ONJ	1.0	0%	0%	0%	0%	1%	1%	1%	1%	4%
Fracture healing complications	95.5	13%	31%	52%	69%	82%	92%	99%	100%	100%
Serious hypocalcemia	9.0	3%	6%	10%	14%	16%	20%	28%	36%	64%
Serious infection	1249	78%	100%	100%	100%	100%	100%	100%	100%	100%
Serious dermatologic adverse events	0.4	0%	0%	0%	0%	0%	0%	0%	0%	1%
Pancreatitis	130	15%	39%	63%	81%	93%	97%	100%	100%	100%
Serious hypersensitivity	8.4	3%	6%	9%	11%	15%	18%	26%	35%	59%
Malignancy	1668	89%	100%	100%	100%	100%	100%	100%	100%	100%
5 Years Post Launch										
ONJ	1.0	1%	1%	2%	3%	5%	5%	7%	10%	23%
Fracture healing complications	95.5	28%	67%	92%	99%	100%	100%	100%	100%	100%
Serious hypocalcemia	9	6%	12%	21%	28%	38%	46%	63%	75%	97%

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^a Power calculated using the Fisher's 2-sided exact test with $\alpha = 0.05$ (Agresti, 1990) based on a group ratio of 10:1 between denosumab- and comparator-exposed person-years.

Table D-3. Power to Detect Relative Risk for the Adverse Events of Special Interest, United HealthCare^a

Outcomes	Background Incidence Rate (per 100,000 Person-years)	Relative Risk								
		1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	10.0
5 Years Post Launch (continued)										
Serious infection	1249	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious dermatologic adverse events	0.4	0%	0%	0%	1%	1%	1%	1%	2%	5%
Serious hypersensitivity	8.4	6%	12%	20%	26%	35%	45%	59%	73%	96%
Pancreatitis	130	34%	80%	97%	100%	100%	100%	100%	100%	100%
Malignancy	1668	100%	100%	100%	100%	100%	100%	100%	100%	100%
10 Years Post Launch										
ONJ	1	2%	4%	6%	10%	11%	14%	20%	26%	51%
Fracture healing complications	95.5	47%	93%	100%	100%	100%	100%	100%	100%	100%
Serious hypocalcemia	9.0	10%	21%	37%	51%	66%	76%	89%	96%	100%
Serious infection	1249	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious dermatologic adverse events	0.4	1%	1%	1%	2%	3%	4%	6%	7%	18%
Pancreatitis	130	61%	98%	100%	100%	100%	100%	100%	100%	100%
Serious hypersensitivity	8.4	9%	20%	35%	49%	63%	74%	88%	95%	100%
Malignancy	1668	100%	100%	100%	100%	100%	100%	100%	100%	100%

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^a Power calculated using the Fisher's 2-sided exact test with $\alpha = 0.05$ (Agresti, 1990) based on a group ratio of 10:1 between denosumab- and comparator-exposed person-years.

Table D-4. Power to Detect Relative Risk for Adverse Events of Special Interest, Nordic National Registries^a

Outcomes	Background Incidence Rate (per 100,000 Person-years)	Relative Risk								
		1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	10.0
2 Years Post Launch										
ONJ	1.0	4%	7%	11%	15%	20%	24%	35%	42%	74%
Serious dermatologic adverse events	0.4	2%	3%	4%	6%	8%	10%	13%	18%	39%
Fracture healing complications	17.5	21%	54%	82%	94%	99%	100%	100%	100%	100%
Serious hypocalcemia	95.5	74%	100%	100%	100%	100%	100%	100%	100%	100%
Serious infection	1249	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious dermatologic adverse events	0.4	2%	3%	4%	6%	8%	10%	13%	18%	39%
Pancreatitis	130	84%	100%	100%	100%	100%	100%	100%	100%	100%
Serious hypersensitivity	8.4	13%	31%	51%	71%	83%	92%	98%	100%	100%
Malignancy	1668	100%	100%	100%	100%	100%	100%	100%	100%	100%
5 Years Post Launch										
ONJ	1.0	7%	15%	24%	35%	45%	56%	74%	84%	99%
Fracture healing complications	95.5	99%	100%	100%	100%	100%	100%	100%	100%	100%
Serious hypocalcemia	9.0	27%	71%	94%	99%	100%	100%	100%	100%	100%

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^a Power calculated using the Fisher's 2-sided exact test with $\alpha = 0.05$ (Agresti, 1990) based on a group ratio of 10:1 between denosumab- and comparator-exposed person-years.

Table D-4. Power to Detect Relative Risk for Adverse Events of Special Interest, Nordic National Registries³

Outcomes	Background Incidence Rate (per 100,000 Person-years)	Relative Risk								
		1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	10.0
5 Years Post Launch (continued)										
Serious infection	1249	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious dermatologic adverse events	0.4	5%	8%	12%	17%	22%	29%	38%	50%	80%
Pancreatitis	130	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious hypersensitivity	8.4	27%	69%	92%	99%	100%	100%	100%	100%	100%
Malignancy	1668	100%	100%	100%	100%	100%	100%	100%	100%	100%
10 Years Post Launch										
ONJ	1	11%	27%	45%	62%	76%	84%	96%	99%	100%
Fracture healing complications	95.5	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious hypocalcemia	9.0	53%	95%	100%	100%	100%	100%	100%	100%	100%
Serious infection	1249	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious dermatologic adverse events	0.4	7%	12%	23%	31%	41%	49%	65%	79%	97%
Pancreatitis	130	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious hypersensitivity	8.4	49%	93%	100%	100%	100%	100%	100%	100%	100%
Malignancy	1668	100%	100%	100%	100%	100%	100%	100%	100%	100%

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³ Power calculated using the Fisher's 2-sided exact test with $\alpha = 0.05$ (Agresti, 1990) based on a group ratio of 10:1 between denosumab- and comparator-exposed person-years.

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CLINICAL REVIEW

Application Type	BLA
Application Number(s)	125,320 (re-submission)
Priority or Standard	Priority
Submit Date(s)	1/25/10
Received Date(s)	1/25/10
PDUFA Goal Date	7/25/10
Division / Office	Division of Reproductive and Urologic Products Office of Drug Evaluation 3
Reviewer Name	Stephen Voss M.D. <i>Stephen Voss M.D. 4/26/10</i>
Clinical Team Leader	Theresa Kehoe M.D. <i>Theresa Kehoe M.D. 4/26/10</i>
Review Completion Date	April 23, 2010
Established Name	Denosumab
(Proposed) Trade Name	PROLIA™
Therapeutic Class	RANK ligand (RANKL) inhibitor
Applicant	Amgen, Inc.
Formulation(s)	Single use prefilled syringe containing 60 mg in a 1 mL solution; Single use vial containing 60 mg in a 1 mL solution
Dosing Regimen	60 mg SC injection Q6months
Indication(s)	Treatment of Osteoporosis
Intended Population(s)	Postmenopausal Women

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends approval of denosumab 60 mg administered subcutaneously every 6 months for the indication of the treatment of postmenopausal osteoporosis (PMO). This recommendation is based on the demonstration of decreased incidence of new vertebral fracture in postmenopausal women with osteoporosis with denosumab compared to placebo, and the risk/benefit profile.

Several significant safety issues, including infections, over suppression of bone remodeling, skin hypersensitivity reactions, and a potential signal for malignancy were identified in the denosumab clinical program. These can be adequately addressed by various avenues of risk management, such as labeling and phase 4 requirements and commitments.

Given these safety concerns and the fact that this is a new molecular entity and first in class, denosumab use should be limited to postmenopausal osteoporotic women at high risk of fracture defined as a history of osteoporotic fracture or multiple risk factors for fracture; or women with PMO who have failed or are intolerant to other osteoporosis therapies.

1.2 Risk Benefit Assessment

Osteoporosis affects over 10 million Americans and is a major cause of morbidity and mortality in older adults. The lifetime risk of an osteoporotic fracture is ~50% for Caucasian women, and 30% of women > 50 years old have vertebral fractures. Fractures of the spine and especially the hip often result in chronic pain, deformity, disability and/or death, as well as great economic cost. Mortality rates in the first year after a hip or vertebral fracture are significantly higher than in the general population (Hasserius et al. 2005; Ioannidis et al. 2009), and approximately 20% of women die within a year of hip fracture (Johnell and Kanis 2004).

Despite increasing availability of effective diagnosis and treatment, osteoporosis continues to be significantly under-diagnosed and under-treated. Even when appropriate therapy is initiated, adherence to therapy is frequently poor. Literature reports that over half of the women who start bisphosphonate therapy discontinue treatment within one year, in part due to side effects and intolerability; this lower adherence correlates with poorer outcomes (Weycker et al. 2006; Rabenda et al. 2008; Rabenda et al. 2009). Existing therapies also are associated with potential long-term safety issues which are not yet fully defined. Thus, the possible benefit of new and different approaches to osteoporosis treatment is apparent.

Data presented in the original denosumab BLA demonstrated the effectiveness of denosumab in decreasing the risks of new vertebral fractures over a 36-month period in postmenopausal women with osteoporosis. Also demonstrated were reduced risks of new non-vertebral fracture and hip fracture over the same time period of treatment. For the primary endpoint of new vertebral fractures, treatment with denosumab resulted in a 4.8% absolute risk reduction and a 68% relative risk reduction in fracture incidence relative to placebo. A 1.5% absolute risk reduction and a 20% relative risk reduction of non-vertebral fractures was seen with denosumab therapy relative to placebo. For hip fractures, there was a 0.3% absolute risk reduction and a 40% relative risk reduction. The number needed to treat to prevent one new vertebral fracture was 21; for non vertebral fracture it was 70; and for hip fracture it was 227. The risk reductions for vertebral, non-vertebral, and hip fractures were statistically significant. The magnitude of treatment benefits with denosumab appears to be similar to that of bisphosphonates approved for the treatment of osteoporosis, although no head-to-head fracture trials have been conducted. The BLA resubmission reviewed here includes no new data on efficacy.

From a safety perspective, there are several safety signals for denosumab, particularly serious infections, a potential signal for malignancy, skin/hypersensitivity reactions, and over suppression of bone turnover. These safety concerns will be briefly summarized below, and described in detail in Section 7 of this review.

- **Serious infections, including skin infections:** Denosumab, like some other monoclonal antibodies, may have immunosuppressive properties that increase infection risk. There was a higher incidence of serious infections (placebo vs. denosumab 133 (3.4%) vs. 159 (4.1%)) in PMO fracture trial 20030216. In the other 3 primary efficacy trials, there was also a consistent safety signal of serious infections. In trial 20040132 there were 1(0.6%) vs. 8(4.9%) serious infections; in trial 20040135 there were 1(0.8%) vs. 3(2.3%); and in trial 20040138 there were 33(4.6%) vs. 43(5.9%). The number needed to harm for serious infections for trial 20030216 was 152 over a 3 year duration. In trial 20030216, signals were noted for endocarditis (0 vs. 3 cases), serious skin infections such as cellulitis and erysipelas requiring hospitalization (3 vs. 14 cases), serious urinary tract infections (17 vs. 28 cases), and serious ear infections (0 vs. 5 cases). In the extension study 20060289, there continues to be a trend for rates of serious infection somewhat greater than placebo.
- **Oversuppression of bone remodeling:** Denosumab at the selected clinical dose resulted in significant suppression of bone remodeling as evidenced by histomorphometry and bone biomarkers findings. Suppressed bone remodeling was suggested by the absence of tetracycline label in bone biopsies in approximately 35% of subjects exposed to denosumab. With currently marketed antiresorptive therapies (bisphosphonates), long-term suppression of remodeling is considered a potential cause of significant adverse outcomes such as osteonecrosis of the jaw

(ONJ), delayed fracture healing and atypical fractures. With bisphosphonates, these delayed events generally have not appeared until post-marketing; however, a case of ONJ was recently reported in a clinical trial of denosumab. The suppression of bone remodeling is reversible upon the discontinuation of denosumab, resulting in loss of the improvement in bone density and, potentially, loss of the fracture benefit. Therefore, treatment would likely need to be continued indefinitely, and remodeling oversuppression may become a major safety issue.

- **Malignancies:** There were early signals of a risk of malignancy in the denosumab clinical development program, with 3 subjects in a high-dose denosumab group (100 mg Q6months) in the Phase 2 dose-finding trial dying from a malignancy. There was also an increased incidence (over placebo) of new malignancies in trial 20030216, specifically malignancies of the breast, gastrointestinal tract, and reproductive systems. In the open-label extension study 20060289, overall rates of new malignancies continue to be higher than those of the 20030216 placebo group. The evidence is inconclusive; this potential risk warrants continued scrutiny in postmarketing.
- **Dermatologic adverse events:** There were greater numbers of subjects in the denosumab group who developed skin conditions in PMO fracture trial 20030216, such as dermatitis, eczema and pruritus (epidermal and dermal conditions: 316(8.4%) vs. 421(11%) ($p < 0.001$). However, these subjects continued receiving denosumab every 6 months and in most cases, these conditions did not recur with subsequent dosing. In PMO prevention trial 20040132, rashes occurred in 5 placebo subjects (3%) vs. 14 denosumab subjects (8.5%). In extension study 20060289, rates of these skin conditions did not appear to increase over time.

The current BLA resubmission includes some new safety data, which upon review does not substantially alter the safety profile of denosumab established by the original BLA.

Given the magnitude of treatment benefit with denosumab and its overall safety profile, denosumab should be approved for the treatment of osteoporosis in postmenopausal women. Because of the potential safety issues and the fact that this is a first in class agent, benefit clearly exceeds risk only for women with high risk of fracture, defined as a history of osteoporotic fracture or multiple risk factors for fracture; or for women who have failed or are intolerant to other osteoporosis therapies. The aforementioned safety concerns can be adequately addressed by various avenues of risk management, such as labeling, a REMS, and phase 4 requirements and commitments.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

In order to insure that the benefit of denosumab exceeds the risk in the PMO population, a Risk Evaluation and Mitigation Strategy (REMS) is necessary to communicate (beyond labeling) the risks of serious infections including skin infection; dermatologic adverse events; and suppression of bone turnover. As requested by the Agency, Amgen has submitted a REMS proposal in this submission, including a Medication Guide for patients, a Communication Plan for healthcare providers, and a schedule of assessments. This proposal has been reviewed by the Division of Risk Management and was discussed during a telephone conference on 4/13/10, and substantial agreement between FDA and Applicant has been reached.

1.4 Recommendations for Postmarket Requirements and Commitments

In the initial BLA submission, Amgen summarized their routine pharmacovigilance activities, including review of adverse event data from clinical trial and postmarketing sources. In addition, they proposed a 10-year prospective observational PMO study (Protocol 20090522) using large administrative databases such as United Healthcare and the Medicare 5% sample, electronic medical records from closed medical systems such as Kaiser Permanente, and the Scandinavian registry database. The purpose of this study would be to identify prospectively 9 Adverse Events of Special Interest (AESI) suspected to occur in denosumab treated patients:

- Osteonecrosis of the jaw (ONJ)
- Atypical fracture
- Fracture healing complications
- Hypocalcemia leading to hospitalization or emergency room (ER) visit
- Infections leading to hospitalization, ER visit, or administration of parenteral anti-infective medication
- Dermatologic adverse events leading to hospitalization or ER visit
- Acute pancreatitis leading to hospitalization
- Hypersensitivity leading to hospitalization or ER visit
- New primary malignancy

A preliminary study (Protocol 20090521) of the feasibility of this proposed study has been carried out, with results included in the resubmission. These protocols have been reviewed by the Office of Surveillance and Epidemiology (OSE), Division of Epidemiology, and were discussed during a telephone conference on 4/13/10.

In addition, the review team believes that there is opportunity for prospective recording of the 9 above-listed AESIs by healthcare providers because of the requirement that denosumab be administered every 6 months by these providers. This method would be

especially useful for obtaining adequate information to ascertain adverse events that are difficult to classify, such as atypical fractures or delayed fracture healing. Amgen has submitted Protocol 20090601, a proposal for such a study. This 10-year study/program would recruit denosumab prescribers to solicit information about potential AESIs from patients, and submit the information to Amgen either electronically or by mail/phone/fax. This proposal, including the questionnaires for gathering the information, was reviewed by OND and OSE, and comments were also discussed with Amgen during the 4/13/10 teleconference.

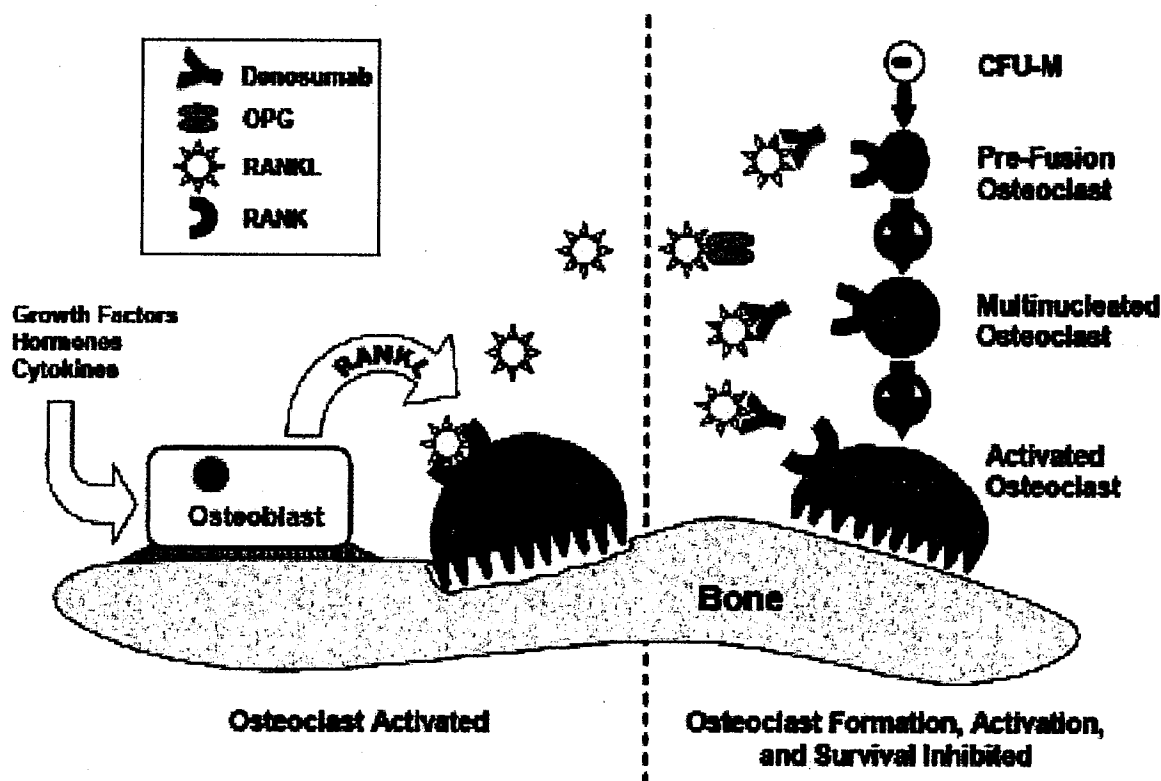
These 2 studies (20090522 and 20090601) will be considered postmarketing requirements. In addition, postmarketing commitments will be requested by the Division of Clinical Pharmacology to investigate the potential for drug-drug interactions with denosumab, and by the Office of Biotechnology Products.

The Maternal Health Team (MHT) has been in discussion with Amgen regarding their proposed surveillance program (PMC) to gather information on women who become pregnant with off-label use. If an indication involving women of childbearing potential were to be sought in the future, MHT recommends that a pregnancy exposure registry (prospective observational cohort study) be required at that time, as well as more complete nonclinical embryofetal toxicity studies.

2 Introduction and Regulatory Background

2.1 Product Information

Prolia (denosumab) is a fully human IgG2 monoclonal antibody against RANKL (RANK ligand), which is the receptor activator of nuclear factor kappa B (RANK). RANKL is essential for normal osteoclast function. Both RANKL and its endogenous inhibitor, osteoprotegerin (OPG) are made by osteoblasts. Pre-osteoclasts and osteoclasts express RANK on their cell membrane, and stimulation by RANKL initiates intracellular signaling cascades which promote osteoclast formation, differentiation, and activation, leading to enhanced resorption of bone. (**Figure 1**) By binding and thus inactivating RANKL, denosumab causes profound suppression of osteoclast function and bone resorption, resulting in an increase in cortical and trabecular bone mass.



CFU-M = colony-forming unit-macrophage; OPG = Osteoprotegerin; RANK = receptor activator of nuclear factor- κ B ; RANKL = RANK ligand

Adapted from Boyle WJ et al. *Nature*. 2003;423:337-342

Figure 1 Mechanism of action of denosumab

In addition to bone, RANKL is highly expressed in lymphoid tissue and dendritic cells, and is important in B- and T-cell maturation; absence of RANKL in knockout mice leads to the complete failure of lymph node development.

2.2 Tables of Currently Available Treatments for Proposed Indications

Osteoporosis is a skeletal disorder characterized by increased bone resorption resulting in low bone mass and microarchitectural deterioration of bone, causing an increase in fragility and susceptibility to fracture. It is more common in women, particularly after menopause when hormonal changes (especially loss of estrogen) lead to more rapid loss of bone. Currently, diagnosis is generally based on bone mineral density (BMD) measurement by dual-energy X-ray absorptiometry (DXA), according to criteria established by the World Health Organization in 1994. By these criteria, BMD T-scores (the number of standard deviations above or below the young adult mean value) are assigned to categories of normal (T-score ≥ -1); low bone mass or osteopenia (T-score

-1 to -2.5); or osteoporosis (T-score < -2.5). In addition to BMD, other factors have also been found to be independent predictors of fracture, particularly age and prior history of fracture.

There are currently 10 products (not including generic versions) approved for the treatment of postmenopausal osteoporosis (PMO) (Table 1)

Table 1. Approved Products for Osteoporosis Treatment

Class	Drug	Route	Dose
Bisphosphonates	Fosamax (alendronate)	Oral	10 mg daily
		Oral	70 mg weekly (tablet/solution)
	Fosamax Plus D	Oral	70 mg/2800 IU weekly
		Oral	70 mg/5600 IU weekly
	Actonel (risedronate)	Oral	5 mg daily
		Oral	35 mg weekly
		Oral	75 mg 2 days/month
		Oral	150 mg monthly
	Actonel with Calcium	Oral	35 mg once weekly 1250 mg Ca ⁺⁺ days 2-7
	Boniva (ibandronate)	Oral	2.5 mg daily
		Oral	150 mg monthly
		IV	3 mg every 3 months
	Reclast (zoledronic acid)	IV	5 mg yearly
Estrogen agonist/ antagonist	Evista (raloxifene)	Oral	60 mg daily
PTH analog	Forteo (teriparatide)	SC	20 mcg daily
Calcitonin*	Miacalcin	SC	100 IU every other day
	Miacalcin	Nasal	200 IU daily
	Fortical	Nasal	200 IU daily

* Approval based on BMD, not fracture efficacy

2.3 Availability of Proposed Active Ingredient in the United States

Denosumab is the first RANKL inhibitor to be developed, and is also the first biologic product and the first monoclonal antibody to seek an indication for the treatment of PMO. It is not currently marketed in any form in the U.S.

2.4 Important Safety Issues With Consideration to Related Drugs

The most commonly prescribed drugs for the treatment of PMO are the bisphosphonates, which like denosumab are potent antiresorptive agents. Safety issues

that are possibly related to over-suppression of bone turnover with long term bisphosphonate use include osteonecrosis of the jaw (ONJ), atypical fractures of the femur, and impairment of fracture healing. Other safety issues with bisphosphonates include upper GI tract irritation with oral dosing; musculoskeletal pain; renal impairment with IV dosing and, due to long residence time of the drugs in bone, potential for fetal toxicity after previous maternal use.

As noted in the initial BLA Clinical Review, there are 27 therapeutic monoclonal antibody or antibody fusion protein products approved for various conditions. Many of these have had major safety issues including serious infections, opportunistic infections, severe infusion reactions, anaphylaxis and malignancies; 20 of the 27 have labeled boxed warnings.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On May 21, 2001, Amgen Inc. submitted original IND 9837 for denosumab. On December 20, 2008, Amgen Inc. submitted Biologic License Applications (BLAs) seeking to market denosumab for 4 separate indications:

- BLA 125320: Treatment of postmenopausal osteoporosis
- BLA 125331: Prevention of postmenopausal osteoporosis
- BLA 125332: Treatment and prevention of bone loss in patients undergoing hormone ablation for breast cancer
- BLA 125333: Treatment and prevention of bone loss in patients undergoing hormone ablation for prostate cancer

The first 2 applications listed (for PMO) were reviewed by the Division of Reproductive and Urologic Products, and the last 2 (for bone loss due to hormone ablation, or HALT) were reviewed by the Division of Biologic Oncology Products. Review of the Phase 3 studies showed that in the PMO population, denosumab 60 mg SC q 6 months is effective in decreasing the incidence of new morphometric vertebral fractures (absolute reduction 4.8%, relative reduction 68%, p-value <0.0001), nonvertebral fractures (absolute reduction 1.5%, relative reduction 20%, p-value 0.0106), and hip fractures (absolute reduction 0.3%, relative reduction 40%, p-value 0.0362). In addition, denosumab was effective in increasing bone mineral density (BMD) in postmenopausal women with low bone mass not in the osteoporotic range. However, the following safety concerns were identified:

- Hypocalcemia;
- Serious infections;
- 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;
- Dermatologic adverse events; and
- Pancreatitis.

An Advisory Committee meeting was convened on August 13, 2009 to discuss all 4 indications. With regard to osteoporosis, the committee recommended approval for treatment (BLA 125,320) but not prevention (BLA 125,331). On the question of whether the benefit of denosumab exceeded the risk for all PMO patients, or for only a subgroup at high fracture risk, many committee members felt that restricting treatment to a high-risk group may be warranted until more information is known about the long-term effects of denosumab. The Committee also voted to recommend a Risk Evaluation and Mitigation Strategy (REMS), including a Medication Guide to inform patients about the risks of the drug, and a Communication Plan to inform providers about the major safety concerns. Some members felt that a registry was also warranted.

On October 16 and 19, 2009, Complete Response actions were taken on all 4 indications. In regard to the treatment of PMO, the reviewers felt that denosumab should be approved based on a favorable risk/benefit profile in high fracture risk patients; the decision for a CR action on this indication was based on: (1) lack of full agreement on product labeling and postmarketing activities, especially the REMS; and (2) lack of an adequate feasibility assessment for the proposed postmarketing observational study. With regard to the second indication, prevention of PMO, the Division agreed with the Advisory Committee that the intended population (younger, and with BMD not as low as the PMO population) would benefit less from denosumab than the PMO population in terms of fracture reduction, at least in the short term, with possibly greater risk of safety issues related to even longer courses of therapy.

The resubmission, dated January 25, 2010, provides a complete response to the Agency requests relative to the application for the treatment of PMO (BLA 125320/0): it outlines plans for the REMS and the postmarketing studies, and includes a further labeling proposal and a requested safety update. It contains no new efficacy data. It does not respond to Agency concerns relative to the proposed PMO prevention indication, but indicates that this may be revisited at a later date. This is considered to be a Class 2 resubmission.

On February 26, 2010, the Applicant submitted revisions to the REMS documents and to the proposed labeling to reflect changes regarding the first case of ONJ observed with denosumab.

2.6 Other Relevant Background Information

In addition to treatment and prevention of PMO and bone loss due to hormone ablation, denosumab is being investigated under (b) (4)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

No new site inspections were conducted for this resubmission. As noted in the original BLA Clinical Review, Amgen determined that there were Good Clinical Practice (GCP) and protocol violations at one clinical site in Lithuania (Site 803) for trial 20030216, based on an inspection by the Lithuanian Health Care Ministry and a joint Amgen, (b) (4) quality assurance audit. This site was subsequently closed and the data from this site was excluded from all safety and efficacy analyses.

Sites were chosen for inspection by the Division of Scientific Investigations (DSI) if they enrolled a large number of subjects, did not have a recent history of inspections, and had a proportionally increased number of protocol violations and/or low numbers of adverse events reported compared to other trial sites. Based on a review of site information and inspection records, DSI inspected 3 individual clinical trial sites from trial 20030216 and 1 clinical site from Study 20010223. One Form 483 was issued related to an incident which the reviewers felt would be unlikely to impact data integrity. Review of all other records noted above revealed no significant discrepancies/regulatory violations. DSI's final assessment was that the data appear acceptable in support of the application. In addition, Amgen, Incorporated (Thousand Oaks, CA) was also inspected by DSI with no significant issues raised.

On October 18, 2009, GCP inspection report for trial 20030216 was received from European Medicines Agency (EMA). This report describes several protocol deviations, the most significant of which involved the primary outcome measure, morphometric vertebral fractures. The EMA inspector noted that fracture status was changed by a second reader for 288 trial subjects. Further information requested of the Applicant revealed that in 80% of these cases, the change in X-ray interpretation involved the screening or baseline film. Of these, 70% involved a change from "no prevalent" fracture to "prevalent" fracture occasioned by comparison with a later film. Changes in fracture status at baseline would not impact the primary endpoint analysis and therefore were not required to be adjudicated according to the study imaging charter. The remaining 63 cases involved a change in interpretation of an on-study film, i.e. a change in incident fracture status. These changes could potentially impact the primary endpoint and therefore underwent the required secondary review and adjudication process in all

except 4 subjects. The Applicant provided sensitivity analysis showing that the changes in these 4 subjects did not impact the primary efficacy analysis.

3.2 Compliance with Good Clinical Practices

No new clinical studies were reported in this resubmission. In the opinion of the clinical reviewers of the original BLAs, studies submitted to BLAs 125,320 and 125,331 appear to have been conducted in compliance with a) their protocols, b) Independent Ethics Committee (IEC) requirements, c) informed consent regulations and d) International Conference on Harmonization / Good Clinical Practices Guidelines, with one notable exception of the Good Clinical Practice (GCP) violations at one clinical site in Lithuania (Site 803) for trial 20030216 (see above).

3.3 Financial Disclosures

No new clinical studies requiring financial disclosure were reported in this resubmission. The Clinical Review of the original BLA notes that the majority of investigators and co-investigators had no financial conflicts of interest to declare. Twenty-six investigators in major studies had financial arrangements to disclose, however these represented a relatively small number of the total number of subjects in these studies.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please refer to Dr. Sarah Kennett's review for complete details.

Other than stability data, no new CMC information was included in this resubmission. Important issues related to CMC aspects of denosumab noted on prior reviews are as follows:

- Denosumab was derived using XenoMouse technology with Chinese hamster ovary (CHO) cells to create a fully human antibody sequence within an IgG2k framework. The drug substance is manufactured at two different sites: Amgen, Colorado (ACO) and Boehringer Ingelheim Pharma, Germany (BIP).
- Two processes (CP1 and CP2) were used for drug substance manufacturing. CP1 material came from the master cell bank and was used in phase 1 trials. CP2 material came from the working cell bank and was used during phase 2 and all pivotal phase 3 clinical trials. There were minor differences (b) (4) seen during development between these two processes. Nonhuman primate PK studies and clinical BE studies have been performed to

ensure that there are not clinically significant differences between the denosumab manufactured through CP1 and CP2 processes.

- Denosumab has (b) (4); there is a difference in charge variants between ACO and GIP. The variation is due to cell culture raw materials and is bounded by base media and enzymatic reaction saturation. Variants have equal *in vitro* potency. This variation is not expected to have a clinical effect.
- Drug product is manufactured at Amgen, Puerto Rico (AML). It is supplied as a 1.0 mL (60 mg/mL) single-use, sterile, preservative-free solution intended for delivery by subcutaneous (SC) injection, either by prefilled syringe (PFS) or single-use vial. In addition to denosumab 60 mg, the solution contains 4.7% sorbitol, 17 mM acetate and NaOH for adjustment to pH 5.2. In addition, PFS formulation also contains 0.01% polysorbate 20.
- Drug Substance and Drug Product Stability- Stability programs conform to ICH guidance and data is sufficient to establish product shelf-life according to the CMC review. For details, please refer to CMC review.

4.2 Clinical Microbiology

Sections 3.2.S and 3.2.P of the original BLA pertaining to microbial control of the drug substance and drug product manufacturing processes were reviewed by the Division of Manufacturing and Product Quality (DMPQ), Biotech Manufacturing Team (BMT). Pre-approval inspections of the ACO and BIP sites were conducted. The BLA was recommended for approval from a microbial control, sterility assurance and product quality microbiology perspective. Please refer to Dr. Patricia Hughes' review for details. No new microbial control data were presented in this BLA resubmission.

4.3 Preclinical Pharmacology/Toxicology

Important issues are summarized here; for details please see Dr. Kimberly Hatfield's reviews.

Denosumab is a fully human IgG₂ monoclonal antibody that binds to the receptor activator of nuclear factor- κ B (RANK) ligand (RANKL). The antibody is specific to human and non-human primate RANKL, therefore the cynomolgus monkey was the species mainly used for nonclinical studies. Although the antibody does not bind to rodent RANKL, some studies were enabled by use of genetically altered (RANKL knock-in) mice in which human RANKL replaced murine RANKL. In addition, because osteoprotegerin (OPG) is like denosumab a regulator of RANKL, an OPG-Fc fusion molecule was created for use in rodent studies. Such studies in young rats showed disruption of epiphyseal plates which negatively affected growth, as well as interference with tooth eruption, causing reviewers to conclude that denosumab should not be used in pediatric populations or in pregnant women.

A 16-month pharmacology study was conducted in ovariectomized (OVX) cynomolgus monkeys, a model which mimics postmenopausal bone loss. Once monthly treatment with denosumab for 12 months decreased biomarkers of bone formation (osteocalcin, sALP) and resorption (CTX, TRAP-5b, NTx), prevented OVX-induced BMD changes in both cortical and cancellous bone, and increased bone strength in most examined bones. Following cessation of treatment, BMD and bone parameters returned to baseline levels.

High levels of RANKL expression were seen in skeletal and lymphoid tissues. In addition, RANKL mRNA expression has been detected in keratinocytes of skin, mammary epithelial cells, heart, skeletal muscle, lung, stomach, placenta, thyroid gland and brain. The RANK/RANKL signaling pathway interacts with the immune system in several ways including lymphocyte development and lymph node organogenesis, monocyte / dendritic cell maturation, activation and longevity, antigen presentation and CD40 ligand-independent T helper cell activation. The absence of RANKL or RANK genes in knock-out mice leads to the complete failure of lymph node development and an absence of lactation by inhibiting mammary gland maturation. A 6/12-month trial in monkeys showed possible signs of immunosuppression, based on the deaths of 2 males with high dose from protozoal infection, and an increased incidence of oral abscesses.

Carcinogenicity studies were not conducted with denosumab due to lack of an appropriate species for testing. Reproductive toxicity studies in monkeys were considered by reviewers to be insufficient to support use during pregnancy – not an issue currently since the indication sought is use only in postmenopausal women.

4.4 Clinical Pharmacology

No new Clinical Pharmacology data was included in the resubmission; Dr. Jee Eun Lee's review is limited to the issue of drug-drug interactions with denosumab, which has not been studied to date. Because of the lack of data, reviewers had previously recommended that Section 7 of the label (Drug Interactions) (b) (4)

(b) (4) and it has been agreed that this discussion will be left out of the label.

However, as per Dr. Lee's review, this rationale is not completely convincing, and she is recommending that the Applicant conduct an *in vivo* drug-drug interaction study as a postmarketing commitment.

Important clinical pharmacology issues from the original BLA are summarized here; please refer to Drs. Chongwoo Yu and Sarah Schrieber's original clinical pharmacology review and Dr. Ping Ji's original pharmacometrics review for complete details.

4.4.1 Mechanism of Action

As noted in the proposed label, denosumab binds to RANKL, a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption. Denosumab prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone. Denosumab interrupts osteoclastogenesis, unlike bisphosphonates which only inhibit function of mature osteoclasts. Also unlike bisphosphonates, denosumab is not incorporated into bone matrix.

4.4.2 Pharmacodynamics

As reflected in the bone resorption markers CTX and TRAP5b, denosumab causes robust suppression of bone resorption by approximately 85% within 3 days, with a nadir at approx. 1-3 months after a dose, at which point many subjects had CTX levels below the limit of quantitation. This level of suppression subsides somewhat toward the end of the 6 month dosing cycle, but remains 45-80% below baseline. Continued treatment causes sustained suppression of resorption and continued increases in BMD. Because of the tight coupling of bone formation and resorption, there is also, after a delay, a marked suppression of bone formation markers e.g. serum P1NP and osteocalcin. After denosumab is discontinued, resorption markers display a "rebound" effect whereby they increase to 40-60% above pretreatment levels within 3-6 months (i.e. 9-12 months after last dose), then return to baseline levels at 18 months (i.e. 24 months after last dose). Concurrently, BMD levels also return to near baseline 12-24 months after discontinuation (i.e. 18-30 months after last dose).

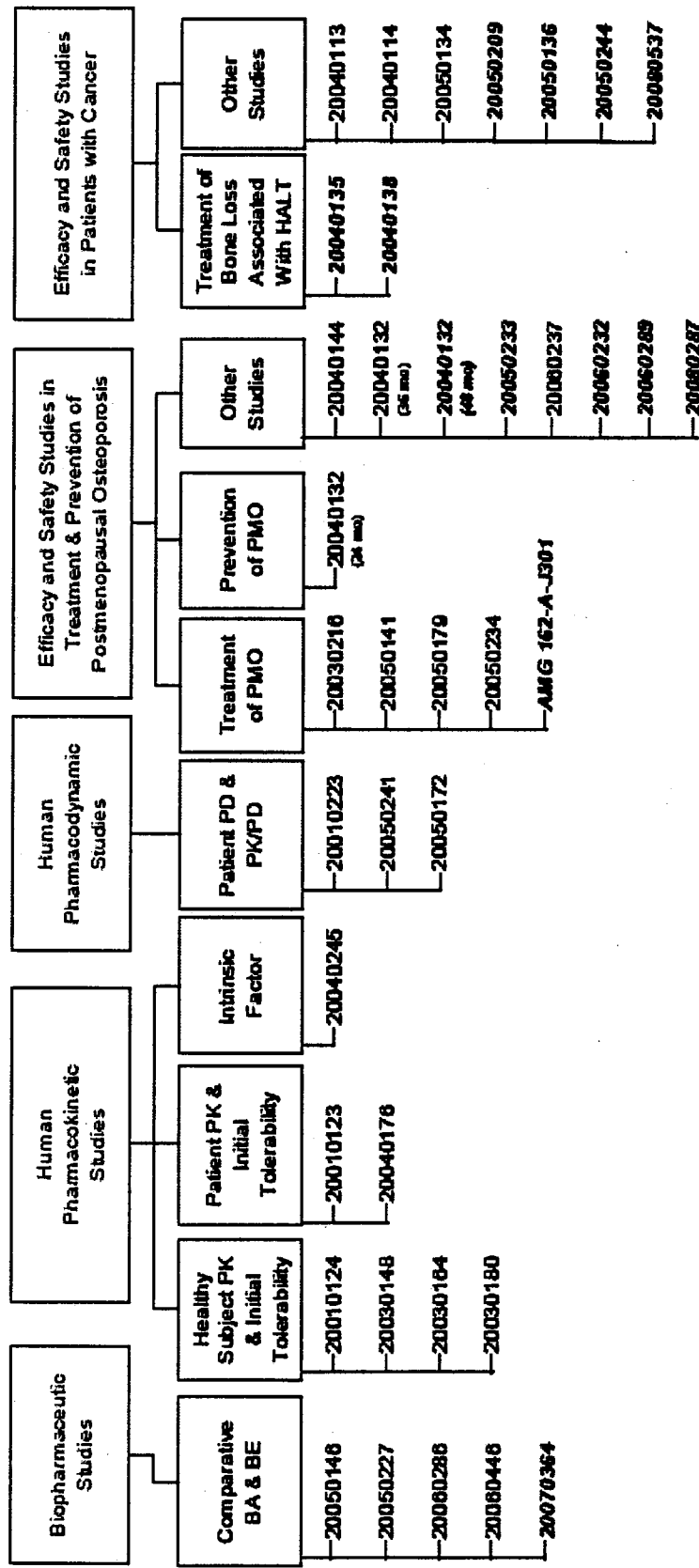
4.4.3 Pharmacokinetics

Denosumab is given at a dose of 60 mg SC every 6 months for the PMO indication. A C_{max} of 6.75 ± 1.89 µg/mL is reached after a median time of 10 days (range 3-21 days). Mean plasma half life is 19.7 ± 8.5 days, and there is no accumulation with repeated doses for up to 4 years. Pharmacokinetics are not affected by age, gender, race or renal function. Less than 1% of subjects treated for up to 5 years developed binding antibodies; none developed neutralizing antibodies. Although body weight was identified as a covariate for clearance, it did not appear to affect BMD changes or fracture rates, therefore the fixed dose of 60 mg Q6M was considered by reviewers to be appropriate for all patients.

5 Sources of Clinical Data

The original marketing application for denosumab (BLAs 125320, 125331, 125332, 125333) submitted in December 2008 included data from 30 clinical studies performed between June 2001 and September 2008. In addition, data from the 120-day Safety Update, submitted 4/15/09, with data cut-off date of 12/2/08, was reviewed in the initial cycle. As requested in the Complete Response letter of 10/16/09, Amgen has provided an additional CR Safety Update, providing data from 12 ongoing and recently completed clinical studies, which is the main focus of this review. **Figure 2** depicts the entire clinical program for denosumab; studies with data reported in this CR Safety Update are indicated in ***bold italic*** text.

Figure 2. Denosumab Clinical Studies



BA = bioavailability; BE = bioequivalence; HALT = hormone ablation therapy; PD = pharmacodynamics; PK = pharmacokinetics; PMO = postmenopausal osteoporosis; SRE = skeletal-related event.

Bold italic text: data from these studies provided in this Safety Update; plain text: no data from this Study provided in this Safety Update.

Source: Complete Response Safety Update, p. 60

5.1 Tables of Studies/Clinical Trials

Table 2 lists the 4 primary phase 3 trials (for 4 different indications) reviewed in the original BLA. The phase 2 dose-finding trial, 20010223, was also reviewed in detail in the initial cycle. These trials are mentioned here because this CR Safety Update review will consider data from the extension studies linked to 20030216 and 20010223, and the off-treatment phases of 20040132, 20040135, and 20040138.

Table 2. Primary Phase 3 Trials Reviewed in Original BLA

Clinical Trial	Indication, # of Subjects, Duration, Dose	Trial Design
20030216	Treatment of PMO 7808 enrolled 3-year 60 mg SC Q6M	Randomized, placebo-controlled, parallel group trial evaluating effects of denosumab on the incidence of new morphometric vertebral fracture in postmenopausal women (age 60-90, mean 72) with osteoporosis (T-score < -2.5 at lumbar spine and/or total hip but not < -4.0); 23% had baseline vertebral fracture
20040132	Prevention of PMO 332 enrolled 60 mg SC Q6M 2 years on treatment, then monitored for additional 2 years off-treatment	Randomized, placebo-controlled, parallel group trial evaluating effects of denosumab on lumbar spine BMD loss in postmenopausal women (age ≤ 90, mean 59) with low bone mass (T-score -1.0 to -2.5 at lumbar spine)
20040135	Prevention and treatment of bone loss in pts undergoing hormone ablation therapy (HALT) for breast Ca 252 enrolled 60 mg SC Q6M 2 years on treatment, then monitored for additional 2 years off-treatment	Randomized, placebo-controlled, parallel-group trial in women receiving adjuvant aromatase inhibitor therapy following definitive local therapy
20040138	Prevention and treatment of bone loss in pts undergoing hormone ablation therapy (HALT) for prostate Ca 1468 enrolled 60 mg SC Q6M 3 years on treatment, then monitored for additional 2 years off-treatment	Randomized, placebo-controlled, parallel group trial evaluating effects of denosumab on bone mass in subjects who were ≥ 70 years, or <70 years with low bone mass or history of fracture

The trials listed in **Table 3**, along with off-treatment phases of trials 20040132, 20040135 and 20040138, account for most of the new data presented in this CR Safety Update:

Table 3. Key Trials with new data in CR Safety Update

Study	Indication, # of Subjects, Duration, Dose, and Study Status	Information provided in Original BLA and 120-Day Safety Update	Information provided in this Complete Response Safety Update
20060289 Phase 3, open-label, single-arm, extension study in women with PMO who completed Trial 20030216	Treatment of PMO 4550 enrolled 7-year (total exposure in parent + extension studies = 10 years) 60 mg SC Q6M Study ongoing	Safety data up to 12/2/08	Safety data up to 7/1/09
20050233 Phase 3, open-label, single-arm, extension study in postmenopausal women with low BMD who completed dose-finding Phase 2 Trial 20010223	PMO 200 enrolled 4-years (total exposure in parent + extension studies = 8 years) 60 mg SC Q6M Study ongoing	Interim analysis up to 6 years (4 yr in trial 20010223 and 2 yr in Study 20050233), and safety data up to 12/2/08	Complete safety analysis up to 6 yrs; last 6-yr subject visit on 4/23/09
20060232 Phase 3b, randomized, crossover, open-label trial in postmenopausal women with low BMD	PMO 250 enrolled 2-years: denosumab 60 mg SC Q6M for 12M followed by alendronate 70 mg PO Qwk for 12M, or reverse order Study ongoing	Safety data up to 12/2/08	Complete safety analysis up to 12 months; last subject visit for 12 months = 6/25/09
20080287 Phase 2 study to characterize effects of discontinuing denosumab on bone histology and histomorphometry	15 planned; 4 enrolled No treatment Enrollment ongoing	None	Subject narratives of bone biopsy results

The CR Safety Update also includes limited data from other trials which will not be reviewed here: **AMG162-A-J301** and **20050209**, which are ongoing and in which safety data are still blinded; **20080537**, an open-label extension of 20040138 with minimal data as of yet; **20070364**, a phase 1 BE study comparing 2 manufacturing processes; and **20050136** and **20050244**, phase 3 studies in patients with advanced cancer.

5.2 Review Strategy

All of the efficacy data and almost all of the safety data to support approval of denosumab for the treatment of PMO were already submitted and reviewed in the initial BLA cycle. This review focused on the Complete Response Safety Update submitted 1/25/10, and will summarize both the old and new safety data. Because the CR Safety Update contains no new efficacy data, section 6 of this review is omitted.

5.3 Discussion of Individual Studies/Clinical Trials

Please see Appendix 9.4 for discussion of individual studies/trials.

6 Review of Efficacy

Efficacy Summary

The efficacy of denosumab in the treatment of PMO was established by Trial 20030216, a three year, randomized, double-blind, placebo-controlled trial in postmenopausal osteoporotic women. The full study reports were included in the initial submission of BLA 125,320 in December 2008 and reviewed. Denosumab 60 mg SC q 6 months is effective in decreasing the incidence of new morphometric vertebral fractures (absolute reduction 4.8%, relative reduction 68%, p-value <0.0001), nonvertebral fractures (absolute reduction 1.5%, relative reduction 20%, p-value 0.0106), and hip fractures (absolute reduction 0.3%, relative reduction 40%, p-value 0.0362). The Division's conclusion that efficacy sufficient to justify approval had been shown is reflected in the currently proposed label. Please refer to Clinical Review of original BLA for details regarding efficacy.

7 Review of Safety

Safety Summary

Important safety issues are summarized below and discussed in detail in the sections that follow.

- **Deaths:** There have been a total of 203 deaths in the denosumab osteoporosis clinical development program. In trial 20030216 (PMO treatment indication), the incidence of all-cause mortality was higher with placebo (90 deaths = 2.3%) than denosumab (70 deaths = 1.8%). As noted in the CR Safety Update, in the ongoing extension study 20060289, there have been 20 deaths in subjects originally on placebo, and 15 deaths in subjects originally on denosumab. There were no deaths in trial 20040132 (PMO prevention indication) during either the on-treatment or off-treatment periods. The number of subjects who died during the key hormone ablation studies was not higher for denosumab (45 subjects)

compared to placebo (47) groups; in the post-treatment observation periods of these trials deaths remained balanced (17 prior-denosumab, 22 prior-placebo).

- **Cardiovascular:** In the entire ISS population in the original BLA, cardiovascular AEs were similarly distributed between the two groups. Adjudicated serious cardiovascular events were similar between the two treatment groups in trials 20030216 and 20040138. There were no differences in aortic calcification scores at 3 years between treatment arms in trial 20030216. There is so far no evidence from extension studies 20050233 or 20060289 that cardiovascular AEs increase over time. There is no evidence that denosumab causes clinically significant QT interval changes.
- **Infections:** In the PMO clinical program, subjects exposed to denosumab had an increased incidence of serious bacterial infections compared to placebo across multiple studies. There were more serious infections of the skin, ear, abdomen (especially diverticulitis) and urinary tract. Also, endocarditis, infected arthritis and skin ulcers occurred more commonly in denosumab-exposed subjects. There have been 4 cases of endocarditis in denosumab subjects (including 3 cases in Trial 20030216 and one in Study 20050233), compared to one case with placebo (in Trial 20040138). Streptococcal infections, including erysipelas and cellulitis, occurred more frequently among denosumab subjects. Three denosumab-exposed subjects in Phase I studies developed pneumonia requiring hospitalization following a single dose of denosumab. While one of these subjects was found to have lung cancer, the other two were young, healthy males less than 35 years old. Extension study 20060289 data, reported in the CR Safety Update, so far shows a continued trend of somewhat higher-than-expected incidences of serious infections and of pneumonia, though there is no evidence that this risk increases further with longer time of exposure. The off-treatment phase of studies 20040132, 20040135 and 20040138 suggest that some increased susceptibility to infection may persist. There does not appear to be an increase in opportunistic infections with denosumab, but immune-suppressed patients have not been studied. SAEs of infection will be monitored in postmarketing studies 20090522 and 20090601.
- **ONJ:** At the time of the Complete Response Safety Update, no cases of ONJ had been positively adjudicated in the PMO or hormone ablation trials (although confirmed cases had occurred in patients with advanced cancer, an ONJ risk factor, at a much higher dose). However, a safety report issued 2/26/10 described a positively adjudicated case of ONJ from ongoing extension study 20060289 in an 83 year old woman who had undergone multiple tooth extractions and other dental procedures. The onset was only ~1.5 years after her first dose of denosumab, as she had been assigned to placebo during the double-blind period. PMR studies will monitor for additional cases and attempt to determine the frequency of ONJ with denosumab.

- **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 trial (Trial 20010223) died of a new malignancy; all subjects received denosumab 100 mg Q6 months for at least 15 months. Overall, subjects in the denosumab group in the primary PMO safety population had an increased incidence of breast cancer, pancreatic cancer, gastrointestinal cancer and reproductive cancers. Breast cancer was the most common adverse event that led to discontinuation of investigational product in the primary PMO safety population, with 20 denosumab (0.5%) and 10 placebo (0.25%) subjects discontinuing due to breast cancer. In extension study 20060289 data, reported in the CR Safety Update, comparison of neoplasm AE rates with the parent study shows no evidence that longer-term exposure to denosumab increases even further the risk of female reproductive, breast, or other specific classes of neoplasms, with the possible exceptions of thyroid, esophageal and colorectal cancer. However, the overall rate of malignancies is somewhat higher in both prior-treatment groups in the extension study relative to both double-blind groups, especially the placebo group. Considering the modest numbers of cases, the issue of malignancy is unresolved, and further study is warranted. To this end, study 20060289 will extend for 7 years, therefore (including the parent study) large numbers of subjects will be observed over 7-10 years of continuous denosumab exposure. In addition, new malignancies will be an outcome of special interest in postmarketing studies 20090522 and 20090601.
- **Pancreatitis:** In PMO trials, 8 denosumab subjects developed pancreatitis (9 events) compared to 4 placebo subjects; all of the denosumab events were considered serious, compared to just one for placebo. Of the 8 denosumab subjects, 3 had had previous histories of pancreatitis, and in one other case it appears the event was gallstone induced. The CR Safety Update reports on 3 additional cases: 2 SAEs apparently gallstone-related (1 from extension study 20050233 and 1 from off-treatment period of 20040138), and 1 nonserious AE from extension study 20060289. The temporal relationship of these events was highly variable, which is not unusual for idiosyncratic drug induced pancreatitis. Denosumab may be a risk factor for serious pancreatitis based on trial 20030216. The strength of the evidence and the number of cases are not sufficiently compelling to warrant inclusion in labeling under Warnings and Precautions, but pancreatitis should be included under Adverse Reactions.
- **Skin and soft tissue disorders:** In the primary PMO trials, subjects in the denosumab group were more likely to develop skin and soft tissue related AEs, 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. There is so far no evidence from extension study 20050289 that these AEs increase with longer term use.

- **Bone biopsy/histomorphometry:** Bone remodeling is essential for repair of micro-cracks which develop over time, in order to preserve bone strength. Bone histomorphometry results raise concerns about the degree of remodeling suppression. The denosumab group had markedly suppressed bone resorption and bone formation parameters. 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. These potential delayed effects will continue to be monitored for up to 10 years in the extension study and are events of special interest in the postmarketing studies 20090522 and 20090601. After denosumab is discontinued, there is some evidence that bone remodeling returns to baseline over time, but histomorphometry evidence to confirm this is not yet complete.
- **Hypocalcemia:** Hypocalcemia is a known class effect of antiresorptive drugs. Denosumab-induced hypocalcemia appears to be transient (nadir at day 8-11 of approx. -2 to -3%) with spontaneous resolution and no serious sequelae observed. However, virtually all subjects studied received calcium/vitamin D supplements; therefore, outside of the controlled clinical trial environment, more patients may experience hypocalcemia. Patients with renal dysfunction appear to have much greater reductions in serum calcium. Hypocalcemia will be listed in the Contraindications and the Warnings and Precautions sections of the labeling document.
- **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 impairment in renal or hepatic function.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

In the initial BLA review, the 4 pivotal Phase 3 trials listed above in **Table 2** were used to evaluate the safety of denosumab 60 mg SC Q6M. New safety data (including AE datasets, hyperlinked CRFs, SAE narratives, subject listings and tabulations) reviewed here (see **Table 3** above) include those from:

- the open-label extension (20050233) of the Phase 2 dose-finding trial (20010223)
- the open-label extension (20060289) of the PMO treatment trial (20030216)
- the off-treatment phase of the other 3 pivotal trials (for other indications – 20040132, 20040135, 20040138)
- a Phase 3 study comparing denosumab with alendronate (20060232)
- a study of bone histology/histomorphometry after denosumab discontinuation (20080287)
- a safety report submitted on 2/26/10 regarding a case of ONJ

7.1.2 Categorization of Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), and the submitted application was coded in MedDRA version 11.0. The Applicant adhered to the definition and reporting requirements for serious adverse events, as defined by the ICH guidelines. The National Cancer Institute Common Toxicity Criteria (CTCAE Criteria, version 3.0) was used to grade the severity of laboratory result abnormalities. These criteria employ a grading system of 0 (laboratory values within normal limits) to 4 (severe toxicity) to classify the increase or decrease in the laboratory parameter.

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

In the review of the original BLA application, safety data were pooled by indication: Trials 20030216 and 20040132 were integrated to evaluate safety in the PMO population and trials 20040135 and 20040138 were integrated to evaluate safety in the HALT population. The Quantitative Safety and Pharmacoepidemiology Group (QSPG) also provided statistical safety analysis.

Data in this CR Safety Update have not been pooled across trials/studies because of significant differences in study population and design. However, in order to investigate possible changes in denosumab AEs over time, the Applicant compared AE rates in trial 20030216 and follow-up study 20060289 by adjusting for subject-years of exposure for each treatment group and each prior-treatment group, respectively. Thus, in the group exposed to continuous denosumab for 4-5 years, the rate of each AE during the first 3 years could be compared to its rate in the subsequent 1-2 years. This may be informative with a drug such as denosumab, where potential AEs (e.g. malignancy) may have a very long latency.

Reviewer comment: This method of comparison is probably valid because AEs were assessed at the same intervals and using the same procedures in both parent and follow-up study. It is not clear whether the change from double-blind to open label would affect reporting of AEs. Rates of reporting of serious AEs did not change markedly through this transition, but overall AEs (especially musculoskeletal and GI, but not infections or neoplasms) were reported less frequently in the extension study.

7.2 Adequacy of Safety Assessments

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

As of the 7/1/09 cutoff date for the studies included in the CR Safety Update, more than 10,000 subjects have been exposed to denosumab in North and South America, Europe, Australia, and Japan. Most studies have enrolled > 90% Caucasian women, so there is relatively little experience with other populations, especially African/African-American or Asian.

A total of 7983 subjects were treated with ≥ 1 dose of denosumab in the phase 2 and 3 PMO trials, and 931 subjects were treated with ≥ 1 dose of denosumab in the phase 3 HALT (hormone ablation therapy) trials. The great majority of these, including all of those from the phase 3 PMO trials (n=4050) and the HALT trials (n=931), were administered the 60 mg Q6M dose currently proposed, and most were women with PMO, the proposed target population.

With the additional long-term data from the extension studies (20050223 and 20060289) included in the CR Safety Update, there is now information on ≥ 4 year denosumab exposure in 2312 subjects (mostly at the 60 mg Q6M dose), and ≥ 6 -year exposure in 111 subjects, mostly continuous exposure. (**Table 4**) The mean ages at baseline for these two extension studies were 66.1 and 74.8, respectively, with about 90% Caucasian and all women with either PMO or osteopenia.

Table 4 Number of Subjects Receiving Denosumab and Duration of Cumulative Exposure by Study Type (Overall Safety Analysis Set)

	Denosumab						
	≥ 1 Dose	≥ 1 Year	≥ 2 Years	≥ 3 Years	≥ 4 Years	≥ 5 Years	≥ 6 Years
Overall total exposure	10362	8694	4809	4028	2312	128	111
Phase 1 studies ^a	925	0	0	0	0	0	0
Bone loss due to hormone ablation therapy studies ^b	931	798	711	484	0	0	0
Postmenopausal osteoporosis studies	7983	7575	4098	3544	2312	128	111
Key phase 3 studies ^c	4050	3867	3656	3331	0	0	0
Additional phase 2 and 3 studies ^d	3933	3708	442	213	2312	128	111
Phase 2 studies in other indications ^e	523	321	0	0	0	0	0

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Exposure is defined as time on Study during the treatment period and does not include Study specified off-treatment periods.

^a Includes studies 20010123, 20010124, 20030148, 20030164, 20030180, 20040176, 20040245, 20050146, 20050227, 20050241, 20060286, 20060446, and 20070364

^b Includes studies 20040135 (24 months), 20040138 (36 months), and 20080537

^c Includes studies 20030216 and 20040132 (24 months)

^d Includes studies 20010223, 20050141, 20050172, 20050179, 20050233 (24 months), 20050234, 20060232 (12 months), 20060237 (12 months), and 20060289

^e Includes studies 20040113 (advanced cancer), 20040114 (25 weeks - advanced cancer), 20040144 (12 months - rheumatoid arthritis), and 20050134 (multiple myeloma)

Source: Table 3, p. 68, Complete Response Safety Update

7.2.2 Explorations for Dose Response

Seven different dose regimens were evaluated in trial 20010223, the primary phase 2 dose-finding trial. Reviewers concluded that there was no clear difference in dose-response between these regimens in terms of either safety or efficacy. Nevertheless, only one dose (60 mg Q6M) was chosen for the phase 3 trials including the proposed PMO-treatment indication. All of the new data included in the CR Safety Update is from subjects receiving this dose. It is unclear whether the safety issues which have emerged could be mitigated by use of a lower dose of denosumab.

7.2.3 Special Animal and/or In Vitro Testing

Reviewers of the initial BLA submission concluded that the pharmacology/toxicology program was adequate overall, though with 2 caveats: (1) only one species, the monkey, was considered relevant for testing, thus carcinogenicity studies were considered not feasible; and (2) reproductive toxicity studies were incomplete; this was not considered a major problem as the target population is limited to postmenopausal women.

7.2.4 Routine Clinical Testing

It appears that adequate investigations have been done to assess potential monoclonal antibody effects such as infection and malignancy, and to evaluate prospectively for cardiovascular safety, ONJ, and delayed fracture healing complications.

7.2.5 Metabolic, Clearance, and Interaction Workup

No metabolism studies have been conducted, as monoclonal antibodies are not expected to be metabolized by the CYP enzymes. However, the clinical pharmacology review staff plans to recommend a postmarketing commitment to evaluate this. Reviewers of the initial BLA felt that clearance data were consistent with at least 2 mechanisms of elimination for denosumab: target mediated, saturable disposition that predominates at lower serum concentrations; and a nonsaturable mechanism at higher concentrations.

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

Evaluation for potential monoclonal antibody effects of infection, malignancy and hypersensitivity was considered adequate. Issues related to the mechanism of suppression of bone resorption (hypocalcemia, ONJ, impaired fracture healing) were adequately addressed: for example, potential ONJ cases were adjudicated by an expert committee, and specific searches for symptoms of hypocalcemia were performed in addition to serum calcium levels.

7.3 Major Safety Results

7.3.1 Deaths

In the phase 2 dose-finding trial (20010223) of 412 subjects over 4 years, there were 4 deaths, 3 of which were due to malignancies; all 3 of these were in the highest-dose (100 mg Q6M) dose cohort of 41 subjects, which raised concern among reviewers. In the 200 subjects who enrolled in the subsequent extension study (20050233), over the first 2 years there were 5 deaths, and 3 were due to malignancies.

In the pivotal phase 3 PMO trial 20030216 of 7808 subjects, fatal adverse events occurred in 70 subjects (1.8%) in the denosumab group and 90 subjects (2.3%) in the placebo group (see Table 27, BLA Clinical Review). Deaths were adjudicated to classify each as to the most likely cause and whether the cause was cardiovascular. The most common causes of death by MedDRA SOC were neoplasms (~29% in both treatment groups) and cardiac disorders (~26% in both treatment groups). Reviewers looked in detail at all of these deaths and did not identify any fatality-related safety signals.

There were 4550 subjects who enrolled in the open-label extension of this trial, study 20060289. The CR Safety Update reports 35 deaths up to the cutoff date of 7/1/09: 15 in the continuous-denosumab cohort and 20 in the prior-placebo cohort. None were considered IP-related by the investigator. The most frequent AEs by PT were: "death" i.e. unknown cause (6 cases), cardiopulmonary failure (3), and pulmonary embolism, CVA and multi-organ failure (2 each). There were 8 fatal AEs for neoplasms (all different malignancies), and 5 fatal cardiac AEs. One fatal AE was attributed to an infection (sepsis/pneumonia in an 81 y/o).

There were no deaths in trial 20040132 (PMO prevention indication) during either the on-treatment or off-treatment periods.

In other ongoing studies with data reported in the CR Safety Update, there have been no deaths reported to date in the phase 3 trials 20060232 or AMG 162-A-J301. In the off-treatment follow-up period of phase 3 study 20040135 (hormone-ablation breast cancer) there have been 4 deaths (2% of subjects). Two of these deaths were in the prior-denosumab group and were both from metastatic breast cancer; the other 2, in prior-placebo subjects, were from hepatic failure and breast cancer. In the off-treatment follow-up period of phase 3 study 20040138 (androgen-deprivation prostate cancer), there have been 25 deaths (3.6% of subjects): 15 in prior-denosumab and 14 in prior-placebo subjects. The cause was prostate cancer with or without bone metastases in 5 and 4 of these cases respectively. There were also 5 deaths due to new malignancies in the prior-denosumab group (acute leukemia, lymphoma, pancreatic carcinoma, metastatic rectal cancer and malignant tongue neoplasm), and just one in the prior-placebo group (malignant brain neoplasm).

Reviewer comment: Overall, there is no evidence of excess mortality associated with denosumab in the PMO or HALT populations at the proposed dose.

7.3.2 Nonfatal Serious Adverse Events

In study 20030216, nonfatal SAEs were reported for 25.0% of denosumab subjects vs. 24.2% of placebo subjects (see Table 86, Clinical Review of initial BLA). Greater numbers of SAEs occurred in denosumab vs. placebo subjects in the following SOC classes: cardiac disorders (265 vs. 195); infections (186 vs. 148); neoplasms (161 vs. 129); and gastrointestinal disorders (181 vs. 131); other classes were generally

balanced. When classified by High Level Group Term, the categories of coronary artery disorders, unspecified infections, and urinary tract signs and symptoms occurred more commonly in denosumab subjects.

According to the CR Safety Update, serious AEs were reported for 13.4% of extension study subjects in study 20060289 up to the cutoff date, with incidence about equal between prior-treatment groups. (Table 5) SAEs in the cardiac, infection and skin classes will be discussed in sections 7.3.4.1, 7.4.3.2 and 7.3.4.8 respectively. The most frequent SOC was Injury, poisoning and procedural complications, and the most frequent of these were fractures. There were greater numbers in the prior-placebo relative to the prior-denosumab group of femoral neck fractures (10 vs. 5 subjects) and femur fractures (4 vs. 2 subjects). Of the 6 cases of "femur fracture", 5 were described as intertrochanteric and the other as a "subtrochanteric fracture of femoral neck left" (sic). The most frequent SAEs by Preferred Term were osteoarthritis (0.6% of subjects), pneumonia (0.4%), femoral neck fracture (0.3%), and fall (0.3%). SAEs considered possibly treatment related occurred in 0.4% of subjects, and none of the PTs of these events occurred in > 1 subject.

Table 5 Study 20060289: Subject Incidence of SAEs by System Organ Class

System Organ Class	Placebo/ Denosumab 60 mg Q6M (N=2203) n	Denosumab/ Denosumab 60 mg Q6M (N=2346) n
Total number of subjects reporting SAEs	304 (13.8%)	306 (13.0%)
Injury, poisoning and procedural complications	53	45
Cardiac disorders	43	48
Neoplasms benign/malignant/unspecified	38	48
Infections and infestations	43	36
Nervous system disorders	32	40
Musculoskeletal and connective tissue disorders	36	33
Gastrointestinal disorders	40	18
Vascular disorders	20	20
Respiratory, thoracic, and mediastinal disorders	15	16
General disorders and administration site conditions	12	17
Hepatobiliary disorders	9	14
Eye disorders	10	9
Reproductive system and breast disorders	11	8
Metabolism and nutrition disorders	4	10
Renal and urinary disorders	8	8
Ear and labyrinth disorders	9	5
Blood and lymphatic system disorders	7	5
Psychiatric disorders	4	7

System Organ Class	Placebo/ Denosumab 60 mg Q6M (N=2203) n	Denosumab/ Denosumab 60 mg Q6M (N=2346) n
Investigations	5	3
Skin and subcutaneous tissue disorders	1	5
Endocrine disorders	5	0
Immune system disorders	1	2
Missing system organ class	3	0
Surgical and medical procedures	0	2
Source: Table 03-6.4.1, CR Safety Update n = number of subjects reporting ≥ 1 event		

Adjusted by subject-years of exposure, there were no pronounced differences between parent and extension studies, or between prior-placebo and prior-denosumab subjects within the extension study, for most SAEs by SOC class or PT. SAEs of infection including pneumonia and sepsis, however, were somewhat more frequent in the extension study (see section 7.4.3.2 below).

7.3.3 Dropouts and/or Discontinuations

In the 2 key PMO trials, 2.3% of denosumab subjects and 2.0% of placebo subjects withdrew from the study because of an AE; 4.8% of denosumab subjects and 5.1% of placebo subjects discontinued study drug because of an AE.

In extension studies 20060289 and 20050233, there were 73/4550 (1.6%) and 7/200 (3.5%) subjects respectively who discontinued denosumab due to AE. In study 20060289, these AEs were balanced between prior-treatment groups; 3 were due to infections.

7.3.4 Significant Adverse Events

7.3.4.1 Cardiovascular Safety

The target population of postmenopausal women is at high risk of cardiovascular disease. Although preclinical studies in monkeys did not present a cardiac safety signal, concern was raised because of literature reports suggesting a possible association between OPG levels and aortic wall calcification, cardiovascular disease and mortality. Denosumab could in theory have a similar effect, or in binding RANKL could result in elevated OPG levels. Therefore, adjudication of cardiovascular SAEs was performed by Amgen in the Phase 3 trials 20030216 and 20040138. In addition, Agency reviewers conducted an independent analysis of cardiovascular AEs and SAEs in a broader safety

database encompassing all phase 2 and 3 trials. They concluded that there was no significant cardiovascular safety signal with denosumab observed in either adjudicated or unadjudicated CV-related outcomes. Also, there was no clear increase in OPG levels in denosumab subjects. Aortic calcification was also assessed on lateral lumbar spine X-rays in 2363 subjects in Trial 20030216; at months 12, 24 and 36, there was no difference between denosumab and placebo. (However as noted by reviewers, this is probably a crude marker for atherosclerosis.)

Review of safety data from the CR Safety Update shows that in extension study 20060289, cardiac AEs were reported for 6.1% of subjects and cardiac SAEs for 2.0% of subjects; there were no apparent differences between prior-placebo and prior-denosumab groups. (Table 6)

Table 6 Study 20060289: Subject Incidence of Cardiac SAEs by PT (Most frequent)

Preferred Term	Placebo/ Denosumab 60 mg Q6M (N=2203) n (%)	Denosumab/ Denosumab 60 mg Q6M (N=2346) n (%)	All (N=4549) n (%)
All cardiac SAEs	43 (2.0)	48 (2.0)	91 (2.0)
Atrial fibrillation	8 (0.4)	5 (0.2)	13 (0.3)
Angina pectoris	6 (0.3)	6 (0.3)	12 (0.3)
Coronary artery disease	6 (0.3)	6 (0.3)	12 (0.3)
Myocardial infarction	5 (0.2)	6 (0.3)	11 (0.2)
Angina unstable	3 (0.1)	4 (0.2)	7 (0.2)
Myocardial ischemia	1 (< 0.1)	4 (0.2)	5 (0.1)
Cardiac failure	1 (< 0.1)	3 (0.1)	4 (< 0.1)
Source: CR Safety Update, Table 03-6.4.1 Data from Trial 20030216 start through 7/1/09			

Vascular AEs occurred in 10.7% of extension subjects and SAEs for 0.9% of subjects.

Within the continuous-denosumab group, rates in the double-blind and extension phases were similar for serious cardiac AEs (2.6 vs. 2.2 per 100 subject-years respectively), and serious vascular AEs (0.8 vs. 0.9 respectively).

For studies 20050233 and 20060232, cardiac and vascular AEs were reported in ≤ 6% and ≤ 8% of subjects respectively, and there were no fatal cardiovascular events.

Reviewer comment: There is no evidence of cardiovascular safety issues with denosumab.

7.3.4.2 Infections

Because RANKL is expressed on activated T and B lymphocytes and in lymph nodes, inhibition by denosumab could potentially impair lymphocyte function and increase risk of infections. A 12-month toxicity study in monkeys showed possible signs of immune suppression at high dose including deaths due to protozoal infection, increased incidence of abscesses of teeth and jaws, and decreases in lymphocyte counts.

In Phase 1 studies, 3 subjects were hospitalized for pneumonia. One was a 75 y/o with history of smoking and COPD who was soon thereafter diagnosed with lung cancer. However, the other 2 were healthy males, age 33 and 34, who developed pneumonia on study day 13 for one subject, and on study day either 12 or 74 (records unclear) for the other subject. Unfortunately, hospital records were unavailable for these 2 subjects despite an apparently diligent effort.

In Phase 2 and 3 studies, denosumab and placebo groups had similar rates of overall infections, but denosumab subjects had a higher incidence of serious bacterial infections, including skin infections; abdominal and gastrointestinal infections (especially diverticulitis); urinary tract infections; pneumonia; and ear infections. Subjects were more likely to be hospitalized for cellulitis with denosumab compared to placebo. In Trial 20030216, 3 denosumab subjects developed endocarditis, vs. 0 with placebo; 7 denosumab subjects developed SAEs of erysipelas, vs. 0 placebo; and 8 denosumab subjects developed infective arthritis (all nonserious), vs. 0 placebo. There did not appear to be an increase in opportunistic infections, and older subjects did not appear to be at higher risk. During the review of the initial BLA, a consult was requested of the Division of Anti-Infective and Ophthalmology Products, and there was agreement that the apparent increase in serious infections should be communicated in labeling and in a REMS, and should be monitored closely in postmarketing activities.

In the extension study 20060289, according to the CR Safety Update, AEs of infection were reported for 30.2% of subjects and SAEs of infection for 1.7% of subjects. There were minimal differences between prior-placebo and prior-denosumab groups: 31.0% vs. 29.4% of subjects for all AEs and 2.0% vs. 1.5% of subjects for SAEs. There were no pronounced differences between prior-treatment groups in the subject incidence of overall AEs in the most frequent HLT or PT categories or in serious AEs in the most frequent PTs. (See **Tables 16 and 17**, Appendix 9.4.4)

Within the continuous-denosumab group, rates of overall infection AEs did not significantly increase from the double-blind to the extension phase: 38.9 vs. 39.8 per 100 subject-years respectively. (**Table 7**) The 7 most commonly reported infection AEs by PT in the extension study were the same ones, in almost the same order of relative frequency, as those in the double-blind phase; adjusted for exposure, rates in double-blind vs. extension phases were comparable except for slightly higher pneumonia rates in the extension (see below).

Table 7 Subject-Year-Adjusted AE Rates of Infection: Most frequent events

	Trial 20030216		Study 20060289		
	Placebo (n=3876) Subj-yr= 10719	Denosumab 60 mg Q6M (n=3886) Subj-yr= 10826	Placebo/ Denosumab 60 mg Q6M (n=2203) Subj-yr= 2495	Denosumab/ Denosumab 60 mg Q6M (n=2346) Subj-yr= 2660	All (n=4549) Subj-yr= 5155
Preferred term	e (r)	e (r)	e (r)	e (r)	e (r)
Number, % of subjects with AEs of infection	2110 (54.4%)	2055 (52.9%)	684 (31.0%)	690 (29.4%)	1374 (30.2%)
Total # of infection AEs	4309(40.2)	4313 (39.8)	997 (40.0)	1034 (38.9)	2031 (39.4)
Nasopharyngitis	799 (7.5)	762 (7.0)	160 (6.4)	149 (5.6)	309 (6.0)
Cystitis	328 (3.1)	327 (3.0)	84 (3.4)	93 (3.5)	177 (3.4)
Bronchitis	376 (3.5)	393 (3.6)	79 (3.2)	94 (3.5)	173 (3.4)
Influenza	412 (3.8)	404 (3.7)	80 (3.2)	76 (2.9)	156 (3.0)
Urinary tract Infection	338 (3.2)	335 (3.1)	80 (3.2)	68 (2.6)	148 (2.9)
Pneumonia	195 (1.8)	188 (1.7)	67 (2.7)	59 (2.2)	126 (2.4)
Upper respiratory tract infection	204 (1.9)	241 (2.2)	52 (2.1)	52 (2.0)	104 (2.0)
Source: Table 6, Complete Response Safety Update Data from Trial 20030216 start through 7/1/09 e = number of events; r = event rate per 100 subject-years					

Serious infection AEs occurred in 1.7% of subjects in the extension study 20060289. (Table 8) The most common serious adverse events of infection were pneumonia (0.4% of subjects) and sepsis, diverticulitis, and bronchitis (0.1% each). There were no compelling differences between prior-treatment groups other than a possible imbalance in subjects with SAEs of sepsis (1 in prior-placebo vs. 4 in prior-denosumab group).

**Table 8 Study 20060289: Subject Incidence of Infection SAEs by PT
(Most frequent)**

	Placebo/ Denosumab 60 mg Q6M (N=2203) n (%)	Denosumab/ Denosumab 60 mg Q6M (N=2346) n (%)	All (N=4549) n (%)
All serious infections	43 (2.0)	36 (1.5)	79 (1.7)
Pneumonia	9 (0.4)	8 (0.3)	17 (0.4)
Sepsis	1 (< 0.1)	4 (0.2)	5 (0.1)
Diverticulitis	3 (0.1)	2 (< 0.1)	5 (0.1)
Bronchitis	4 (0.2)	1 (< 0.1)	5 (0.1)
Pneumonia bacterial	2 (< 0.1)	2 (< 0.1)	4 (< 0.1)
Appendicitis	0 (0.0)	3 (0.1)	3 (< 0.1)
Erysipelas	1 (< 0.1)	2 (< 0.1)	3 (< 0.1)
Urinary tract infection	1 (< 0.1)	2 (< 0.1)	3 (< 0.1)
Pneumonia pneumococcal	2 (< 0.1)	1 (< 0.1)	3 (< 0.1)
Source: CR Safety Update, Table 03-6.4.1 Data from Trial 20030216 start through 7/1/09			

Adjusted for subject-years of exposure, rates of these SAEs and of overall infection SAEs in the continuous-denosumab extension group were similar to slightly higher than those in the double-blind denosumab group. (Table 9)

Table 9 Subject-Year-Adjusted SAE Rates of Infection: Most frequent events

	Trial 20030216		Study 20060289		
	Placebo (n=3876) Subj-yr= 10719	Denosumab 60 mg Q6M (n=3886) Subj-yr= 10826	Placebo/ Denosumab 60 mg Q6M (n=2203) Subj-yr= 2495	Denosumab/ Denosumab 60 mg Q6M (n=2346) Subj-yr= 2660	All (n=4549) Subj-yr= 5155
Preferred term	e (r)	e (r)	e (r)	e (r)	e (r)
Number, % of subjects with SAEs of infection	134 (3.5%)	160 (4.1%)	43 (2.0%)	36 (1.5%)	79 (1.7%)
Total # of infection SAEs	155 (1.4)	194 (1.8)	53 (2.1)	43 (1.6)	96 (1.9)
Pneumonia	37 (0.3)	35 (0.3)	11 (0.4)	9 (0.3)	20 (0.4)
Diverticulitis	6 (< 0.1)	9 (< 0.1)	3 (0.1)	4 (0.2)	7 (0.1)
Sepsis	4 (< 0.1)	3 (< 0.1)	1 (< 0.1)	4 (0.2)	5 (< 0.1)
Bronchitis	7 (< 0.1)	4 (< 0.1)	4 (0.2)	1 (< 0.1)	5 (< 0.1)
Appendicitis	7 (< 0.1)	7 (< 0.1)	0 (0.0)	4 (0.2)	4 (< 0.1)
Pneumonia bacterial	2 (< 0.1)	2 (< 0.1)	2 (< 0.1)	2 (< 0.1)	4 (< 0.1)
Erysipelas	0 (0.0)	7 (< 0.1)	1 (< 0.1)	2 (< 0.1)	3 (< 0.1)
Urinary tract Infection	10(< 0.1)	16 (0.1)	1 (< 0.1)	2 (< 0.1)	3 (< 0.1)
Pneumonia pneumococcal	1 (< 0.1)	0 (0.0)	2 (< 0.1)	1 (< 0.1)	3 (< 0.1)
Cystitis	2 (< 0.1)	6 (< 0.1)	3 (0.1)	0 (0.0)	3 (< 0.1)
Lobar pneumonia	2 (< 0.1)	0 (0.0)	0 (0.0)	2 (< 0.1)	2 (< 0.1)
Lower respiratory tract infection	3 (< 0.1)	10 (< 0.1)	1 (< 0.1)	1 (< 0.1)	2 (< 0.1)
Source: Table 03-6.11.5, Complete Response Safety Update					
Data from Trial 20030216 start through 7/1/09					
e = number of events; r = event rate per 100 subject-years					

Serious AEs of pneumonia/pneumonia bacterial/pneumococcal pneumonia/lobar pneumonia/lower respiratory tract infection/bronchopneumonia combined occurred at rates of 0.48 per 100 subject-years in the double-blind placebo group and 0.49 in the double-blind denosumab group; and in the extension study, 0.68 in the prior-placebo group and 0.56 in the prior-denosumab group. Overall AEs of pneumonia (serious + nonserious) occurred at rates of 1.8 per 100 subject-years of exposure in placebo subjects compared with 1.7 in denosumab subjects in the double blind period; in the

extension study 20060289, these rates were slightly higher: 2.7 per 100 subject-years in the prior-placebo group compared with 2.2 in the prior-denosumab group.

One serious adverse event of infection was fatal (sepsis/pneumonia; Subject 6436107, continuous-denosumab group). Unlike in parent trial 20030216, there were no cases of endocarditis or infective arthritis in this extension study.

Serious AEs of **skin infection** were reported for 4 subjects in study 20060289: 3 with erysipelas and 1 with necrotizing fasciitis. Overall frequency of skin infection SAEs was not greater in the extension study compared to the parent study. (Table 10)

Table 10 Subject-Year-Adjusted SAE Rates of Skin Infection

Preferred term	Trial 20030216		Study 20060289		All (n=4549) Subj-yr= 5155
	Placebo (n=3876) Subj-yr= 10719	Denosumab 60 mg Q6M (n=3886) Subj-yr= 10826	Placebo/ Denosumab 60 mg Q6M (n=2203) Subj-yr= 2495	Denosumab/ Denosumab 60 mg Q6M (n=2346) Subj-yr= 2660	
	e (r)	e (r)	e (r)	e (r)	e (r)
Number, % of subjects with SAEs of infection	3 (< 0.1%)	15 (0.4%)	1 (< 0.1%)	3 (0.1%)	4 (< 0.1%)
Total # of skin infection SAEs	3 (<0.1)	17 (0.2)	1 (<0.1)	3 (0.1)	4 (<0.1)
Erysipelas	0 (0.0)	7 (<0.1)	1 (<0.1)	2 (<0.1)	3 (<0.1)
Necrotizing fasciitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Cellulitis	1 (<0.1)	6 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Infected skin ulcer	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Skin bacterial infection	0 (0.0)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Staphylococcal infection	1 (< 0.1)	1 (< 0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Subcutaneous abscess	1 (< 0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Source: Table 8, Complete Response Safety Update Data from Trial 20030216 start through 7/1/09 e = number of events; r = event rate per 100 subject-years					

The phase 3 trials 20040132, 20040135 and 20040138 all had higher rates of serious infection AEs with denosumab relative to placebo during the treatment phase. In the off-

treatment periods of all 3 trials, there were higher overall rates of infection AEs in prior-denosumab compared to prior-placebo subjects. SAEs of infection were even between these off-treatment groups (14 each, for the 3 trials combined), however SAEs of pneumonia were more common in prior-denosumab subjects (8 vs. 1). In ongoing trial 20060232 as well, infection AEs have been more common in denosumab subjects compared to the control group (alendronate).

In the extension study 20050233, 4 subjects (out of 200) experienced SAEs of infection; all recovered. One of these, an 83-year-old in her 5th year of continuous denosumab (including the first 2 years on a high dose of 100 mg Q6M), developed staphylococcal septicemia and endocarditis, and despite several weeks of appropriate antibiotic therapy went on to develop CHF and severe mitral regurgitation leading to valve replacement. Together with the 3 cases in Trial 20030216, this case represents the fourth reported case of endocarditis associated with denosumab. The other infection SAEs in study 20050233 were: diverticulitis resulting in colectomy; pneumonia in a diabetic with ketoacidosis; and aspiration pneumonia following cholecystectomy after an episode of gallstone pancreatitis.

Reviewer comment: Data from the open-label extension studies appear to be consistent with those in the initial trials, indicating that serious AEs of infection are more common with denosumab than placebo in the PMO population, consistent with the drug's potential to interact with the immune system. This trend appears to persist with continuous exposure beyond 3 years, with no clear evidence of either improvement or worsening. The effect appears to involve multiple classes of bacterial infections; opportunistic infections have not been seen. No population appears to be at greater risk, though immunosuppressed subjects have not been studied. This trend, particularly the occurrence of 4 cases of endocarditis in denosumab-treated subjects, is of concern and warrants inclusion in labeling section 5.2 WARNINGS AND PRECAUTIONS/ Serious Infections.

7.3.4.3 Osteonecrosis of the Jaw

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. Bisphosphonates, which like denosumab cause major suppression of bone remodeling, have been associated with ONJ in postmarketing reports. Most reports have occurred in cancer patients treated with IV bisphosphonates, but long-term (>3-year) use of oral bisphosphonates for osteoporosis has also been associated with ONJ, especially following dental procedures.

As with bisphosphonates, ONJ with denosumab was first seen in cancer patients receiving high doses (12x the dose for PMO or HALT indications). An adjudication committee was established for possible ONJ cases in the PMO and HALT trials of

denosumab. The definition of ONJ used, which was developed by the American Dental Association and the American Society of Bone and Mineral Research, is the following:

- 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.

There were 21 potential ONJ cases reported in the initial BLA, and 7 more in the CR Safety Update; none were adjudicated positive for ONJ. However on 2/26/10, one case of adjudicated-positive ONJ in a PMO subject was reported from Study 20060289. This involved an 83 y/o Lithuanian female with a medical history that included hypertension, ischemic heart disease, vascular dementia, denture use (no information on correctness of fit) and breast cancer although there was no history of chemotherapy or of radiation to the head, face or jaw. Her only concomitant medications were calcium and vitamin D; there was no history of prior use of glucocorticoids or immune suppressants; she had been on alendronate from May 2004 to July 2004. She enrolled in Trial 20030216 in December 2004 and was randomized to the placebo arm. She completed this study and entered the extension study 20060289 in January 2008. She apparently received 4 doses of open label denosumab under this study, the last being on July 13, 2009. She underwent tooth extractions in 2008, and then between February and June 2009 she underwent additional extractions as well as several other dental procedures. In August 2009 (about 1.5 yrs after initiating denosumab therapy), she experienced pain in the jaw and was diagnosed with osteomyelitis of the mandible in the area of one of the extractions. Partial alveoli resection was performed in September with temporary improvement, however the pain recurred and additional surgery performed in October; after this the event was reported to have resolved. The investigator reported that this AE of osteomyelitis of the mandible was possibly denosumab-related and met Amgen's pre-defined criteria for ONJ, and was adjudicated positive for ONJ.

Reviewer comment: This represents the first occurrence of a case of ONJ in any osteoporosis clinical trial; with oral bisphosphonates these cases have only appeared in postmarketing, i.e. with longer exposure periods. This is not surprising, given that bone remodeling is suppressed to an even greater degree with denosumab, compared to bisphosphonates. This concern will be noted in Section 5.4 of labeling (WARNINGS AND PRECAUTIONS/Osteonecrosis of the Jaw), as well as REMS documents and postmarketing requirements.

7.3.4.4 Delayed Fracture Healing

Healing of fractures involves remodeling of the initial callus; drugs that interfere with this process, especially antiresorptives, may in theory delay or prevent normal healing. Animal studies have demonstrated such delays with bisphosphonates and with denosumab. In Trial 20030216, the small number of reported cases of fracture healing

complications was balanced between denosumab and placebo; a small substudy which prospectively evaluated healing of wrist fractures by assessment of cortical bridging on 3- and 6-month X-rays also showed no difference between treatment groups. However, reviewers concluded that this evidence was not strong enough to eliminate the concern, and recommended that this issue be addressed in labeling, REMS documents, and postmarketing observational studies. There have been no reports of AEs related to fracture healing complications in either of the extension studies (20060289 or 20050233).

7.3.4.5 Malignancy

Because denosumab is species-specific, carcinogenicity studies could not be performed due to lack of an appropriate animal model. Denosumab is a monoclonal antibody which may have immunosuppressive effects, therefore it potentially could increase cancer risk, and clinical trials have raised some concern. In the dose-finding trial 20010223, there were 3 subjects (out of 412) who died of a new malignancy; all 3 were in one of the higher dose cohorts (100 mg Q6M, N=41). Six additional malignancies (exclusive of skin) were reported in 200 subjects in the first 2 years of the extension of this trial (20050233).

Reviewers pooled data from the PMO trials (placebo N=4041; denosumab N=4050), and found greater numbers of malignancies with denosumab for many types, particularly female reproductive (21 vs. 9), GI tract (35 vs. 24), breast (35 vs. 30), and malignant endocrine neoplasms (mainly thyroid, 7 vs. 2). The only major category more common with placebo was malignant respiratory neoplasms (16 vs. 25). In trial 20030216, there was one case in a denosumab subject of Schofflers tumor, a very rare inflammatory pseudotumor of the abdominal wall belonging to the reactive tumor-like fibromatoses. RANKL was originally found in dendritic cells of the skin, and reviewers felt there could be a connection of this case with denosumab. Considering all of the evidence, reviewers concluded that the data relative to malignancy is relevant to the benefit-risk assessment for denosumab, particularly in regard to long-term use for osteoporosis.

In extension study 20060289, AEs related to malignant neoplasms were reported in 2.6% of subjects, and were not more common overall in continuous-denosumab compared to prior-placebo subjects. (**Table 11**) By preferred term, the most common ($\geq 0.1\%$ overall) were basal cell carcinoma (0.7%), breast cancer (0.2%), colon cancer (0.2%), thyroid neoplasm (0.2%), and lung neoplasm malignant (0.1%).

Table 11 Study 20060289: Subject Incidence of Selected Neoplasms by HLT

High Level Term	Placebo/ Denosumab 60 mg Q6M (N=2203) n (%)	Denosumab/ Denosumab 60 mg Q6M (N=2346) n (%)	All (N=4549) n (%)
All malignancies	61 (2.8)	59 (2.5)	120 (2.6)
Rectal cancer			
Large intestine carcinoma	4	7	11
Colon cancer			
Esophageal carcinoma			
Esophageal adenocarcinoma	0	3	3
Breast neoplasms unspec. malignant			
Breast/nipple neoplasms malignant	6	8	14
Respiratory tract/pleural neo. malignant			
Non-small cell neoplasms resp. malignant	4	5	9
Resp. tract/pleural neo/malignant.unspec.			
Uterine neoplasms malignant			
Ovarian neoplasms malignant	1	2	3
Endometrial cancer			
Thyroid neoplasms malignant			
Endocrine neoplasms malignant/unspec.	7	4	11
Source: CR Safety Update, Table 03-6.10.3			
Data from Trial 20030216 start through 7/1/09			

Comparison of neoplasm AE rates in studies 20030216 and 20060289, adjusted for length of exposure, shows no evidence that longer-term exposure to denosumab heightens the risk of female reproductive, breast, or other specific classes of neoplasms, with the possible exceptions of thyroid, esophageal and colorectal cancer. (**Table 12**) However, the overall rate of malignancies is somewhat higher in both prior-treatment groups in the extension study relative to both double-blind groups, especially the placebo group.

Table 12 Subject-Year-Adjusted AE Rates of Selected Neoplasms

High Level Group Term Preferred term	Trial 20030216		Study 20060289		All (n=4549) Subj-yr= 5155
	Placebo (n=3876) Subj-yr= 10719 e (r)	Denosumab 60 mg Q6M (n=3886) Subj-yr= 10826 e (r)	Placebo/ Denosumab 60 mg Q6M (n=2203) Subj-yr= 2495 e (r)	Denosumab/ Denosumab 60 mg Q6M (n=2346) Subj-yr= 2660 e (r)	
Number, % of subjects reporting AEs	166 (4.3%)	188 (4.8%)	61 (2.8%)	59 (2.5%)	120 (2.6%)
Total # of AEs	196 (1.8)	220 (2.0)	64 (2.6)	63 (2.4)	127 (2.5)
GI Neoplasms - all	24 (0.2)	35 (0.3)	9 (0.4)	12 (0.5)	21 (0.4)
Colon cancer/ Rectal cancer/ Large intestine Ca/ Colon cancer metastatic/ Colon neoplasm/ Colorectal cancer/ Intestinal adenoCa/ Rectal Ca stage III/ Rectal neoplasm	13 (0.12)	18 (0.17)	4 (0.16)	8 (0.30)	12 (0.23)
Esophageal carcinoma/ Esophageal adenoCa/ Esoph. squam. cell Ca	1 (< 0.1)	1 (< 0.1)	0 (< 0.1)	3 (0.11)	3 (< 0.1)
AdenoCa pancreas/ Pancreatic carcinoma/ PancreaticCa metastatic	3 (< 0.1)	8 (< 0.1)	2 (< 0.1)	0 (0.0)	2 (< 0.1)
Gastric cancer/ Metastatic gastric Ca	3 (< 0.1)	7 (< 0.1)	1 (< 0.1)	0 (0.0)	1 (< 0.1)
Breast neoplasms	28 (0.3)	34 (0.3)	6 (0.2)	8 (0.3)	14 (0.3)
Respiratory and mediastinal neoplasms	25 (0.2)	16 (0.1)	4 (0.2)	5 (0.2)	9 (0.2)
Thyroid neoplasm/ Thyroid cancer	2 (< 0.1)	6 (< 0.1)	6 (0.24)	4 (0.15)	10 (0.19)
Reproductive neoplasms female malign/unspec.	10 (< 0.1)	20 (0.2)	1 (< 0.1)	2 (< 0.1)	3 (< 0.1)
Basal cell carcinoma	41 (0.4)	32 (0.3)	18 (0.7)	14 (0.5)	32 (0.6)
Hematopoietic neoplasms excl. leukemia/lymphoma	0 (0.00)	3 (< 0.1)	1 (< 0.1)	0 (0.0)	1 (< 0.1)
Source: Table 03-6.13.2, Complete Response Safety Update					
Data from Trial 20030216 start through 7/1/09					
e = number of events; r = event rate per 100 subject-years					

Reviewer comment: So far, the trends toward higher numbers of breast and female reproductive cancers with denosumab are less apparent in the extension study compared to the parent study. However, the rates of overall malignancies, and of colorectal, esophageal and thyroid cancers, are greater in the extension phase groups

compared to the previous placebo group. This effect may be partly explained by the fact that extension study subjects were on average 3 years older than double-blind subjects and thus at somewhat higher baseline risk of malignancy. Because there is no placebo control in the extension study, and the number of cases is relatively modest, the issue of malignancy remains unresolved. Further study is warranted in view of the potential for some therapeutic monoclonal antibodies to cause malignancy, and the long latency period of malignancies.

7.3.4.6 Ocular Adverse Events

Bisphosphonates have been associated rarely with eye inflammation including uveitis, and denosumab was associated with a higher incidence of cataracts (34 cases, vs. 9 with placebo) in trial 2004138. The off-treatment phase of this trial reports 3 additional prior-denosumab and 5 additional prior-placebo subjects with cataract AEs. In the PMO studies, reviewers found that eye disorders (including cataracts and glaucoma) were balanced between denosumab and placebo. In study 20060289, exposure-adjusted AE rates of cataract within the continuous-denosumab cohort were similar between double-blind and extension phases (3.0 vs. 2.9 per 100 subject-years respectively). Corresponding figures for glaucoma were 0.6/0.8.

Reviewer comment: There do not appear to be any eye-related safety signals with denosumab.

7.3.4.7 Pancreatitis

In the pivotal PMO studies, there were 8 subjects (9 events) (0.2%) with pancreatitis in the denosumab group compared to 4 subjects (0.1%) in the placebo group. One subject in the denosumab group reportedly died from pancreatitis. One placebo subject discontinued IP due to pancreatitis. All nine events of pancreatitis were serious in the denosumab group while only one was serious in the placebo group. The temporal relationship between duration of denosumab exposure and the development of pancreatitis was highly variable; most cases in the denosumab group were confounded by prior episodes of pancreatitis or risk factors for the development of pancreatitis. Reviewers considered these findings to be of unclear significance.

In extension study 20060289, there was only one AE (nonserious) of pancreatitis. In extension study 20050233, there was one SAE of pancreatitis, apparently caused by an impacted gallstone. In the off-treatment phase of trial 20040138, there was one case of acute pancreatitis in conjunction with biliary sepsis and believed to be caused by passage of a gallstone.

Reviewer comment: Pancreatitis may be a risk factor for serious pancreatitis, based on trial 20030216. Extension studies do not appear to show a greater risk over time.

7.3.4.8 Skin and soft tissue disorders

PMO studies showed that denosumab subjects were more likely to develop skin disorders (other than skin infections) compared to placebo subjects, including bullous conditions, pruritic conditions, skin rashes, dermatitis and eczema. Reviewers concluded that this increase is clinically significant and should be included in labeling. Most subjects were able to remain on the drug and some events spontaneously resolved.

In study 20060289, AEs of eczema (including dermatitis, allergic dermatitis, and contact dermatitis) were reported for 0.9% of subjects. Comparing double-blind and extension phases within the continuous-denosumab cohort, exposure adjusted adverse event rates were similar for preferred terms of eczema (0.6 and 0.5 per 100 subject-years, respectively), dermatitis (0.2 and 0.3, respectively), allergic dermatitis (0.4 and 0.1, respectively), and contact dermatitis (< 0.1 and < 0.1, respectively). Adverse events of rash were reported for 0.9% of subjects. Within the continuous-denosumab cohort, exposure-adjusted adverse event rates of rash were similar (1.1 and 0.9 per 100 subject-years, respectively). Adverse events in the high-level term of bullous conditions were blister and dermatitis herpetiformis (2 subjects (< 0.1%) for each term). No events of Stevens-Johnson syndrome or toxic epidermal necrolysis were reported in the study. SAEs of skin disorders, especially skin ulcer, occurred more frequently in prior-denosumab compared to prior-placebo subjects.

Reviewer comment: There is so far no clear evidence from extension study 20050289 that AEs of skin disorders increase with longer term use.

7.3.4.9 Diverticular Disorders and Diverticulitis

Data from the pooled primary PMO studies (20030216 and 20040132) showed higher frequencies of SAEs with denosumab vs. placebo in the PTs of diverticulum (7 vs. 3), diverticulum intestinal (8 vs. 2), diverticulitis (10 vs. 7), and diverticulitis intestinal hemorrhagic (1 vs. 0). However, in the extension study 20060289, subject-year of exposure-adjusted rates of both AEs and SAEs of diverticulitis were intermediate between those of the 2 double-blind groups.

Reviewer comment: Diverticulitis-related AEs and SAEs appear to be more common with denosumab compared to placebo; there is no evidence from the extension study that this increased risk changes over time.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In the primary PMO trials 20030216 and 20040132, adverse events were comparable (~93% overall) between treatment groups. In extension study 20060289, AEs were reported for 73.4% of prior-placebo subjects and 74.6% of prior-denosumab subjects. The 6 most common AEs were (in slightly different order) also the 6 most common in the parent study: arthralgia (8.0% of subjects), back pain (7.7%), hypertension (7.0%), nasopharyngitis (5.9%), osteoarthritis (4.7%), and pain in extremity (3.9%). The rate of overall AE reporting adjusted for exposure declined from the parent to the extension study, particularly in the SOC classes of musculoskeletal and connective tissue disorders (58.5 to 41.3 per 100 subject-years) and gastrointestinal disorders (25.3 to 18.8 per 100 subject-years). However, there was no major change in reporting of infections (40.0 to 39.4 per 100 subject-years) or neoplasms (3.2 to 3.5 per 100 subject-years).

7.4.2 Laboratory Findings

Hypocalcemia

Bone resorption plays an important role in calcium homeostasis, and inhibitors of absorption (e.g. bisphosphonates) may cause hypocalcemia. In trial 20030216, mean serum calcium was lower at month 1 in the denosumab group (9.54 mg/dL vs. 9.83 mg/dL), with much smaller difference at later timepoints and virtually none by month 24. There was an imbalance of subjects with hypocalcemia (< 8.5 mg/dL) at month 1 in denosumab subjects vs. placebo (33 vs. 3). However, this study did not capture levels at the nadir in serum calcium which was shown in Trial 20040245 to occur at day 8-11. Thus, serum calcium was measured at day 10 (\pm 5) in Study 20060289, the open-label extension of Trial 20030216. In this study there were significant decreases in serum calcium at day 10, especially in the placebo-to-denosumab group, compared to the denosumab-denosumab group. Combining these 2 groups, at day 10, 3.3% of subjects had a serum calcium < 8.5 mg/dL, however only 0.3% had serum calcium < 8.0 mg/dL, and 0.07% had serum calcium < 7.5 mg/dL. The lowest serum calcium of 7.0 mg/dL, in a subject with history of renal impairment, was associated with AE of nausea; the other hypocalcemic subjects appeared asymptomatic (no AEs of hypoesthesia, oral hypoesthesia, paresthesia, oral paresthesia, or tetany). Five AEs of hypocalcemia were reported, all in prior-placebo subjects, and none were considered serious. Note that all subjects in this study were supplemented with 1 gm calcium and vitamin D daily throughout this study and the preceding 3-year parent study.

There were no hypocalcemia AEs reported in PMO studies 20050233 or 20060232, HALT study 20080537, or phase 1 study 20070364.

Hypocalcemia was shown to be more frequent and severe in subjects with abnormal renal function in Studies 20040245 and 20060289. In the former, a phase 1 study investigating PK with varying renal function, enrollment was halted because of severe hypocalcemia (< 7.5 mg/dL or symptomatic), primarily in the group with creatinine clearance < 30 mL/min. After the protocol was amended to include daily calcium/vitamin D supplementation, serum calcium levels were similar among the groups at all levels of renal function, except the most severe (ESRD) group, which still had a lower median nadir albumin-adjusted serum concentration (7.9 mg/dL). In Study 20060289, mean percent declines at day-10 in serum calcium were similar in subgroups of renal function (~ -2 to -3%), except for subjects with creatinine clearance of 15-30 mL/min (-5.5% placebo-denosumab, -3.6% denosumab-denosumab).

Reviewer comment: Denosumab induced hypocalcemia appears to be transient, occurring primarily within the first month after dosing, especially after the first dose. Most cases have been mild and asymptomatic. However, almost all subjects were supplemented with calcium/vitamin D. In the real world setting many patients would probably not take supplements, and hypocalcemia would likely be more common. The agreed-upon labeling discusses hypocalcemia in Contraindications and Warnings and Precautions sections, including the need for calcium/vitamin D supplementation and the increased risk in subjects with renal dysfunction (Creatinine clearance < 30 mL/min).

Serum phosphorus mean levels declined from baseline compared to placebo in clinical trials 20030216 and 20040132. The mechanism is presumed to be related to decreased bone resorption, similar to the declines in serum calcium. The decline in phosphorus was greatest at month 1 (it was not measured at day 10), at which point levels were on average $\sim 8\%$ below baseline. Thereafter, like serum calcium, levels returned to baseline by month 24. There is no evidence that these changes were clinically significant.

Parathyroid hormone levels increased at month 1 in trial 20030216, due to the declines in serum calcium, and returned to baseline by month 6.

There were no other significant changes in clinical laboratory parameters seen in clinical trials/studies, including parameters of hepatic and renal function. Please consult BLA Clinical Review for details.

7.4.3 Vital Signs

Clinical trials have shown no evidence of significant alterations in vital signs, weight or BMI. AEs such as bradycardia, tachycardia, arrhythmia etc. occurred at comparable rates in placebo and denosumab groups in trial 20030216 and in the extension study 20060289.

7.4.4 Electrocardiograms (ECGs)

Denosumab, a fully human monoclonal antibody, with a molecular weight of approximately 144 kDa, is not anticipated to have a direct effect on ion channels. Therefore, a thorough QT trial was not required. As outlined in the BLA Clinical Review, multiple clinical studies included ECGs at various time points, including around Tmax. There were no significant differences between treatment groups in QTc intervals, nor any relationship between QTc and serum calcium or denosumab levels. There were several more outliers with QTc > 500 msec and/or Δ QTc > 60 msec, however the IRQT team noted that subjects with underlying ECG abnormalities had not been excluded. They concluded that the ECG evaluations were adequate and that there are no large QT interval effects with denosumab, and also noted that there was no imbalance in reports of sudden death between treatment groups. The CR Safety Update does not include any additional ECG data.

7.4.5 Special Safety Studies/Clinical Trials

Bone Biopsies

Transiliac bone biopsies were performed in 3 denosumab clinical trials. Data were presented and reviewed in the original BLA cycle, and will be summarized here; for details please refer to BLA Clinical Review.

Evaluable biopsies obtained:

- Trial 20030216: 115 biopsies in 92 subjects (47 denosumab, 45 placebo) at month 24 and/or 36
- Trial 20010223: 86 subjects (72 denosumab, 9 placebo, 5 alendronate) at baseline or month 12
- Trial 20050234: 36 subjects (15 denosumab, 21 alendronate) at month 12

Qualitative histology of all specimens showed normal lamellar bone with no woven bone and no osteomalacia. Normal osteoid was seen in all placebo (62/62) subjects and 48/53 (91%) of denosumab subjects. However, at month 24, 5 denosumab subjects did not have apparent osteoid, a finding that may be due to suppressed bone turnover. Another denosumab subject, who had normal histology at month 24, had cortical trabecularization at month 36, which may be an indicator of reduced bone strength.

Quantitative histomorphometry showed abundant evidence of suppression of bone remodeling. There were significant decreases with denosumab in static parameters of bone formation (osteoblast/osteoid interface, osteoid surface, osteoid width) and bone resorption (eroded surface/bone surface, osteoclast number). Activation frequency, a very sensitive measure of remodeling activity, was markedly reduced at month 24 and 36. There was a marked increase in biopsy samples which showed no tetracycline label (21% at 1 year, 35% at 2 years and 36% at 3 years, vs. 0 with placebo). Absence of label connotes severe suppression of bone formation. There was no clear evidence of

impairment of mineralization: mineralization lag time was not prolonged in most, and osteoid thickness was not increased; however because of absent label, dynamic parameters could be assessed in only a limited number of denosumab biopsies. Reviewers concluded that the evidence of possible over-suppression of bone turnover may have consequences for long-term adverse effects.

The only bone histomorphometry data presented in the CR Safety Update is from study 20080287, designed to investigate the reversibility of denosumab suppression of bone remodeling. Results from the first 4 subjects, who had received their last denosumab dose 27-33 months before a biopsy, show normal histology with double label in all; parameters of bone formation rate were WNL in all and mineral apposition rate was normal to slightly below normal. A total of ~15 subjects is planned. (See Appendix 9.4.5)

7.4.6 Immunogenicity

As a therapeutic protein, denosumab has the potential to elicit an immune response with hypersensitivity and/or reduction in efficacy. Preclinical studies showed development of binding antibodies in 78% of monkeys and neutralizing antibodies in 22%; the latter corresponded to ~30-53% reduction in exposure based on AUC. This was not unexpected since denosumab is a fully humanized protein.

Clinical studies have all included immunoassays for antibodies (> 8000 subjects receiving at least one dose of denosumab). The highest frequency of binding antibodies in any study was 2/129 (1.6%) in Trial 20040135. In Trial 20030216, 25/3886 subjects (0.6%) tested positive. None of these were positive for neutralizing antibodies. In the CR Safety Update, no binding or neutralizing antibodies have been seen in any of the studies reported.

In trial 20040216, the PTs of drug hypersensitivity, angioedema, urticaria and anaphylactic shock were generally balanced between denosumab and placebo groups. In study 20060289, hypersensitivity and drug hypersensitivity were reported for 0.2% and 0.1% of subjects, respectively. In study 20050233, only one AE of hypersensitivity ("environmental allergies") and one of drug hypersensitivity ("Flagyl allergy") were reported. None of these events in either study was considered denosumab related.

Reviewer comment: There is no evidence that denosumab is immunogenic, or that it elicits hypersensitivity reactions.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

As reported in the BLA Clinical Review, the dose-finding trial (20010223) for the osteoporosis indications examined 7 different SC doses of denosumab, including 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 trial. There was a greater reduction in corrected calcium from baseline at higher doses of denosumab. There was no clear dose response observed in terms of markers of bone remodeling or bone histomorphometry. There were no other noteworthy trends in dose-related adverse events when the adverse event, laboratory parameters and physical findings were examined by cumulative yearly denosumab dose.

7.5.2 Time Dependency for Adverse Events

Hypocalcemia is maximal at about 10 days following a dose of denosumab, although it is not clear that this results in clinically significant AEs. Otherwise, there is no good evidence of a significant relationship between time of denosumab exposure and specific adverse events. However, malignancies were slightly more common in the extension phase of the PMO trial 20030216; this specific risk would be expected to have a very long latency. Also as noted in section 7.4.5, a trend of progressive suppression of bone remodeling was seen at 12, 24, and 36 months; this may eventually be reflected in late AEs such as ONJ or atypical fractures. It is not clear if the risk for serious infections changes over time.

7.5.3 Drug-Demographic Interactions

In the primary PMO trials, reviewers looked at AEs and SAEs of infection in relation to age groups of ≥ 75 years and ≥ 80 years, and found that elderly subjects treated with denosumab did not appear to be more susceptible to infections than younger subjects. No pediatric studies have been conducted. Studies predominantly enrolled women; however, trial 20040138 was conducted in men and denosumab was found to be efficacious, with no apparent difference in safety issues. Since most patients in the osteoporosis trials were Caucasian, the effects of race/ethnicity on the safety and efficacy of denosumab are not known.

7.5.4 Drug-Disease Interactions

Impairment of renal function appears to have little if any effect on the PK/PD profile of denosumab. However, as discussed in section 7.4.2, hypocalcemia is significantly more frequent and severe in subjects with more severe dysfunction ($\text{CrCL} < 30 \text{ mL/min}$), especially in the absence of calcium/vitamin D supplementation.

7.5.5 Drug-Drug Interactions

Monoclonal antibodies in general do not directly affect hepatic enzymes involved in drug metabolism, however in some cases by affecting cytokines they may do so indirectly. No drug/drug interaction studies have been conducted with denosumab to date, however the Division of Clinical Pharmacology intends to require postmarketing studies to confirm the lack of potential for drug interactions.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Because denosumab does not bind to rodent RANKL, carcinogenicity studies are not feasible. Denosumab is a monoclonal antibody which may have immunosuppressive effects, therefore it potentially could increase cancer risk. As noted above (7.3.4.5), phase 2 and 3 trials appeared to show a modest excess of some malignancies in denosumab treated groups. As this issue is not entirely resolved, the postmarketing studies 20090522 and 20090601 will include new primary malignancies as an outcome of interest.

7.6.2 Human Reproduction and Pregnancy Data

Reproductive and developmental toxicity studies in pregnant and neonatal mice lacking the RANKL signaling pathway resulted in fetal lymph node agenesis (prenatal exposure) and impaired dentition and bone growth (neonatal exposure). Maturation of mammary glands in pregnant mice was also affected, causing impairment in lactation. An embryofetal trial in monkeys showed no major effects on organogenesis or on the mother, but dosing did not continue into late pregnancy when antibodies are more likely to cross the placenta, and fetal lymph nodes were not examined. Thus, reviewers consider that this study is not adequate to support use in women with childbearing potential.

The proposed indication is limited to postmenopausal women. A total of 4 subjects have become pregnant after receiving denosumab while participating in clinical trials; one delivered a healthy infant, and outcomes in the other 3 cases have not been reported. Denosumab will be labeled as Pregnancy Category C. The Applicant has proposed a postmarketing pregnancy surveillance program to gather more information about outcomes with off-label use.

7.6.3 Pediatrics and Assessment of Effects on Growth

As noted in the initial BLA Clinical Review, denosumab has not been studied in pediatric patients, and animal studies have shown negative effects on epiphyseal growth plates

and developing bones and teeth. Therefore the label is to indicate that it should not be given to pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose was not reported during the denosumab PMO and hormone ablation studies. In the dose-finding trial (trial 20010223), subjects received repeated fixed SC doses of denosumab up to 210 mg every 6 months for up to 24 months. Also, cumulative doses up to 1080 mg over 6 months have been evaluated in subjects with advanced cancer in Study 20040114 without dose-limiting toxicity.

There is no suggestion of drug abuse potential at this time.

The “off-treatment” effects of denosumab were evaluated for 2 years following treatment (30 months from last dose) in trial 20040132 and for up to 2 years following treatment (18 to 30 months from last dose) in Trial 20010223 (“dose-finding” trial). Within 6 months of discontinuing denosumab, bone resorption markers rose from markedly-below to markedly-above baseline; within 12 months, BMD returned to approximately baseline levels in these subjects.

7.7 Additional Submissions / Safety Issues

Subsequent to the Complete Response on 1/25/10, a safety report was submitted on 2/26/10 describing a case of ONJ, which is discussed above in section 7.3.4.3.

8 Postmarket Experience

Denosumab has not been approved for use in other countries and there is no postmarket experience for this product.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

See separate document.

9.3 Advisory Committee Meeting

As noted above and discussed at length in the clinical review of the initial BLA application, an Advisory Committee meeting was held on August 13, 2009. The committee voted unanimously in favor of approval of denosumab in the treatment (but not the prevention) of PMO. A few members expressed their concerns about the long term safety and felt that the benefit would exceed the risk only for a subgroup at high risk for fracture. A majority (12 to 1) also endorsed implementation of a REMS to mitigate the risks.

9.4 Review of Individual Studies

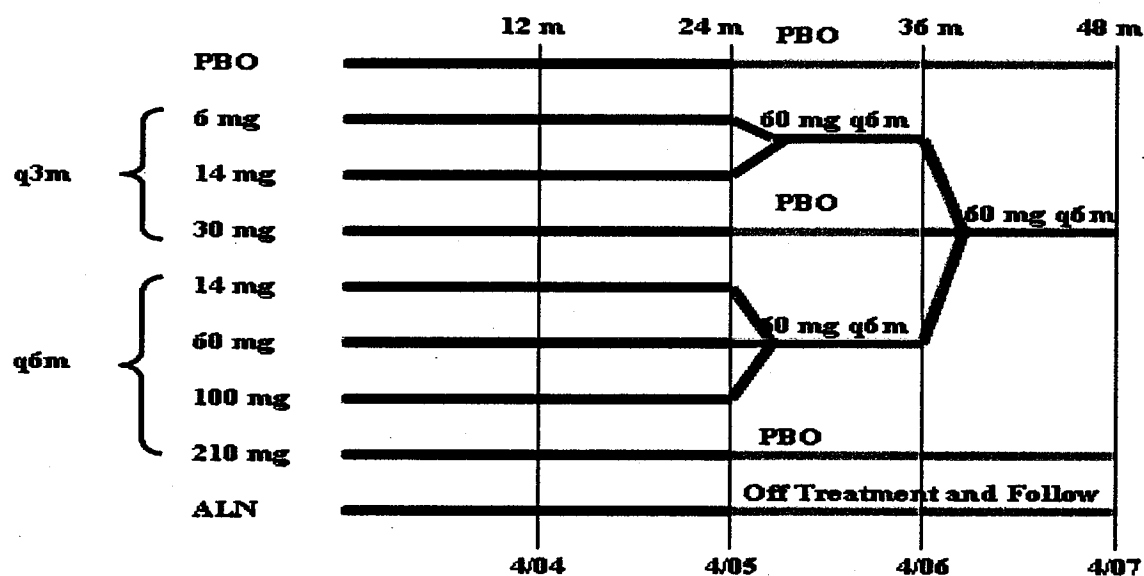
9.4.1 Trial 20010223

This was the primary phase 2 dose-finding trial for denosumab. The final report of this trial was reviewed in the initial BLA cycle, and safety findings will be summarized here for the purpose of providing context for the results of extension study 20050233.

Trial 20010223 was a 4-year, randomized-double-blind trial in 412 postmenopausal women (mean age 62.5, range 43-83; 86% Caucasian, 9.5% Hispanic) with low BMD (mean T-scores: lumbar spine -2.1, total hip -1.4). For the first 2 years of the trial, subjects were assigned to one of 7 different dose regimens of denosumab (6 mg, 14 mg

or 30 mg Q3M; or 14 mg, 60 mg, 100 mg or 210 mg Q6M); or to placebo-control; or to active-control of open-label alendronate 70 mg Qwk (**Figure 3**). For the last 2 years of the trial, 5 of the 7 denosumab cohorts (6 mg or 14 mg Q3M; and 14 mg, 60 mg, or 100 mg Q6M) were given 60 mg SC Q6M. The 30 mg Q3M cohort was off treatment for the 3rd yr (placebo at months 24 and 30), then back on for the 4th yr (denosumab 60 mg SC at months 36 and 42). The high-dose 210 mg Q3M cohort, as well as the placebo cohort, were given placebo for the last 2 years. The alendronate cohort was also followed, off-treatment, for the last 2 years. There were approx. 40 subjects in each cohort. Subjects were told to take daily supplements of calcium (≥ 1 gm/day) and vitamin D (≥ 400 IU). An average of 64% of all subjects completed the 4-year trial, and 4-6% withdrew because of AEs; there were no major differences in discontinuations between denosumab, placebo and alendronate groups.

Figure 3 Design of Trial 20010223



Source: Clinical Trial Report for Trial 20010223, page 4 of 9933.

All 7 denosumab cohorts showed increases in lumbar spine BMD at month 12 (the primary endpoint) ranging from 3.0% to 6.7%. Except for one of the lowest denosumab doses (14 mg Q6M), BMD gains in each group were similar to alendronate, which showed a 4.5% increase. (Placebo group showed a -0.8% BMD decline.) BMD at other sites (total hip, distal radius, total body) also increased from baseline. Bone resorption, as measured by serum CTX1, was profoundly suppressed at each dose of denosumab. Although Agency reviewers concluded that there was not a clear dose-response effect in either CTX1 or in BMD, the Applicant chose only a single dose (60 mg Q6M) for Phase 3 studies involving PMO or HALT indications. In the 2 cohorts that stopped denosumab after 24 months, there was then a transient increase in bone turnover markers to above-baseline values, and a decline in BMD, which approached baseline

levels by month 36. One of these 2 cohorts was then re-treated during the fourth year, resulting in BMD and bone turnover marker effects similar to those seen with the initial treatment.

Transiliac bone biopsies with histomorphometry, double tetracycline labeling and microCT were performed in a subset of subjects within 1 month prior to the first dose and the Month 12 dose. Dynamic parameters such as the activation frequency were consistent with markedly impaired resorption with denosumab. Two denosumab subjects had a mineral apposition rate below normal at month 12. There was a higher-than-expected rate in the denosumab samples of no label or single label. The most sensitive indicator of a mineralization defect, mineralization lag time, was not abnormal for the denosumab group overall; however, 4 denosumab subjects did have prolonged MLT > 100 days. Bone histology and microCT evaluation showed no abnormalities.

Safety data

Reviewers of the original BLA focused on data from the first 24 months of this trial, because of the changes in dose during the last 24 months. There were 4 deaths during this trial, all in denosumab groups. Three of the four deaths involved neoplasms, including a lung adenocarcinoma, gastric cancer NOS and a frontal lobe tumor NOS. All of these events occurred in the denosumab 100 mg Q6M cohort (3/41 subjects); they occurred at 33, 18, and 15 mos into the trial. The reviewers considered that "it is highly unusual that 3 deaths due to neoplasms would occur in a trial of this size and duration". The 4th death was a CVA.

During the first 24 months of the trial, serious adverse events occurred in 11%, 18%, and 17% of placebo, denosumab and alendronate subjects, respectively. The most common SOC classes for SAE's in denosumab subjects were Neoplasms, Injury, Cardiac, Nervous System and Infections. The incidence of these SAEs did not appear to be different between placebo, denosumab and alendronate, with the exception of infections: there were 6 denosumab subjects with serious infections, compared to none with placebo or alendronate. (Note however that there were > 6x as many subjects with denosumab compared to the other groups.)

Adverse events leading to withdrawal occurred in 4.8% of denosumab subjects, vs. 2.2% of placebo subjects and 17.4% with alendronate (note that alendronate was open-label). Higher doses of denosumab did not appear to make discontinuation more likely.

Common AEs that appeared to be more frequent with denosumab compared to placebo included hypertension (12.4% vs. 2.2%), urinary tract infection (10.5% vs. 0%), rash (5.7% vs. 0%), insomnia (5.4% vs. 0%), and seasonal allergy (5.1% vs. 2.2%). There did not appear to be any obvious dose related AEs from analysis by SOC.

Adverse Events of Special Interest in Trial 20010223

Infections:

The overall rates of infection were similar between the treatment groups, though as noted above, there were more serious infections with denosumab. Higher doses of denosumab did not appear to increase the infection risk. Three percent of denosumab subjects were hospitalized for an infection, vs. none in the other groups. There were no unusual or opportunistic infections seen, and no deaths due to infection.

Immune cell counts were assessed in a subset of 91 subjects. During the study, denosumab had no clinically significant effect on counts of T and B cell subtypes or natural killer cells by flow cytometry, or on total WBC or lymphocyte counts.

Hypocalcemia:

Despite supplementation, mean serum calcium declined in the denosumab cohorts, with decreases ranging from 3.0% to 4.3% on day 4 of treatment (3 days after 1st dose) and 1.1% to 3.9% at 1 month. One denosumab subject had an asymptomatic episode of hypocalcemia (8.0 mg/dL at month 2). There were no reported hypocalcemia AEs, defined as those considered clinically significant. Serum levels of iPTH increased during the first month after dosing, presumably compensating for the low calcium. Serum phosphorus also declined transiently.

Suppression of Bone Turnover:

There were no reports of ONJ, atypical fractures or impaired fracture healing through month 24.

Cardiac Events:

There were no differences between treatment groups in serious or non-serious cardiovascular events through month 24, and no cardiac deaths through month 48. ECGs performed at screening, month 1 and month 12 showed no differences in QTc parameters.

Neoplasms:

As noted above, there were 3 fatal malignancies in the denosumab group during the trial. Overall incidence of neoplasms, however, was similar in denosumab and placebo groups, and the numbers of subjects in the trial were too small to draw conclusions.

Laboratory/Vital Signs:

There were no significant changes in lab parameters, vital signs or physical findings during the trial, nor any dose-related changes in vital signs for the denosumab cohorts.

9.4.2 Study 20050233

This is an ongoing, open-label, single-arm extension of dose-finding Trial 20010223, which lasted 4 years. Enrolled were 200 completers of any one of the 9 arms of the parent study, all of whom were then placed on denosumab 60 mg SC Q6M for the extension study. The extension study is planned to run for 4 additional years, at the end of which many subjects will have been treated with denosumab for 8 years continuously. The Complete Response Safety Update summarizes interim analysis from the first 2 years of the extension study. Some of the safety data to be discussed here was presented in the 120-Day Safety Update and was therefore reviewed in the initial BLA cycle, but will be included here as well.

Subject Demographics, Disposition, and Exposure

Out of the 9 treatment cohorts in the parent trial 20010223, the 5 cohorts who were administered denosumab for all 4 years (the “continuous-treatment” cohort) were consolidated into one in extension study 20050233 for analysis purposes. (Table 13) This group of 124 subjects, representing most of the 200 subjects in the extension study, represents 6 years of continuous denosumab exposure. The mean age at baseline of the extension trial was 66.1 (range 49-85) with 89% Caucasian. The 24-month analysis indicates that 176/200 subjects (88%) of the subjects received all 4 doses in the extension study. As of the cutoff date of 4/23/09, 33 subjects (17%) had discontinued denosumab, 7 subjects (4%) due to AEs.

Table 13 Study 20050233: Treatment Groups

Cohort	Years 1-4 Study 20010223	Years 5-6 Study 20050233	N (Current Study)
“Continuous Treatment”	Denosumab Years 1-2: 6 mg Q3M; 14 mg Q3M; 14 mg Q6M; 60 mg Q6M; or 100 mg Q6M	Denosumab 60 mg Q6M	124
“Placebo”	Years 1-4: placebo	Denosumab 60 mg Q6M	23
“Off-treatment”	Years 1-2: denosumab 210 mg Q6M Years 3-4: placebo	Denosumab 60 mg Q6M	17
“Retreatment”	Years 1-2: denosumab 30 mg Q3M Year 3: placebo Year 4: denosumab 60 mg Q6M	Denosumab 60 mg Q6M	14
“Alendronate”	Years 1-2: alendronate 70 mg PO QW Years 3-4: no treatment	Denosumab 60 mg Q6M	22

Source: CR Safety Update, p.98

Safety Results

During the initial 2 years of this extension study, the most common AEs were upper respiratory infection (14% of subjects) and arthralgia (12% of subjects). AEs considered to be related to denosumab occurred in 10%. There were 7 AEs leading to treatment withdrawal: 2 due to neoplasms (breast Ca *in situ* and breast Ca), and 1 each for back pain, muscle spasms, musculoskeletal pain, noncardiac chest pain and injection site reaction. Investigators considered 2 of these to be related to study drug: breast Ca *in situ* and muscle spasms, both in continuous-treatment cohort.

Serious AEs

Serious AEs were reported for 26 subjects (13%). None occurred more than once with the exception of lung cancer (3 cases) and noncardiac chest pain (2 cases). SAEs considered related to denosumab occurred in 2 subjects: breast cancer *in situ* and staphylococcal bacteremia.

Deaths

Although the summary lists 3 deaths during Study 20050233 (1.5%), 2 other subjects died after discontinuing study participation due to a cancer diagnosis. Subject 307006, an 80 y/o female in the retreatment cohort, died unexpectedly at home approx. 6 months after initiation of open-label denosumab and 3 weeks after last dose. The investigator was unable to obtain any other information. Other than hypertension, the narrative gives no medical history and the cause of death was considered unknown. Subject 309030, a 72 y/o woman in continuous-treatment cohort with a history of heavy smoking and emphysema, became ill 23 months after first open-label dose in the extension study with fatal exacerbation of COPD.

Subject 321004, a 70 y/o female, continuous cohort, was diagnosed with liver, lung and bone cancer (primary not specified or unknown) approx. 13 months after first open-label dose. No medical history or smoking history was provided. The date of the last denosumab dose and date of death were unknown.

Subject 309093, a 72-year-old woman, continuous cohort, with family history of colon Ca, was diagnosed with metastatic colon cancer 11 months after first open-label dose and died of metastasis approx. 10 months later. Her study participation ended soon after diagnosis of the cancer, thus her death was not considered to be on study.

Subject 309097, a 58 year old woman in the initial-placebo cohort, with history of heavy smoking and COPD, was diagnosed with stage IV lung Ca 25 months after open-label initiation and 1 month after last dose. She soon withdrew from the study, and died about 1 month later.

Adverse Events of Special Interest in Study 20050233

Infections:

AEs of infections were reported for 80 subjects (40%) in Study 20050233.

SAEs of infections, none of which were fatal, occurred in 3 subjects (1.5%) according to the 24-month analysis tables; however an additional case of aspiration pneumonia is reported in the SAE narratives.

Subject 307082, an 83-year-old female, represents the 4th case of endocarditis reported in subjects receiving denosumab. She had a history of hypertension, heartburn and overactive bladder, and was on the highest dose (100 mg Q6M) in the continuous treatment group of Trial 20010223. Seven months after beginning the extension study she was hospitalized with fever/chills, neck/upper back pain, confusion and leukocytosis. Blood cultures were positive for *Staphylococcus aureus*. Meningitis was suspected but not confirmed by CSF culture. IV ceftriaxone was begun. The investigator considered the event possibly related to denosumab so the study drug was permanently discontinued. The patient improved and was discharged from hospital after 12 days. She was re-admitted approx. 1 week later with acute CHF and mitral regurgitation, and was treated with IV furosemide and continued ceftriaxone. She improved and was discharged 2 days later, however 12 days later was admitted for the 3rd time with exacerbation of symptoms. An echocardiogram showed endocarditis of the mitral valve with calcified vegetation, small perforation of the posterior leaflet, aneurysm near the commissure and severe valvular insufficiency. Treatment included mitral valve replacement and she recovered. This SAE (CHF/endocarditis) was considered by the investigator to be unrelated to study drug.

Subject 317008, a 67 y/o female with a history of acute diverticulitis, in the parent trial alendronate cohort, was hospitalized 22 months after open label 1st dose of denosumab with recurrent diverticulitis. She underwent laparoscopic sigmoid colectomy and recovered. The event was considered unrelated to denosumab and this treatment was continued.

Subject 311072, a 52 y/o female with history of type 2 diabetes, reflux and smoking, in the parent trial alendronate cohort, was hospitalized 2 yrs after initiation of open label with diabetic ketoacidosis, WBC 28,000 and infiltrate on CXR and was treated for pneumonia. She recovered and episode was considered unrelated to study drug.

Subject 329030, a 63 y/o female, in the continuous-treatment cohort, with a history of hypertension and esophageal reflux, was hospitalized for abdominal pain 22 mos after initiation of open label tx, and 4 mos after last dose of IP. She was diagnosed with acute pancreatitis with a gallstone blocking the pancreatic duct. She underwent laparoscopic cholecystectomy, and postoperatively developed respiratory distress due to aspiration pneumonia. She subsequently improved and was discharged on the 6th hospital day. These SAEs were considered unrelated to denosumab.

Skin infections, both nonserious, occurred in 2 subjects, one of which ("skin infection" in subject 323006) was considered possibly treatment related.

Hypocalcemia: As expected, median serum calcium declined at 1 month after the first open-label denosumab dose: from -1.0% to -2.9% for all treatment groups except for -6.3% in the initial-210 mg Q6M group (which had been off treatment for the preceding 2 years). There were no AEs of hypocalcemia reported in this study, and no subjects had a decrease in serum calcium from Grade 0 to Grade 2 or higher (i.e. < 8.0 mg/dL).

Suppression of Bone Turnover:

No adjudicated positive events of ONJ have occurred in Study 20050233, and all 10 of the nonvertebral fractures seen in this study have been reported to have healed without evidence of delayed healing or nonunion.

Cardiovascular Events:

Twelve subjects (6%) experienced cardiovascular disorders, none fatal. Four of these were considered serious: 1 each of angina, atrial fib/flutter, CHF/mitral regurgitation, and post-traumatic leg hematoma.

Neoplasms:

Malignancies were reported for 6 subjects (3%) during the initial 2 years of the extension study: 2 cases of lung Ca, 1 of colon Ca, 1 of breast Ca, 1 of breast Ca *in situ*, and 1 of bone/hepatic/lung neoplasm malignant. Also, one case of non-Hodgkin's lymphoma was diagnosed in the 3rd year of the extension study. In addition there were 4 cases of basal cell Ca and 1 of basal cell/squamous cell Ca of skin.

Subjects 321004, 309093 and 309097, diagnosed with liver/lung/bone, colon, and lung Ca respectively, died of their malignancies (see above). The nonfatal non-skin malignancies were:

Subject 303004, a 66 y/o female in the continuous-treatment cohort, with no medical history reported except for 30 year smoking, was found on a routine exam to have an apical lung mass which was resected and found to be a bronchogenic adenocarcinoma. She recovered and event was reported to have resolved on 7/3/08. Dates of onset, last dose not given.

Subject 311070, a 73 y/o female in continuous-treatment cohort; 6 mos post initiation of open label and 6 mos post last dose of denosumab, she had an abnormal mammogram and bx showed infiltrating ductal Ca with lobular features and 1/17 positive nodes. She underwent partial mastectomy with axillary dissection.

Subject 319012, a 65 y/o female in continuous-treatment cohort, with "no risk factors such as exposure to estrogen, oral contraceptives, radiation therapy, and familial tendency", was diagnosed 5 mos after initiation with ductal Ca in situ of the breast, and underwent lumpectomy and radiation.

Subject 326003, a 76 y/o female, in continuous-treatment cohort and 5 mos post first open label dose, was found to have a cecal tumor and gallstones. Right hemicolectomy was done and the cecal tumor was a benign adenoma.

Subject 314001, an 86 y/o female, who in the parent trial was on the highest denosumab dose (210 mg Q6M) for 2 yrs then 2 yrs off, was diagnosed with non-Hodgkin's lymphoma approx. 2.5 years after initiation of open label denosumab.

Reviewer comment: It is concerning that there were 3 fatal malignancies in the parent study and 3 more in this extension study along with 4 other internal malignancies (not

reported as fatal). However, two were lung cancers in heavy smokers, and overall numbers are not large enough to be very conclusive.

Skin Disorders

Adverse events of eczema and contact dermatitis were reported for 1 and 4 subjects, respectively, all in the continuous treatment cohort. None of these events were serious and none were considered denosumab related.

9.4.3 Trial 20030216

This was the pivotal phase 3 safety/efficacy study of denosumab in the treatment of postmenopausal osteoporosis (PMO). The final report of this trial was reviewed in the initial BLA cycle, and relevant safety findings will be summarized here for the purpose of providing context for the results of extension study 20060289.

The primary objective of this 3-year, multinational, randomized, double-blind trial was to assess fracture endpoints in postmenopausal women with osteoporosis (T-score ≤ -2.5 at lumbar spine or total hip). Subjects were randomized 1:1 to receive either denosumab 60 mg SC Q6M or placebo, and all received daily calcium (≥ 1 g) and vitamin D (≥ 400 IU) supplementation throughout the trial. Exclusion criteria included a T-score < -4.0 at lumbar spine or total hip; significant or recent exposure to other osteoporosis therapies; hypocalcemia (< 8.5 mg/dL); low serum 25(OH) vitamin D (< 12 ng/mL); or metabolic conditions or drugs with potential to affect bone.

There were 7868 subjects enrolled, and the ITT population consisted of 7808 subjects. Overall, 3206 subjects (84%) in the denosumab group and 3272 subjects (82%) in the placebo group completed the 3-year study. Adverse events leading to withdrawal of the IP occurred in 4.9% of the denosumab group and 5.2% of the placebo group.

All participants were females, a majority of whom were Caucasian (92.7%); most of the remainder were Hispanic (6.0%). The mean age (\pm SD) at randomization was 72 ± 5 (range, 60-91), with 32% being > 75 years old. The mean (\pm SD) BMI was $26 \text{ kg/m}^2 (\pm 4)$ and the average number of years since menopause was 24 years. Baseline subject demographics were balanced between the treatment groups. The same proportions of each group reported a history of a fracture (53%) or a nonvertebral fracture (39%); baseline spine X-rays showed prevalent (baseline) vertebral fractures in 23% of both groups. Mean baseline BMDs were -2.8 (lumbar spine), -1.9 (total hip), and -2.2 (femoral neck), and were similar between treatment groups.

Safety Results in Trial 20030216:

The safety analysis subset of all randomized subjects who received at least 1 dose of IP consisted of 3876 subjects receiving placebo and 3886 subjects receiving denosumab. A total of 6 doses were planned; 75% of placebo subjects and 79% of denosumab subjects received all 6 doses.

Table 14 Trial 20030216: Adverse Events rates

Adverse events	Placebo	Denosumab
	n (%)	n (%)
N, enrolled	3906	3902
N, safety	3876	3886
Deaths	90 (2.3)	70 (1.8)
Nonfatal Serious	972 (25.1)	1004 (25.8)
Leading to trial discontinuation	81 (2.1)	93 (2.4)
Leading to investigational product discontinuation	202 (5.2)	192 (4.9)
At least one adverse event	3607 (93.1)	3605 (92.8)

Source: Table 84, BLA Clinical Review

Deaths

Fatal adverse events occurred in 70 subjects (1.8%) in the denosumab group and 90 subjects (2.3%) in the placebo group (see Table 85, BLA Clinical Review). Deaths were adjudicated to classify each as to the most likely cause and whether the cause was cardiovascular. The most common cause of death by MedDRA SOC was neoplasms (approximately 29% in both treatment groups) and cardiac disorders (26% in both treatment groups). Denosumab group had a higher incidence of death reported in the SOC of infections (8.6% vs. 6.7%).

Nonfatal SAEs

These were reported for 25.0% of denosumab subjects vs. 24.2% of placebo subjects (see Table 86, Clinical Review of initial BLA). Greater numbers of SAEs occurred in denosumab vs. placebo subjects in the following SOC classes: cardiac disorders (265 vs. 195); infections (186 vs. 148); neoplasms (161 vs. 129); and gastrointestinal disorders (181 vs. 131).

AEs leading to withdrawal of IP

These occurred in 192 denosumab subjects vs. 202 placebo subjects (see Table 87, BLA Clinical Review). However, there were more AE-related discontinuations with denosumab in the following SOC classes: neoplasms (58 vs. 48); skin and subcutaneous tissue disorders (13 vs. 9); general disorders (14 vs. 7); and cardiac disorders (14 vs. 3). Notable differences (by PTs) between the treatment groups (where # denosumab > # placebo) include: breast cancer (20 denosumab vs. 10 placebo); gastric cancer (5 vs. 1); neoplasm (4 vs. 1); lung adenocarcinoma (2 vs. 0); abdominal pain (4 vs. 0); pancreatic cancer (3 vs. 1); pruritus (3 vs. 0); and pruritic rash (2 vs. 0). AE related

withdrawals declined from the 1st to the 2nd year, and from the 2nd to the 3rd year, about equally in both treatment groups.

Common AEs

The overall proportion of subjects reporting at least one adverse event was comparable between the two treatment groups (Placebo 92.6% vs. Denosumab 92.2%). Most frequently reported AEs by SOC are musculoskeletal (~64%); infections (~52%); GI disorders (~37%); and nervous system disorders (~27%) (see Table 90, BLA Clinical Review). The most common adverse events reported by Preferred Terms (>10% in either treatment group) were back pain (~35%), arthralgia (~20%), hypertension (~16%), nasopharyngitis (~15%), pain in extremity (~11%), and osteoarthritis (~11%); these were similarly distributed between the treatment groups.

Adverse Events of Special Interest in Trial 20030216

Infections

Overall, infection AEs were similar in the treatment groups: 2108 placebo subjects with 4307 events vs. 2055 denosumab subjects with 4316 events. However, infection SAEs were more common with denosumab (4.0% vs. 3.3%). The disparity was mostly due to imbalances in serious bacterial infections (25 vs. 15) especially streptococcal infections (7 vs. 1); abdominal and gastrointestinal infections (28 vs. 22); ear infections (5 vs. 0); and urinary tract infections (28 vs. 17) (See Table 94 and 95, Clinical Review of initial BLA). Mycobacterial, rickettsial and viral infection SAEs were similar between groups. In terms of breakdown by Preferred Terms, there were imbalances in serious cases of erysipelas (7 denosumab subjects vs. 0 placebo), and endocarditis (3 denosumab subjects vs. 0 placebo). There were few details provided on the 3 endocarditis cases and causative organisms were not reported in any. There were more denosumab subjects who had multiple serious infections (10 vs. 6). The incidence of infections leading to death was similar between the two groups (6 in each). There were no opportunistic infections, but some unusual infections were more common, e.g. arthritis infective (nonserious) occurred in 8 denosumab vs. 0 placebo subjects.

Hypocalcemia

In this trial, serum calcium levels were measured at screening; trial day 1; and months 1, 6, 12, 18, 24, 30 and 36. Mean serum calcium was lower at month 1 in the denosumab group (9.54 mg/dL vs. 9.83 mg/dL), with much smaller difference at the other timepoints. There were greater numbers of subjects with hypocalcemia (corrected calcium < 8.5 mg/dL) in the denosumab group compared to placebo at each timepoint, with the greatest difference by far at Month 1 (33 subjects vs. 3) (see Table 55, BLA Clinical Review).

Osteonecrosis of the Jaw

A pre-defined list of MedDRA preferred terms was used to identify cases of potential ONJ cases to be adjudicated by an expert committee. The committee did not consider any of the 12 cases sent for adjudication to be a bona fide case of ONJ.

Cardiac Events

Cardiovascular (CV) related AEs (unadjudicated) occurred in 13.3% of denosumab subjects and 12.7% of placebo subjects (Table 99, Clinical Review of initial BLA). The former group had higher numbers with previous history of CAD, possibly explaining the mild discrepancy. The number of events adjudicated by a review committee as CV related was 247 in the denosumab group and 233 in the placebo group. Treatment groups were similar in incidence of any adjudicated CV SAE, CV death, acute coronary syndrome, stroke/transient ischemic attack, congestive heart failure and other vascular disorder (see Table 100, BLA Clinical Review). Studies of subsets found no difference between treatment groups in osteoprotegerin levels (see Figure, p. 213, BLA Clinical Review) or in aortic calcifications measured on lateral X-rays.

Neoplasms

Malignancies were more common in denosumab subjects compared to placebo: 307 (7.9%) vs. 274 (7.1%). There were more subjects in the denosumab group with benign and malignant breast neoplasms (34 vs. 29), GI neoplasms (35 vs. 24), benign endocrine neoplasms (19 vs. 12), and reproductive neoplasms (19 vs. 9). Respiratory neoplasms were more common with placebo (15 denosumab vs. 24 placebo) (see Table 93, BLA Clinical Review). Malignancy related SAEs mirrored these trends. There were 26 subjects in the placebo group and 20 in the denosumab group who died with an AE of malignancy. Noteworthy was one case of Schofflers tumor in a denosumab subject; this is a very rare inflammatory pseudotumor of connective tissue and could conceivably be related to the effects of RANKL on dendritic cells.

Eye Disorders

Eye-related AEs and SAEs were less overall in denosumab compared to the placebo group, including cataracts. There was an increased incidence of blurred vision in the denosumab group, but all but one of these was non-serious (Tables 96 and 97, BLA Clinical Review). Reviewers felt that there were no eye-related safety signals.

Musculoskeletal system

This was the most frequent class of AEs in both treatment groups. Rates of overall AEs and of individual AEs by PT were very similar between groups (Table 102, BLA Clinical Review).

Nervous system

There were no signals with possible exceptions of memory impairment (52 denosumab vs. 37 placebo); sciatica (178 vs. 149); and Parkinsonism/Parkinson's disease combined (21 vs. 14).

Gastrointestinal disorders

AEs were balanced overall, with exceptions of rectal hemorrhage (24 denosumab vs. 15 placebo), diverticulum (37 vs. 21), and diverticulum intestinal (33 vs. 20). SAEs were more common with denosumab (145 vs. 103), with imbalances in diverticular disorders

(15 vs. 6), exocrine pancreas disorders (8 vs. 2) and in GI ulcerations and perforations (15 vs. 9). Pancreatitis was noted in 8 subjects in the denosumab compared to 3 in the placebo group. Among these, all 8 subjects in the denosumab group had a serious event, vs. none in the placebo group. One subject, SID 20030216-835096 had 4 episodes of pancreatitis. Of the 8 subjects, 3 had a prior history of pancreatitis, and in another subject, gallstone pancreatitis was diagnosed leading to cholecystectomy. The temporal relationship between denosumab administration and event onset was highly variable.

Skin and soft tissue disorders

More denosumab subjects had AEs of skin and soft tissue disorders compared to placebo, mainly in the HLT epidermal and dermal conditions (421 vs. 316). In terms of HLT categories, there were more AEs with denosumab vs. placebo in bullous conditions (9 vs. 3), photosensitivity conditions (6 vs. 1), pruritis (107 vs. 92), rashes, eruptions and exanthems NEC (102 vs. 84), dermatitis and eczema (141 vs. 77), and dermatitis ascribed to specific agent (6 vs. 1). There were 4 subjects with "toxic skin eruptions" in the denosumab group vs. none with placebo. (Tables 106 and 107, BLA Clinical Review). Of these events, reviewers and dermatology consultants considered the increases in pruritic conditions, skin rashes, dermatitis and eczema to be clinically significant and deserving of mention in labeling.

Other

There were slightly more denosumab subjects listed with AEs of elevated cholesterol or triglycerides, however lipid profiles were not collected prospectively; reviewers considered this possibly worthy of future study. There was no evidence of significant alterations of hepatic or renal function tests or vital signs related to denosumab.

Bone biopsy substudy

A total of 115 transiliac bone biopsies were obtained (62 placebo, 53 denosumab). One hundred-three subjects consented to participate in the substudy, 92 subjects (45 placebo, 47 denosumab) received ≥ 1 dose of investigational product and had ≥ 1 evaluable biopsy, and 23 subjects (17 placebo, 6 denosumab) underwent sequential biopsy evaluation. After 24 or 36 months of treatment, there was no evidence of osteomalacia or woven bone, however 5 subjects in the denosumab group at month 24 did not have osteoid that could be visualized, which could be related to suppressed bone turnover. In the denosumab subjects, absence of tetracycline label in 35% at month 24 biopsy and 38% at month 36 was felt to be consistent with suppressed bone formation. Dynamic bone formation parameters such as activation frequency, bone formation rate and mineralizing surface were markedly suppressed.

Fracture healing

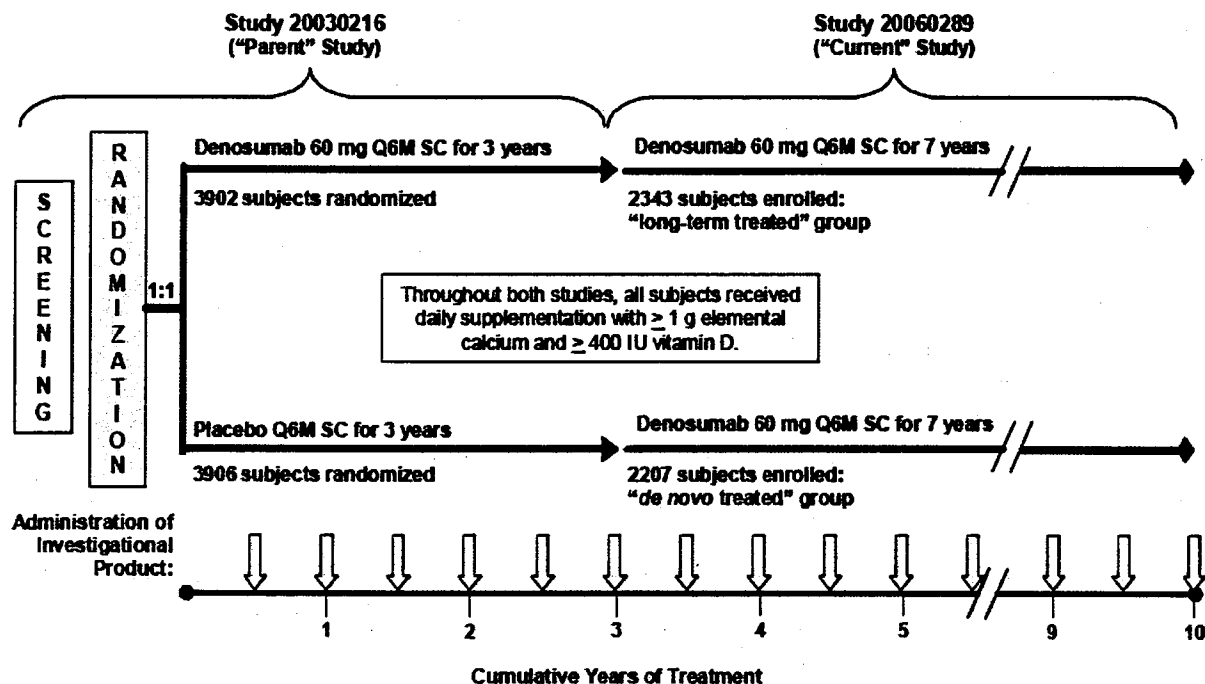
Information on fracture healing complications was collected for all nonvertebral fractures in this trial. Complications were infrequent and balanced between treatment groups; 2 subjects in each group had delayed healing, and one placebo subject had non-union. In

addition, a small substudy evaluated cortical bridging by serial X-rays to assess healing progression (cortical bridging) at 3 and 6 months post wrist fracture. However, enrollment in this study was low, and reviewers concluded that it provided no useful information.

9.4.4 Study 20060289

This is an ongoing multicenter, open-label, single-arm extension study to evaluate the long-term safety and efficacy of denosumab in the treatment of PMO. To enter this study, subjects had to have successfully completed Trial 20030216 (the parent study), which was a 3-year randomized, placebo-controlled trial of denosumab 60 mg Q6M vs. placebo injections, in postmenopausal women with osteoporosis. In the extension study, all subjects are placed on open-label denosumab 60 mg Q6M. This extension study is planned to run for 7 years, marking a total denosumab exposure period of 7-10 years (Figure 4).

Figure 4 Schema for Studies 20030216 and 20060289



Source: Complete Response Safety Update

The primary objective of Study 20060289 is to describe the long-term safety and tolerability of denosumab, as assessed by AE monitoring, immunogenicity evaluation, and safety laboratory parameters. The CR Safety Update includes clean source-verified data for a complete safety analysis for this study through the 7/1/09 cutoff date. Some of the safety data to be discussed here were already presented in the original BLA or the

120-Day Safety Update, and were therefore reviewed in the initial BLA cycle, but will be included here as well.

Subject Demographics, Disposition, and Exposure

Of the 6478 subjects who completed the 3 years of Trial 20030216 (83% of those randomized), 4550 (70%) enrolled in the open-label extension (2343 from prior-denosumab and 2207 from prior-placebo groups). Mean age at extension study entry was 74.8 ± 5.0 years, and 93% were Caucasian. The 4550 enrollees had had a mean age of 71.8 ± 5.0 years at entry into the parent-study, and their demographics were similar to the subjects who completed the parent study but did not enroll in the extension.

As of the 7/1/09 cutoff date, 6.4% of subjects had withdrawn from the extension study; the most common reasons for withdrawal were consent withdrawn (3.8%), adverse event (1.0%), and death (0.7%). As of 7/1/09, 69% of subjects had received 3 doses and 24% had received 4 doses of denosumab in the extension study. Thus, in the continuous-denosumab group, 69% had received a total of 9 doses (parent + extension = ≥ 4 yrs exposure) and 24% had received a total of 10 doses (≥ 4.5 yrs exposure). Total denosumab exposure was 10,826 subject-years in the parent study (only denosumab group) and 5155 subject-years in the extension.

Safety Results in Study 20060289

In the CR Safety Update, data summaries are presented for subjects according to their treatment group in the parent study, i.e. denosumab or placebo. In addition to presenting subject incidences, in order to compare the AE rates seen in the extension study with those in the parent study, Amgen has adjusted AE rates for subject-years of exposure for each treatment group in each study, giving event rates per 100 subject-years. Ascertainment of AEs followed the same procedures in parent and extension studies and occurred at the same timepoints i.e. at Q6month study visits and by telephone contact at the 3-month midpoint between visits.

Adverse Events

Adverse events were reported for 73.4% of prior-placebo subjects and 74.6% of prior-denosumab subjects in the first two years of this extension study. (In the original three year trial, adverse events were reported for 92.6% of placebo subjects and 92.2% of denosumab subjects.) Adjusted for subject-years of exposure, the rate of overall AEs dropped from 236.2 per 100 subject years in parent trial 20030216 (237.2 placebo/ 235.2 denosumab) to 205.7 per 100 subject years in the extension study (211.0 prior-placebo, 200.7 prior-denosumab). This drop was largely due to the SOC classes of musculoskeletal and connective tissue disorders (58.5 to 41.3 per 100 subject-years) and gastrointestinal disorders (25.3 to 18.8 per 100 subject-years). Most other SOC classes did not change over time, e.g. infections and infestations (40.0 to 39.4 per 100 subject-years); neoplasms (3.2 to 3.5 per 100 subject-years); cardiac (7.6 to 7.4 per 100 subject-years), and vascular (10.9 to 10.8 per 100 subject-years). By contrast, the SOC

class Metabolism and nutrition disorders increased somewhat (6.0 to 7.5 per 100 subject-years), mostly due to diabetes mellitus (0.6 to 1.0 per 100 subject-years).

By preferred term the most common AEs were arthralgia (8.0% of all extension study subjects), back pain (7.7%), hypertension (7.0%), nasopharyngitis (5.9%), osteoarthritis (4.7%), and pain in extremity (3.9%). There were no marked differences between prior-treatment groups. These were also, in slightly different order, the 6 most common AEs in the parent study. Subject-year-adjusted rates were similar between parent and extension studies for most of the common AEs, but lower in the extension study for some, especially for the most common AE of back pain, which occurred at a rate of 19.0 per 100 subject years in the parent study but only 8.1 per 100 subject years in the extension study.

Serious AEs occurred in 13.4% of subjects, fatal AEs in 0.8%, and AEs leading to IP discontinuation in 1.6%. Overall, 3.8% of subjects experienced AEs considered IP-related, 0.4% had SAEs considered IP-related, and there were no deaths considered IP-related. IP-related AEs leading to IP discontinuation occurred in 0.2%.

Serious Adverse Events

Serious adverse events in the first two years of the extension study were reported for 13.8% of prior-placebo subjects and 13.0% of prior-denosumab subjects. In the original three year trial, serious adverse events were reported by 24.2% of placebo subjects and 25.0% of denosumab subjects. Adjusted for subject-years of exposure, the rate of overall SAEs was 16.8 per 100 subject years in parent trial 20040216 and 18.0 per 100 subject years in the extension study (19.0 in prior-placebo and 17.2 in prior-denosumab subjects). Thus, although reporting of AEs declined over time, reporting of SAEs did not.

For SAEs, the most frequent SOC was Injury, poisoning and procedural complications, and the most frequent of these were fractures. There were greater numbers in the prior-placebo relative to the prior-denosumab group of femoral neck fractures (10 vs. 5 subjects) and femur fractures (4 vs. 2 subjects). The most frequent SAEs by Preferred Term were osteoarthritis (0.6% of subjects), pneumonia (0.4%), femoral neck fracture (0.3%), and fall (0.3%). SAEs considered possibly treatment related occurred in 0.4% of subjects, and none of the PTs of these events occurred in > 1 subject. (Table 15)

Table 15 Study 20060289: Subject Incidence of SAEs by System Organ Class

System Organ Class	Placebo/ Denosumab 60 mg Q6M (N=2203) n	Denosumab/ Denosumab 60 mg Q6M (N=2346) n
Total number of subjects reporting SAEs	304	306
Injury, poisoning and procedural complications	53	45
Cardiac disorders	43	48
Neoplasms benign/malignant/unspecified	38	48
Infections and infestations	43	36
Nervous system disorders	32	40
Musculoskeletal and connective tissue disorders	36	33
Gastrointestinal disorders	40	18
Vascular disorders	20	20
Respiratory, thoracic, and mediastinal disorders	15	16
General disorders and administration site conditions	12	17
Hepatobiliary disorders	9	14
Eye disorders	10	9
Reproductive system and breast disorders	11	8
Metabolism and nutrition disorders	4	10
Renal and urinary disorders	8	8
Ear and labyrinth disorders	9	5
Blood and lymphatic system disorders	7	5
Psychiatric disorders	4	7
Investigations	5	3
Skin and subcutaneous tissue disorders	1	5
Endocrine disorders	5	0
Immune system disorders	1	2
Missing system organ class	3	0
Surgical and medical procedures	0	2
Source: Table 03-6.4.1, CR Safety Update n = number of subjects reporting ≥ 1 event		

Adjusted by subject-years of exposure, there were no pronounced differences between parent and extension studies, or between prior-placebo and prior-denosumab subjects within the extension study, for most SAEs by SOC class or PT. Serious cardiac or vascular AEs did not appear to increase over time of denosumab exposure. SAEs of infection including pneumonia and sepsis, however, were somewhat more frequent in the extension study (see below).

Deaths

The CR Safety Update reports 35 deaths in study 20060289 up to the cutoff date of 7/1/09: 15 in the continuous-denosumab cohort and 20 in the prior-placebo cohort. None were considered IP-related by the investigator. The most frequent AEs by PT were: "death" i.e. unknown cause (6 cases), cardiopulmonary failure (3), and pulmonary

embolism, CVA and multi-organ failure (2 each). There were 8 fatal AEs for neoplasms (all different malignancies), and 5 fatal cardiac AEs. One fatal AE was attributed to an infection (sepsis/pneumonia).

Withdrawals Due to Adverse Events

There were 73 subjects (1.6%) who withdrew from IP due to an AE. Of these, 9 involved an AE that was considered IP-related; 4 of these were dermatologic (drug eruption, erythema, rash pruritic, rash).

Adverse Events of Special Interest

Infections

AEs of infection were reported for 30.2% of extension study subjects, with minimal difference between prior-placebo and prior-denosumab groups. (**Tables 16 and 17**) The 7 most commonly reported AEs by PT in the extension study were the same, in almost the same order of relative frequency, as those in the double-blind phase; adjusted for exposure, rates in double-blind vs. extension phases were comparable except for slightly higher pneumonia rates in the extension (see below).

**Table 16 Study 20060289: Subject Incidence of Infection AEs by HLT
(Most frequent)**

	Placebo/ Denosumab 60 mg Q6M (N=2203) n (%)	Denosumab/ Denosumab 60 mg Q6M (N=2346) n (%)	All (N=4549) n (%)
All infections	684 (31.0)	690 (29.4)	1374 (30.2)
Upper respiratory tract infections	238 (10.8)	247 (10.5)	485 (10.7)
Lower respiratory tract/lung infections	148 (6.7)	157 (6.7)	305 (6.7)
Urinary tract infections	125 (5.7)	140 (6.0)	265 (5.8)
Influenza viral infections	76 (3.4)	75 (3.2)	151 (3.3)
Viral infections NEC	36 (1.6)	39 (1.7)	75 (1.6)
Infections NEC	40 (1.8)	35 (1.5)	75 (1.6)
Abdominal and GI infections	33 (1.5)	34 (1.4)	67 (1.5)
Herpes viral infections	27 (1.2)	33 (1.4)	60 (1.3)
Dental/oral soft tissue infections	22 (1.0)	23 (1.0)	45 (1.0)
Fungal infections NEC	16 (0.7)	17 (0.7)	33 (0.7)
Ear infections	18 (0.8)	14 (0.6)	32 (0.7)
Streptococcal infections	10 (0.5)	12 (0.5)	22 (0.5)
Skin structures/soft tissue infections	12 (0.5)	9 (0.4)	21 (0.5)
Bacterial infections NEC	7 (0.3)	11 (0.5)	18 (0.4)
Female reproductive tract infections	4 (0.2)	7 (0.3)	11 (0.2)
Candida infections	7 (0.3)	4 (0.2)	11 (0.2)
Sepsis, bacteremia NEC	4 (0.2)	5 (0.2)	9 (0.2)
Source: CR Safety Update, Table 03-6.10.3 Data from Trial 20030216 start through 7/1/09			

**Table 17 Study 20060289: Subject Incidence of Infection AEs by PT
(Most frequent)**

	Placebo/ Denosumab 60 mg Q6M (N=2203) n (%)	Denosumab/ Denosumab 60 mg Q6M (N=2346) n (%)	All (N=4549) n (%)
All infections	684 (31.0)	690 (29.4)	1374 (30.2)
Nasopharyngitis	139 (6.3)	129 (5.5)	268 (5.9)
Bronchitis	70 (3.2)	82 (3.5)	152 (3.3)
Influenza	76 (3.4)	75 (3.2)	151 (3.3)
Cystitis	60 (2.7)	72 (3.1)	132 (2.9)
Urinary tract infection	63 (2.9)	63 (2.7)	126 (2.8)
Pneumonia	56 (2.5)	52 (2.2)	108 (2.4)
Upper respiratory tract infection	48 (2.2)	50 (2.1)	98 (2.2)
Sinusitis	24 (1.1)	31 (1.3)	55 (1.2)
Herpes zoster	18 (0.8)	26 (1.1)	44 (1.0)
Source: CR Safety Update, Table 03-6.10.1 Data from Trial 20030216 start through 7/1/09			

Within the continuous-denosumab group, rates of infection AEs did not decrease from the double-blind to the extension phase: 38.9 vs. 39.8 per 100 subject-years respectively. (Table 18)

Table 18 Subject-Year-Adjusted AE Rates of Infection: Most frequent events

	Trial 20030216		Study 20060289		
	Placebo (n=3876) Subj-yr= 10719	Denosumab 60 mg Q6M (n=3886) Subj-yr= 10826	Placebo/ Denosumab 60 mg Q6M (n=2203) Subj-yr= 2495	Denosumab/ Denosumab 60 mg Q6M (n=2346) Subj-yr= 2660	All (n=4549) Subj-yr= 5155
Preferred term	e (r)	e (r)	e (r)	e (r)	e (r)
Number, % of subjects with AEs of infection	2110 (54.4%)	2055 (52.9%)	684 (31.0%)	690 (29.4%)	1374 (30.2%)
Total # of infection AEs	4309(40.2)	4313 (39.8)	997 (40.0)	1034 (38.9)	2031 (39.4)
Nasopharyngitis	799 (7.5)	762 (7.0)	160 (6.4)	149 (5.6)	309 (6.0)
Cystitis	328 (3.1)	327 (3.0)	84 (3.4)	93 (3.5)	177 (3.4)
Bronchitis	376 (3.5)	393 (3.6)	79 (3.2)	94 (3.5)	173 (3.4)
Influenza	412 (3.8)	404 (3.7)	80 (3.2)	76 (2.9)	156 (3.0)
Urinary tract Infection	338 (3.2)	335 (3.1)	80 (3.2)	68 (2.6)	148 (2.9)
Pneumonia	195 (1.8)	188 (1.7)	67 (2.7)	59 (2.2)	126 (2.4)
Upper respiratory tract infection	204 (1.9)	241 (2.2)	52 (2.1)	52 (2.0)	104 (2.0)
Source: Table 6, Complete Response Safety Update Data from Trial 20030216 start through 7/1/09 e = number of events; r = event rate per 100 subject-years					

Serious infection AEs occurred in 1.7% of extension study subjects. (Table 19) The most common serious adverse events of infection were pneumonia (0.4%) and sepsis, diverticulitis, and bronchitis (0.1% each). There were no notable differences between prior-treatment groups, with a possible exception of 1 SAE of sepsis in the prior-placebo group vs. 4 in the prior-denosumab group.

**Table 19 Study 20060289: Subject Incidence of Infection SAEs by PT
(Most frequent)**

	Placebo/ Denosumab 60 mg Q6M (N=2203) n (%)	Denosumab/ Denosumab 60 mg Q6M (N=2346) n (%)	All (N=4549) n (%)
All serious infections	43 (2.0)	36 (1.5)	79 (1.7)
Pneumonia	9 (0.4)	8 (0.3)	17 (0.4)
Sepsis	1 (< 0.1)	4 (0.2)	5 (0.1)
Diverticulitis	3 (0.1)	2 (< 0.1)	5 (0.1)
Bronchitis	4 (0.2)	1 (< 0.1)	5 (0.1)
Pneumonia bacterial	2 (< 0.1)	2 (< 0.1)	4 (< 0.1)
Appendicitis	0 (0.0)	3 (0.1)	3 (< 0.1)
Erysipelas	1 (< 0.1)	2 (< 0.1)	3 (< 0.1)
Urinary tract infection	1 (< 0.1)	2 (< 0.1)	3 (< 0.1)
Pneumonia pneumococcal	2 (< 0.1)	1 (< 0.1)	3 (< 0.1)
Source: CR Safety Update, Table 03-6.4.1 Data from Trial 20030216 start through 7/1/09			

Adjusted for subject-years of exposure, rates of these SAEs and of overall infection SAEs in the continuous-denosumab extension group were similar to slightly higher than those in the double-blind denosumab group. (Table 20)

Table 20 Subject-Year-Adjusted SAE Rates of Infection: Most frequent events

	Trial 20030216		Study 20060289		
	Placebo (n=3876) Subj-yr= 10719	Denosumab 60 mg Q6M (n=3886) Subj-yr= 10826	Placebo/ Denosumab 60 mg Q6M (n=2203) Subj-yr= 2495	Denosumab/ Denosumab 60 mg Q6M (n=2346) Subj-yr= 2660	All (n=4549) Subj-yr= 5155
Preferred term	e (r)	e (r)	e (r)	e (r)	e (r)
Number, % of subjects with SAEs of infection	134 (3.5%)	160 (4.1%)	43 (2.0%)	36 (1.5%)	79 (1.7%)
Total # of infection SAEs	155 (1.4)	194 (1.8)	53 (2.1)	43 (1.6)	96 (1.9)
Pneumonia	37 (0.3)	35 (0.3)	11 (0.4)	9 (0.3)	20 (0.4)
Diverticulitis	6 (< 0.1)	9 (< 0.1)	3 (0.1)	4 (0.2)	7 (0.1)
Sepsis	4 (< 0.1)	3 (< 0.1)	1 (< 0.1)	4 (0.2)	5 (< 0.1)
Bronchitis	7 (< 0.1)	4 (< 0.1)	4 (0.2)	1 (< 0.1)	5 (< 0.1)
Appendicitis	7 (< 0.1)	7 (< 0.1)	0 (0.0)	4 (0.2)	4 (< 0.1)
Pneumonia bacterial	2 (< 0.1)	2 (< 0.1)	2 (< 0.1)	2 (< 0.1)	4 (< 0.1)
Erysipelas	0 (0.0)	7 (< 0.1)	1 (< 0.1)	2 (< 0.1)	3 (< 0.1)
Urinary tract Infection	10(< 0.1)	16 (0.1)	1 (< 0.1)	2 (< 0.1)	3 (< 0.1)
Pneumonia pneumococcal	1 (< 0.1)	0 (0.0)	2 (< 0.1)	1 (< 0.1)	3 (< 0.1)
Cystitis	2 (< 0.1)	6 (< 0.1)	3 (0.1)	0 (0.0)	3 (< 0.1)
Lobar pneumonia	2 (< 0.1)	0 (0.0)	0 (0.0)	2 (< 0.1)	2 (< 0.1)
Lower respiratory tract infection	3 (< 0.1)	10 (< 0.1)	1 (< 0.1)	1 (< 0.1)	2 (< 0.1)
Source: Tables 7 and 03-6.11.5, Complete Response Safety Update					
Data from Trial 20030216 start through 7/1/09					
e = number of events; r = event rate per 100 subject-years					

Serious AEs of pneumonia/pneumonia bacterial/pneumococcal pneumonia/lobar pneumonia/lower respiratory tract infection/bronchopneumonia combined occurred at rates of 0.48 per 100 subject-years in the double-blind placebo group and 0.49 in the double-blind denosumab group; and in the extension study, 0.68 in the prior-placebo group and 0.56 in the prior-denosumab group. Overall AEs of pneumonia (serious + nonserious) occurred at rates of 1.8 per 100 subject-years of exposure in placebo subjects compared with 1.7 in denosumab subjects in the double blind period; in the

extension study 20060289, these rates were slightly higher: 2.7 per 100 subject-years in the prior-placebo group compared with 2.2 in the prior-denosumab group.

There was one SAE of infection (sepsis/pneumonia) which was fatal (Subject 6436107). This was an 81 y/o in the prior-denosumab group with history of hypertension and acute pulmonary edema who became ill about 5.5 months after her last (8th) dose of denosumab. She was hospitalized with diagnosis of bronchopneumonia and sepsis and cause of death reported as sepsis.

There were no reported cases of endocarditis in this extension study, nor any infections with opportunistic pathogens. There were 2 serious ear infections: 1 each of chronic otitis media and ear infection, both in prior-placebo subjects. There were no cases of infective arthritis.

Serious AEs of **skin infection** were reported for 4 subjects: 3 with erysipelas and 1 with necrotizing fasciitis. Overall frequency of skin infection SAEs was not greater in the extension study compared to the parent study. (Table 21)

Table 21 Subject-Year-Adjusted SAE Rates of Skin Infection

Preferred term	Trial 20030216		Study 20060289		All (n=4549) Subj-yr= 5155
	Placebo (n=3876) Subj-yr= 10719	Denosumab 60 mg Q6M (n=3886) Subj-yr= 10826	Placebo/ Denosumab 60 mg Q6M (n=2203) Subj-yr= 2495	Denosumab/ Denosumab 60 mg Q6M (n=2346) Subj-yr= 2660	
	e (r)	e (r)	e (r)	e (r)	e (r)
Number, % of subjects with SAEs of infection	3 ($< 0.1\%$)	15 (0.4%)	1 ($< 0.1\%$)	3 (0.1%)	4 ($< 0.1\%$)
Total # of skin infection SAEs	3 (< 0.1)	17 (0.2)	1 (< 0.1)	3 (0.1)	4 (< 0.1)
Erysipelas	0 (0.0)	7 (< 0.1)	1 (< 0.1)	2 (< 0.1)	3 (< 0.1)
Necrotizing fasciitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)	1 (< 0.1)
Cellulitis	1 (< 0.1)	6 (< 0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Infected skin ulcer	0 (0.0)	1 (< 0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Skin bacterial infection	0 (0.0)	2 (< 0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Staphylococcal infection	1 (< 0.1)	1 (< 0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Subcutaneous abscess	1 (< 0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Source: Table 8, Complete Response Safety Update Data from Trial 20030216 start through 7/1/09 e = number of events; r = event rate per 100 subject-years					

Subject 6652012, an 81-year-old woman who received denosumab for 3 years in Trial 20030216, was reported to have **erysipelas** of the right leg 8 days after receiving the first dose of denosumab in the current trial and was treated with amoxicillin. Thirteen days later, the subject was noted to have a bullous rash with increased pain and erythema. The subject was hospitalized with an admission diagnosis of necrotizing fasciitis and erysipelas of the right leg. Cutaneous exam revealed external and internal right leg ulceration that was clean and without signs of infection. Wound culture revealed *Pseudomonas aeruginosa*, *Enterobacter cloacae*, and *Enterococcus faecalis*. The ulcer was incised and the subject was treated with intravenous antibiotics. The subject clinically improved and was eventually discharged from the hospital on oral antibiotics. Investigational product was discontinued.

Subject 6631051, an 82-year-old woman who received 3 years of placebo in Trial 20030216, developed erysipelas (left leg) approximately 2 months after initiating treatment with denosumab in the current trial. The subject was hospitalized. Treatment included antibiotic therapy, and the subject was discharged 6 days later.

Hypocalcemia

Because PK studies with denosumab showed that serum calcium declines to a nadir at about 10 days after a dose, levels were measured at day 10 \pm 5 after the first dose in this extension study. This complete dataset was submitted in the 120-Day Safety Update and reviewed with the initial BLA. Median decreases in serum calcium at day 10 were greater in the placebo-to-denosumab group (-3.1%) compared to the denosumab-to-denosumab group (-2.0%). Combining these 2 groups, at day 10, 3.3% of subjects had a serum calcium < 8.5 mg/dL, however only 0.3% had serum calcium < 8.0 mg/dL, and 0.07% had serum calcium < 7.5 mg/dL. The lowest serum calcium of 7.0 mg/dL, in a subject with history of renal impairment, was associated with AE of nausea; the other hypocalcemic subjects appeared asymptomatic (no AEs of hypoesthesia, oral hypoesthesia, paresthesia, oral paresthesia, or tetany). Five AEs of hypocalcemia were reported, all in prior-placebo subjects, only one of these had a serum calcium < 8 mg/dL, and none were considered serious. Note that all subjects in this study were supplemented with 1 gm calcium and vitamin D daily throughout this study and the preceding 3-year parent study.

Suppression of Bone Turnover

At the time of the CR Safety Update, there had been 7 cases of potential ONJ sent to the adjudication committee, and none were confirmed positive. However, one case adjudicated positive for ONJ was reported later (see discussion in section 7.3.4.3).

No adverse events were reported indicating either atypical fractures or fracture healing complications (i.e, fracture, malunion, non-union, or delayed union; impaired healing; epiphyses delayed fusion; callus formation delayed; and primary, secondary, or tertiary sequestrum).

Cardiovascular Events

During the extension study, the most common serious adverse events of cardiac disorders ($\geq 0.3\%$ overall) were atrial fibrillation (0.3%), angina pectoris (0.3%), and coronary artery disease (0.3%). (Table 22) There were 210 cardiac AEs and 58 cardiac SAEs in the continuous-denosumab group, and there were 171 cardiac AEs and 47 cardiac SAEs in the de novo-denosumab group. There were 5 cardiac deaths, 3 in prior-placebo and 2 in prior-denosumab subjects; these were due to cardiopulmonary failure (3), cardiac failure (1), and myocardial ischemia (1)..

Table 22 Study 20060289: Subject Incidence of Cardiac SAEs by PT (Most frequent)

Preferred Term	Placebo/ Denosumab 60 mg Q6M (N=2203) n (%)	Denosumab/ Denosumab 60 mg Q6M (N=2346) n (%)	All (N=4549) n (%)
All cardiac SAEs	43 (2.0)	48 (2.0)	91 (2.0)
Atrial fibrillation	8 (0.4)	5 (0.2)	13 (0.3)
Angina pectoris	6 (0.3)	6 (0.3)	12 (0.3)
Coronary artery disease	6 (0.3)	6 (0.3)	12 (0.3)
Myocardial infarction	5 (0.2)	6 (0.3)	11 (0.2)
Angina unstable	3 (0.1)	4 (0.2)	7 (0.2)
Myocardial ischemia	1 (< 0.1)	4 (0.2)	5 (0.1)
Cardiac failure	1 (< 0.1)	3 (0.1)	4 (< 0.1)
Source: CR Safety Update, Table 03-6.4.1 Data from Trial 20030216 start through 7/1/09			

Within the continuous-denosumab cohort, cardiac SAE event rates were 2.6 per 100 subject-years of exposure during the double-blind phase compared to 2.2 in the extension phase. Similar figures for the most common individual PTs were: atrial fibrillation 0.3/0.2; coronary artery disease 0.1/0.3; angina pectoris 0.3/0.2; myocardial infarction 0.2/0.2; angina unstable 0.1/0.2; myocardial ischaemia 0.1/0.2.

Reviewer comment: Cardiac AE rates may not be comparable in the double-blind and extension phase rates because they were adjudicated by committee in the parent study but apparently not in the extension study.

AEs and SAEs of vascular disorders were reported at exposure-adjusted rates that were similar between studies 20030216 and 20060289. The most common SAEs were hypertension (0.2%) and deep vein thrombosis (0.1%). One subject (6853093, (prior-placebo group) experienced an SAE of vasculitis that was considered possibly IP-related.

Neoplasms

AEs related to malignant neoplasms were reported in 2.6% of extension subjects. There were no major imbalances between prior-treatment groups except for possibly esophageal cancer. (**Table 23**) By preferred term, the most common ($\geq 0.1\%$ overall) were basal cell carcinoma (0.7%), breast cancer (0.2%), colon cancer (0.2%), thyroid neoplasm (0.2%), and lung neoplasm malignant (0.1%). Eight subjects died of adverse events in the neoplasms SOC.

Table 23 Study 20060289: Subject Incidence of Selected Neoplasms by HLT

High Level Term	Placebo/ Denosumab 60 mg Q6M (N=2203) n (%)	Denosumab/ Denosumab 60 mg Q6M (N=2346) n (%)	All (N=4549) n (%)
All malignancies	61 (2.8)	59 (2.5)	120 (2.6)
Rectal cancer			
Large intestine carcinoma	4	7	11
Colon cancer			
Esophageal carcinoma			
Esophageal adenocarcinoma	0	3	3
Breast neoplasms unspec. malignant			
Breast/nipple neoplasms malignant	6	8	14
Respiratory tract/pleural neo. malignant			
Non-small cell neoplasms resp. malign.	4	5	9
Resp. tract/pleural neo. malign unspec.			
Uterine neoplasms malignant			
Ovarian neoplasms malignant	1	2	3
Endometrial cancer			
Thyroid neoplasms malignant			
Endocrine neoplasms malignant/unspec.	7	4	11
Source: CR Safety Update, Table 03-6.10.3 Data from Trial 20030216 start through 7/1/09			

In the primary PMO trials, the original BLA reviewers identified the following categories of malignant neoplasms as occurring more frequently in denosumab subjects relative to placebo: female reproductive; gastrointestinal; breast; thyroid; and hematopoietic. Comparison of neoplasm AE rates in studies 20030216 and 20060289, adjusted for length of exposure, shows no evidence that longer-term exposure to denosumab heightens the risk of these or other specific classes of neoplasms, with the possible exceptions of colorectal, esophageal and thyroid cancer. (**Table 24**) However, the overall rate of malignancies is somewhat higher in both prior-treatment groups in the extension study relative to both double-blind groups, especially the placebo group.

Reviewer comment: Some of this difference in overall malignancies may be explained by the fact that extension study subjects were on average 3 years older than double-blind subjects and thus at somewhat higher baseline risk of malignancy.

Table 24 Subject-Year-Adjusted AE Rates of Selected Neoplasms by HLG/PT

High Level Group Term Preferred term	Trial 20030216		Study 20060289		All (n=4549) Subj-yr= 5155
	Placebo (n=3876) Subj-yr= 10719	Denosumab 60 mg Q6M (n=3886) Subj-yr= 10826	Placebo/ Denosumab 60 mg Q6M (n=2203) Subj-yr= 2495	Denosumab/ Denosumab 60 mg Q6M (n=2346) Subj-yr= 2660	
	e (r)	e (r)	e (r)	e (r)	e (r)
Number, % of subjects reporting AEs	166 (4.3%)	188 (4.8%)	61 (2.8%)	59 (2.5%)	120 (2.6%)
Total # of AEs	196 (1.8)	220 (2.0)	64 (2.6)	63 (2.4)	127 (2.5)
GI Neoplasms - all	24 (0.2)	35 (0.3)	9 (0.4)	12 (0.5)	21 (0.4)
Colon cancer/ Rectal cancer/ Large intestine Ca/ Colon cancer metastatic/ Colon neoplasm/ Colorectal cancer/ Intestinal adenoCa/ Rectal Ca stage III/ Rectal neoplasm	13 (0.12)	18 (0.17)	4 (0.16)	8 (0.30)	12 (0.23)
Esophageal carcinoma/ Esophageal adenoCa/ Esoph. squam. cell Ca	1 (< 0.1)	1 (< 0.1)	0 (< 0.1)	3 (0.11)	3 (< 0.1)
AdenoCa pancreas/ Pancreatic carcinoma/ PancreaticCa metastatic	3 (< 0.1)	8 (< 0.1)	2 (< 0.1)	0 (0.0)	2 (< 0.1)
Gastric cancer/ Metastatic gastric Ca	3 (< 0.1)	7 (< 0.1)	1 (< 0.1)	0 (0.0)	1 (< 0.1)
Breast neoplasms	28 (0.3)	34 (0.3)	6 (0.2)	8 (0.3)	14 (0.3)
Respiratory and mediastinal neoplasms	25 (0.2)	16 (0.1)	4 (0.2)	5 (0.2)	9 (0.2)
Thyroid neoplasm/ Thyroid cancer	2 (< 0.1)	6 (< 0.1)	6 (0.24)	4 (0.15)	10 (0.19)
Reproductive neoplasms female malign/unspec.	10 (< 0.1)	20 (0.2)	1 (< 0.1)	2 (< 0.1)	3 (< 0.1)
Basal cell carcinoma	41 (0.4)	32 (0.3)	18 (0.7)	14 (0.5)	32 (0.6)
Hematopoietic neoplasms excl. leukemia/lymphoma	0 (0.00)	3 (< 0.1)	1 (< 0.1)	0 (0.0)	1 (< 0.1)
Source: Table 03-6.13.2, Complete Response Safety Update Data from Trial 20030216 start through 7/1/09 e = number of events; r = event rate per 100 subject-years					

Skin disorders

In study 20060289, AEs of eczema (including dermatitis, allergic dermatitis, and contact dermatitis) were reported for 0.9% of subjects. Comparing double-blind and extension phases within the continuous-denosumab cohort, exposure adjusted AE rates were similar for preferred terms of eczema (0.6 and 0.5 per 100 subject-years, respectively), dermatitis (0.2 and 0.3, respectively), allergic dermatitis (0.4 and 0.1, respectively), and contact dermatitis (< 0.1 and < 0.1, respectively). AEs of rash were reported for 0.9% of subjects. Within the continuous-denosumab cohort, exposure-adjusted AE rates of rash were similar (1.1 and 0.9 per 100 subject-years, respectively). AEs in the high-level term of bullous conditions were blister and dermatitis herpetiformis (2 subjects (< 0.1%) for each term). No events of Stevens-Johnson syndrome or toxic epidermal necrolysis were reported in the study. Skin-related SAEs occurred in 6 subjects, including skin ulcer events in 1 prior-placebo and 3 prior-denosumab subjects, and 1 subject each (both prior-denosumab) with drug eruption or rash pruritic. The rate of skin ulcer SAEs, which did not occur in any placebo subjects in the parent study, increased slightly in the denosumab group from double-blind to extension phase.

Hypersensitivity

AEs of hypersensitivity and drug hypersensitivity were reported for 0.2% and 0.1% of subjects, respectively. Most of these list a specific allergen e.g pollen, drugs other than denosumab, insect bites, etc., and none were considered denosumab related.

Pancreatitis

Only one non-serious AE of acute pancreatitis was reported in the prior-placebo group, with none in the prior-denosumab group and no SAEs in either group.

Diverticulitis

Combined events (overall and serious) of diverticulitis, diverticulum intestinal and diverticulum, when adjusted for subject-years of exposure, occurred at somewhat higher rates in both prior-treatment groups compared with the original placebo group. (Table 25)

Table 25 Subject-Year-Adjusted AE and SAE Rates of Diverticulitis/diverticulum

Preferred Term	Trial 20030216		Study 20060289		All (n=4549) Subj-yr= 5155
	Placebo (n=3876) Subj-yr= 10719	Denosumab 60 mg Q6M (n=3886) Subj-yr= 10826	Placebo/ Denosumab 60 mg Q6M (n=2203) Subj-yr= 2495	Denosumab/ Denosumab 60 mg Q6M (n=2346) Subj-yr= 2660	
	e (r)	e (r)	e (r)	e (r)	e (r)
AEs – total	67 (0.63)	112 (1.0)	19 (0.76)	26 (1.0)	45 (0.87)
Diverticulitis	25	37	8	12	20
Diverticulum intestinal	21	35	5	8	13
Diverticulum	21	40	6	6	12
SAEs - total	11 (0.10)	24 (0.22)	4 (0.16)	5 (0.19)	9 (0.17)
Diverticulitis	6	9	3	4	7
Diverticulum intestinal	2	8	0	1	1
Diverticulum	3	7	1	0	1

Source: Tables 03-6.11.1 and 03-6.11.5, Complete Response Safety Update

Data from Trial 20030216 start through 7/1/09

e = number of events; r = event rate per 100 subject-years

Clinical Laboratory Evaluations

CTCAE abnormalities of hematology/chemistry parameters (other than calcium) of Grade 3 or 4 were seen in 1.8% of subjects. For each parameter, < 1% of subjects had such an outlier, and the 2 prior-treatment groups were similar.

Immunogenicity

Although 0.6% of the denosumab-treated subjects in the parent trial 20030216 had a positive result for denosumab binding antibodies, none of the subjects in this extension study has tested positive.

9.4.5 Study 20080287

Study 20080287 is an ongoing, multi-center, cohort study to characterize bone histology and histomorphometry in postmenopausal women with low bone mass or osteoporosis who were previously treated with denosumab, in order to determine reversibility of denosumab suppression of remodeling. Subjects eligible for enrollment were completers of either trial 20050179, 20050141, 20060237, or 20030216 who had discontinued denosumab for ≥ 12 months prior to screening. No treatment is given, other than 2 cycles of tetracycline x 3 days, separated by 14 days, for labeling, followed by a transiliac bone biopsy 5-14 days after the last dose.

Biopsy results are presented for the first 4 subjects (total of ~15 is planned). These women age 54-65 had previously participated in trial 20050141 and had received their last of 2 denosumab doses 27-33 months before the biopsy. Histology on all 4 specimens showed normal lamellar bone and osteoid with absence of pathological findings and with double label seen in all. (Table 26)

Table 26 Study 20080287: Dynamic Histomorphometry Variables on 1st 4 subjects

	Reference Range	Subject No.			
		287201001	287201002	287201003	287201004
Mineral apposition rate (MAR) ($\mu\text{m/day}$)	0.89 ± 0.18	0.776	0.717	0.693	0.631
Bone formation rate volume-based (BFR/BV) (%/yr)	26.2 ± 16.4	30.88	27.34	13.82	34.51
Activation frequency (AcF) (/yr)	Not provided	0.44	0.34	0.2	0.54
Reference range for postmenopausal women provided by Mayo Clinic Histomorphometry Laboratory Source: Table 04-1.1, CR Safety Update					

Bone turnover markers (serum P1NP, CTx) were also measured; in all 4 subjects, these markers, which had been suppressed by ~60 - >90% within 6 mos of denosumab doses, returned to near baseline at 27-33 months. The Applicant considers that these results are consistent with normal remodeling after withdrawal of denosumab, demonstrating reversibility of its effects on bone.

9.4.6 Trial 20060232

This is an ongoing multicenter, randomized, open-label, crossover trial in postmenopausal women with low BMD evaluating denosumab and alendronate in terms of patient "adherence, preference and satisfaction". A total of 250 subjects were randomized (1:1) to either denosumab 60 mg SC Q6m x 1 year followed by alendronate 70 mg PO QW x 1 year, or vice versa. The mean age was 65.2, and 94% were white. The CR Safety Update provides data through the 12-month interim analysis.

Adverse events have been reported for 90 subjects (72%) on denosumab and 75 subjects (64%) on alendronate, however more alendronate subjects have withdrawn because of AEs (5 vs. 2, 3 of the alendronate withdrawals due to reflux/dyspepsia). (Note that this is an open-label study). A total of 8 subjects experienced SAEs thus far; (3 denosumab, 5 alendronate). For the denosumab group, there was 1 subject each who experienced chest pain, diverticulitis, and osteoarthritis. For the alendronate group, there was 1 subject each who experienced atrial fibrillation, cardiac failure congestive, C. difficile colitis, squamous cell carcinoma, muscle spasms, pain and lumbar spinal stenosis. There were no deaths at the time of the safety update.

Infection AEs have been reported for 33 subjects (26%) on denosumab and 24 subjects (20%) on alendronate. There have been no skin infections. One subject in each group reported contact dermatitis. A denosumab subject had "allergic reaction" but not serious and not considered treatment related. The only malignancies have been 1 basal cell ca in a denosumab subject, and 1 basal cell and 1 squamous cell ca in alendronate subjects. Median serum calcium concentrations decreased from baseline to month 12 in both the denosumab (-2.5%) and alendronate (-3.0%) groups. There have been no AEs of hypocalcemia or ONJ.

9.4.7 Trial 20040132

This was a phase 3 study of the prevention of PMO in women with osteopenia. The initial 24-month double-blind treatment period results were submitted and reviewed in the initial BLA cycle. Data and analysis of the subsequent 24 months of off treatment observation is complete and the final study report is included in this CR submission.

This multicenter trial enrolled postmenopausal women with lumbar spine BMD T-score between -1.0 and -2.5, and no history of a fracture after the age of 25. Subjects were randomized to denosumab 60 mg Q6M or placebo, and all received ≥ 1 gm calcium and ≥ 400 IU vitamin D. Four injections were given at baseline and months 6, 12, and 18. No treatment was given during the off treatment period (months 25-48) though calcium/vitamin D supplements were continued. Serum denosumab concentrations were low at month 24 and were all below LLQ at month 36.

There were 332 subjects enrolled, with 166 randomized to each treatment group. Of these, ~86% completed the 24-month on-treatment phase, and of these 256 subjects (128 from each treatment group, 77% of those randomized) continued into the off-treatment observation phase. Mean age of subjects was 59.1 ± 7.1 and 82% were Caucasian, 7% Hispanic.

The efficacy endpoints of percent change in BMD at various skeletal sites at month 24 were achieved, however BMD returned to near baseline at months 36 to 48. There were clinical low-trauma fractures in 2 denosumab and 7 placebo subjects in the initial 24 months; in the last 24 months these occurred in 4 subjects in each group. These prior-

denosumab fractures were: femoral neck, fibula, radius, hand. The prior-placebo fractures were: humerus, fibula, radius, hand. Morphometric vertebral fractures were identified in 1 placebo subject in the first phase, and in 2 prior-denosumab subjects in the latter phase.

Safety results

During the off-treatment period, 84% of prior-denosumab subjects and 77% of prior-placebo subjects reported AEs. There were no deaths during this phase. Serious AEs were reported for 7 subjects (5.5%) in prior-denosumab group and 9 subjects (7.0%) in prior-placebo group. Other than 2 breast cancers in prior-placebo subjects, no preferred term SAE appeared more than once. There were no adjudicated positive cases of ONJ, or reports of delayed fracture healing.

Infections

During the initial 24 months (on-treatment phase) of this trial, there was an imbalance of serious infections, which occurred in 8 denosumab subjects (4.9%), vs. 1 placebo subject (0.6%). These included pneumonia (3 denosumab vs. 1 placebo subject), diverticulitis (2 denosumab) and sepsis (2 denosumab).

In the off-treatment phase, AEs of infection occurred in 43.8% of prior-denosumab and 40.6% of prior-placebo subjects. There were 11 UTI/cystitis/pyelonephritis AEs in prior-denosumab subjects and 5 in prior-placebo subjects. Other categories of nonserious infections including skin infections were balanced between the groups. One prior-denosumab subject had an AE of Mycobacterium avium complex infection. There were 2 infection SAEs in the off-treatment period: 1 pneumonia (prior-denosumab, day 848, ~10 months after last dose) and 1 diverticulitis (prior-placebo).

Malignancies

In the on-treatment period, subjects receiving denosumab reported 5 malignancies (ovarian cancer, uterine cancer, breast cancer, basal cell carcinoma, T-cell lymphoma). In the placebo group, there were 2 reported malignancies (B-cell lymphoma, squamous cell skin carcinoma).

In the off-treatment period, there were 3 reports of malignancies in the prior-denosumab group (meningioma, metastatic atypical carcinoid and melanoma). One of these (metastatic atypical carcinoid) was considered by the investigator to be treatment related. In the prior-placebo group, there were also 3 reported malignancies (2 breast cancers, 1 squamous cell skin carcinoma).

9.4.8 Trial 20040135

This was a randomized, double-blind, placebo-controlled trial to evaluate denosumab in the treatment of bone loss in subjects undergoing aromatase inhibitor therapy for

nonmetastatic breast cancer, with T-score -1.0 to -2.5). This 4-year trial enrolled 252 subjects (denosumab -127, placebo - 125). Subjects received therapy for 24 months (denosumab 60 mg Q6M vs. placebo) and were monitored for an additional 24 months; 69% completed all 4 years. Efficacy and safety data from the double-blind period were reviewed in the initial BLA cycle. Safety data and analysis from the off-treatment phase is submitted in the CR Safety Update. Subjects had a mean age of 59.8 (range 38-84); 93.5% were white.

More subjects in the prior-denosumab group (15) than prior-placebo subjects (6) reported a fracture during the off-treatment period. (Table 27) This includes 3 denosumab subjects who had vertebral fractures, although one of these was reportedly due to "moderate trauma" and the other was a pathologic fracture due to metastasis. The report notes that bisphosphonate use in this phase was more common in the prior-placebo group (26 vs. 14 subjects, excluding those who began a bisphosphonate after a fracture).

Table 27 Study 20040135: Fracture AEs by Preferred Term (Off-Treatment Phase)

Preferred Term	All Fractures		Fractures confirmed by Central reader	
	Placebo (N=90) n	Prior-Denosumab (N=96) n	Placebo (N=90) n	Prior-Denosumab (N=96) n
Number of subjects with Fractures	6 (6.7%)	15 (15.6%)	5 (5.6%)	12 (12.5%)
Radius fracture	1	4	1	4
Thoracic vertebral fracture	0	3	0	2
Fibula fracture	2	2	1	2
Foot fracture	1	2	1	1
Lumbar vertebral fracture	0	2	0	1
Rib fracture	0	2	0	2
Tibia fracture	0	2	0	2
Fracture	0	1	0	0
Fractured sacrum	0	1	0	1
Pelvic fracture	0	1	0	1
Ulna fracture	1	0	1	0
Wrist fracture	1	0	1	0

Source: CR Safety Update

Reviewer comment: This apparent excess of fractures in the off-treatment phase is of doubtful significance; no such effect was seen in the off-treatment phases of trials 20040132 or 20040138.

Safety results

During the off-treatment phase, AEs occurred in ~70% of both prior-treatment groups and appear fairly balanced between groups. However, AEs in the Musculoskeletal and connective tissue disorders SOC were reported in 34.4% of prior-denosumab subjects and 26.7% of prior-placebo subjects, due in part to the PT of arthralgia (11 vs. 4 subjects). SAEs occurred in 9 prior-denosumab and 4 prior-placebo subjects; none were considered treatment related. There were 4 deaths in the off treatment phase (2% of subjects). Two of these deaths were in the prior-denosumab group and were both from metastatic breast cancer; the other 2, in prior-placebo subjects, were from hepatic failure and breast cancer. There were no adjudicated positive cases of ONJ, or reports of delayed fracture healing.

Infections

Infection AEs occurred in 22 prior-denosumab and 17 prior-placebo subjects. There were 2 infection SAEs in each group: lobar pneumonia and pneumonia in prior-denosumab subjects, and cellulitis and C. difficile colitis in prior-placebo subjects.

Malignancies

In the off-treatment phase, there were 4 prior-denosumab and 9 prior-placebo subjects who were reported with neoplasm AEs. Most of these were related to breast cancer progression. There was 1 new pancreatic carcinoma in a prior-denosumab subject and 1 new multiple myeloma in a prior-placebo subject.

9.4.9 Trial 20040138

This was a randomized, double-blind, placebo-controlled trial to evaluate denosumab in the treatment of bone loss in subjects undergoing androgen-deprivation therapy for nonmetastatic prostate cancer. Subjects had either age ≥ 70 , history of osteoporotic fracture, and/or T-score < -1.0 . This 5-year trial enrolled 1468 subjects (denosumab - 734, placebo - 734). Subjects received therapy for 36 months (denosumab 60 mg Q6M vs. placebo); 55% of those randomized then entered a 24-month off-treatment safety follow-up phase, which is ongoing. A large number of those who entered this follow-up phase (27%) have dropped out, but only 3 because of AEs; most dropped out in order to enroll in an open-label study (20080537). Complete efficacy and safety data from the double-blind period were reviewed in the initial BLA cycle. Safety data and analysis from the off-treatment phase is submitted in the CR Safety Update. Off-treatment phase subjects had a mean age of 74.3 (range 48-92); 83% were white, 4% African American, and 12% Hispanic.

Fractures were reported in 3 prior-denosumab subjects and 6 prior-placebo subjects, including 1 subject in each treatment group who developed a vertebral fracture in the off-treatment period and 2 prior-denosumab and 4 prior-placebo subjects who were diagnosed with nonvertebral fractures that were likely to be osteoporotic.

Safety results

In the off-treatment period, adverse events occurred in 41% of prior-denosumab subjects and in 37% of prior-placebo subjects. AEs in the Musculoskeletal and connective tissue disorders SOC were reported in 11.5% of prior-denosumab subjects and 8.3% of prior-placebo subjects. The most frequent AE was arthralgia (13 prior-denosumab subjects vs. 8 prior-placebo subjects). Serious AEs occurred in 13.9% of prior-denosumab and 13.5% of prior-placebo subjects. There were more AEs (13 vs. 7) and SAEs (5 vs. 1) for hematuria in prior-denosumab compared to prior-placebo subjects. There was one SAE of pancreatitis in a prior-denosumab subject associated with cholangitis and septicemia, which was believed to be caused by passage of a gallstone. There were no adjudicated positive cases of ONJ, or reports of delayed fracture healing.

There were 15 deaths in prior-denosumab subjects and 14 in prior-placebo subjects. The cause was prostate cancer with or without bone metastases in 5 and 4 of these cases respectively. There were also 4 deaths due to new malignancies in the prior-denosumab group (acute leukemia/lymphoma, pancreatic carcinoma, metastatic rectal cancer and malignant tongue neoplasm), and just one in the prior-placebo group (malignant brain neoplasm).

Infections

Infection AEs were reported in 41 (9.9%) prior-denosumab subjects and 31 (8.0%) prior-placebo subjects. Infection SAEs occurred in 11 subjects in each group, but there were more AEs (8 vs. 2) and SAEs (5 vs. 1) for pneumonia in prior-denosumab compared to prior-placebo subjects. No other imbalances were apparent. There was one case of endocarditis in a prior-placebo subject.

Malignancies

Neoplasm-related AEs occurred in 29 prior-denosumab (7.0%) vs. 21 prior-placebo (5.4%) subjects; most of these were related to prostate Ca ± metastases which occurred in 17 vs. 13 subjects respectively. Neoplasm-related SAEs occurred in 15 prior-denosumab vs. 10 prior-placebo subjects. There were more subjects with new malignancies (14 vs. 8) in the prior-denosumab, compared to the prior placebo group, resulting in more deaths (4 vs. 1). (**Table 28**)

Table 28 Study 20040138: Number of subjects with AEs of malignancies, exclusive of prostate Ca/metastases (off-treatment phase)

Preferred Term	Prior- placebo (N=386) n	Prior- denosumab (N=416) n
Total	8	14
Bladder cancer Bladder neoplasm Bladder transitional cell carcinoma Transitional cell carcinoma	3	3
Acute leukemia Lymphoma (same pt)	0	1*
Basal cell carcinoma Skin cancer	0	2
Colon cancer Rectal cancer metastatic Rectal cancer Gastrointestinal carcinoma ("recurrence bowel Ca")	1	3 (1*)
Pancreatic carcinoma	0	1*
Lung neoplasm (2 lung nodules)	0	1
Myeloproliferative disorder	0	1
Tongue neoplasm malignant	0	1*
Metastases to liver ("metastatic small cell Ca")	0	1
Brain neoplasm malignant	1*	0
Hepatic neoplasm	1	0
Oropharyngeal cancer	1	0
Squamous cell carcinoma (lower lip)	1	0
N = number of subjects who had a visit in the safety follow-up phase through 7/1/09 n = number of subjects reporting ≥ 1 event in safety follow-up phase * = fatal AE		



FDA CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM

DATE: October 16, 2009

TO: BLAs 125320 and 125331
PROLIA (denosumab) Injection, 60 mg/mL
Amgen, Inc.

FROM: Julie Beitz, M.D.
Director, Office of Drug Evaluation III

RE: Complete Response Actions

Denosumab is a fully human IgG2 monoclonal antibody that targets receptor activator of nuclear factor kappa B ligand (RANKL), a member of the tumor necrosis factor superfamily of cytokines. RANKL promotes osteoclast formation, differentiation and activation, as well as B cell and T cell differentiation and dendritic cell maturation. Blockade of RANKL is believed to result in increased bone mass. The applicant has submitted information in support of the following indications for denosumab: treatment and prevention of postmenopausal osteoporosis, and treatment and prevention of bone loss associated with hormone ablative therapies in patients with breast and prostate cancer.

This memo documents my concurrence with the Division of Reproductive and Urologic Product's (DRUP's) recommendation for complete response actions for denosumab, administered by subcutaneous injection every 6 months, for the treatment (BLA 125320) and prevention (BLA 125331) of postmenopausal osteoporosis. In addition, the Division of Biologic Oncology Products recommends complete response actions for the treatment and prevention of bone loss in patients undergoing hormone ablation for breast (BLA 125332) and prostate cancer (BLA 125333).

REGULATORY HISTORY

BLA 125320 was received on December 19, 2008 and granted a standard review. Given that the BLA contained data regarding several distinct indications, it was administratively split as follows: BLAs 125320 and 125331 support the treatment and prevention of postmenopausal osteoporosis, respectively, while BLAs 125332 and 125333 support the treatment and prevention of bone loss in patients undergoing hormone ablation for breast

and prostate cancer, respectively. The Division of Reproductive and Urologic Products has reviewed the postmenopausal osteoporosis indications while the Division of Biologic Oncology Products has reviewed the oncology indications.

All of the applicant's proposed indications were discussed before the Reproductive Health Drugs Advisory Committee (RHDAC) on August 13, 2009. Several safety concerns associated with denosumab use were addressed including, the occurrence of serious infections, the potential for the development of new malignancies and for tumor progression in patients with existing cancer, bone histomorphometry findings that suggest suppression of bone remodeling which may lead to future complications with long-term use (e.g., delayed fracture healing, osteonecrosis of the jaw, or atypical fracture), and serious dermatologic adverse events. In addition, if denosumab were to be approved, we sought 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.

Facility inspections of the drug substance manufacturing sites were found acceptable, however inspection of the drug product manufacturing site (Puerto Rico) resulted in a 483 issued on September 11, 2009 that cited concerns regarding quality control. On October 15, 2009, the Office of Compliance recommended that the site was acceptable based on new information received and Amgen's intent to provide corrective actions to adequately address the CGMP deficiencies. Of note, Amgen was able to identify the defective syringe lots and show they were not used in the manufacture of denosumab.

On October 2, 2009, the applicant was notified that a REMS would be required for denosumab if it is approved. The elements of the REMS would be a Medication Guide, a communication plan, and a timetable for assessments of the REMS. Amgen submitted a proposed REMS on October 8, 2009.

Before BLA 125320 for the treatment of postmenopausal osteoporosis may be approved, the sponsor must submit adequate information demonstrating the feasibility of, and the methodologies to be used in, Study 20090522. This is a required postmarketing observational study in administrative databases designed to assess the long-term risks of denosumab. Careful review of Study 20090601, a long-term, targeted surveillance study, and of Study 20090589, the pregnancy exposure registry study, will also be needed. Both will be required postmarketing studies. Product labeling remains unresolved at this time. Review of the REMS will be deferred to the next cycle.

(b) (4)



EFFICACY

Two randomized, placebo-controlled trials evaluated the efficacy of subcutaneous injections of denosumab 60 mg relative to placebo in subjects with postmenopausal osteoporosis. These are summarized below:

Treatment of Postmenopausal Osteoporosis. Study 20030216 was a 3-year study that enrolled 7808 women (3902 on denosumab, 3906 on placebo). Enrolled subjects were women aged 60-91 years (mean age 72) with a mean BMD T-score of -2.8 at the lumbar spine or total hip. Nearly a quarter of enrolled subjects had at least one prevalent fracture at baseline. Treatment with denosumab resulted in a 68% reduction in the risk of new vertebral fracture at year 3 compared to placebo (95% CI: 59, 74; $p < 0.0001$). Denosumab reduced the risk of new vertebral fracture regardless of age, baseline rate of bone turnover, baseline BMD or history of fracture, or prior use of osteoporosis medications. Denosumab also demonstrated superiority over placebo treatment in reducing the incidence of hip fracture and non-vertebral fractures at year 3.

Approximately 45% of enrolled subjects were considered to be at high risk of fracture (defined as having 2 of the following: age > 70 , prevalent fracture at baseline, or baseline BMD T-score of ≤ -3.0). Treatment with denosumab in these subjects resulted in a 65% reduction in the risk of new vertebral fracture ($p < 0.0001$). In addition, a significant reduction in the risk of hip fracture (but not non-vertebral fracture) was demonstrated with denosumab treatment.

Prevention of Postmenopausal Osteoporosis. Study 20040132 is a 4-year study that enrolled 332 women (166 on denosumab; 166 on placebo) with a mean age of 59 and a mean BMD T-score of -1.6. Subjects were treated with denosumab or placebo for 24 months and then monitored for an additional 24 months. This study is still ongoing. Denosumab resulted in a treatment difference of 7% (95% CI: 6.2, 7.8; $p < 0.0001$) in lumbar spine BMD from baseline to month 24; the effect in women ≤ 5 years since menopause was similar to that for women > 5 years since menopause. Positive effects on lumbar spine BMD were observed regardless of baseline weight and BMD. Treatment differences in BMD from baseline to month 24 were also noted at the total hip, femoral neck, trochanter, distal third radius, and whole body. In the off-treatment period, BMD gains with denosumab therapy were rapidly lost in the first year after treatment was discontinued.

SAFETY

The denosumab clinical development program included data from approximately 14,000 subjects enrolled in 30 clinical studies. The following is a summary of some of the major clinical safety concerns.

Deaths. Overall, there were 354 deaths involving 185 subjects with underlying malignancy and 169 subjects with osteoporosis or low bone mass. There were no deaths on Study 20040132 (postmenopausal osteoporosis prevention). In Study 20030216 (postmenopausal osteoporosis treatment), the causes of death in both treatment groups

were similar to what would be expected in women over 60 (i.e., deaths related to cardiac events, respiratory events, the nervous system and malignancies).

Serious Adverse Events. Rates of serious adverse events were similar in denosumab- and placebo-treated subjects, but varied by study population. In subjects receiving postmenopausal osteoporosis treatment, serious adverse event rates for denosumab and placebo treatment were higher (24% and 22%) compared to rates for subjects being evaluated for postmenopausal osteoporosis prevention (11% and 5.5%).

Serious Infections. RANKL is expressed on activated T and B lymphocytes and in lymph nodes. Therefore, a RANKL inhibitor such as denosumab may increase the risk of infection. In phase 1 studies, two relatively healthy subjects were hospitalized with pneumonia following treatment with denosumab.

Overall, in the postmenopausal osteoporosis studies, the incidence of infections resulting in death was 0.2% in both treatment groups, and the incidence of non-fatal serious infections was 4.0% in denosumab-treated subjects as compared to 3.3% in placebo-treated subjects. The numeric imbalance in the incidence of serious infections was accounted for by events of cellulitis, erysipelas, diverticulitis, and urinary tract infection. Opportunistic infections were rare (0.1%) and were balanced between treatment groups.

Four cases of endocarditis occurred in elderly subjects aged 75, 75, 82 and 83 years, respectively, after varying lengths of denosumab treatment. No causative organism was found in three cases. One case of *S. aureus* bacteremia required mitral valve replacement. The events were reported as resolved in two cases, ongoing in one and the fourth case died. In the denosumab development program, endocarditis was also diagnosed in one placebo-treated subject and one alendronate-treated subject.

New Malignancies. Denosumab cannot be tested in a traditional 2-year rodent study to evaluate carcinogenic potential; while the applicant did evaluate a knock-in human RANKL transgenic mouse model and a surrogate rodent antibody, this was not considered an appropriate model for carcinogenicity testing.

In subjects with postmenopausal osteoporosis, new malignancies were reported in 4.9% of denosumab-treated subjects as compared to 4.3% of placebo-treated subjects. There were imbalances in the numbers of the following malignancies in denosumab-treated subjects as compared to placebo-treated subjects: breast (35 vs. 30), gastrointestinal (35 vs. 24), and reproductive tract (21 vs. 9) cancer. Breast cancer was listed as the most common adverse event that led to study discontinuation in denosumab-treated subjects with postmenopausal osteoporosis, involving 20 denosumab-treated versus 10 placebo-treated subjects.

Serious Dermatologic Adverse Events. Serious skin and soft tissue conditions, excluding infections, were reported more frequently in denosumab-treated subjects as compared to placebo-treated subjects (11% vs. 8.4%). These conditions included bullous conditions, photosensitivity, pruritis, skin rashes, dermatitis and eczema.

Pancreatitis. In postmenopausal osteoporosis subjects, there were 8 serious reports of pancreatitis on denosumab as compared to one serious report and 3 non-serious reports on placebo. Many of these subjects had underlying risk factors for pancreatitis.

Cardiovascular Adverse Events. An unadjudicated analysis of data from 20 phase 2 and 3 clinical studies was performed by DRUP. Overall, 632 (13%) placebo-treated subjects and 723 (11%) denosumab-treated subjects had a cardiovascular adverse event, most commonly angina pectoris, atrial fibrillation, palpitations, coronary artery disease, and arrhythmia. The incidence of serious cardiovascular adverse events was 4.6% in denosumab-treated subjects and 5% in placebo-treated subjects. Subgroup analysis did not show any concerning trends in subjects > 75 years. There was no dose-related increase in cardiovascular adverse events.

The applicant established an expert committee to adjudicate cardiovascular events in Study 20030216 (postmenopausal women) and Study 20040138 (men with prostate cancer) based on theoretical concerns that inhibition of RANKL by denosumab could result in elevated levels of osteoprotegerin, which in turn may be associated with aortic wall calcification, cardiovascular disease and mortality. The point estimate for the hazard ratio for cardiovascular death was 0.7 (95% CI: 0.4, 1.2) for Study 20030216 and 0.97 (95% CI: 0.7, 1.3) for Study 20040138. Time to first any adjudicated cardiovascular event analysis did not suggest worsening cardiovascular outcomes over time in either low cardiovascular risk or high cardiovascular risk subjects. The incidence of any adjudicated serious cardiovascular adverse event (cardiovascular death, acute coronary syndrome, stroke/transient ischemic attack, congestive heart failure, arrhythmia, and other vascular disorder) was similar in the two treatment groups.

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 Study 20030216 (64 on placebo and 96 on denosumab). There was no increase in osteoprotegerin levels in denosumab-treated subjects compared to placebo-treated subjects.

A total of 2363 subjects were assessed for aortic wall calcification. The mean change from baseline in aortic wall calcification score at month 12, 24 and 36 was minimal in both treatment groups.

Hypocalcemia. Hypocalcemia is a known class effect of antiresorptive drugs. Denosumab-induced hypocalcemia was transient, occurring in the first month after dosing (nadir at day 8-11) with spontaneous resolution and without any serious sequelae. Subjects with severe renal impairment (creatinine clearance < 30 mL/min) and subjects receiving dialysis are at increased risk for hypocalcemia and should be adequately supplemented with calcium and vitamin D.

Osteonecrosis of the Jaw. Osteonecrosis of the jaw, or avascular necrosis of the jaw, has been associated with long-term (> 3 years) bisphosphonate use and IV bisphosphonate use. Although no adjudicated cases of osteonecrosis of the jaw were observed in subjects with postmenopausal osteoporosis, cases have been positively adjudicated in patients with multiple myeloma and other cancers who received higher doses of denosumab for prevention of bone metastases.

Immunogenicity. The presence of binding antibodies to denosumab was evaluated in over 8000 subjects who received at least one dose of denosumab. Positive results were found in less than 1% of subjects. There was no apparent correlation between positive binding antibody tests and altered pharmacokinetic profile, toxicity profile, or clinical response. None of the subjects who were positive for binding antibodies tested positive for neutralizing antibodies.

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

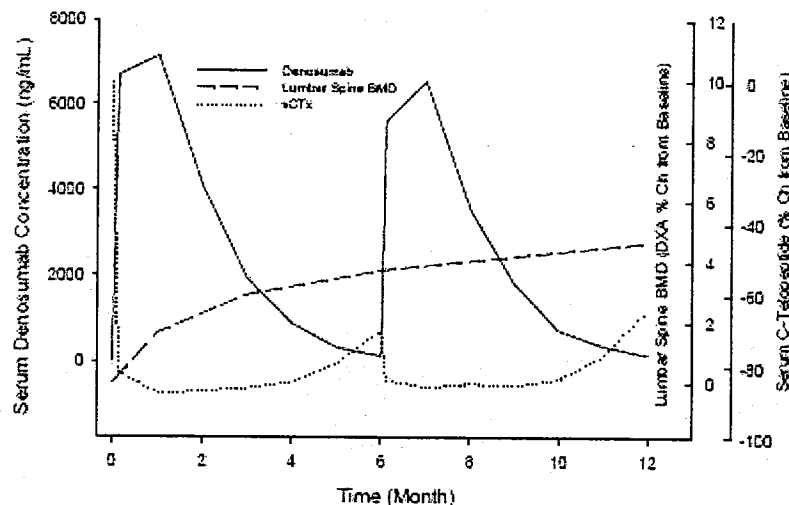
Study 20050234 provided bone histomorphometry data for postmenopausal subjects with low BMD (T-scores between -2.0 and -4.0) previously treated with alendronate who either continued alendronate or switched from alendronate to denosumab. In this study, evidence for further suppression of bone remodeling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

Although the clinical consequence of these findings is unclear, the possibility of oversuppression of bone turnover with chronic denosumab exposure remains an outstanding concern in need of further study.

CLINICAL PHARMACOLOGY

Following subcutaneous administration of denosumab 60 mg, C_{max} for denosumab is attained at 1 month post-dose, which coincides with a rapid, dramatic, and sustained reduction in the bone resorption marker, sCTX1. Following C_{max} , serum denosumab concentrations decrease with a mean half-life of approximately 30 days. During months 4 and 5 post-dose, serum denosumab concentrations decrease to a level at which binding to RANKL is no longer saturated. Although this level corresponds to more rapid elimination of denosumab and a lessening in denosumab's effect on sCTX1 levels, there is no adverse effect on lumbar spine BMD (see figure below).

Figure 1: Mean Serum Denosumab Concentration and Mean Percent Change From Baseline for Serum CTX1 and Lumbar Spine BMD Following Two 60-mg Q6M Doses of Denosumab to Postmenopausal Women with Low BMD (Study 20010223)



It should be noted that the applicant selected the 60 mg denosumab dose administered every 6 months because no additional efficacy was observed at higher doses or shorter intervals. Although this dose and schedule appear to be appropriate for subjects receiving denosumab for treatment of postmenopausal osteoporosis, the Divisions of Clinical Pharmacology 3 and 5 have recommended that additional dose finding be performed in subjects with low bone mass receiving denosumab for osteoporosis prevention. This evaluation is requested because this population, compared with the osteoporosis treatment population, is much younger and will require a longer duration of denosumab treatment.

SUMMARY

Denosumab has been shown to be effective in reducing the risk of fracture in women with postmenopausal osteoporosis and in increasing bone mineral density in women with low bone mass. However, several potentially serious risks were reported more frequently with denosumab use: serious infections, including serious skin infections, and serious dermatologic adverse events. In addition, the degree to which denosumab may oversuppress bone turnover remains an open question. Long-term monitoring of denosumab users for the occurrence of atypical fracture, osteonecrosis of the jaw, and delayed fracture healing is needed.

Considering all the available data, the RHDAC unanimously (15 to 0) recommended approval of denosumab for the treatment of postmenopausal osteoporosis; however, many Committee members advised that the indicated population be limited to those subjects with a high risk of fracture given the concerns regarding the long-term risks of denosumab treatment. Women at high risk for fracture include those 70 years and over and those with a history of osteoporotic fracture.

A majority of Committee members also advised that denosumab have a risk evaluation and mitigation strategy or REMS if it is approved (12 in favor, 1 against, and 3 absent). The Committee recommended the implementation of a Medication Guide and a communication plan to advise denosumab users and healthcare providers, respectively, of

the risks associated with denosumab. Some members also suggested that a registry was warranted to better monitor safety outcomes in denosumab users prospectively.

The Committee voted (2 to 13) against approval of denosumab for prevention of postmenopausal osteoporosis. Given that women under 70 with low bone mass are at relatively low risk of fracture, available information regarding the long-term risks of the product did not outweigh the benefits of chronic use in this population.

DRUP and I are in general agreement with the recommendations of the RHDAC.

RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

In accordance with section 505-1 of the Federal Food, Drug, and Cosmetic Act, we have determined that a REMS is necessary for PROLIA (denosumab) to ensure that the benefits of the drug outweigh the risk of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover. We have determined that the REMS for this product must include a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

The applicant was notified of this determination on October 2, 2009 and submitted a proposed REMS and supporting documentation on October 8, 2009.

POSTMARKETING REQUIREMENTS UNDER 505(o)

In accordance with section 505(o)(3)(A), based on the signals of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover described above, we have determined that, if BLA 125320 (treatment of postmenopausal osteoporosis) is approved, postmarketing studies will be needed to further assess these risks. The applicant will be required to conduct:

1. A long-term observational study in administrative databases to prospectively evaluate the incidence of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover in postmenopausal women administered denosumab (Protocol 20090522);
2. A long-term, targeted surveillance study in postmenopausal women administered denosumab to prospectively evaluate the incidence of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover (Protocol 20090601); and
3. A long-term pregnancy exposure registry study in denosumab users who become pregnant on the drug (Protocol 20090589).

The applicant has submitted amendments to the BLA containing its proposed postmarketing studies to address these issues. DRUP and the Division of Epidemiology will continue review and discussion of these postmarketing study proposals so that the complete response to the action letter contains adequately designed and acceptable studies.

TRADENAME REVIEW

The Division of Medication Error Prevention and Analysis has found the proposed tradename PROLIA to be acceptable.

Julie Beitz MD 10-16-09

Julie Beitz, M.D.
Director
Office of Drug Evaluation III

Deputy Division Director Review

Date	October 16, 2009
From	George S. Benson, MD <i>GS Benson</i>
Subject	Deputy Division Director Review
NDA/BLA#	BLA # 125320/000 BLA # 125331/000
Applicant	Amgen, Inc.
Date of Submission	December 19, 2008
PDUFA Goal Date	October 19, 2009
Proprietary Name/ Established name	Prolia/ denosumab
Dosage forms/Strength	60 mg subcutaneous injection administered every six months
Proposed Indications	1. treatment of postmenopausal osteoporosis (BLA #125320) 2. prevention of postmenopausal osteoporosis (BLA #125331)
Recommendation	Complete response (BLA # 125320) Complete response (BLA # 125331)

Reviewers:

DRUP: Kim Hatfield Celia Peacock Margie Kober Vaishali Popat Adrienne Rothstein Lynnda Reid Theresa Kehoe Martin Kaufman Audrey Gassman George Benson OTS/DB3: Sonia Castillo Mahboob Sobhan OTS/OCP3: Chongwoo Yu Jang-Ik Lee Hae-Young Ahn	DBOP: Suzanna Demko Michael Orr Melanie Pierce Ann Pilaro Jeff Summers Patricia Keegan Rick Pazdur OTS/DB5: Kyung Lee Mark Rothmann OTS/DCP5: Sarah Schrieber Hong Zhao DSI: Roy Blay Pharmacometric Ping Ji Pravin Jadhav	DAIOP: Peter Kim Thomas Smith Katherine Laessig DCRP/IRQT: Aliza Thompson Suchitra Balakrishnan Christeine Garnett Norman Stockbridge DDDP: Denise Cook Fred Hyman Jake Kelsey David Kettl Susan Walker ODE III Julie Beitz Maria Walsh	OBP/DMA: Michele Dougherty Sarah Kennett Chana Fuchs DMPO: Maan Abduldayem Bo Chi Patricia Hughes Donald Obenhuber Michael Pacanowski Kalavati Suvarna OSE/QSPG: Anita Abraham Jenise Gillespie- Pederson Leslie Kenna Paul Schuette John Yap Mandi Yu George Rochester	OSE: Sandra Griffith Carlos Grillasca OSE/DRISK: Eilizabeth Donohue Suzanne Robotton Mary Dempsey OSE/ DMEPA Judy Park Kellie Talor OSE/ DPV2 Mark S. Miller DDMAC Janice Maniwang Cynthia Collins OSE/RMS Maria Wasilik
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1. Introduction
2. Background
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6. Clinical Microbiology
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10. Pediatrics
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1. Introduction

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

BLA 125320: Treatment of postmenopausal osteoporosis

BLA 125331: Prevention of postmenopausal osteoporosis

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

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

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

2. Background

Denosumab is the first biologic product and the first monoclonal antibody submitted for the indications of prevention and treatment of postmenopausal osteoporosis. Denosumab is a human monoclonal IgG2 that targets receptor activator of nuclear factor kappa B ligand (RANKL). The mechanism of action involves the antibody binding to RANK ligand and inhibiting the interaction of RANKL and its receptor (RANK). Inhibition of the RANK-RANKL interaction prevents receptor activation and the downstream signaling from the receptor. RANKL-induced RANK signaling is essential for the formation, function, and survival of mature osteoclasts which are responsible for bone

resorption. The resulting decrease in bone resorption leads to an increase in bone mass. RANKL is also involved in the immune system where it is important in B-cell and T-cell differentiation as well as dendritic cell maturation.

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

The denosumab original IND (IND 9837) was submitted on May 21, 2001. At that time, therapeutic monoclonal antibodies were reviewed in the Center for Biologic Evaluation and Research (CBER). Subsequently, all therapeutic proteins including monoclonal antibodies were transferred to the Center for Drug Evaluation and Research (CDER). There was no special protocol assessment requested for the pivotal fracture trial (20030216). The BLA was submitted on December 19, 2008. Three pre-BLA meetings were held (February 5, 2008, for the structure and content of the BLA, July 8, 2008, for CMC issues, and October 21, 2008, for clinical issues).

3. CMC

4. Nonclinical Pharmacology/Toxicology

5. Clinical Pharmacology

6. Clinical Microbiology

The CMC, nonclinical pharmacology/toxicology, clinical pharmacology, and clinical microbiology are well summarized in the cross discipline team leader review and are reproduced in Appendix A of this review.

A GMP inspection of the drug product manufacturing site in Puerto Rico revealed significant deficiencies which are listed on the 483 form issued to the site (see page 3 of Appendix A). At the time of finalizing this review, no recommendation has been received from Compliance.

Addendum: *On October 15, a signed memorandum was received from Compliance which stated that "the DMPQ is providing an acceptable recommendation based on new information received and the firm's intent to provide corrective actions to adequately address the CGMP deficiencies."*

7. Efficacy/Statistics

Each of the two postmenopausal osteoporosis indications was supported by a single primary study. Trial 20030216 was a large (approximately 8000 subjects) trial whose primary endpoint was incidence of new morphometric (radiographic) vertebral fractures

at month 36 and was submitted to support the treatment of postmenopausal osteoporosis indication. Trial 20040132 was a smaller (332 subjects) trial whose primary endpoint was change from baseline in lumbar spine BMD at month 24 and was submitted to support the prevention of postmenopausal osteoporosis indication.

Trial 20030216 (submitted to support the treatment of postmenopausal osteoporosis indication)

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

Study treatments: Eligible subjects were randomized 1:1 to receive denosumab 60 mg or placebo subcutaneous injection, administered by a healthcare professional, every 6 months. All subjects were to receive daily calcium > 1000 mg daily. Subjects also received vitamin D (400 – 800 IU) supplementation, based on their baseline 25 hydroxyvitamin D level (12 – 20 ng/ml – 800 IU, > 20 ng/mL – 400 IU).

Efficacy measures: Trial 20030216 had one primary, two secondary, and fifty-six tertiary/exploratory efficacy endpoints. The primary endpoint was incidence of new morphometric vertebral fracture at month 36. The secondary endpoints were time to first nonvertebral fracture and time to first hip fracture. A fixed sequence testing procedure was employed for the primary and secondary endpoints in the order mentioned above (vertebral, nonvertebral, hip) for multiplicity adjustment to maintain the overall significance level at 0.05. There was no fixed testing procedure or multiplicity adjustment for the 57 tertiary and exploratory endpoints.

Lateral spine x-rays were performed at screening and months 12, 24, and 36 for all subjects. All lateral spine x-rays were assessed at a central reading facility using the Genant semi-quantitative scoring method. Quantitative morphometry was not performed. 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. Hip fracture included fractures of the femoral neck, femur intertrochanter, and femur subtrochanter. All clinical fractures were to be reported as adverse events and were radiographically confirmed by the central reading facility.

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

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

Laboratory measurements of bone turnover markers included bone resorption markers serum c-telopeptides (CTX) and tartrate resistant acid phosphatase 5b (TRAP 5b); and the bone formation markers serum bone specific alkaline phosphatase (BSAP) and procollagen type 1 amino-terminal propeptide (P1NP). Bone turnover markers were measured at baseline and months 6, 12, 18, 24, and 30 for subjects enrolled in the bone turnover marker substudy. All samples were evaluated by a specialized central laboratory (b) (4) except for serum CTX, which was evaluated by the Sponsor.

Results:

A total of 7868 subjects were enrolled into the study. Eighty-three percent of the enrolled population completed the study (3208 in the placebo group and 3272 in the denosumab group). Baseline subject demographics were generally well balanced across the treatment groups. The average age of enrollees was approximately 72 years with an age range of 60 – 91 years. Ninety-five percent of the enrolled population was age 65 years or older and 32% were age 75 years or older. Subjects were not required to have a baseline fracture to qualify for study enrollment. Overall 24% of the enrolled population had at least one prevalent fracture at baseline and 44% had sustained a fracture after age 55 years. The mean lumbar spine BMD T-score was -2.8 standard deviations below the mean bone mass

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

As outlined in Table 1, 264/3691(7.2%) subjects in the placebo group and 86/3702 (2.3%) subjects in the denosumab group sustained at least one new morphometric vertebral fracture during the three years of the trial.

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

Trial 20030216: Subjects with At Least One New Morphometric Vertebral Fracture, mITT, LOCF		
	Placebo	Denosumab
N, mITT	3691	3702
Crude incidence, n (%)	264 (7.2)	86 (2.3)
Absolute Risk Reduction (95% CI)	4.8 (3.9 , 5.8)	
Relative Risk Reduction (95% CI)	68 (59 , 74)	
Odds Ratio (95% CI)	0.31 (0.24 , 0.39)	
p-value	<0.0001	
Source: compiled by medical reviewer based on 20030216 study report and statistical review		

The absolute risk reduction is 4.8% with a relative risk reduction of 68% ($p < 0.0001$). Subgroup analyses including race, age, geographic location, BMI, baseline lumbar spine BMD T-score, and baseline total hip BMD T-score revealed similar results. Thus, the primary endpoint was met and is highly statistically significant.

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

Over the three-year treatment period, 531 subjects [293 (7.5%) in the placebo group and 238 (6.1%) in the denosumab group] sustained a nonvertebral fracture (Table 2).

Table 2. Subjects with Nonvertebral Fractures

Trial 20030216: Subjects with Nonvertebral Fracture at Month 36, ITT		
	Placebo	Denosumab
N, ITT	3906	3902
Crude incidence, n (%)	293 (7.5)	238 (6.1)
Kaplan-Meier Estimate (%)	8.0	6.5
Absolute Risk Reduction (95% CI)	1.5 (0.3 , 2.7)	
Hazard Ratio (95% CI)	0.80 (0.67 , 0.95)	
p-value	0.0106	
Source: compiled by reviewer based on 20030216 study report and statistical review		

Based on Kaplan-Meier estimates, the three-year event rates for nonvertebral fracture were 8.0 in the placebo group and 6.5 in the denosumab group, with an absolute risk reduction of 1.5 (95% CI: 0.3, 2.7).

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

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

Table 3. Subjects with Hip Fracture at Month 36

Trial 20030216: Subjects with Hip Fracture at Month 36, ITT		
	Placebo	Denosumab
N, ITT	3906	3902
Crude incidence, n (%)	43 (1.1)	26 (0.7)
Kaplan-Meier Estimate (%)	1.2	0.7
Absolute Risk Reduction (95% CI)	0.3 (-0.1, 0.7)	
Hazard Ratio (95% CI)	0.60 (0.37, 0.97)	
p-value	0.0362	
Source: compiled by reviewer based on 20030216 study report and statistical review		

Based on Kaplan-Meier estimates, the three-year event rates for hip fracture were 1.2 in the placebo group and 0.7 in the denosumab group, with an absolute risk reduction of 0.3% (95% CI: -0.1, 0.7).

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

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

Table 4. Percent Change in BMD at 36 Months

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

Biochemical Markers of Bone Turnover: Biochemical markers of bone turnover were evaluated in the bone marker substudy which enrolled 160 subjects, as well as in all subjects in the pharmacokinetic substudy and the bone biopsy substudy. The endpoint in the bone marker substudy include change in the bone resorption markers serum C-telopeptide of type 1 collagen (CTX) and tartrate resistant acid phosphatase 5b (TRAP 5b) levels at hour 6-8, day 1 and months 1, 6, 12, 24, and 36; and change in the bone formation markers bone specific alkaline phosphatase (BSAP) and procollagen type 1 N-terminal peptide (P1NP) levels at months 1, 6, 12, 24, and 36.

Treatment with denosumab resulted in levels of suppression of the markers of bone resorption CTX and TRAP5b. The nadir of bone resorption markers appears to occur at 1 – 3 months after administration of the denosumab dose. The level of CTX suppression seen with denosumab has not been noted with any other antiresorptive agent and the long-term clinical consequences of this degree of suppression is not clear.

Trial 20040132 (submitted to support the prevention of postmenopausal osteoporosis indication)

The Sponsor also submitted one key efficacy trial, 20040132, to support the approval of denosumab for the indication of prevention of postmenopausal osteoporosis. Trial 20040132 is a randomized, double-blind, placebo- and active-controlled, 4-year, 2-period study trial evaluating the safety and efficacy of denosumab use in the prevention of the postmenopausal osteoporosis population. The first 24 months of the study is considered the “on-treatment” period, where all subjects received study drug. The second 24 months of the study is the “off-treatment” period, where subjects were followed off study drug. Subjects were randomized to receive either placebo or denosumab 60 mg SC every six months. The primary endpoint of the study was the percent change from baseline in lumbar spine BMD at month 24. This trial is ongoing and this review focuses on the data to month 24.

Study population: Subjects enrolled in this trial study were not more than 90 years old, and had low bone mass, defined as a lumbar spine bone mineral density T-score of -1.0 to -2.5. Patients with a history of fracture after age 25 years were excluded from enrollment. Subjects previously on iv bisphosphonate, fluoride, or strontium therapy were excluded from the study. Subjects previously on oral bisphosphonate therapy for less than 3 months could be enrolled in the study. If the cumulative exposure were more than 3 months but less than 3 years, subjects could be enrolled only after a wash-out period of one year. For subjects on other osteoporosis therapies, subjects could be enrolled after a 6 week wash-out period. Subjects were stratified based on years since menopause (≤ 5 years, > 5 years).

Study treatments: Eligible subjects were randomized 1:1 to receive denosumab 60 mg or placebo subcutaneous injection, administered by a healthcare professional, every 6 months (day 1 and months 6, 12, and 18). All subjects were to receive daily calcium > 1000 mg daily. Subjects also received vitamin D (400 – 800 IU) supplementation based on their baseline 25 hydroxyvitamin D level (12 – 20 ng/ml – 800 IU, > 20 ng/mL – 400 IU).

Efficacy measures: Trial 20040132 had one primary, eight secondary, and ninety exploratory efficacy endpoints. The primary endpoint of the study was the percent change from baseline in lumbar spine BMD (as determined by DXA) at month 24. The secondary endpoints were the percent change from baseline in total hip, femoral neck, trochanter, distal radius and total body BMD (as determined by DXA) at month 24; and percent change from baseline of trabecular volumetric BMD, cortical volumetric BMD and total volume (as determined by quantitative computed tomography [QCT]) of the distal radius. The overall significance level for the primary and secondary endpoints was 0.05 by using a Bonferroni adjustment divided equally between the strata (0.025 for each stratum). The approach for handling multiplicity for the primary and secondary endpoints within each time-since-menopause stratum included a hierarchical testing strategy.

Results:

Disposition: A total of 332 subjects were enrolled into the study. Eighty-five percent of the enrolled population completed the study. There was comparable subject disposition between the treatment groups.

Demographics: Baseline subject demographics were generally well balanced across the treatment groups. The average age of enrollees was 59 years with an age range of 43 – 83 years. Twenty-two percent of the enrolled population was age 65 years or older and 5% were age 75 years or older. The mean time since menopause was 3.6 years in the ≤ 5 years stratum, 16 years in the > 5 years stratum, and 9.4 years overall. The mean lumbar spine BMD T-score was -1.6 standard deviations below the mean bone mass of young healthy adults.

Bone Mineral Density, Primary Endpoint: Change in bone mineral density of the lumbar spine at month 24 was the primary endpoint of the study. Treatment with denosumab significantly increased bone mineral density of the lumbar spine compared to placebo (Table 5). Results were consistent across the strata as well as within the subgroups tested (baseline weight and baseline BMI).

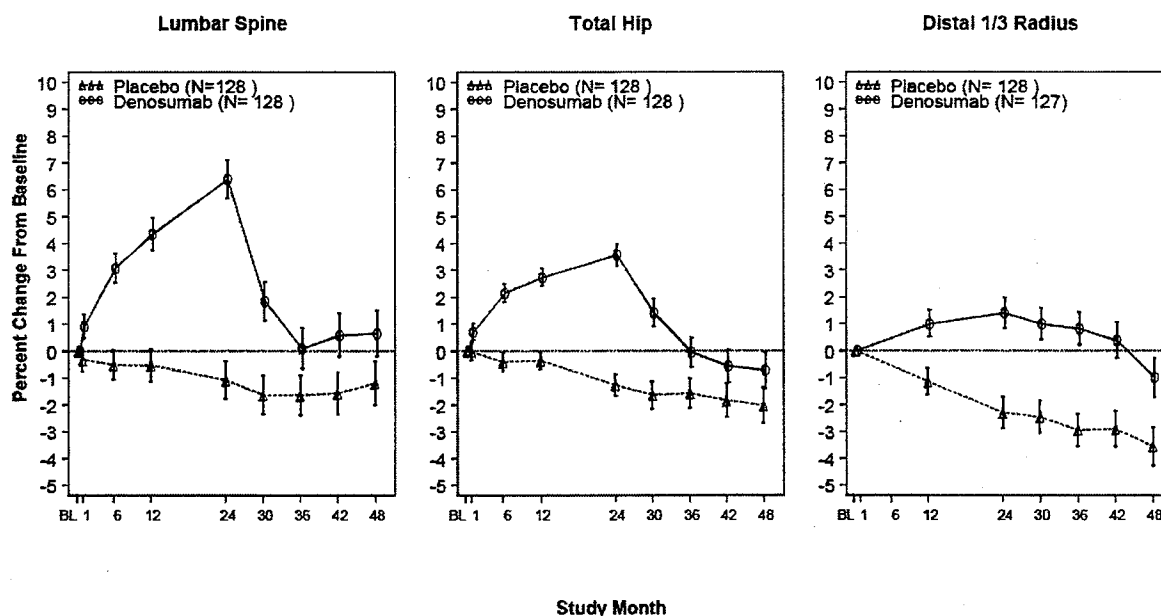
Table 5. Percent Change in Lumbar Spine BMD at Month 24

Trial 20040132: Percent Change in Lumbar Spine BMD at Month 24, mITT, LOCF		
	Placebo	Denosumab
Overall population	163	163
LS mean percent change	-0.6	6.5
LS mean difference (95% CI)	7.0 (6.2 , 7.8)	
p-value	<0.0001	
≤ 5 years post menopause	80	79
LS mean percent change	-1.2	6.2
LS mean difference (95% CI)	7.4 (6.1 , 8.7)	
p-value	<0.0001	
> 5 years post menopause	83	84
LS mean percent change	0.1	6.8
LS mean difference (95% CI)	6.7 (5.4 , 8.0)	
p-value	<0.0001	
Source: compiled by reviewer based on 20040132 study report as well as statistical and clinical review documents		

Fracture: In this study clinical fractures were reported as adverse events. Lateral spine x-rays were evaluated by the central imaging vendor at screening, month 24, and also planned at month 48. New morphometric vertebral fractures were reported in one placebo subject and no denosumab subjects. Clinical fractures were reported in seven (4%) placebo-treated subjects and 2 (1%) denosumab treated subjects.

Trial 20040132 was designed to evaluate the changes in bone mineral density and bone turnover markers in the off-treatment period (months 24-48). The bone mineral density gains achieved with denosumab therapy were rapidly lost in the first year after treatment was discontinued (Figure 1).

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



Source: Applicant. Page 148, 120 day safety update.

Serum CTX also increased in the off-treatment period, to levels well above baseline.

Efficacy summary:

In the osteoporosis treatment trial, denosumab, 60 mg given every six months is effective in decreasing the incidence of new morphometric vertebral fractures (absolute reduction 4.8%, relative reduction 68%, p-value <0.0001), nonvertebral fractures (absolute reduction 1.5%, relative reduction 20%, p-value 0.0106), and hip fractures (absolute reduction 0.3%, relative reduction 40%, p-value 0.0362). BMD was also assessed and the changes compared to placebo highly statistically significant.

In the osteoporosis prevention trial, BMD changes were highly statistically significant.

Thus, the efficacy of denosumab for both the treatment and prevention of osteoporosis has been adequately demonstrated in the postmenopausal population.

8. Safety

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

The safety database for trial 20030216 includes 7762 subjects (3876 placebo, 3886 denosumab) who received at least one dose of study medication. Overall, 75.5% of the placebo group and 79.6% of the denosumab group received all six doses of study medication. The safety database for trial 20040132 (prevention of postmenopausal osteoporosis trial) is smaller and includes 329 subjects (165 placebo, 164 denosumab) who received at least one dose of study medication. Overall, 85% of both treatment groups received all four doses of study medication.

Summary of Safety Events:

The adverse event rates between the placebo and denosumab treatment groups were balanced except for serious adverse events which occurred more frequently in trial 20040132 (the prevention of PMO trial that enrolled younger postmenopausal women) (Table 6).

Table 6. Summary of Safety Events in the Two Primary Trials for the Postmenopausal Osteoporosis Indications

Denosumab PMO Trials: Summary of Safety Events						
	20030216		20040132		All	
	placebo	denosumab	placebo	denosumab	placebo	denosumab
N, enrolled	3906	3902	166	166	4072	4068
N, safety*	3876	3886	165	164	4041	4050
Discontinued	700 (18)	630 (16)	22 (13)	24 (14)	722 (18)	654 (16)
N, completed	3208 (82)	3272 (84)	144 (87)	142 (86)	3350 (82)	3414 (84)
Death	90 (2.3)	70 (1.8)	0 (0)	0 (0)	90 (2.2)	70 (1.7)
Serious Adverse Event	972 (25.1)	1004 (25.8)	9 (5.5)	18 (11.0)	981 (24.2)	1022 (25.2)
Withdrawal due to AE	81 (2.1)	93 (2.4)	2 (1.2)	1 (0.6)	83 (2.1)	94 (2.3)
Study Drug Permanently Discontinued due to AE	202 (5.2)	192 (4.9)	6 (3.6)	5 (3.0)	208 (5.1)	197 (4.9)
Adverse Event	3607 (93.1)	3605 (92.8)	157 (95.2)	156 (95.1)	3764 (93.1)	3761 (92.9)
*including all patients who received at least one dose of denosumab regardless of assigned treatment group						
Source: compiled by reviewer based on 20030216 study report as well as statistical and clinical review documents						

Deaths: In trial 20030216, 160 subjects (90 in the placebo group and 70 in the denosumab group) died during the study. No subjects died in the PMO prevention trial 20040132. All deaths in trial 20030216 were adjudicated by an independent cardiovascular adjudication committee to determine whether the deaths were caused by a cardiovascular event. The most common SOC for cause of death were neoplasms, cardiac disorders, general disorders and nervous system disorders. These causes of death are expected for the general population of the age of the enrolled population.

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

Serious Adverse Events: In trial 20030216, nonfatal serious adverse events occurred in 1792 subjects [868 (22%) in the placebo group and 924 (24%) in the denosumab group]. In trial 20040132 (treatment phase to 24 months), nonfatal serious adverse events occurred in 27 subjects [9 (5.5%) in the placebo group and 17 (11%) in the denosumab group]. The most common SAEs in denosumab treated subjects were infection, pathogen unspecified [112 (2.8%) placebo, 134 (3.3%) denosumab], and coronary artery disorders [69 (1.7%) placebo, 98 (2.4%) denosumab]. Bone and joint injuries which included fracture and joint disorders were more common in the placebo group [108 (2.7%) placebo, 99 (2.4%) denosumab]. The differences in SAEs between treatment groups are small.

Adverse Events Leading to Study Withdrawal: In trial 20030216, 174 subjects [81 (2%) placebo, 93 (2%) denosumab] discontinued the trial due to an adverse event. In trial 20040132 (treatment phase to 24 months), three subjects [2 (1%) in the placebo group and 1 (3%) in the denosumab group] withdrew from the study due to adverse events. The most commonly reported AEs leading to discontinuation were breast cancer [2 (0.1%) placebo, 11 (0.3%) denosumab], back pain [9 (0.2%) placebo, 4 (0.1%) denosumab] and constipation [4 (0.1%) placebo, 4 (0.1%) denosumab].

Adverse Events Leading to Discontinuation of Study Drug (Investigational Product): Subjects had the option of discontinuing study drug and remaining in the study for collection of further data. In trial 20030216, 394 subjects [202 (5%) in the placebo group and 192 (5%) in the denosumab group] discontinued study drug. In trial 20040132 (treatment phase to 24 months), 6 subjects [5 (4%) in the placebo group and 5 (3%) in the denosumab group] discontinued study drug. The most common reason for study drug discontinuation was cancer in the denosumab group [19 (0.5%) placebo, 40 (1%) denosumab] and fracture in the placebo group [20 (0.5%) placebo, 6 (0.2%) denosumab]. Breast cancer was the most common malignancy reported followed by colon cancer, gastric cancer, ovarian cancer and pancreatic cancer.

Adverse Events: In trial 20030216, 93% of the enrolled population reported at least one adverse event during the trial. The most commonly reported adverse events System Organ Classes (SOC) were musculoskeletal and connective tissue disorders, infections and infestations, and gastrointestinal disorders. In trial 20040132 (treatment phase to 24 months), the most commonly reported adverse events (>10% in either treatment group) were: arthralgia, nasopharyngitis, back pain, headache, pain in extremity, upper respiratory tract infection, constipation, urinary tract infection, shoulder pain, influenza and sinusitis.

Adverse Events of Special Interest: The following adverse events of interest, identified by either the sponsor or the review team, were reviewed and discussed at the August 13, 2009, Advisory Committee Meeting.

Hypocalcemia: Hypocalcemia is a known adverse event seen with anti-resorptive therapies. From Phase 1 studies, the nadir in serum calcium appears to occur approximately 10 days after denosumab dosing. Laboratory testing in the phase 3 trial 20030216 was performed at one month post dose and likely fails to capture true nadir. However, at month 1, 3 (0.08%) subjects in the placebo group and 33 (0.8%) subjects in the denosumab group were noted to have calcium levels below 8.5 mg/dL. The large majority of patients with a serum calcium level below 8.5 mg/dL were asymptomatic.

Of note, in a Phase 1 trial of subjects with all degrees of renal function, subjects with baseline creatinine clearance less than 30 mL/min developed significant hypocalcemia (Ca <7.5 mg/dL or symptoms). Subjects in this trial did not receive calcium and vitamin D supplementation, which may have contributed to the extent of the hypocalcemia. The trial was stopped and the protocol was amended to require calcium and vitamin D supplementation. After supplementation was initiated, the calcium nadir in the severe renal disease group was improved to the levels of the other groups.

If denosumab is approved, hypocalcemia will be a labelled contraindication for its use.

Cardiovascular Adverse Events: During the development program for denosumab, a concern was raised regarding the potential for denosumab to promote arterial wall calcification and atherosclerosis. Reports in the published literature suggested a possible association between osteoprotegerin levels and arterial wall calcification, cardiovascular disease, and mortality. Inactivation of RANKL by denosumab could result in elevated levels of osteoprotegerin (OPG) as it binds to the same target.

The Sponsor established a cardiovascular adjudication committee to review possible cardiovascular events in trial 20030216 (postmenopausal osteoporosis fracture trial) and trial 20040138 (bone loss due to hormone ablation in prostate cancer). In addition, the reviewing Division recommended an assessment of arterial wall calcification/thickness. Because the large fracture study was already underway making baseline measurements using newer technologies impossible, an analysis of changes in abdominal aortic calcification (as assessed using lateral lumbar spine radiographs) was also conducted in a subset of subjects in trial 20030216.

The medical officer review of baseline cardiovascular risk factors showed the two treatment groups to be similar. Osteoprotegerin levels were measured in the PK substudy of trial 20030216 and there was no clear increase in osteoprotegerin levels with denosumab therapy.

A total of 1098 cardiovascular adverse events from trial 20030216 (526 in placebo-treated subjects and 572 in the denosumab-treated subjects) were submitted for adjudication. The number of positively adjudicated events was 233 in placebo-treated subjects and 247 in the denosumab-treated subjects. The incidence of any adjudicated

cardiovascular event analysis did not suggest worsening cardiovascular outcomes over time in either low cardiovascular risk or high cardiovascular risk subjects. The incidence of any adjudicated cardiovascular serious adverse event (cardiovascular death, acute coronary syndrome, stroke/transient ischemic attack, congestive heart failure, arrhythmia, and other vascular disorder) was similar in the two treatment groups.

The distribution of baseline aortic calcification scores was similar between the two treatment groups with 23% of subjects having a baseline score of zero. At month 36, the mean changes in aortic calcification scores were small and balanced across the treatment groups.

I agree with the cross discipline team leader, primary medical officers, and Cardiorenal consultant's conclusion that no clear cardiovascular safety signal is seen.

Infections: RANKL is expressed on activated T and B lymphocytes, in lymph nodes, and plays a role in dendritic cell (antigen presenting cells) maturation. Therefore, it is biologically plausible that the RANKL inhibitor denosumab could increase the risk of infection as T and B lymphocytes are responsible for foreign antigen recognition.

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

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

In trial 20030216, fatalities due to infection occurred in 6 (0.2%) subjects in each treatment group. Serious adverse events of infection were reported by 292 subjects (133 (3.4%) placebo, 159 (4.1%) denosumab) and adverse events of infection were reported by 4163 subjects [2108 (54.4%) placebo, 2055 (52.9%) denosumab]. In trial 20040132, an imbalance in serious adverse events of infection was noted. Infection SAEs were reported by 9 subjects: one (0.6%) in the placebo group and 8 (4.9%) in the denosumab group. Adverse events of infection were reported by 200 subjects [101 (61.2%) placebo, 99 (60.4%) denosumab].

Opportunistic infections were not increased in the subjects receiving denosumab.

Serious adverse events related to infections occurred at a higher incidence in denosumab subjects compared with placebo. Specifically, serious bacterial infections occurred in 15 (0.4%) of placebo subjects and 25 (0.6%) of denosumab subjects and serious infections due to an unspecified pathogen occurred in 115 (2.8%) of placebo subjects and 138 (3.4%) of denosumab subjects. In trial 20030216, denosumab treated subjects appeared to have a higher incidence of skin, abdominal, ear, and urinary tract infections. Skin

infection serious adverse events occurred in 3 (0.1%) placebo subjects and 14 (0.4%) denosumab subjects. Gastrointestinal infection serious adverse events occurred in 22 (0.5%) placebo subjects and 28 (0.7%) denosumab subjects. Serious ear infection adverse events occurred in no placebo subjects and 5 (0.1%) denosumab subjects. The majority of these cases were labyrinthitis. Serious urinary tract infection adverse events occurred in 17 (0.4%) placebo subjects and 28 (0.7%) denosumab subjects. Also of concern is the imbalance in endocarditis serious adverse events, which occurred in no placebo-treated subjects and three denosumab-treated subjects.

A Division of Anti-Infective and Ophthalmology Products consultant agreed that patients on denosumab appeared to have infections more frequently, had more severe cellulitis and more serious abdominal and lower respiratory tract infections. The consultant recommended that the label include information related to the potential risks for infections in the Warnings and Precautions section. In addition, the recommendations included that the Sponsor commit to continue to collect information on all infection-related adverse events for an indefinite time during the postmarketing period.

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

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

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

Dermatologic Adverse Events: An imbalance in dermatologic adverse events (skin infections are not included) was noted in the postmenopausal osteoporosis database. A total of 501 (12.4%) placebo-treated subjects and 610 (15.1%) denosumab-treated

subjects reported an adverse event related to skin and soft tissue disorders. These events did not include skin infections and were generalized, not specific to the drug injection site. This imbalance was mainly due to imbalances observed in HLGT “Dermal and Epidermal conditions”, driven by dermatitis, eczema, and rashes. Of note, dermal and epidermal adverse events including toxic skin reactions and bullous conditions occurred at approximately a 10-fold increased incidence in denosumab treated subjects. The Division of Dermatology and Dental Products was consulted to assist in the evaluation of these cases and their relationship to denosumab therapy. After review, denosumab could not be clearly implicated as causative nor could it be definitively ruled out as the cause.

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

Diverticular Events: In trial 20030216, an imbalance in diverticular disorders was noted. Serious adverse events related to diverticular disease were reported in 14 (0.3%) subjects in the placebo group and 23 (0.6%) subjects in the denosumab group. Serious adverse events of diverticulitis were reported in 7 (0.2%) subjects in the placebo group and 10 (0.2%) subjects in the denosumab group.

Ocular Adverse Events: Adverse events of cataracts were noted with increased frequency in the denosumab treated subjects in the prostate cancer trial 20030138 [9 (1.2%) of the placebo group and 34 (4.7%) of the denosumab group]. In the PMO database, adverse events related to the eye were reported in 537 (13%) placebo treated subjects and 513 (12.6%) denosumab treated subjects. Cataracts were reported in 253 (6.3%) of the placebo group and 229 (5.7%) of the denosumab group. Based on the available data, there is no clear safety signal for ocular adverse events in the PMO population. The reason(s) for the increased number of cataracts in the men in the prostate cancer trial is not clear.

Bone histomorphometry:

Parameters of bone resorption are expected to decrease with anti-resorptive agents including denosumab. Iliac crest bone biopsies were performed in a subset of subjects in three studies. Absence of double tetracycline labeling in bone biopsy specimens (suggestive of suppressed bone turnover and formation) was observed in 21% of denosumab-treated subjects at month 12, in 35% of subjects at month 24, and in 38% of subjects at month 36. Absence of labeling was not observed in any placebo-treated subject tested. (The cross discipline team leader’s review of the bone histomorphometry data is presented in Appendix B of this review).

Study 20050234 provided bone histomorphometry data for postmenopausal subjects with low BMD (T-scores between -2.0 and -4.0) previously treated with alendronate who

either continued alendronate or switched from alendronate to denosumab. In this study, evidence for further suppression of bone remodeling following initiation of denosumab treatment was noted.

Over suppression of bone resorption may be related to ONJ, atypical fracture, and delayed fracture healing. Although the clinical consequence of these histomorphometry findings is unclear, the possibility of over suppression of bone turnover with chronic denosumab therapy remains an outstanding clinical concern and requires further study.

Safety summary:

The three safety issues of primary concern are serious infections (including skin infections), dermatologic adverse events, and sequelae of over suppression of bone.

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

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

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

In addition, hypocalcemia is a recognized adverse event with all anti-resorptive therapies and should be labeled accordingly. Hypocalcemia should be a contraindication to denosumab use.

The adverse events and concerns noted for the treatment population also apply to the prevention population, and may be more concerning because of the long-term treatment that would be required to support continued fracture reduction efficacy.

9. Advisory Committee Meeting

An Advisory Committee meeting was held on August 13, 2009, to discuss the four biologic licensing applications/indications for denosumab. Because all four indications were to be discussed, the Committee was comprised of some representative members from the Reproductive Health Advisory Committee and the Oncology Advisory Committee as well as experts in the fields of bone/osteoporosis, infectious diseases, dermatology and epidemiology. The issues that the Committee were asked to consider

with regard to the risk/benefit profile for denosumab included the following safety concerns:

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

The questions (in italics) and the votes and discussion of the Committee members are presented below. Questions related to the bone loss due to hormone ablation in breast and prostate cancer indications are not presented here.

Benefit/Risk Profile – Treatment of postmenopausal osteoporosis

Question 1a [Vote: Yes/No]: Is there a population of postmenopausal women with osteoporosis in which the benefit of treatment with denosumab is likely to outweigh the risks?

The Committee vote was unanimous 15 (yes), 0 (no) that there is a population of postmenopausal women with osteoporosis in which the benefits of denosumab therapy are likely outweigh the risks.

Question 1b [Discussion]: If yes, would this population be:

- (1) all women with postmenopausal osteoporosis,*
- (2) limited to a subgroup at a high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or women who have failed or are intolerant to other osteoporosis therapies*

Many committee members believed that limiting the treatment population to those at high risk of fracture may be warranted until more information is known about the long-term risks of the therapy.

Benefit/Risk Profile – Prevention of postmenopausal osteoporosis

Question 2a [Vote: Yes/No]: Is there a population of postmenopausal women with low bone mineral density who do not meet the criteria for treatment of osteoporosis in which the benefit of prevention of osteoporosis with denosumab is likely to outweigh the risks?

The Committee vote was 2 (yes) and 13 (no) that there is a population of postmenopausal women with low bone mineral density who do not meet the criteria for treatment of osteoporosis in which the benefits of denosumab therapy are likely outweigh the risks.

Risk Evaluation and Mitigation Strategies

Question 6a [Vote: Yes/No]: If approved, do you recommend that denosumab have a Risk Evaluation and Mitigation Strategy or REMS?

The Committee vote was 12 (yes), 1 (no), 3 (absent) that denosumab should have a REMS.

Question 6b [Discussion]: If so, which elements should be included in the REMS?

- (1) A Medication Guide to inform patients about the risks of the drug?*
- (2) A Communication Plan to disseminate information to healthcare providers?*
- (3) Other?*

The Committee members believed that a Medication Guide to inform patients about the risks of the drug and a Communication Plan to educate providers about major safety concerns were warranted. Some members also suggested that, given the need for providers to administer the drug, a registry was also warranted to better monitor safety outcomes in denosumab users prospectively.

10. Pediatrics

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

11. Other Relevant Regulatory Issues

Risk Evaluation and Mitigation Strategies (REMS)

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

The sponsor was notified of this determination on October 2, 2009, and submitted a proposed REMS and supporting documentation on October 9, 2009.

Postmarketing Requirements

Based on the signals of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover described above, the Division, in consultation with OSE, determined that, if BLA 125320 (treatment of postmenopausal osteoporosis) is approved, postmarketing studies will be needed to further assess these risks. The sponsor will be required to conduct:

1. A long-term observational study in administrative databases to prospectively evaluate the incidence of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover in postmenopausal women administered denosumab [submitted as Protocols 20090521 (Phase A) and 20090522 (Phase B)]
2. A long-term (b) (4) surveillance study in postmenopausal women administered denosumab to prospectively evaluate the incidence of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover
3. A long-term pregnancy exposure registry in denosumab users who become pregnant on the drug. [Submitted as Protocol 20090589]

The sponsor has submitted amendments to the BLA containing its proposed postmarketing studies to address these issues. DRUP will continue discussion of these postmarketing study proposals so that the complete response to the action letter contains adequately designed and acceptable studies.

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

Division of Medication Errors and Analysis (DMEPA):

The Sponsor's proposed tradename (Prolia) was found to be acceptable.

Division of Scientific Investigations (DSI):

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

Office of Surveillance and Epidemiology/DEPI:

The Office of Surveillance and Epidemiology, Division of Epidemiology was consulted regarding the proposed observational study protocols. Their recommendation is that the results from Phase A (protocol 20090521), including the development and validation of the methodology and background adverse event rate assessments, be acceptable before accepting Phase B as adequate and before approving the product.

Because of the difficulty with diagnosis and coding of some of the adverse events of interest, the clinical team also believes that the method of administration of denosumab (by a healthcare provider) provides a unique opportunity to collect data regarding the adverse events of concern in patients being treated with denosumab outside of the controlled clinical trial environment. This approach would complement the observational

database approaches proposed and could be dispensed as a short survey with the drug or provided to prescribers. The survey would include evaluation of the occurrence of new fractures including fracture location, fracture healing complications, osteonecrosis of the jaw, infections including skin infections, and dermatologic adverse events.

12. Labeling

Physician labeling continues to be negotiated at the time of this review. The major issue under discussion includes the language for the indication. The Applicant originally proposed "treatment of osteoporosis in postmenopausal women." The clinical review team believes that the population should be restricted to one at higher risk of fracture, which also appeared to be supported by the Advisory Committee.

13. Decision/Action/Risk Benefit Assessment

Treatment of Osteoporosis in Postmenopausal Women

I agree with the cross discipline team leader and primary medical officers that BLA 125320 receive a complete response action. The clinical reviewers agree with the OSE/DEPI reviewers that there is concern that the proposed postmarketing observational study will not successfully capture the safety information regarding denosumab use. Therefore, it will be necessary for the sponsor to complete study 20090521 (Part A) and submit the data for review prior to approval.

In the osteoporosis treatment population, denosumab, 60 mg given every six months is effective in decreasing the incidence of new morphometric vertebral fractures (absolute reduction 4.8%, relative reduction 68%, p-value <0.0001), nonvertebral fractures (absolute reduction 1.5%, relative reduction 20%, p-value 0.0106), and hip fractures (absolute reduction 0.3%, relative reduction 40%, p-value 0.0362). BMD was also assessed and the changes compared to placebo highly statistically significant. Thus, the efficacy of denosumab has been adequately demonstrated in this patient population.

Multiple safety issues have been identified, including serious infections (including skin infections), dermatologic adverse events, and the potential for the occurrence of events related to over suppression of bone turnover (osteonecrosis of the jaw, delayed fracture healing, and atypical fractures). Hypocalcemia is a known adverse event associated with antiresorptive therapy. I believe that all of these events can be adequately labeled to provide information to both healthcare providers and patients. Following agreement on the feasibility of the Postmarketing Safety Assessment (Protocol 20090521), I believe that denosumab could be approved for the treatment of postmenopausal osteoporosis in a high risk population. Labeling and review of the REMS (including the Medication Guide) have not been completed.

REMS

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

Postmarketing Requirements:

Three postmarketing studies have been recommended by the clinical reviewers and OSE. I agree with this recommendation.

1. A long-term observational study in administrative databases to prospectively evaluate the incidence of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover in postmenopausal women administered denosumab [submitted as Protocols 20090521 (Phase A) and 20090522 (Phase B)]
2. A long-term, (b) (4) surveillance study in postmenopausal women administered denosumab to prospectively evaluate the incidence of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover
3. A long-term pregnancy exposure registry in denosumab users who become pregnant on the drug. [Submitted as Protocol 20090589]

Prevention of Osteoporosis in Postmenopausal Women

I agree with the recommendation of the cross discipline team leader and the primary medical officers that denosumab receive a Complete Response action for BLA 125331 (prevention of osteoporosis in postmenopausal women). Based upon BMD data, denosumab is effective in this group of patients. (b) (4)

When asked the question "Is there a population of postmenopausal women with low bone mineral density who do not meet the criteria for treatment of osteoporosis in which the benefit of prevention of osteoporosis with denosumab is likely to outweigh the risks?," the Advisory Committee voted 2 (yes) and 13 (no).

Appendix A

3. CMC/Device

Please refer to Drs. Sarah Kennett and Michele Dougherty's review and Drs. Kalavati Suvarna and Donald Obenhuber's product quality reviews for complete details.

3.1 General product quality considerations

Denosumab is a full-length human monoclonal IgG2 antibody. Denosumab binds specifically to the D-E loop of human receptor activator of nuclear factor kappa B ligand (b) (4) depending on the assay method used.

Denosumab drug substance is manufactured at two different sites: Amgen, Colorado (ACO) and Boehringer Ingelheim Pharma, Germany (BIP). There is a difference in charge variants between ACO and BIP. The variation is due to cell culture raw materials and is bounded by base media and enzymatic reaction saturation. The noted variants have equal *in vitro* potency and are not expected to have a clinical effect.

Denosumab was derived by immunizing human IgG2/kappa Xeno-mouse animals with Chinese hamster ovary (CHO) cells stably expressing the cDNA for human RANKL.

(b) (4)

In the denosumab clinical program, two processes (CP1 and CP2) were used for drug substance manufacturing. CP1 material came from the master cell bank and was used in phase 1 trials. CP2 material came from the working cell bank and was used in the phase 2 trials and all pivotal phase 3 clinical trials. There were minor differences (b) (4) (b) (4) seen during development between these two processes.

Nonclinical studies as well as clinical bioequivalence studies were performed to ensure there are not clinically significant changes between the denosumab manufactured through the CP1 and CP2 processes

Please refer to Dr. Obenhuber's review for complete details of the denosumab drug product manufacturing process. Drug product is manufactured at Amgen, Puerto Rico (AML). Denosumab drug product is supplied as a single-use, sterile, preservative-free solution intended for delivery by subcutaneous injection, supplied in either a 60 mg/mL prefilled syringe (PFS) or 60 mg/mL vial presentation with a 1.0 mL deliverable volume to support dosing of 60 mg every 6 months (Q6M). Each prefilled syringe contains: 60 mg denosumab, 4.7% sorbitol, 17 mM acetate, 0.01 % polysorbate 20, sodium hydroxide for pH adjustment in Water for Injection, USP (pH of 5.2). Each vial contains: 60 mg denosumab, 4.7% sorbitol, 17 mM acetate, sodium hydroxide for pH adjustment in Water for Injection, USP (pH of 5.2).

The only difference in the formulations for these presentations is the addition of 0.01 % (w/v) polysorbate to the formulation used for the PFS.

3.2 Facilities review/inspection

Facilities inspections of the ACO and BIP sites for the denosumab drug substance manufacturing were conducted by the Biotech Manufacturing Team of the Division of Manufacturing and Product Quality (DMPQ).

A pre-approval inspection for denosumab drug substance production at the Boehringer Ingelheim Pharma (BIP) facility was conducted from May 11 to May 20, 2009. The BIP facility is responsible for manufacture of denosumab drug substance and for QC testing. A form 483 was issued at the end of this inspection. Observations made during the inspection pertain to inadequate actions taken in response to a deviation where contaminated harvest with a bioburden excursion of too numerous to count was used to manufacture drug substance and procedures were not established to ensure that the

process step identified as the source of contamination is successfully performed. This inspection was classified VAI.

A pre-approval inspection for denosumab drug substance production at the Amgen Colorado (ACO) facility was conducted from June 8 to June 12, 2009 by BMT reviewers Kalavati Suvana and Maan Abduldayem, product reviewer Sarah Kennett, and district investigators Nancy Schmidt and Kimberley Buytaert-Hoefen. ACO is responsible for manufacture of denosumab drug substance, for QC testing (except mycoplasma and in vitro viral testing), and for stability sample storage and testing. No form 483 was issued.

Facilities inspection of the AML site specifically for the denosumab drug product was not performed based on the compliance history, current GMP status, and previous inspections of manufacturing processes similar to the denosumab manufacturing process. A routine GMP inspection of the Puerto Rico site (AML) was concluded on 9/11/09. Findings included low level syringe breakage identified on the Enbrel SureClick manufacturing line. The Applicant was issued a 483 which included the following observation:



A final review and recommendation from the Office of Compliance is pending at the time of this review.

All other facilities listed in the BLA, including contract facilities for mycoplasma, viral, sterility and container closure integrity testing, were not inspected. Inspections were not conducted as the activities in these sites are either low risk and/or these sites are in compliance as per 21 CFR 210, 211 and 600.

3.3 Other notable issues

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

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

1. To perform stability testing on at least one marketed drug product lot of both the 3 cc glass vial and the 1 ml glass syringe; annually, for each year in which respective drug product is manufactured and for each site at which it is manufactured, using the post-approval stability protocol specified in the BLA. The first update will be included in an annual report to be submitted by [Amgen to provide date]
2. To modify the acceptance criteria for the pre-filled syringe extrusion and breakloose specification. This specification was added during review and acceptance criterion is currently listed as "report". Data, analysis and justification for a quantitative limit will be included in a prior approval supplement submitted by June 30, 2010.
3. To re-evaluate the release and shelf-life specifications and in-process limits for denosumab drug substance and drug product after 30 commercial manufacturing runs to reflect increased manufacturing experience. The revisions to the quality control system, the corresponding data from the 30 commercial manufacturing runs, and the analysis plan used to create the revisions will be provided by XXXX, 20XX. [Amgen, provide date]
4. To confirm validation of the updated SE-HPLC method (MET-001208). The method was revised to add column conditioning using material containing the high molecular weight species. The protocol and final report will be included in an annual report to be submitted by [Amgen to provide date].

4. Nonclinical Pharmacology/Toxicology

Please refer to Dr. Kimberly Hatfield's review for complete details.

4.1 General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).

Denosumab is a fully human IgG₂ monoclonal antibody that binds to the receptor activator of nuclear factor- κ B (RANK) ligand (RANKL). The antibody is specific to human and non-human primate RANKL. Denosumab also does not bind to rodent RANKL. For this reason, studies in two animal species were not possible and the cynomolgus monkey was the species mainly used. Other studies were done using genetically altered mice (human RANKL knock-in mice where human RANKL was expressed instead of murine RANKL). In addition, the Applicant conducted studies in rodents using an osteoprotegerin-Fc fusion molecule. The rationale for this approach was that OPG is an endogenous regulator of RANKL activity and like denosumab, OPG binding to RANKL inhibits RANKL activity.

A 16-month pharmacology study was conducted in ovariectomized (OVX) cynomolgus monkeys, a model which mimics postmenopausal bone loss. Once monthly treatment with denosumab for 12 months decreased biomarkers of bone formation (osteocalcin, sALP) and resorption (CTx, TRAP-5b, NTx), and increased bone mineral density (BMD), prevented OVX-induced BMD changes in both cortical and cancellous bone, and increased bone strength in most examined bones. Following cessation of treatment, BMD and bone parameters returned to original baseline levels.

High levels of protein expression were observed in skeletal and lymphoid tissues. In addition, RANKL mRNA expression has been detected in keratinocytes of skin, mammary epithelial cells, heart, skeletal muscle, lung, stomach, placenta, thyroid gland and brain.

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

4.2 Carcinogenicity

Genotoxicity: Genotoxicity potential was not been studied. The standard genotoxicity studies routinely conducted for pharmaceuticals are not applicable to monoclonal antibodies and therefore are not recommended. Denosumab is not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity: The carcinogenicity potential of denosumab has not been assessed. Denosumab does not bind to rodent RANKL and therefore an appropriate model was not available. Although the Sponsor generated a knock-in human RANKL transgenic mouse and a surrogate rodent antibody (OPG-Fc fusion protein), these models were not considered relevant for carcinogenicity testing. It should also be noted that huRANKL KI mice have lower osteoprotegerin levels than wild type mice.

In the two long term studies (12-month toxicity and 16-month pharmacology), there were no incidences of tumor formation indicated with the exception of squamous metaplasia (benign) in two females, one each dosed at 1 and 50 mg/kg/month for 12 months. However, standard organ histopathology was not conducted in the 16-month pharmacology study.

Nonclinical evidence that suggests a potential that denosumab may be associated with increased carcinogenicity risk relates to the findings that the product appears to be immunosuppressive. Immunosuppressive agents, in general, increase the risk of cancer.

4.3 Reproductive and Developmental toxicology

Reproductive and developmental studies were performed in cynomolgus monkeys. There was no evidence of impairment of fertility following once weekly administration of denosumab through 2 menstrual cycles, mating and gestational day 20 of presumed pregnancy. When administered to pregnant monkeys once weekly during the time of major organogenesis (gestational days 20-50) there were no observed adverse effects on the mother or fetus. However, IgG antibodies do not readily cross the placenta during this period and therefore, this study only assessed potential secondary or indirect effect on the fetus due to maternal exposure. Although there were no gross teratogenic effects observed, only limited fetal tissues were examined histologically. Of particular note, the lymph nodes, where RANK signaling plays a major role in the developing immune system, were not examined.

Inhibition of the RANK/RANKL in knock-out mice resulted in lymph node agenesis, and postnatal impairment of bone growth, dentition and tooth eruption. These mice also showed altered maturation of the maternal mammary gland during pregnancy, leading to impaired lactation postpartum.

Young mice (2 weeks of age at initiation of treatment) treated with OPG-Fc for 6 weeks had significant decreases in body weight gain and axial skeletal length. Decreased upper

and lower incisor length, and delayed molar eruption proportional to the magnitude of bone resorption suppression were also observed.

4.4 Other notable issues

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

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

5. Clinical Pharmacology/Biopharmaceutics

Please refer to Drs. Chongwoo Yu and Sarah Schrieber's clinical pharmacology review and Dr. Ping Ji's pharmacometrics review for complete details.

5.1 General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.

Denosumab is administered as a subcutaneous injection. A validated, conventional sandwich enzyme-linked immunosorbent assay (ELISA) was used to quantify serum denosumab concentrations. The mean maximum serum denosumab concentrations (C_{max}) of 6.75 $\mu\text{g/ml}$ (standard deviation [SD]: 1.89 $\mu\text{g/ml}$) was reached in the median time of 10 days (range: 3 to 21 days) following a 60 mg SC dose after at least 12 hrs of fasting prior to denosumab administration. After C_{max} , serum denosumab concentrations decline over a period of 4 to 5 months with a mean half-life of 25.4 days (SD: 8.5 days; n=46; Study 20010223). No accumulation in serum denosumab concentrations was observed with repeated doses of 60 mg once every 6 month (Q6M), and denosumab PK did not appear to change with time (up to 4 years exposure). Denosumab PK was not affected by the formation of binding antibodies to denosumab and was similar in men and women.

The serum concentration time profiles of denosumab are best characterized as a two-compartment model with first-order absorption and a parallel linear and non-linear

elimination. Approximately dose-proportional increases in exposure (based on $AUC_{0-\tau}$) were observed for doses ≥ 60 mg (i.e., in the range of fixed doses of 60 to 210 mg in Study 20010223 in the PMO population). Across the range of doses tested, denosumab plasma concentrations declined at a faster rate when serum denosumab concentration dropped below approximately 1 $\mu\text{g/ml}$. The mechanism behind this change in elimination rate is likely related to denosumab binding to RANKL (i.e., target-mediated disposition). This non-linear elimination mechanism predominates at low serum denosumab concentrations (i.e., < 1 $\mu\text{g/ml}$ in this case) and becomes saturated as serum denosumab concentration increases.

Comparability: The Biopharmaceutics program demonstrated the comparability between denosumab drug substance and drug product produced for the pivotal Phase 3 clinical trials and those intended for commercial use.

Drug substance: During the development of denosumab, there were process changes of manufacturing the drug substance. Denosumab drug substance used in the nonclinical and early clinical studies was manufactured using an initial version of the commercial process, designated CP1 at Amgen Thousand Oaks (ATO). Denosumab drug substance manufactured at ATO using an optimized process with increased product yields and improved process robustness, designated as CP2 has been used in all of the later clinical trials. Although the Sponsor has assessed the comparability of denosumab produced using the CP1 and CP2 processes in a nonclinical study with cynomolgus monkeys, the PK comparability of denosumab produced using CP1 and CP2 processes in human is unknown. It should be noted that the Sponsor is proposing to use PK data obtained from studies conducted using CP2 process drug substance for labeling purposes.

Manufacturing site change and product preparation: The drug substance used in the pivotal Phase 3 trials was manufactured at ATO while the to-be-marketed drug substance was manufactured at Amgen Colorado (ACO) and Boehringer-Ingelheim Pharma (BIP). The Sponsor is proposing to have both a vial and a prefilled syringe (PFS) product preparation. PK and PD comparability assessments were conducted by the Sponsor to establish comparability across the different manufacturing sites as well as the different product preparations. Assessments of PK and PD comparability were based on the rate (maximum observed serum denosumab concentration [C_{max}]) and extent (area under the serum denosumab concentration-time curve from time zero to 16 weeks [$AUC_{0-16 \text{ weeks}}$]) of denosumab exposure and were supported by PD parameters (e.g., area under the effect curve from time zero to 16 weeks [$AUEC_{0-16 \text{ weeks}}$] for reductions in sCTX1). In addition, the safety profiles including immunogenicity were also compared and appeared to be consistent between the drug substances from the three different manufacturing sites. In the Clinical Pharmacology studies performed in healthy volunteers (Studies 20050227, 20060286, and 20050146), the PK and PD comparability of denosumab drug substances manufactured at 3 manufacturing sites (ATO, ACO, and BIP) and using 2 drug product preparations (PFS and vial) was established.

5.2 Drug-drug interactions

Because denosumab is a monoclonal antibody and is not eliminated via hepatic metabolic mechanisms (e.g., by cytochrome P450 [CYP] enzymes), hepatic impairment and drug interaction studies (e.g., with CYP inhibitors or inducers) were not considered appropriate by the Sponsor and have therefore not been conducted. However, considering that the effect of denosumab, an anti-cytokine antibody, on CYP activities is unknown, a post-marketing commitment (PMC) recommendation is being made to the Sponsor to address denosumab's effect on CYP activities and drug interaction potential.

5.3 Pathway of Elimination

Intrinsic Factors: Based on the pharmacometrics review, age and gender were not significant covariates in the population PK analysis. In the population PK analysis both race and solid tumor were identified as covariates for clearance. The PK of denosumab did not appear to be affected by these covariates.

The appropriateness of fixed dosing regimen of 60 mg Q6M was evaluated through the effect of body weight on new vertebral fractures and BMD levels. Although body weight was identified as a covariate for clearance, body weight did not appear to affect the incidence of new vertebral fracture over the 36 months period or the change in the BMD levels. While denosumab PK parameters are dependent on body weight, these differences in exposure did not affect the response to denosumab. Therefore, the proposed dosing regimen was found to be appropriate for all patients recommended for use.

5.4 Demographic interactions/special populations

A renal impairment study (Study 20040245) was conducted and included 55 patients with normal, mild, moderate, severe, and end-stage renal disease, defined by creatinine clearance (CrCL). Overlap was observed in denosumab exposure across renal impairment cohorts, and no notable relationship was apparent between denosumab PK and renal impairment. No dose adjustment is necessary in patients with renal impairment.

5.5 Thorough QT study or other QT assessment

Because denosumab is a monoclonal antibody and therefore, a large protein product that is unlikely to interact with cardiac cell ion channels, a thorough QT study was not required or performed. However, the clinical reviewers were concerned regarding the QT effects noted for denosumab and an IRQT consult was obtained. Despite the lack of a thorough QT study, the clinical development program did include an intensive assessment of the effects of denosumab on electrocardiograms, with particular emphasis on the QTc interval. ECGs were obtained at baseline, around Cmax and at several time points during the follow-up period in most clinical studies. In all studies, ECG

assessments were based on automated readings using machines provided by the investigative sites. Paper copies of ECGs were collected and manually read (semi-automated) in a blinded fashion for Studies 20010223 and 20040132. The remaining studies did not have ECGs centrally read.

Outliers (patients with absolute post-dose QTcF over 500 ms or over 60 ms change from baseline) were noted in several studies although underlying ECG abnormalities were also noted in several of the studies. Notably, subjects were not excluded because of baseline QTc prolongation. There was no imbalance in the reports of sudden death between the denosumab and comparator groups. The final recommendation from the IRQT team was that the sponsor's ECG evaluations appear adequate and there are no large effects on the QT interval due to denosumab.

5.6 Other notable issues

In Study 20010223, the percent change from baseline in sCTX1 and lumbar spine BMD following 2 consecutive doses of various denosumab concentrations given every 3 or 6 months to postmenopausal women with low BMD was assessed. Denosumab treatment was associated with an increase in BMD of the lumbar spine. The gain in lumbar spine BMD of all active treatment groups was significantly greater compared to placebo. The gain in lumbar spine BMD following 60 mg Q6M dosing is comparable to that observed following 100 and 210 mg Q6M dosing and greater than that observed following 14 mg Q6M dosing. However, all dose groups achieved similar increases in BMD after 48 months. There was no dose-response relationship for safety established.

(b) (4)

(b) (4)

The Clinical Pharmacology Review Team recommends the following post marketing commitments (PMC):

Anti-cytokine antibodies such as tocilizumab, an anti-IL-6 monoclonal antibody, showed the alteration of CYP substrate drug exposure by affecting the effect of cytokine on drug metabolism. Thus, denosumab may affect the exposure to CYP substrate drugs by altering the concentration of RANKL, a cytokine that affects B- and T-cell differentiation, and dendritic cell maturation.

Therefore, the sponsor should conduct an in vitro study to assess whether RANKL modulates expression of major CYP enzymes (e.g., CYP 3A4, CYP 1A2, CYP 2C9, CYP 2C19, and CYP 2D6). If, upon review, there is no significant modulation of any

of the major CYP enzyme(s) observed, further exploration would not be necessary. If the results of the in vitro study are positive, a drug interaction study or studies will be needed to further characterize the effect of denosumab on the metabolism of CYP probe drugs in PMO patients.

As an alternative to the in vitro study and the subsequent drug interaction study above, the sponsor may conduct a drug interaction study to determine the potential of denosumab to alter CYP substrate metabolism in PMO patients (e.g., using a cocktail of the major CYP probe drugs).

6. Clinical Microbiology

Denosumab is not an antimicrobial agent. Clinical microbiology studies are not applicable to this BLA. The microbiology product quality of the denosumab drug substance has been discussed in Sections 3.1 and 3.2 of this review.

Appendix B

Bone Histomorphometry

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 the table below, 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.

Denosumab Bone Histomorphometry Studies: Labeling status												
Study	20010223						20050234		20030216			
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
evaluatable, 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 from denosumab group												

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 the table below.

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. 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.

Trial 20030216: 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

Source: compiled by reviewer from study 20030216 study report

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 the table below.

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.

Study 20050234: 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
Source: compiled by reviewer from the 20050234 study report		

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 the figure of CTX changes on page 34 of this review, 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 the actual values that were the limit of quantitation (<0.049 ng/mL) up to read as a value of 0.049. The following table details the trabecular label status in terms of the actual month one CTX value (classified as either 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.

Trail 20030216: Comparison of Trabecular label Status and Month 1 serum CTX Status				
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. 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.

Clinical Review Addendum for BLA 125320 and 125321 (Denosumab)

BLA	125320/000 and BLA 125321/000
Sponsor:	AMGEN
Drug:	Denosumab
Dose and Route of administration:	60 mg q 6 months subcutaneous injection
Proposed Indication:	Treatment of Osteoporosis Prevention of Osteoporosis
Review type	Review Addendum
Date Addendum Completed	10/15/2009
Recommended Regulatory Action:	Complete Response
Reviewers:	Vaishali Popat, MD, MPH <i>SS Patel, MD, MPH</i> Adrienne Rothstein, PharmD <i>Adrienne Rothstein, PharmD</i> Theresa Kehoe, MD <i>Theresa Kehoe, MD</i>
Team Leader:	

Amgen, Inc. submitted an original Biologic Licensing Application (BLA) for denosumab, a monoclonal antibody against the receptor activator of nuclear factor-kappa B ligand (RANKL) on 12/19/2008. The application seeks 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; and treatment and prevention of bone loss associated with hormone ablation therapy for prostate cancer. The indications related to postmenopausal osteoporosis were reviewed by the Division of Reproductive and Urologic Products (DRUP).

On September 11, 2009 the Applicant submitted the following two protocols as components of a Risk Evaluation and Mitigation Strategy for review:

1. Denosumab Global Safety Methodology and Background Rate Assessment Among Women With Postmenopausal Osteoporosis (PMO) Using Multiple Observational Databases (Denosumab Methodology and Background Assessment [DMBA]) (protocol 20090521, Phase A)
2. Denosumab Global Safety Assessment Among Women With Postmenopausal Osteoporosis (PMO) Using Multiple Observational Databases (Denosumab Postmarketing Global Safety Assessment [DPMGSA]) (protocol #20090522, Phase B)

The Office of Surveillance and Epidemiology (OSE), Division of Epidemiology (DEPI) was consulted for an evaluation of the proposed studies. The initial evaluation was received by DRUP on October 5, 2009, after completion of the clinical review (see Clinical Review dated September 14, 2009). This addendum to the Clinical Review provides an update related to these proposed epidemiologic studies.

Protocol P20090521 is herein called the feasibility study. Protocol P20090522 is herein referred to as the observational study. The feasibility study will be used to validate the study methodology and adverse event rate assessments for the observational study. The Applicant proposed completing the analysis of the feasibility study by the end of 2010 (post-approval). The observational study is planned to be conducted between June 2010

and December 2015. The analysis of the feasibility data would not be completed before the start of the observational study, as currently proposed by the Applicant.

In their evaluation of the proposed epidemiologic studies, DEPI noted concerns about the difficulty in capturing denosumab use and identifying some of the adverse events of interest in these administrative databases. Specifically, they noted that events such as osteonecrosis of the jaw and atypical fracture may be treated outside the healthcare plan or may be difficult to identify and may not be adequately captured in the proposed study. DEPI recommended the following:

- Expand the scope of the feasibility study to include all postmenopausal women, not just postmenopausal women with osteoporosis.
- Conduct the feasibility study to assess the development and validation of the observational study methodology *prior* to approving denosumab and initiating the observational study.

We concur with these recommendations for the Applicant. Therefore, the recommendation for Regulatory Action is Complete Response for both postmenopausal osteoporosis indications.

Cross-Discipline Team Leader Review

Date	October 13, 2009
From	Theresa Kehoe, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	BLA # 125320/000
Supplement#	BLA # 125331/000
Applicant	Amgen, Inc
Date of Submission	December 20, 2008
PDUFA Goal Date	October 19, 2009
Proprietary Name / Established (USAN) names	Prolia denosumab
Dosage forms / Strength	60 mg q6 months subcutaneous injection administered by a healthcare provider
Proposed Indication(s)	1. Treatment of postmenopausal osteoporosis (BLA 125320) 2. Prevention of postmenopausal osteoporosis (BLA125331)
Recommendation:	BLA 125320 (Treatment) = Complete Response BLA125331 (Prevention) = Complete Response

1. Introduction

Amgen, Inc. has submitted this original biologic licensing application (BLA) seeking to market 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; and treatment and prevention of bone loss associated with hormone ablation therapy for prostate cancer. The postmenopausal osteoporosis indications are under review by the Division of Reproductive and Urologic Products while the bone loss due to hormone ablation in breast and prostate cancer indications are under review by the Division of Biologic Oncology Products. Each indication has been assigned a separate BLA number as follows:

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

This memo will focus on the postmenopausal osteoporosis indications. The Applicant has submitted two pivotal trials in support of the two postmenopausal osteoporosis (PMO) indications. For treatment of postmenopausal osteoporosis, the basis for approval 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 basis for approval of 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. These trials as well as the dose-finding study 20010223 are the main clinical focus of this review.

2. Background

Denosumab represents the first biologic product and the first monoclonal antibody agent seeking approval for the prevention and treatment of postmenopausal osteoporosis. Denosumab is a full-length human monoclonal IgG2 that targets receptor activator of nuclear factor kappa B ligand (RANKL). RANKL exists in both transmembrane and soluble forms, and denosumab is fully capable of binding to either form. The mechanism of action for this antibody involves the antibody binding to RANKL and inhibiting the interaction of RANKL and its receptor (RANK). Inhibition of the RANK-RANKL interaction prevents receptor activation and clustering as well as the downstream signaling from the receptor. RANKL-induced RANK signaling is essential for the formation, function, and survival of mature osteoclasts, which are responsible for bone resorption. The resulting decrease in bone resorption leads to an increase in bone mass. 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 appears to be modulated by various cytokines, glucocorticoids, and PTH and it is produced by osteoblastic lineage cells and activated T cells.

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

As outlined in the 1994 osteoporosis guidance document entitled **“Guidelines for Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis”** a clinical trial assessing the effects of treatment on the incidence of new vertebral fractures at three years is required for approval of an osteoporosis indication. In the pivotal fracture trial, bone mineral density is a generally 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, as outlined in the 1994 osteoporosis guidelines, because the monoclonal antibody is species specific. All nonclinical studies were performed in the monkey.

On 5/21/01, original IND 9837 was submitted to FDA. At that time, therapeutic monoclonal antibodies were reviewed in the Center for Biologic Evaluation and Research (CBER). Subsequently, all therapeutic proteins including monoclonal antibodies were transferred to the Center for Drug Evaluation and Research (CDER). On 4/20/2004, a pre phase 3 meeting was held for the PMO indication. There was no special protocol assessment requested for the pivotal fracture trial (20030216). Instead, there was a lengthy discussion between FDA and Amgen about various issues, including appropriateness of the dose selection. The BLA was submitted on 12/19/2008 with the data cut-off date of 05/31/2008 as agreed upon between the Agency and the Applicant. There were 3 pre BLA meetings (on February 5, 2008 for the structure and content of BLA, on July 8, 2008 for CMC issues and on October 21, 2008 for clinical issues).

3. CMC/Device

Please refer to Drs. Sarah Kennett and Michele Dougherty's review and Drs. Kalavati Suvarna and Donald Obenhuber's product quality reviews for complete details.

3.1 General product quality considerations

Denosumab is a full-length human monoclonal IgG2 antibody. Denosumab binds specifically to the D-E loop of human receptor activator of nuclear factor kappa B ligand (b) (4):

(b) (4) depending on the assay method used.

Denosumab drug substance is manufactured at two different sites: Amgen, Colorado (ACO) and Boehringer Ingelheim Pharma, Germany (BIP). There is a difference in charge variants between ACO and BIP. The variation is due to cell culture raw materials and is bounded by base media and enzymatic reaction saturation. The noted variants have equal *in vitro* potency and are not expected to have a clinical effect.

Denosumab was derived by immunizing human IgG2/kappa Xeno-mouse animals with Chinese hamster ovary (CHO) cells stably expressing the cDNA for human RANKL (b) (4)

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(b) (4)

In the denosumab clinical program, two processes (CP1 and CP2) were used for drug substance manufacturing. CP1 material came from the master cell bank and was used in phase 1 trials. CP2 material came from the working cell bank and was used in the phase 2 trials and all pivotal phase 3 clinical trials. There were minor differences (b) (4) seen during development between these two processes. Nonclinical studies as well as clinical bioequivalence studies were performed to ensure there are not clinically significant changes between the denosumab manufactured through the CP1 and CP2 processes

Raw materials used in the manufacture of denosumab are from approved suppliers and are **accepted based on manufacturers' certification documents** or testing procedures established at Amgen. (b) (4)

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Please refer to Dr. Obenhuber's review for complete details of the denosumab drug product manufacturing process. Drug product is manufactured at Amgen, Puerto Rico (AML). Denosumab drug product is supplied as a single-use, sterile, preservative-free solution intended for delivery by subcutaneous injection, supplied in either a 60 mg/mL prefilled syringe (PFS) or 60 mg/mL vial presentation with a 1.0 mL deliverable volume to support dosing of 60 mg every 6 months (Q6M). Each prefilled syringe contains: 60 mg denosumab, 4.7% sorbitol, 17 mM acetate, 0.01 % polysorbate 20, sodium hydroxide for pH adjustment in Water for Injection, USP (pH of 5.2). Each vial contains: 60 mg denosumab, 4.7% sorbitol, 17 mM acetate, sodium hydroxide for pH adjustment in Water for Injection, USP (pH of 5.2). The only difference in the formulations for these presentations is the addition of 0.01 % (w/v) polysorbate to the formulation used for the PFS.

3.2 Facilities review/inspection

Facilities inspections of the ACO and BIP sites for the denosumab drug substance manufacturing were conducted by the Biotech Manufacturing Team of the Division of Manufacturing and Product Quality (DMPQ).

A pre-approval inspection for denosumab drug substance production at the Boehringer Ingelheim Pharma (BIP) facility was conducted from May 11 to May 20, 2009. The BIP facility is responsible for manufacture of denosumab drug substance and for QC testing. A form 483 was issued at the end of this inspection. Observations made during the inspection pertain to inadequate actions taken in response to a deviation where contaminated harvest with a bioburden excursion of too numerous to count was used to manufacture drug substance and procedures were not established to ensure that the process step identified as the source of contamination is successfully performed. This inspection was classified VAI.

A pre-approval inspection for denosumab drug substance production at the Amgen Colorado (ACO) facility was conducted from June 8 to June 12, 2009 by BMT reviewers Kalavati Suvarna and Maan Abduldayem, product reviewer Sarah Kennett, and district investigators Nancy Schmidt and Kimberley Buytaert-Hoefen. ACO is responsible for manufacture of denosumab drug substance, for QC testing (except mycoplasma and in vitro viral testing), and for stability sample storage and testing. No form 483 was issued.

Facilities inspection of the AML site specifically for the denosumab drug product was not performed based on the compliance history, current GMP status, and previous inspections of manufacturing processes similar to the denosumab manufacturing process. A routine GMP inspection of the Puerto Rico site (AML) was concluded on 9/11/09. Findings included low level syringe breakage identified on the Enbrel SureClick manufacturing line. The Applicant was issued a 483 which included the following observation:

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(b) (4)

This finding is a serious failure of the quality control unit at the drug product manufacturing plant that likely affects all products produced at the plant. A final review and recommendation from the Office of Compliance is pending at the time of this review.

All other facilities listed in the BLA, including contract facilities for mycoplasma, viral, sterility and container closure integrity testing, were not inspected. Inspections were not conducted as the activities in these sites are either low risk and/or these sites are in compliance as per 21 CFR 210, 211 and 600.

3.3 Other notable issues

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

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

1. To perform stability testing on at least one marketed drug product lot of both the 3 cc glass vial and the 1 ml glass syringe; annually, for each year in which respective drug product is manufactured and for each site at which it is manufactured, using the post-approval stability protocol specified in the BLA. The first update will be included in an annual report to be submitted by [Amgen to provide date]
2. To modify the acceptance criteria for the pre-filled syringe extrusion and breakloose specification. This specification was added during review and acceptance criterion **is currently listed as "report"**. **Data, analysis** and justification for a quantitative limit will be included in a prior approval supplement submitted by June 30, 2010.

3. To re-evaluate the release and shelf-life specifications and in-process limits for denosumab drug substance and drug product after 30 commercial manufacturing runs to reflect increased manufacturing experience. The revisions to the quality control system, the corresponding data from the 30 commercial manufacturing runs, and the analysis plan used to create the revisions will be provided by XXXX, 20XX. [Amgen, provide date]
4. To confirm validation of the updated SE-HPLC method (MET-001208). The method was revised to add column conditioning using material containing the high molecular weight species. The protocol and final report will be included in an annual report to be submitted by [Amgen to provide date].

4. Nonclinical Pharmacology/Toxicology

Please refer to Dr. Kimberly Hatfield's review for complete details.

4.1 General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).

Denosumab is a fully human IgG₂ monoclonal antibody that binds to the receptor activator of nuclear factor- κ B (RANK) ligand (RANKL). The antibody is specific to human and non-human primate RANKL. Denosumab also does not bind to rodent RANKL. For this reason, studies in two animal species were not possible and the cynomolgus monkey was the species mainly used. Other studies were done using genetically altered mice (human RANKL knock-in mice where human RANKL was expressed instead of murine RANKL). In addition, the Applicant conducted studies in rodents using an osteoprotegerin-Fc fusion molecule. The rationale for this approach was that OPG is an endogenous regulator of RANKL activity and like denosumab, OPG binding to RANKL inhibits RANKL activity.

A 16-month pharmacology study was conducted in ovariectomized (OVX) cynomolgus monkeys, a model which mimics postmenopausal bone loss. Once monthly treatment with denosumab for 12 months decreased biomarkers of bone formation (osteocalcin, sALP) and resorption (CTx, TRAP-5b, NTx), and increased bone mineral density (BMD), prevented OVX-induced BMD changes in both cortical and cancellous bone, and increased bone strength in most examined bones. Following cessation of treatment, BMD and bone parameters returned to original baseline levels.

High levels of protein expression were observed in skeletal and lymphoid tissues. In addition, RANKL mRNA expression has been detected in keratinocytes of skin, mammary epithelial cells, heart, skeletal muscle, lung, stomach, placenta, thyroid gland and brain.

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

4.2 Carcinogenicity

Genotoxicity. Genotoxicity potential was not been studied. The standard genotoxicity studies routinely conducted for pharmaceuticals are not applicable to monoclonal antibodies and therefore are not recommended. Denosumab is not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity. The carcinogenicity potential of denosumab has not been assessed. Denosumab does not bind to rodent RANKL and therefore an appropriate model was not available. Although the Sponsor generated a knock-in human RANKL transgenic mouse and a surrogate rodent antibody (OPG-Fc fusion protein), these models were not considered relevant for carcinogenicity testing. It should also be noted that huRANKL KI mice have lower osteoprotegerin levels than wild type mice.

In the two long term studies (12-month toxicity and 16-month pharmacology), there were no incidences of tumor formation indicated with the exception of squamous metaplasia (benign) in two females, one each dosed at 1 and 50 mg/kg/month for 12 months. However, standard organ histopathology was not conducted in the 16-month pharmacology study.

Nonclinical evidence that suggests a potential that denosumab may be associated with increased carcinogenicity risk relates to the findings that the product appears to be immunosuppressive. Immunosuppressive agents, in general, increase the risk of cancer.

4.3 Reproductive and Developmental toxicology

Reproductive and developmental studies were performed in cynomolgus monkeys. There was no evidence of impairment of fertility following once weekly administration of denosumab through 2 menstrual cycles, mating and gestational day 20 of presumed pregnancy. When administered to pregnant monkeys once weekly during the time of major organogenesis (gestational days 20-50) there were no observed adverse effects on the mother or fetus. However, IgG antibodies do not readily cross the placenta during this period and therefore, this study only assessed potential secondary or indirect effect on the fetus due to maternal exposure. Although there were no gross teratogenic effects observed, only limited fetal tissues

were examined histologically. Of particular note, the lymph nodes, where RANK signaling plays a major role in the developing immune system, were not examined.

Inhibition of the RANK/RANKL in knock-out mice resulted in lymph node agenesis, and postnatal impairment of bone growth, dentition and tooth eruption. These mice also showed altered maturation of the maternal mammary gland during pregnancy, leading to impaired lactation postpartum.

Young mice (2 weeks of age at initiation of treatment) treated with OPG-Fc for 6 weeks had significant decreases in body weight gain and axial skeletal length. Decreased upper and lower incisor length, and delayed molar eruption proportional to the magnitude of bone resorption suppression were also observed.

4.4 Other notable issues

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

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

5. Clinical Pharmacology/Biopharmaceutics

Please refer to Drs. Chongwoo Yu and Sarah Schrieber's **clinical pharmacology** review and Dr. Ping Ji's **pharmacometrics** review for complete details.

5.1 General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.

Denosumab is administered as a subcutaneous injection. A validated, conventional sandwich enzyme-linked immunosorbent assay (ELISA) was used to quantify serum denosumab concentrations. The mean maximum serum denosumab concentrations (C_{max}) of 6.75 µg/ml

(standard deviation [SD]: 1.89 µg/ml) was reached in the median time of 10 days (range: 3 to 21 days) following a 60 mg SC dose after at least 12 hrs of fasting prior to denosumab administration. After C_{max} , serum denosumab concentrations decline over a period of 4 to 5 months with a mean half-life of 25.4 days (SD: 8.5 days; n=46; Study 20010223). No accumulation in serum denosumab concentrations was observed with repeated doses of 60 mg once every 6 month (Q6M), and denosumab PK did not appear to change with time (up to 4 years exposure). Denosumab PK was not affected by the formation of binding antibodies to denosumab and was similar in men and women.

The serum concentration time profiles of denosumab are best characterized as a two-compartment model with first-order absorption and a parallel linear and non-linear elimination. Approximately dose-proportional increases in exposure (based on $AUC_{0-\tau}$) were observed for doses ≥ 60 mg (i.e., in the range of fixed doses of 60 to 210 mg in Study 20010223 in the PMO population). Across the range of doses tested, denosumab plasma concentrations declined at a faster rate when serum denosumab concentration dropped below approximately 1 µg/ml. The mechanism behind this change in elimination rate is likely related to denosumab binding to RANKL (i.e., target-mediated disposition). This non-linear elimination mechanism predominates at low serum denosumab concentrations (i.e., < 1 µg/ml in this case) and becomes saturated as serum denosumab concentration increases.

Comparability. The Biopharmaceutics program demonstrated the comparability between denosumab drug substance and drug product produced for the pivotal Phase 3 clinical trials and those intended for commercial use.

Drug substance: During the development of denosumab, there were process changes of manufacturing the drug substance. Denosumab drug substance used in the nonclinical and early clinical studies was manufactured using an initial version of the commercial process, designated CP1 at Amgen Thousand Oaks (ATO). Denosumab drug substance manufactured at ATO using an optimized process with increased product yields and improved process robustness, designated as CP2 has been used in all of the later clinical trials. Although the Sponsor has assessed the comparability of denosumab produced using the CP1 and CP2 processes in a nonclinical study with cynomolgus monkeys, the PK comparability of denosumab produced using CP1 and CP2 processes in human is unknown. It should be noted that the Sponsor is proposing to use PK data obtained from studies conducted using CP2 process drug substance for labeling purposes.

Manufacturing site change and product preparation: The drug substance used in the pivotal Phase 3 trials was manufactured at ATO while the to-be-marketed drug substance was manufactured at Amgen Colorado (ACO) and Boehringer-Ingelheim Pharma (BIP). The Sponsor is proposing to have both a vial and a prefilled syringe (PFS) product preparation. PK and PD comparability assessments were conducted by the Sponsor to establish comparability across the different manufacturing sites as well and the different product preparations. Assessments of PK and PD comparability were based on the rate (maximum observed serum denosumab concentration [C_{max}]) and extent (area under the serum denosumab concentration-time curve from time zero to 16 weeks [$AUC_{0-16 \text{ weeks}}$]) of denosumab exposure and were

supported by PD parameters (e.g., area under the effect curve from time zero to 16 weeks [AUEC_{0-16 weeks}] for reductions in sCTX1). In addition, the safety profiles including immunogenicity were also compared and appeared to be consistent between the drug substances from the three different manufacturing sites. In the Clinical Pharmacology studies performed in healthy volunteers (Studies 20050227, 20060286, and 20050146), the PK and PD comparability of denosumab drug substances manufactured at 3 manufacturing sites (ATO, ACO, and BIP) and using 2 drug product preparations (PFS and vial) was established.

5.2 Drug-drug interactions

Because denosumab is a monoclonal antibody and is not eliminated via hepatic metabolic mechanisms (e.g., by cytochrome P450 [CYP] enzymes), hepatic impairment and drug interaction studies (e.g., with CYP inhibitors or inducers) were not considered appropriate by the Sponsor and have therefore not been conducted. However, considering that the effect of denosumab, an anti-cytokine antibody, on CYP activities is unknown, a post-marketing **commitment (PMC) recommendation is being made to the Sponsor to address denosumab's** effect on CYP activities and drug interaction potential.

5.3 Pathway of Elimination

Intrinsic Factors: Based on the pharmacometrics review, age and gender were not significant covariates in the population PK analysis. In the population PK analysis both race and solid tumor were identified as covariates for clearance. The PK of denosumab did not appear to be affected by these covariates.

The appropriateness of fixed dosing regimen of 60 mg Q6M was evaluated through the effect of body weight on new vertebral fractures and BMD levels. Although body weight was identified as a covariate for clearance, body weight did not appear to affect the incidence of new vertebral fracture over the 36 months period or the change in the BMD levels. While denosumab PK parameters are dependent on body weight, these differences in exposure did not affect the response to denosumab. Therefore, the proposed dosing regimen was found to be appropriate for all patients recommended for use.

5.4 Demographic interactions/special populations

A renal impairment study (Study 20040245) was conducted and included 55 patients with normal, mild, moderate, severe, and end-stage renal disease, defined by creatinine clearance (CrCL). Overlap was observed in denosumab exposure across renal impairment cohorts, and no notable relationship was apparent between denosumab PK and renal impairment. No dose adjustment is necessary in patients with renal impairment.

5.5 Thorough QT study or other QT assessment

Because denosumab is a monoclonal antibody and therefore, a large protein product that is unlikely to interact with cardiac cell ion channels, a thorough QT study was not required or performed. However, the clinical reviewers were concerned regarding the QT effects noted for denosumab and an IRQT consult was obtained. Despite the lack of a thorough QT study, the clinical development program did include an intensive assessment of the effects of denosumab on electrocardiograms, with particular emphasis on the QTc interval. ECGs were obtained at baseline, around Cmax and at several time points during the follow-up period in most clinical studies. In all studies, ECG assessments were based on automated readings using machines provided by the investigative sites. Paper copies of ECGs were collected and manually read (semi-automated) in a blinded fashion for Studies 20010223 and 20040132. The remaining studies did not have ECGs centrally read.

Outliers (patients with absolute post-dose QTcF over 500 ms or over 60 ms change from baseline) were noted in several studies although underlying ECG abnormalities were also noted in several of the studies. Notably, subjects were not excluded because of baseline QTc prolongation. There was no imbalance in the reports of sudden death between the denosumab and comparator groups. The final recommendation from the IRQT team was that the sponsor's ECG evaluations appear adequate and there are no large effects on the QT interval due to denosumab.

5.6 Other notable issues

In Study 20010223, the percent change from baseline in sCTX1 and lumbar spine BMD following 2 consecutive doses of various denosumab concentrations given every 3 or 6 months to postmenopausal women with low BMD was assessed. Denosumab treatment was associated with an increase in BMD of the lumbar spine. The gain in lumbar spine BMD of all active treatment groups was significantly greater compared to placebo. The gain in lumbar spine BMD following 60 mg Q6M dosing is comparable to that observed following 100 and 210 mg Q6M dosing and greater than that observed following 14 mg Q6M dosing. However, all dose groups achieved similar increases in BMD after 48 months. There was no dose-response relationship for safety established.

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The Clinical Pharmacology Review Team recommends the following post marketing commitments (PMC):

Anti-cytokine antibodies such as tocilizumab, an anti-IL-6 monoclonal antibody, showed the alteration of CYP substrate drug exposure by affecting the effect of cytokine on drug metabolism. Thus, denosumab may affect the exposure to CYP substrate drugs by altering the concentration of RANKL, a cytokine that affects B- and T-cell differentiation, and dendritic cell maturation.

Therefore, the sponsor should conduct an in vitro study to assess whether RANKL modulates expression of major CYP enzymes (e.g., CYP 3A4, CYP 1A2, CYP 2C9, CYP 2C19, and CYP 2D6). If, upon review, there is no significant modulation of any of the major CYP enzyme(s) observed, further exploration would not be necessary. If the results of the in vitro study are positive, a drug interaction study or studies will be needed to further characterize the effect of denosumab on the metabolism of CYP probe drugs in PMO patients.

As an alternative to the in vitro study and the subsequent drug interaction study above, the sponsor may conduct a drug interaction study to determine the potential of denosumab to alter CYP substrate metabolism in PMO patients (e.g., using a cocktail of the major CYP probe drugs).

6. Clinical Microbiology

Denosumab is not an antimicrobial agent. Clinical microbiology studies are not applicable to this BLA. The microbiology product quality of the denosumab drug substance has been discussed in Sections 3.1 and 3.2 of this review.

7. Clinical/Statistical- Efficacy

Please refer to Drs. Vaishali Popat and Adrienne **Rothstein's clinical** review and Dr. Sonia **Castillo's statistical** review for complete details.

The applicant is seeking two separate indications: 1) treatment of osteoporosis in postmenopausal women and 2) prevention of osteoporosis in postmenopausal women. Each indication is supported by a key efficacy trial and each trial will be discussed separately.

7.1 Dose identification/selection and limitations

The phase 2 dose-finding study was trial 20010223, a four-year, randomized, double-blind, placebo and active-controlled study which evaluated 7 different dose regimens from denosumab (6 mg, 14 mg or 30 mg every 3 months and 14 mg, 60 mg, 100 mg or 210 mg every 6 months). The original dose groups were maintained for the first two years of the study and the primary endpoint was percent change from baseline in lumbar spine BMD at month 12. The 12-month interim analyses of BMD and changes in bone turnover markers were used to choose dosing for the phase 3 program. Years 3 and 4 of the study assessed off-treatment and retreatment effects of denosumab therapy.

The study population was postmenopausal women with low bone mineral density (T-score -1.8 **to -4.0 at the lumbar spine or -1.8 to -3.5 at the hip**). All subjects were instructed to take at least 1000 mg calcium and 400 IU vitamin D daily. A total of 412 subjects (319 denosumab, 46 placebo, 47 alendronate) were enrolled in the trial and 406 (314 denosumab, 46 placebo, 46 alendronate) received at least one dose of study medication. The mean age of the enrolled population was 62.5 years with an age range of **43 – 83 years. Most subjects (86%) were** Caucasian race, and the mean baseline T-score was -2.1 at the lumbar spine and -1.4 at the total hip.

As outlined in the following table, denosumab increased BMD of the lumbar spine from baseline to month 12 in all denosumab cohorts (range: 3.0% to 6.7%). With the exception of the 14 mg q 6month dose cohort, the increases in BMD approximate that achieved by alendronate 70 mg once weekly.

Trial 20010223: Percent Change From Baseline in Lumbar Spine BMD at Month 12 (mITT, LOCF)						
Treatment Arm / Dosing Cohort	Annualized Dose	Difference from Baseline		Difference from Placebo		
		n	Least Squares Mean (SEM) ^a	Least Squares Mean (SEM) ^a	95% C.I.	P-value ^b
Placebo (N = 46)		46	-0.67 (0.46)	--	--	--
Denosumab 6 mg q3m (N = 44)	24 mg	40	4.14 (0.48)	4.81 (0.65)	3.53, 6.09	<0.001
Denosumab 14 mg q6m (N = 54)	28 mg	53	2.92 (0.42)	3.59 (0.61)	2.39, 4.78	<0.001
Denosumab 14 mg q3m (N = 44)	56 mg	43	4.51 (0.47)	5.18 (0.64)	3.92, 6.44	<0.001
Denosumab 30 mg q3m (N = 41)	120 mg	40	5.99 (0.49)	6.66 (0.65)	5.38, 7.94	<0.001
Denosumab 60 mg q6m (N = 47)	120 mg	46	4.29 (0.46)	4.96 (0.63)	3.73, 6.20	<0.001
Denosumab 100 mg q6m (N = 42)	200 mg	41	5.33 (0.48)	6.00 (0.65)	4.72, 7.28	<0.001
Denosumab 210 mg q6m (N = 47)	420 mg	46	4.85 (0.46)	5.52 (0.63)	4.29, 6.76	<0.001
Alendronate 70 mg qw (N = 47)		46	4.49 (0.45)	5.16 (0.63)	3.92, 6.40	<0.001

N = Number of subjects enrolled.
 n = Number of subjects with values at baseline and 1 or more post baseline visits at or prior to month 12.
^a Based on ANCOVA model adjusting for treatment, geographical location, and baseline value.
^b p-values for denosumab vs. placebo are adjusted for multiple comparisons using Hochberg's procedure.
 Nominal p-value is reported for alendronate vs. placebo.
 Source: Primary Clinical Review, page 42, table 5

With regard to dose selection for phase 3, the Applicant stated:

“In study 20010223, doses of 6, 14, and 30 mg denosumab administered every 3 months and 14, 60, 100, and 210 mg administered every 6 months effectively reduced bone loss with a similar dose-response relationship in both subject groups. Evaluation of BMD data from all anatomic sites, serum CTX1, and urine NTX/creatinine indicated that (1) no additional pharmacodynamic (PD) activity was observed when doses higher than 60 mg were administered, and (2) that 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 either using a 3- or a 6-month dosing interval, the 6-month dosing interval was selected because it is more convenient and may increase compliance. Therefore, the denosumab dose used in this study was 60 mg every 6 months.”

However, as outlined in the clinical pharmacology review and the primary clinical review, **pages 42 – 46, there is not a clear dose-response in changes in serum CTX or BMD with the various denosumab doses evaluated.**

7.2 Phase 3/ clinical studies essential to regulatory decision, including design, analytic features, and results

7.2.1 Treatment of Osteoporosis in Postmenopausal Women

The Applicant has submitted one key efficacy trial, 20030216, to support approval of denosumab in the indication of treatment of postmenopausal osteoporosis. Trial 20030216 is a multicenter, double-blind, randomized, placebo-controlled, study to assess the safety and efficacy of denosumab, administered as a subcutaneous injection 60mg every 6 months in the treatment of postmenopausal osteoporosis (PMO). The primary endpoint of the study was incidence of new morphometric (radiographic) vertebral fractures at month 36.

Study population: Subjects enrolled in this trial study were age 60 to 90 years, with diagnosed osteoporosis. Enrollees were required to have a bone mineral density T-score of at least -2.5 but not lower than -4.0 at the lumbar spine and/or total hip. Radiologic evidence of baseline vertebral fracture was not required. Women with a history of metabolic bone disease, hypocalcemia, active parathyroid disease, hyperthyroidism, vitamin D deficiency (< 12 ng/mL), malabsorption, or rheumatoid arthritis were excluded from the study. Subjects previously on iv bisphosphonate, fluoride or strontium therapy were excluded from the study. Subjects previously on oral bisphosphonate therapy for less than 3 months could be enrolled in the study. If the cumulative exposure was more than 3 months but less than 3 years, subjects could be enrolled only after a wash-out period of one year. For subjects on other osteoporosis therapies, subjects could be enrolled after a 6 week wash-out period. Concomitant osteoporosis therapies were not allowed during the trial. Subjects were stratified based on age at entry (60-64 years, 65-69 years, 70-74 years, and ≥ 75 years).

Study treatments: Eligible subjects were randomized 1:1 to receive denosumab 60 mg or placebo subcutaneous injection, administered by a healthcare professional, every 6 months. No dosing adjustments were permitted. All subjects were to receive daily calcium > 1000 mg daily. Subjects also received vitamin D (400 – 800 IU) **supplementation based on their baseline 25 hydroxyvitamin D level (12 – 20 ng/ml – 800 IU, > 20 ng/mL – 400 IU).** The calcium and vitamin D supplements were not provided by the Applicant, they were to be provided by the investigator. The Applicant did reimburse the clinical sites for the cost of the supplements.

Efficacy measures: Trial 20030216 had one primary, two secondary, and fifty-six tertiary/exploratory efficacy endpoints. There were also multiple endpoints in each of the seven substudies. The primary endpoint was incidence of new morphometric vertebral fracture at month 36. The secondary endpoints were time to first nonvertebral fracture and time to first hip fracture. A fixed sequence testing procedure was employed for the primary and secondary endpoints in the order mentioned above (vertebral, nonvertebral, hip) for multiplicity adjustment to maintain the overall significance level at 0.05. There was no fixed testing procedure or multiplicity adjustment for the 56 tertiary and exploratory endpoints. Significance level for each analysis of these endpoints as well as that of the substudy endpoints

was 0.05. All statistical testing was 2-sided. Of the multiple tertiary endpoints, the Applicant seeks labeling for the clinical fracture results and bone mineral density results.

Lateral spine x-rays were performed at screening and months 12, 24 and 36 for all subjects. All lateral spine x-rays were assessed at a central reading facility using the Genant semi-quantitative scoring method. Quantitative morphometry was not performed. Nonvertebral fractures (osteoporotic) were those occurring on study excluding those of the vertebrae (cervical, thoracic, and lumbar), skull, facial bones, mandible, metacarpus, finger phalanges, and toe phalanges. Hip fracture included fractures of the femur neck, femur intertrochanter, and femur subtrochanter. All clinical fractures were to be reported as adverse events and were radiographically confirmed by the central reading facility.

The Applicant further classified nonvertebral fractures into the following categories which were assessed as tertiary endpoints:

- Major nonvertebral fractures: a subset of nonvertebral fractures comprising the pelvis, distal femur (i.e., femur excluding hip), proximal tibia (i.e., tibia excluding ankle), ribs, proximal humerus (i.e., humerus excluding elbow), forearm, and hip, excluding fractures associated with high trauma severity and pathologic fractures.
- Major osteoporotic fractures: clinical vertebral, hip, forearm, and humerus fractures not associated with a pathologic fracture, regardless of trauma severity.
- Any osteoporotic fracture included any new vertebral fractures or osteoporotic nonvertebral fractures, excluding fractures associated with high trauma severity and pathologic fractures.
- Clinical fracture: clinical vertebral and nonvertebral (osteoporotic) fractures

Bone density measurements at the lumbar spine, determined by dual x-ray absorptiometry (DXA), were obtained on all patients at baseline, and month 36. Bone density measurements at the hip were obtained at baseline and months 12, 24, and 36. In the DXA substudy, bone density measurements at the spine and hip were obtained at baseline and months 1, 6, 12, 24, and 36 as well as measurements of the distal radius and total body at baseline and months 12, 24, and 36. All DXA scans were evaluated by a central reading facility (b) (4)

Laboratory measurements of bone turnover markers included bone resorption markers serum c-telopeptides (CTX) and tartrate resistant acid phosphatase 5b (TRAP 5b); and the bone formation markers serum bone specific alkaline phosphatase (BSAP) and procollagen type I amino-terminal propeptide (PINP). Bone turnover markers were measured at baseline and months 6, 12, 18, 24, and 30 for subjects enrolled in the bone turnover marker substudy. All samples were evaluated by a specialized central laboratory (b) (4) except for serum CTX, which was evaluated by the Applicant.

Results:

Disposition. A total of 7868 subjects were enrolled into the study. Because of significant GCP violations at site 803 in Lithuania, the sixty subjects enrolled at this site were excluded from analysis. As outlined in the table below, 83% of the enrolled population completed the study.

Of the 1330 (17%) subjects who withdrew from the study, the most common reason for withdrawal was the withdrawal of consent by 723 (9%) subjects. Adverse events leading to withdrawal occurred in 174 (2%) subjects (81 in the placebo group and 93 in the denosumab group). There was comparable subject disposition between the treatment groups.

Trial 20030216: Disposition		
	Placebo	Denosumab
N, enrolled	3935	3933
N, site 803, excluded	29	31
N, randomized	3906	3902
Discontinued	700 (18)	630 (16)
Did not receive IP	23 (1)	23 (1)
Death	78 (2.0)	62 (1.6)
Adverse Event	81 (2.1)	93 (2.4)
Lost to follow-up	57 (1.5)	57 (1.5)
Withdrew consent	392 (10.1)	331 (8.5)
Protocol violation	11 (0.3)	10 (0.3)
Noncompliance	16 (0.4)	13 (0.3)
Other	42 (1.3)	41 (1.3)
N, completed	3208 (82)	3272 (84)
N, ITT	3883	3879
N, mITT	3691	3702
N, safety	3876	3886*
*including all patients who received at least one dose of denosumab regardless of assigned treatment group		
Source: compiled by reviewer based on 20030216 study report as well as statistical and clinical review documents		

Demographics. As outlined in the table below, baseline subject demographics were generally well balanced across the treatment groups. The average age of enrollees was approximately 72 years with an age range of 60 – 91 years. **Ninety-five percent of the enrolled population was** age 65 years or older and 32% were age 75 years or older. Subjects were not required to have a baseline fracture to qualify for study enrollment. Overall 24% of the enrolled population had at least one prevalent fracture at baseline and 44% had sustained a fracture after age 55 years. The mean lumbar spine BMD T-score was -2.8 standard deviations below the mean bone mass of young healthy adults. Use of bone mineral density alone is not able to predict the risk of fracture in all patients. It has long been recognized that other risk factors in combination with BMD offer a better fracture prediction tool. In 2008, the World Health Organization released **the FRAX™ fracture risk assessment tool.** The Applicant conducted an analysis of fracture risk using the FRAX algorithm. Overall, the 10-year probability of hip fracture was 7% and the 10-year probability of major osteoporotic fracture was 19% in the study population.

Trial 20030216: Patient Demographics		
	Placebo	Denosumab
N	3906	3902
Age (yrs, mean \pm SD)	72.3 \pm 5.2	72.3 \pm 5.2
Age range	60 – 91	60 – 90
Race, n (%)		
White	3629 (93)	3609 (93)
Asian/Japanese	12 (0.3)	16 (0.4)
Black	27 (0.7)	30 (0.8)
Hispanic	232 (6)	241 (6)
Other	6 (0.2)	6 (0.2)
Height (cm, mean)		
Weight (kg, mean)		
BMI (mean)	26 \pm 4.2	26 \pm 4.1
Baseline Vertebral Fx	915 (23)	929 (24)
Any fracture after age 55 years	1718 (44)	1711 (44)
Nonvertebral fracture after age 55 years	1177 (30)	1163 (30)
LS BMD T-score, baseline	-2.84 \pm 0.69	-2.82 \pm 0.70
FRAX, 10-year probability of hip fracture		
mean	7 \pm 7.7	7 \pm 7.9
range	0 - 89	0 - 78
FRAX, 10-year major OP fracture probability		
mean	19 \pm 10.6	19 \pm 10.6
range	3 - 90	3 - 90
Source: compiled by reviewer based on 20030216 study report as well as statistical and clinical review documents		

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

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

Trial 20030216: Subjects with At Least One New Morphometric Vertebral Fracture, mITT, LOCF		
	Placebo	Denosumab
N, mITT	3691	3702
Crude incidence, n (%)	264 (7.2)	86 (2.3)
Absolute Risk Reduction (95% CI)	4.8 (3.9 , 5.8)	
Relative Risk Reduction (95% CI)	68 (59 , 74)	
Odds Ratio (95% CI)	0.31 (0.24 , 0.39)	
p-value	<0.0001	
Source: compiled by reviewer based on 20030216 study report and statistical review		

Nonvertebral fracture. The time to the first nonvertebral fracture was a secondary endpoint. Nonvertebral fractures were defined as fractures excluding traumatic and pathologic fractures as well as fractures of the vertebrae, skull, face, mandible, metacarpus, fingers and toes. Fractures were required to be confirmed by radiologic exam or documented in a radiology report, surgical report or discharge summary. The analyses used the intent to treat population (all subjects that had received at least one dose of study drug) and cumulative incidence was summarized using the Kaplan-Meier estimates.

As outlined in the table below, over the three-year treatment period, 531 subjects (293 (7.5%) in the placebo group and 238 (6.1%) in the denosumab group) sustained a nonvertebral fracture. Based on Kaplan-Meier estimates, the three-year event rates for nonvertebral fracture were 8.0% in the placebo group and 6.5% in the denosumab group, with an absolute risk reduction of 1.5% (95% CI: 0.3, 2.7) and a hazard ratio of 0.80 (95% CI: 0.67 , 0.95, p=0.0106).

Trial 20030216: Subjects with Nonvertebral Fracture at Month 36, ITT		
	Placebo	Denosumab
N, ITT	3906	3902
Crude incidence, n (%)	293 (7.5)	238 (6.1)
Kaplan-Meier Estimate (%)	8.0	6.5
Absolute Risk Reduction (95% CI)	1.5 (0.3 , 2.7)	
Hazard Ratio (95% CI)	0.80 (0.67 , 0.95)	
p-value	0.0106	
Source: compiled by reviewer based on 20030216 study report and statistical review		

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

As outlined in the following table, over the three-year treatment period, 69 subjects (43 (1.1%) in the placebo group and 26 (0.7%) in the denosumab group) sustained a hip fracture. Based on Kaplan-Meier estimates, the three-year event rates for hip fracture were 1.2% in the placebo

group and 0.7% in the denosumab group, with an absolute risk reduction of 0.3% (95% CI: -0.1, 0.7) and a hazard ratio of 0.60 (95% CI: 0.37, 0.97, p=0.0362).

Trial 20030216: Subjects with Hip Fracture at Month 36, ITT		
	Placebo	Denosumab
N, ITT	3906	3902
Crude incidence, n (%)	43 (1.1)	26 (0.7)
Kaplan-Meier Estimate (%)	1.2	0.7
Absolute Risk Reduction (95% CI)	0.3 (-0.1 , 0.7)	
Hazard Ratio (95% CI)	0.60 (0.37 , 0.97)	
p-value	0.0362	
Source: compiled by reviewer based on 20030216 study report and statistical review		

Primary and Secondary Fracture Endpoints in the High Risk Group. The Applicant also conducted an evaluation of the primary and secondary endpoints based on baseline fracture risk. Subjects were considered at high risk of fracture if they met two of the following criteria: age > 70 years, prevalent vertebral fracture at baseline, and baseline BMD T-score of ≤ -3.0 at the lumbar spine, total hip or femoral neck. Subjects who did not meet these criteria were considered at increased risk of fracture. Approximately 45% of the enrolled population met the criteria for being considered at high risk of fracture. Based on these criteria, the incidence of new vertebral fractures in the placebo group was 10.0%, compared to 7.2% of all placebo-treated subjects. This increased incidence of fracture in the placebo group demonstrated the validity of the approach, according to the Applicant. As outlined in the table below, in subjects at high risk of fracture, the absolute risk reduction of morphometric vertebral fractures was 4.8% with a relative risk reduction of 65% (p < 0.0001).

Trial 20030216: Subjects with At Least One New Morphometric Vertebral Fracture, Stratified Based on Baseline Fracture Risk, mITT, LOCF		
	Placebo	Denosumab
N, enrolled	3906	3902
Overall population, N mITT	3691	3702
Crude incidence, n (%)	264 (7.2)	86 (2.3)
Absolute Risk Reduction (95% CI)	4.8 (3.9 , 5.8)	
Odds Ratio (95% CI)	0.31 (0.24 , 0.39)	
p-value	<0.0001	
High risk population, N mITT	1633	1661
Crude incidence, n (%)	163 (10.0)	58 (3.5)
Absolute Risk Reduction (95% CI)	6.5 (4.8 , 8.2)	
Odds Ratio (95% CI)	0.33 (0.24 , 0.44)	
p-value	<0.0001	
Increased risk population, N mITT	1999	1986
Crude incidence, n (%)	96 (4.8)	28 (1.4)
Absolute Risk Reduction (95% CI)	3.4 (2.3 , 4.5)	
Odds Ratio (95% CI)	0.28 (0.19 , 0.43)	
p-value	<0.0001	
Source: compiled by reviewer based on table 14-4.3.11, 20030216 study report		

With regard to the secondary fracture endpoints, results are shown in the table below. Denosumab therapy continued to demonstrate fracture risk reduction in all groups. However, because of the decrease in sample size in each subgroup, the results were not as significant as those seen in the overall population.

Trial 20030216: Primary Efficacy Outcomes, Stratified Based on Baseline Fracture Risk, LOCF		
	Placebo	Denosumab
N, enrolled	3906	3902
Nonvertebral Fracture		
Overall population, N mITT	3906	3902
Crude incidence, n (%)	293 (7.5)	238 (6.1)
Kaplan-Meier Estimate (%)	8.0	6.5
Hazard Ratio (95% CI)	0.80 (0.67 , 0.95)	
p-value	0.0106	
High risk population, N mITT	1752	1761
Crude incidence, n (%)	150 (8.6)	136 (7.7)
Kaplan-Meier Estimate (%)	9.3	8.3
Hazard Ratio (95% CI)	0.88 (0.70 , 1.11)	
p-value	0.2901	
Increased risk population, N mITT	2086	2080
Crude incidence, n (%)	142 (6.8)	98 (4.7)
Kaplan-Meier Estimate (%)	7.1	5.0
Hazard Ratio (95% CI)	0.68 (0.53 , 0.89)	
p-value	0.0037	
Hip Fracture		
Overall population, N mITT	3906	3902
Crude incidence, n (%)	43 (1.1)	26 (0.7)
Kaplan-Meier Estimate (%)	1.2	0.7
Hazard Ratio (95% CI)	0.60 (0.37 , 0.97)	
p-value	0.0362	
High risk population, N mITT	1752	1761
Crude incidence, n (%)	34 (1.9)	18 (1.0)
Kaplan-Meier Estimate (%)	2.1	1.1
Hazard Ratio (95% CI)	0.52 (0.29 , 0.91)	
p-value	0.0208	
Increased risk population, N mITT	1999	1986
Crude incidence, n (%)	96 (4.8)	28 (1.4)
Kaplan-Meier Estimate (%)		
Hazard Ratio (95% CI)	0.28 (0.19 , 0.43)	
p-value	0.4478	
Source: compiled by reviewer based on tables 14-4.14.10 and 14-4.17.1, 20030216 study report		

Other Tertiary Fracture Endpoints: Of the 56 tertiary endpoints, the Applicant seeks to include the following tertiary fracture endpoints in the full prescribing information: incidence of vertebral fractures 0 – 1 years, incidence of vertebral fractures 0 – 2 years, incidence of clinical fracture, incidence of major osteoporotic fracture, and incidence of clinical vertebral fracture. No fixed testing procedure or multiplicity adjustments were defined for the tertiary

endpoints. The significance level for each analysis was 0.05. It should be noted that tertiary endpoints have not been allowed in the full prescribing information with other osteoporosis drugs. For the vertebral fracture endpoints at years 1 and 2, the primary analysis included all subjects who received study drug and had at least one follow-up spinal radiograph and used an ANCOVA model with LOCF imputation. For the other vertebral endpoints, the analyses used the intent to treat population (all subjects that had received at least one dose of study drug) and cumulative incidence was summarized using Kaplan-Meier estimates.

The results of these tertiary endpoints are outlined in the following table. For vertebral fractures occurring in the first year of the trial, the crude incidence was 2.2% in the placebo group and 0.9% in the denosumab group with an absolute risk reduction of 1.4%. For vertebral fractures occurring during the first two years of the trial, the crude incidence was 5.0% in the placebo group and 1.4% in the denosumab group with an absolute risk reduction of 3.5%. Clinical fractures included vertebral fractures were those associated with signs or symptoms (or both) and nonvertebral osteoporotic fractures. The incidence of clinical fractures based on Kaplan-Meier estimates was 10.2% in the placebo group and 7.2% in the denosumab group with an absolute risk reduction of 2.9% (p value < 0.0001). Major osteoporotic fractures comprised clinical vertebral, hip, forearm, and humerus fractures not associated with a pathologic fracture, regardless of trauma severity. The incidence of major osteoporotic fractures based on Kaplan-Meier estimates was 8.0% in the placebo group and 5.3% in the denosumab group with an absolute risk reduction of 2.7% (p value < 0.0001). Clinical vertebral fractures were symptomatic fractures of the vertebrae. The incidence of clinical vertebral fractures based on Kaplan-Meier estimates was 2.6% in the placebo group and 0.8% in the denosumab group with an absolute risk reduction of 1.8% (p value < 0.0001).

Trial 20030216: Tertiary Fracture Endpoints		
	Placebo	Denosumab
N, Vertebral fracture through Year 1 (mITT)	3691	3702
Crude Incidence, n (%)	82 (2.2)	32 (0.9)
Absolute Risk Reduction (95% CI)	1.4 (0.8 , 0.38)	
Relative Risk Reduction (95% CI)	61 (42 , 74)	
Odds Ratio (95% CI)	0.38 (0.25 , 0.58)	
p-value	<0.0001	
N, Vertebral fracture through Year 2 (mITT)	3691	3702
Crude Incidence, n (%)	183(5.0)	53 (1.4)
Absolute Risk Reduction (95% CI)	3.5 (2.7 , 4.3)	
Relative Risk Reduction (95% CI)	71 (61 , 79)	
Odds Ratio (95% CI)	0.28 (0.20 , 0.38)	
p-value	<0.0001	
N, Clinical fracture through Year 3 (ITT)*	3906	3902
Crude Incidence, n (%)	373 (9.5)	265 (6.8)
Kaplan-Meier Estimate (%)	10.2	7.2
Absolute Risk Reduction (95% CI)	2.9 (1.6 , 4.2)	
Hazard Ratio (95% CI)	0.70 (0.59 , 0.81)	
p-value	<0.0001	
N, Major Osteoporotic fracture through Year 3 (ITT)*	3906	3902
Crude Incidence, n (%)	294 (7.5)	196 (5.0)
Kaplan-Meier Estimate (%)	8.0	5.3
Absolute Risk Reduction (95% CI)	2.7 (1.6 , 3.9)	
Hazard Ratio (95% CI)	0.65 (0.55 , 0.78)	
p-value	<0.0001	
N, Clinical vertebral fracture through Year 3 (ITT)*	3906	3902
Crude Incidence, n (%)	92 (2.4)	29 (0.7)
Kaplan-Meier Estimate (%)	2.6	0.8
Absolute Risk Reduction (95% CI)	1.8 (1.2 , 2.4)	
Hazard Ratio (95% CI)	0.31 (0.20 , 0.47)	
p-value	<0.0001	
*absolute risk reduction unadjusted for age		
Source: compiled by reviewer based on 20030216 study report and statistical review		

Year to year evaluation of Fractures: As outlined in Dr. Castillo's review, pages 11-12, the 95% confidence interval for the absolute risk reduction at 36 months for hip fracture included zero, so further investigation of hip fracture data at yearly intervals was done. The hip fracture data was descriptively presented as the number and percentage of hip fractures within each 1-year time interval for year 1, year 2, and year 3. The table below outlines the results. The percentage of hip fractures is greater in the placebo group compared to the denosumab group within the year 1 and year 2 time intervals. However, in the year 3 time interval, the percentage of hip fractures in the denosumab group (0.34%) is greater than the percentage for the placebo group (0.26%). The percentage of hip fractures within year 3 is nearly a threefold increase compared to within year 2. The fluctuation in the percentage of hip fractures in the denosumab group appears to be counterintuitive since one would expect the percentage to either decrease or remain the same with an osteoporosis treatment, which is usually what has been observed with other therapies. Also, the percentage within year 3 is greater in the

denosumab group compared to the placebo group, suggesting that the percentage of hip fractures in the denosumab group has caught up with that in the placebo group.

Study 20030216: Number and Percentage of Hip Fractures within Each 1-Year Time Interval

	Year 1		Year 2		Year 3	
	Number of subjects at beginning of interval	Number of fractures in interval (%)	Number of subjects at beginning of interval	Number of fractures in interval (%)	Number of subjects at beginning of interval	Number of fractures in interval (%)
Denosumab	3902	10 (0.26)	3676	4 (0.12)	3477	12 (0.34)
Placebo	3906	20 (0.51)	3672	14 (0.38)	3430	9 (0.26)

Source: Statistical Review, table 3.7.

Because of the findings noted for hip fracture, similar analyses were conducted for new vertebral and nonvertebral fractures. The table below presents the results for new vertebral fractures. The percentage of new vertebral fractures is greater in the placebo group compared to the denosumab group within all 1-year time intervals. The percentage of new vertebral fractures within year 3 is nearly a threefold increase compared to within year 2. Similar to the findings with hip fracture, the fluctuation in the percentage of new vertebral fractures in the denosumab group appears to be counterintuitive since one would expect the percentage to either decrease or remain the same with an osteoporosis treatment. Trends for nonvertebral fractures were consistent throughout the years.

Study 20030216: Number and Percentage of New Vertebral Fractures within Each 1-Year Time Interval

	Year 1		Year 2		Year 3	
	Number of subjects at beginning of interval	Number of fractures in interval (%)	Number of subjects at beginning of interval	Number of fractures in interval (%)	Number of subjects at beginning of interval	Number of fractures in interval (%)
Denosumab	3902	23 (0.59)	3551	17 (0.48)	3323	46 (1.38)
Placebo	3906	49 (1.25)	3503	89 (2.54)	3175	126 (3.97)

Source: Statistical Review, table 3.8

Bone Mineral Density: Change in bone mineral density of the lumbar spine was evaluated in the entire study population at screening and months 24 and 36. Changes in bone mineral density of the hip were evaluated at screening, months 12, 24 and 36. Changes in bone mineral density were tertiary endpoints. Similar to the tertiary endpoints discussed above, no fixed testing procedure or multiplicity adjustments were defined for the BMD endpoints. The significance level for each analysis was 0.05. The primary analysis included all subjects who received study drug and had at least one follow-up DXA scan and used an ANCOVA model with LOCF imputation

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

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

Biochemical Markers of Bone Turnover: Biochemical markers of bone turnover were evaluated in the bone marker substudy which enrolled 160 subjects, as well as in all subjects in the pharmacokinetic substudy and the bone biopsy substudy. The endpoints in the bone marker substudy include change in the bone resorption markers serum C-telopeptide of type 1 collagen (CTX) and tartrate resistant acid phosphatase 5b (TRAP 5b) levels at hour 6-8, day 1 and months 1, 6, 12, 24, and 36; and change in the bone formation markers bone specific alkaline phosphatase (BSAP) and procollagen type 1 N-terminal peptide (P1NP) levels at months 1, 6, 12, 24, and 36. Similar to the tertiary endpoints, no fixed testing procedure or multiplicity adjustments were defined for the bone marker substudy endpoints. The significance level for each analysis was 0.05.

As outlined in the clinical review pages 55 – 59, **treatment with denosumab resulted in robust suppression of the markers of bone resorption CTX and TRAP5b. The nadir of bone resorption markers appears to occur 1 – 3 months after administration of the denosumab dose.** During the clinical reviewer analyses of bone turnover markers, it was noted that many subjects who had CTX determinations were reported to have levels of CTX below the level of quantitation for the assay used. This is an unusual finding that has not been noted previously with other antiresorptive agents. When data from the bone biomarkers substudy and the PK substudy **were used, 39 – 68% of subjects have serum CTX levels suppressed to the point that they are undetectable by the laboratory assay used (see table below).** Because of these findings, it is not clear how much suppression of CTX levels occurs following denosumab dosing. As outlined in the primary clinical review, an analysis was performed setting the undetectable CTX levels

to the lower level of quantitation (which is how the Applicant handled these findings), set to ½ the lower level of quantitation, and set to zero. For this, the best we can say about the suppression of CTX levels is that 1 month following denosumab dosing, CTX levels are suppressed at least 87%, but may be suppressed as much as 94%. This level of CTX suppression has not been noted with any other antiresorptive agent and the long-term clinical consequences of this degree of suppression is not clear. It is reassuring that the level of suppression trends back upwards at the end of the dosing cycle.

Trial 20030216: Number of Subjects with serum CTX level below level of quantitation										
Month	1	6	12	15	18	21	24	30	33	36
Placebo										
N	437	435	434	368	311	353	413	335	328	396
n	0	0	1	0	0	3	3	0	0	5
(%)	(0)	(0)	(0.2)	(0)	(0)	(0.8)	(0.7)	(0)	(0)	(1.3)
Denosumab										
N	504	501	494	412	358	394	476	388	367	454
n	293	46	32	161	32	266	43	15	180	38
(%)	(58)	(9)	(6)	(39)	(9)	(68)	(9)	(4)	(48)	(8)
Source: reviewer's analysis, albnsp dataset, bone marker and PK substudies										

Bone formation is tightly coupled to bone resorption due to intercellular communication between osteoblasts (formation) and osteoclasts (resorption). After treatment with denosumab, bone formation indices are also suppressed, but lag behind the bone resorption indices discussed above (see Figure 8, page 58 of the primary clinical review). Similar to results seen with serum CTX, up to 36% of subjects treated with denosumab had serum P1NP levels suppressed to below the level of quantitation for the assay method used (see table below). This level of P1NP suppression has not been noted with any other antiresorptive agent and the long-term clinical consequences of this degree of suppression is not clear.

Trial 20030216: Number of Subjects with serum P1NP level below level of quantitation										
Month	1	6	12	15	18	21	24	30	33	36
Placebo										
N	438	405	432	368	311	354	408	335	328	375
n	6	1	2	1	1	1	0	0	2	0
(%)	(1.4)	(0.2)	(0.4)	(0.3)	(0.3)	(0.3)	(0)	(0)	(0.4)	(0)
Denosumab										
N	502	482	492	412	358	394	471	388	367	438
n	5	91	63	101	29	121	46	72	131	50
(%)	(0.9)	(19)	(12)	(24)	(8)	(31)	(9)	(18)	(36)	(12)
Source: reviewer's analysis, albnsp dataset, bone marker and PK substudies										

7.2.2 Prevention of Osteoporosis in Postmenopausal Women

The Applicant has submitted one key efficacy trial, 20040132, to support approval of denosumab in the indication of prevention of postmenopausal osteoporosis. Trial 20040132 is a randomized, double-blind, placebo- and active-controlled, 4-year, 2-period study trial evaluating the safety and efficacy of denosumab use in the prevention of postmenopausal osteoporosis population. The first 24 months of the study is **considered the “on-treatment” period**, where all subjects received study drug. **The second 24 months of the study is the “off-treatment” period, where subjects were followed off of study drug.** Subjects were randomized to receive either placebo or denosumab 60 mg SC every six months. The primary endpoint of the study was the percent change from baseline in lumbar spine BMD at month 24. This trial is ongoing and this review focuses on the data to month 24, and also to month 36 for discussion of the effect after discontinuation of therapy.

Study population: Subjects enrolled in this trial study were not more than 90 years old, with low bone mass, defined as a lumbar spine bone mineral density T-score of -1.0 to -2.5. Patients with a history of fracture after age 25 years were excluded from enrollment. Women with a history of metabolic bone disease, hypocalcemia, active parathyroid disease, hyperthyroidism, vitamin D deficiency (< 12 ng/mL), malabsorption, or rheumatoid arthritis were excluded from the study. Subjects previously on iv bisphosphonate, fluoride or strontium therapy were excluded from the study. Subjects previously on oral bisphosphonate therapy for less than 3 months could be enrolled in the study. If the cumulative exposure was more than 3 months but less than 3 years, subjects could be enrolled only after a wash-out period of one year. For subjects on other osteoporosis therapies, subjects could be enrolled after a 6 week wash-out period. Subjects were stratified based on years since menopause (≤ 5 years, > 5 years).

Study treatments: Eligible subjects were randomized 1:1 to receive denosumab 60 mg or placebo subcutaneous injection, administered by a healthcare professional, every 6 months (day 1 and months 6, 12, and 18). No dosing adjustments were permitted. All subjects were to receive daily calcium > 1000 mg daily. **Subjects also received vitamin D (400 – 800 IU) supplementation based on their baseline 25 hydroxyvitamin D level (12 – 20 ng/ml – 800 IU, > 20 ng/mL – 400 IU).** The calcium and vitamin D supplements were not provided by the Applicant, they were to be provided by the investigator. The Applicant did reimburse the clinical sites for the cost of the supplements.

Efficacy measures: Trial 20040132 had one primary, eight secondary, and ninety exploratory efficacy endpoints. The primary endpoint of the study was the percent change from baseline in lumbar spine BMD (as determined by DXA) at month 24. The secondary endpoints were the percent change from baseline in total hip, femoral neck, trochanter, distal radius and total body BMD (as determined by DXA) at month 24; and percent change from baseline of trabecular volumetric BMD, cortical volumetric BMD and total volume (as determined by quantitative computed tomography [QCT]) of the distal radius. The overall significance level for the primary and secondary endpoints was 0.05 by using a Bonferroni adjustment equally between the strata (0.025 for each stratum). The approach for handling multiplicity for the primary and secondary endpoints within each time-since-menopause stratum included a hierarchical testing

strategy (significance was required for the primary endpoint to test the secondary endpoints) **and Hochberg's procedure for multiplicity** (all secondary endpoints were tested simultaneously with multiplicity adjustments to maintain the overall significance level at 0.025 in each stratum). Of the eight secondary endpoints, the Applicant seeks labeling for (b) (4),

(b) (4)

Results:

Disposition. A total of 332 subjects were enrolled into the study. As outlined in the table below, 85% of the enrolled population completed the study. Of the 46 (14%) subjects who withdrew from the study, the most common reason for withdrawal was the withdrawal of consent by 25 (8%) subjects. There was comparable subject disposition between the treatment groups.

Trial 20040132: Disposition		
	Placebo	Denosumab
N, enrolled	166	166
Discontinued	22 (13)	24 (14)
Did not receive IP	1	2
Adverse Event	2	1
Lost to follow-up	5	7
Withdrew consent	15	10
Protocol violation	0	0
Noncompliance	0	2
Other	0	4
N, completed month 24	144 (87)	142 (86)
N, safety	165	164
*including all patients who received at least one dose of denosumab regardless of assigned treatment group		
Source: compiled by reviewer based on 20040132 study report as well as statistical and clinical review documents		

Demographics. As outlined in the following table, baseline subject demographics were generally well balanced across the treatment groups. The average age of enrollees was 59 **years with an age range of 43 – 83 years.** Twenty-two percent of the enrolled population was age 65 years or older and 5% were age 75 years or older. Subjects were excluded from enrollment if they had sustained a fracture, however, one subjects in the denosumab group did have a vertebral fracture at baseline. The mean time since menopause was 3.6 years in the ≤ 5 years stratum, 16 years in the > 5 years stratum, and 9.4 years overall. The mean lumbar spine BMD T-score was -1.6 standard deviations below the mean bone mass of young healthy adults.

Trial 20040132: Patient Demographics		
	Placebo	Denosumab
N	166	166
Age (yrs, mean \pm SD)	58.9 \pm 7.5	59.8 \pm 7.4
Age range	43 – 83	46 – 83
Race, n (%)		
White	137 (83)	137 (83)
Asian/Japanese	8 (5)	9 (5)
Black	6 (4)	8 (5)
Hispanic	13 (8)	10 (6)
Other	2 (1)	2 (1)
BMI (mean)	26 \pm 4.8	27 \pm 4.8
Time since menopause (yrs, mean \pm SD)	9.4 \pm 8.4	10.5 \pm 9.3
LS BMD T-score, baseline	-1.66 \pm 0.44	-1.55 \pm 0.41
Source: compiled by reviewer based on 20040132 study report as well as statistical and clinical review documents		

Bone Mineral Density, Primary Endpoint. Change in bone mineral density of the lumbar spine at month 24 was the primary endpoint of the study. As outlined in the table below, treatment with denosumab significantly increased bone mineral density of the lumbar spine compared to placebo. Results were consistent across the strata as well as within the subgroups tested (baseline weight and baseline BMI).

Trial 20040132: Percent Change in Lumbar Spine BMD at Month 24, mITT, LOCF		
	Placebo	Denosumab
Overall population	163	163
LS mean percent change	-0.6	6.5
LS mean difference (95% CI)	7.0 (6.2 , 7.8)	
p-value	<0.0001	
≤ 5 years post menopause	80	79
LS mean percent change	-1.2	6.2
LS mean difference (95% CI)	7.4 (6.1 , 8.7)	
p-value	<0.0001	
> 5 years post menopause	83	84
LS mean percent change	0.1	6.8
LS mean difference (95% CI)	6.7 (5.4 , 8.0)	
p-value	<0.0001	
Source: compiled by reviewer based on 20040132 study report as well as statistical and clinical review documents		

Bone Mineral Density, Secondary Endpoints. Change in bone mineral density of the total hip, femoral neck, trochanter, distal radius and whole body at month 24 were secondary endpoints of the study. As outlined in the table below, treatment with denosumab significantly increased bone mineral density at all of the secondary BMD endpoints compared to placebo at month 24. Trabecular bone tends to be more metabolically active than cortical bone with regard to bone turnover. The results in the table below show that sites with more trabecular bone, such as the

trochanter, had greater increases in BMD than sites that are predominantly cortical, such as the radius.

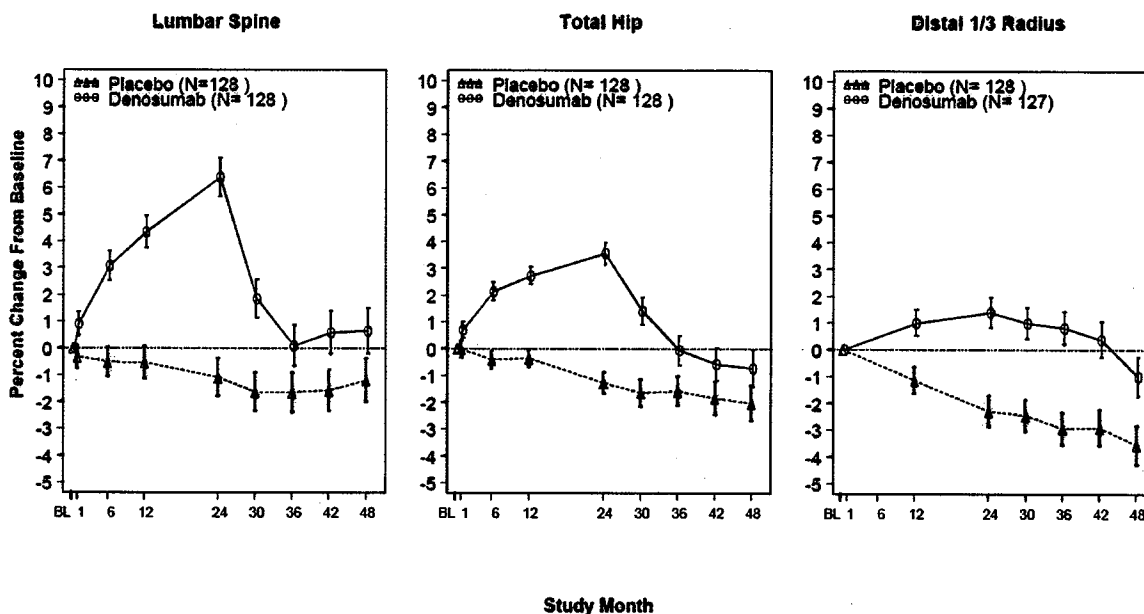
Trial 20040132: Percent Change in BMD at Month 24, mITT, LOCF		
	Placebo	Denosumab
Total Hip, n (mITT)	163	163
LS mean percent change	-1.1	3.4
LS mean difference (95% CI)	4.5 (4.0 , 5.0)	
p-value	<0.0001	
Femoral Neck, n (mITT)	163	163
LS mean percent change	-0.9	2.8
LS mean difference (95% CI)	3.7 (2.9 , 4.4)	
p-value	<0.0001	
Trochanter, n (mITT)	163	163
LS mean percent change	-0.9	5.2
LS mean difference (95% CI)	6.0 (5.3 , 6.6)	
p-value	<0.0001	
Distal 1/3 radius, n (mITT)	156	156
LS mean percent change	-2.1	1.4
LS mean difference (95% CI)	3.5 (2.8 , 4.3)	
p-value	<0.0001	
Whole Body, n (mITT)	154	156
LS mean percent change	-1.4	2.4
LS mean difference (95% CI)	3.8 (3.1 , 4.5)	
p-value	<0.0001	
Source: compiled by reviewer based on 20040132 study report as well as statistical and clinical review documents		

For all of the other secondary and exploratory endpoints, results were consistent with those discussed above.

Fracture: In this study clinical fractures were reported as adverse events. Lateral spine x-rays were evaluated by the central imaging vendor at screening, month 24, and also planned at month 48. New morphometric vertebral fractures were reported in one placebo subject and no denosumab subjects. Clinical fractures were reported in seven (4%) placebo-treated subjects and 2 (1%) denosumab treated subjects.

Trial 20040132 was designed to evaluate the changes in bone mineral density and bone turnover markers in the off-treatment period (months 24-48). As outlined in the primary clinical review pages 70-72 (Figure 10 reproduced below), the bone mineral density gains achieved with denosumab therapy were rapidly lost in the first year after treatment was discontinued.

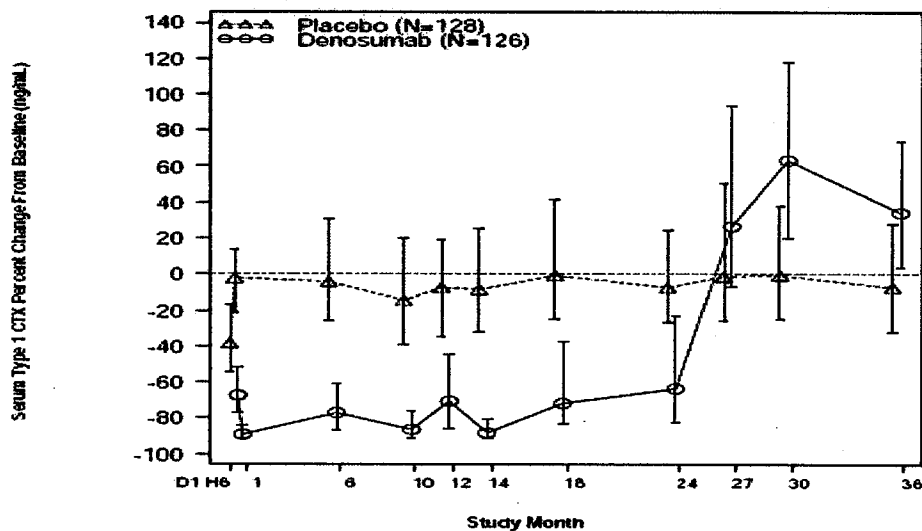
Bone Mineral Density by DXA Percent Change From Baseline by Visit, Least Squares Means and 95% CIs From Repeated Measures Model



Source: Applicant provided figure 6-1, page 148, 120 day safety update. Includes subjects who enrolled in the off-treatment phase with values at baseline and at ≥ 1 postbaseline visit.

As outlined in the figure below, the bone resorption marker, serum CTX also increased in the off-treatment period, to levels well above baseline.

Serum Type 1 CTX Percent Change From Baseline by Visit Median and Interquartile Ranges



Source: Clinical study report 20040132-36 month, figure 7.7 page 92

The results seen with the bone turnover markers suggest that a patient might rebound and develop a high bone turnover state, which is an independent risk factor for fracture. As outlined in the adverse event reports, there was an increase in fractures among subjects treated with denosumab in the first year off therapy. Excluding fractures of the phalanges, a total of eight subjects (three in the placebo group and four in the denosumab group) fractured from month 24 to 36.

7.3 Other efficacy studies

The Applicant has also submitted multiple smaller studies in support of denosumab's efficacy for increasing bone mineral density. These have been reviewed by the primary clinical review team and data are discussed where pertinent.

7.4 Discussion of primary reviewers' comments and conclusions

I agree with Drs. Popat, Rothstein and Castillo's conclusions that denosumab is effective in reducing the incidence of morphometric vertebral, nonvertebral and hip fractures in postmenopausal osteoporotic women. On page 48 of the clinical review, the reviewer states that the findings are not only statistically significant, but also clinically meaningful. It is not clear what constitutes a clinically meaningful result as that would require that a threshold other than statistical significance be set.

In the osteoporosis treatment population, denosumab 60 mg q 6 months is effective in decreasing the incidence of new morphometric vertebral fractures (absolute reduction 4.8%, relative reduction 68%, p-value <0.0001), nonvertebral fractures (absolute reduction 1.5%, relative reduction 20%, p-value 0.0106), and hip fractures (absolute reduction 0.3%, relative reduction 40%, p-value 0.0362). These are the primary and secondary endpoints that should be included in the full prescribing information. When evaluated in a subgroup at high risk of fracture (subjects meeting two of the following three criteria: age > 70 years, prevalent vertebral fracture at baseline, and baseline BMD T-score of ≤ -3.0 at the lumbar spine, total **hip or femoral neck**), denosumab's effectiveness in the primary endpoint, morphometric vertebral fracture, was maintained (absolute reduction 6.5%, relative reduction 67%, p-value <0.0001). In this same population, the effectiveness of denosumab in reduction of nonvertebral fracture was no longer significant (hazard ratio 0.88, p-value 0.2901), although reduction in hip fracture did remain significant (hazard ratio 0.52, p-value 0.0208).

In the osteoporosis prevention population, denosumab 60 mg q 6 months is effective in increasing bone mineral density at all sites evaluated and in all subgroups evaluated. The treatment difference at 24 months was 7.0% at the lumbar spine, 4.5% at the total hip, and 3.7% at the femoral neck (all p-values <0.0001).

7.5 Discussion of notable efficacy issues.

The degree of suppression of bone turnover, both bone resorption and bone formation, and the increase in the number of hip fractures that occurred from in the third year of the fracture trial when compared to year one and two are of concern. In general, the pattern of fracture reduction efficacy tends to be stable from year to year. It is not clear if these findings represent the start of loss of fracture efficacy with long term use. One could postulate a loss of fracture efficacy because of the degree of suppression of bone turnover. Over-suppression of bone **turnover can impair the body's ability** to repair bone micro-cracks, thus potentially allowing them to propagate to the point where biomechanical instability will lead to fracture.

Further long-term data are necessary to assess **denosumab's continued fracture efficacy**.

With regard to product labeling, the Applicant seeks to include the following tertiary fracture endpoints in the full prescribing information: **incidence of vertebral fractures 0 – 1 years, incidence of vertebral fractures 0 – 2 years, incidence of clinical fracture, incidence of major osteoporotic fracture, and incidence of clinical vertebral fracture**. No fixed testing procedure or multiplicity adjustments were defined for the tertiary endpoints. While these endpoints are included in some of the other osteoporosis product labels, in those cases, the endpoints were secondary endpoints with adequate statistical adjustments to allow their inclusion. In the case of denosumab, no such statistical plans were made and for that reason, I believe it is important only to include the primary and secondary endpoints in the full prescribing information. Bone mineral density results were also tertiary endpoints in the fracture study. However, the BMD data essentially provides the basis for approval for all of the other proposed indications and therefore, even though the data were tertiary endpoints, it would be acceptable to include this information in order to provide a reference for the BMD data for the other indications.

8. Safety

8.1 General safety considerations

The safety database for this application is primarily generated by the large three-year fracture trial in postmenopausal women. While the baseline bone disease characteristics are similar between the postmenopausal women and the populations enrolled in the bone loss due to hormone ablation trials, the underlying disease characteristics (cancer) may significantly impact the safety analysis. For this reason, this safety review primarily focuses on the postmenopausal osteoporosis population. The safety database for postmenopausal osteoporosis does provide exposures to meet ICH guidelines for chronic therapy.

8.2 Safety findings from submitted clinical trials – general discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.

The safety database for trial 20030216 includes 7762 subjects (3876 placebo, 3886 denosumab) who received at least one dose of study medication. Overall, 76% of the placebo group and 80% of the denosumab group received all six doses of study medication. The safety database for trial 20040132 includes 329 subjects (165 placebo, 164 denosumab) who received at least one dose of study medication. Overall, 85% of both treatment groups received all four doses of study medication.

Summary of Safety Events: As noted in the table below, the comparable adverse event rates between the placebo and denosumab treatment groups were balanced except for serious adverse events which occurred more frequently in trial 20040132 (the prevention of PMO trial that enrolled younger postmenopausal women).

Denosumab PMO Trials: Summary of Safety Events						
	20030216		20040132		All	
	placebo	denosumab	placebo	denosumab	placebo	denosumab
N, enrolled	3906	3902	166	166	4072	4068
N, safety*	3876	3886	165	164	4041	4050
Discontinued	700 (18)	630 (16)	22 (13)	24 (14)	722 (18)	654 (16)
N, completed	3208 (82)	3272 (84)	144 (87)	142 (86)	3350 (82)	3414 (84)
Death	90 (2.3)	70 (1.8)	0 (0)	0 (0)	90 (2.2)	70 (1.7)
Serious Adverse Event	972 (25.1)	1004 (25.8)	9 (5.5)	18 (11.0)	981 (24.2)	1022 (25.2)
Withdrawal due to AE	81 (2.1)	93 (2.4)	2 (1.2)	1 (0.6)	83 (2.1)	94 (2.3)
Study Drug Permanently Discontinued due to AE	202 (5.2)	192 (4.9)	6 (3.6)	5 (3.0)	208 (5.1)	197 (4.9)
Adverse Event	3607 (93.1)	3605 (92.8)	157 (95.2)	156 (95.1)	3764 (93.1)	3761 (92.9)
*including all patients who received at least one dose of denosumab regardless of assigned treatment group						
Source: compiled by reviewer based on 20030216 study report as well as statistical and clinical review documents						

Deaths: In trial 20030216, 160 subjects (90 in the placebo group a 70 in the denosumab group) died during the study. No subjects died in the PMO prevention trial 20040132. All deaths in trial 20030216 were adjudicated by an independent cardiovascular adjudication committee to determine whether the deaths were caused by a cardiovascular event. As outlined in primary clinical review Table 27, page 85 the system organ class (SOC) classification of deaths was balanced between the two treatment groups. The most common SOC for cause of death were neoplasms, cardiac disorders, general disorders and nervous system disorders, which is expected for the general population of the age of the enrolled population.

It should also be noted that there were four deaths reported in the phase 2 dose-finding trial 20010223. As discussed on page 84 of the primary clinical review, all subjects received

denosumab and three of these subjects died of malignancy (brain tumor in one subject and adenocarcinoma in the other three subjects).

Serious Adverse Events: In trial 20030216, nonfatal serious adverse events occurred in 1792 subjects (868 (22%) in the placebo group and 924 (24%) in the denosumab group). In trial 20040132 (treatment phase to 24 months), nonfatal serious adverse events occurred in 27 subjects (9 (5.5%) in the placebo group and 17 (11%) in the denosumab group). As outlined in the primary clinical review page 88, table 31, the most common SAEs in denosumab treated subjects were infection, pathogen unspecified (112 (2.8%) placebo, 134 (3.3%) denosumab), and coronary artery disorders (69 (1.7%) placebo, 98 (2.4%) denosumab). Bone and joint injuries which included fracture and joint disorders were more common in the placebo group (108 (2.7%) placebo, 99 (2.4%) denosumab). The differences in SAEs between treatment groups are small, but some of these imbalances may be important.

Adverse Events Leading to Study Withdrawal: In trial 20030216, 174 subjects (81 (2%) placebo, 93 (2%) denosumab) discontinued the trial due to an adverse event. In trial 20040132 (treatment phase to 24 months), three subjects (2 (1%) in the placebo group and 1 (3%) in the denosumab group) withdrew from the study due to adverse events. Most events occurred in the SOC Neoplasms (27 (0.7%) placebo, 35 (1%) denosumab), Nervous System Disorders (13 (0.3%) placebo, 17 (0.4%) denosumab) and Musculoskeletal Disorders (15 (0.4%) placebo, 11 (0.3%) denosumab). The most commonly reported AEs leading to discontinuation were breast cancer (2 (0.1%) placebo, 11 (0.3%) denosumab), back pain (9 (0.2%) placebo, 4 (0.1%) denosumab) and constipation (4 (0.1%) placebo, 4 (0.1%) denosumab).

Adverse Events Leading to Discontinuation of Study Drug (Investigational Product): Subjects had the option of discontinuing study drug and remaining in the study for collect further data. In trial 20030216, 394 subjects (202 (5%) in the placebo group and 192 (5%) in the denosumab group) discontinued study drug. In trial 20040132 (treatment phase to 24 months), 6 subjects (5 (4%) in the placebo group and 5 (3%) in the denosumab group) discontinued study drug. The most common reason for study drug discontinuation was cancer in the denosumab group (19 (0.5%) placebo, 40 (1%) denosumab) and fracture in the placebo group (20 (0.5%) placebo, 6 (0.2%) denosumab). Breast cancer was the most common malignancy reported followed by colon cancer, gastric cancer, ovarian cancer and pancreatic cancer.

Adverse Events: In trial 20030216, 93% of the enrolled population reported at least one adverse event during the trial. The most commonly reported adverse events system organ classes were musculoskeletal and connective tissue disorders, infections and infestations, and gastrointestinal disorders (page 199, table 90 of the primary review). As outlined in the primary clinical review, the most commonly reported adverse events (>10% in either treatment group) were: back pain, arthralgia, dizziness, hypertension, nasopharyngitis, pain in extremity, and osteoarthritis.

In trial 20040132 (treatment phase to 24 months), the most commonly reported adverse events (>10% in either treatment group) were: arthralgia, nasopharyngitis, back pain, headache, pain in extremity, upper respiratory tract infection, constipation, urinary tract infection, shoulder pain, influenza and sinusitis.

Adverse Events of Special Interest. The following adverse events of interest have been identified by either the Applicant or the review team.

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

The Quantitative Safety and Pharmacoepidemiology Group (QSPG) group performed hypocalcemia adverse event analyses by MedDRA hierarchy (Preferred Term, High Level Term, High Level Group Term, and System Organ Class). The analyses did not show any difference between the treatment groups. Events of hypocalcemia were analyzed in different strata of Vitamin D (in ng/ml <12, 12-20, 20-32 and >32) and renal function (Cr clearance in ml/min <30, 30-60, 60-90 and >90). No significant differences were detected in any of the vitamin D strata.

Of note, in a Phase 1 trial of subjects with all phases of renal function, subjects with baseline creatinine clearance less than 30 mL/min developed significant hypocalcemia (Ca <7.5 mg/dL or symptoms). Subjects in this trial did not receive calcium and vitamin D supplementation, which may have contributed to the extent of the hypocalcemia. The trial was stopped and the protocol was amended to require calcium and vitamin D supplementation. As outlined in the primary clinical review pages 120-121, after supplementation was initiated, the calcium nadir in the severe renal disease group was improved to the levels of the other groups.

Cardiovascular Adverse Events: During the development program for denosumab, a concern was raised regarding the potential for denosumab to promote arterial wall calcification and atherosclerosis. Reports in the published literature suggested a possible association between OPG levels and arterial wall calcification, cardiovascular disease and mortality (Kiechl S et al. 2004; Mikami S et al. 2008; Nybo M and Rasmussen LM 2008). Inactivation of RANKL by denosumab could result in elevated levels of osteoprotegerin (OPG) as it binds to the same target.

To address these concerns, the Applicant established a cardiovascular adjudication committee to review possible cardiovascular events in trial 20030216 (postmenopausal osteoporosis

fracture trial) and trial 20040138 (bone loss due to hormone ablation in prostate cancer). In addition, the reviewing Division recommended an assessment of arterial wall calcification/thickness. Because the large fracture study was already underway making baseline measurements using newer technologies impossible, an analysis of changes in abdominal aortic calcification (as assessed using lateral lumbar spine radiographs) was also conducted in a subset of subjects in trial 20030216.

The Quantitative Safety and Pharmacoepidemiology Group provided a statistical analysis of the cardiovascular adverse events from the entire denosumab safety database (all four indications). Consultation was also obtained from the Division of Cardiovascular Renal Products.

In the primary clinical review, analysis of cardiovascular **safety can be found on pages 91 – 96**. Baseline cardiovascular risk factors were similar between treatment groups. Osteoprotegerin levels were measured in the PK substudy of trial 20030216. As outlined in the figure on page 213 of the primary clinical review, there was no clear increase in osteoprotegerin levels with denosumab therapy. However, the sensitivity of the osteoprotegerin assay is not known and the level of change in osteoprotegerin that would constitute a clinically significant change is also unclear.

A total of 1098 cardiovascular adverse events from trial 20030216 (526 in placebo-treated subjects and 572 in the denosumab-treated subjects) were submitted for adjudication. The number of positively adjudicated events was 233 in placebo-treated subjects and 247 in the denosumab-treated subjects.

Upon QSPG statistical analysis, bradyarrhythmia and ischemic heart disease are the only signals that appear consistently in the analysis of the data from the nine studies of denosumab in postmenopausal and hormone ablation populations. Bradyarrhythmia had a consistent signal according to the broad MedDRA search strategy. In the analysis of all PMO studies pooled, relative risk was estimated as 2.9 for moderate events and 1.7 for all worse severity levels. This trend was observed in the analysis of study 20030216 alone (RR=3.5), which appears to have heavily influenced the pooled analysis. Severe ischemic heart disease was associated with relative risk estimates greater than one in all eight analyses, with RR ranging from 1.7 to 2.0. There was a consistent estimate of relative risk greater than one across all severity levels for the placebo- controlled and pooled PMO studies. Relative risk estimates ranging from 1.4 to 1.8 having p-values less than 0.05 were observed for all worse severity levels in the pooled placebo-controlled and PMO studies. With regard to ischemic cardiac disease, these analyses were based on all cardiovascular adverse events. When adjudicated adverse events were evaluated, 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 two treatment groups.

An evaluation of the approach used for the QSPG analysis revealed that the standardized MedDRA query for bradycardia includes terms such as conduction defects, accessory pathway, agonal rhythm, AV conduction time shortened, asystole, PR shortened, prolonged

QT, and sinus arrhythmia. The primary review team had noted prolonged outliers in the ECG data from trial 20030216. Based on these concerns and the lack of a thorough QT study prompted a consult to the IRQT team. The conclusions of their review were that there is no relationship between denosumab serum concentration and change in QTcF. In addition, a review of the heart rate vital sign data showed that subjects with documented heart rates < 40 beats per minute were balanced between the two treatment groups (table 60, page 130 of the primary clinical review).

The distribution of baseline aortic calcification scores was similar between the two treatment groups with 23% of subjects having a baseline score of zero. At month 36, the mean changes in aortic calcification scores were small and balanced across the treatment groups.

Based on the data available, there is no clear cardiovascular safety signal seen.

Infections: RANKL is expressed on activated T and B lymphocytes, in the lymph nodes, and plays a role in dendritic cell (antigen presenting cells) maturation. Therefore, it is biologically plausible that the RANKL inhibitor denosumab could increase the risk of infection as T and B lymphocytes are responsible for foreign antigen recognition. Consultation was also obtained from the Division of Anti-Infective and Ophthalmology Products. The primary clinical review analysis of infections can be found on pages 96 – 103. **As outlined in the primary clinical review**, there were safety signals pertaining to infections noted in the preclinical studies. In early phase 1 and 2 studies, there was no clear evidence of decreasing lymphocyte cell counts with denosumab therapy. However, the sample sizes in these studies were small.

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

In trial 20030216, fatalities due to infection occurred in 6 (0.2%) subjects in each treatment group. Serious adverse events of infection were reported by 292 subjects (133 (3.4%) placebo, 159 (4.1%) denosumab) and adverse events of infection were reported by 4163 subjects (2108 (54.4%) placebo, 2055 (52.9%) denosumab). In trial 20040132, an imbalance in serious adverse events of infection was noted. Infection SAEs were reported by 9 subjects: one (0.6%) in the placebo group and 8 (4.9%) in the denosumab group. Adverse events of infection were reported by 200 subjects (101 (61.2%) placebo, 99 (60.4%) denosumab).

As outlined in the primary clinical review, opportunistic infections were not increased in the subjects receiving denosumab. When infection serious adverse events were examined in detail, infections related to bacteria and unspecified pathogens occurred at higher incidence in denosumab subjects compared with placebo. Specifically, serious bacterial infections occurred

in 15 (0.4%) of placebo subjects and 25 (0.6%) of denosumab subjects and serious infections due to an unspecified pathogen occurred in 115 (2.8%) of placebo subjects and 138 (3.4%) of denosumab subjects. In trial 20030216, denosumab-treated subjects appeared to have a higher incidence of skin, abdominal, ear, and urinary tract infections. Skin infection serious adverse events occurred in 3 (0.1%) placebo subjects and 14 (0.4%) denosumab subjects. Gastrointestinal infection serious adverse events occurred in 22 (0.5%) placebo subjects and 28 (0.7%) denosumab subjects. Serious ear infection adverse events occurred in no placebo subjects and 5 (0.1%) denosumab subjects. The majority of these cases were labyrinthitis. Serious urinary tract infection adverse events occurred in 17 (0.4%) placebo subjects and 28 (0.7%) denosumab subjects. Also of concern is the imbalance in endocarditis serious adverse events, which occurred in no placebo-treated subjects and three denosumab-treated subjects in trial 20030216. This occurrence rate is much higher than would be anticipated based on the **published literature = 0.2 – 0.6 cases pretreatment group** based on 11,000 person years of exposure.

Based on the data reviewed, the Division of Anti-Infective and Ophthalmology Products agreed that patients on denosumab appeared to have infections more frequently, had more severe cellulitis and more serious abdominal and lower respiratory tract infections. In addition, given that multiple layers of the immune system may be impacted with denosumab therapy, a specific time to event signal may not yet be evident. The consultants recommended that the label include information related to the potential risks for infections in the Warnings and Precautions section. In addition, the recommendations included that the Applicant commit to continue to collect information on all infection-related adverse events for the indefinite future during the postmarketing period. This could take the form of a postmarketing requirement.

Malignancy: Concerns regarding the incidence of new malignancies in subjects treated with denosumab have been raised for several reasons. No carcinogenicity studies have been performed because of the lack of an animal model and there is biologic plausibility based on **denosumab's effect on the immune system**. In addition, in the dose-finding studies, three subjects all treated with denosumab died due to neoplasms. Breast cancer was a common reason for withdrawal from the trial and cancers (breast cancer followed by colon cancer, gastric cancer, ovarian cancer and pancreatic cancer) was the most common reason for study drug discontinuation. Please refer **to the discussion in the primary clinical review, pages 109 – 111**. In the combined PMO database (studies 20030216 and 20040132) adverse events related to neoplasms were reported in 285 (7.1%) placebo-treated subjects and 316 (7.8%) denosumab-treated subjects. Malignant and unspecified neoplasms were reported in 162 (4.2%) placebo-treated subjects and 192 (4.7%) denosumab-treated subjects. In particular, there were more malignant gastrointestinal, breast, and reproductive malignancies in the denosumab group and more respiratory malignancies in the placebo group (table 47, page 110 of the primary clinical review).

As outlined in the primary clinical review page 204, one case of Schofflers tumor was observed in a subject treated with denosumab in trial 20030216. To date, only 6 such cases are described in the literature (3 in Germany and 3 in Japan). Schofflers tumor is a rare inflammatory pseudotumour of the abdominal wall with aggressive connective tissue

proliferation which frequently infiltrates neighboring abdominal organs. The lesion belongs to the reactive tumor-like fibromatoses. Since RANKL was originally found in dendritic cells of the skin, and this very rare condition occurred in denosumab group, this one case raises concerns about increased possibility of such events. However, it is not possible to assess the risk of this very rare tumor base on one case.

I agree with the primary reviewer's **conclusions that the higher** incidence of several types of malignancies in denosumab subjects is concerning, particularly when considering the long-term use associated with the prevention indication and that the significance of these findings in studies of moderate duration is unclear due to the long latency for malignancies.

Osteonecrosis of the Jaw: Osteonecrosis of the jaw (ONJ) has been noted in patients receiving other potent anti-resorptive therapies and inhibition of bone resorption has been postulated as a possible etiology for ONJ. For the phase 3 program, the Applicant convened an Osteonecrosis of the Jaw Adjudication Committee to evaluate potential cases of ONJ. The definition of ONJ used was that outlined by the American Dental Association in 2008: **"An area of exposed alveolar or palatal bone where gingival or alveolar mucosa is normally found associated with non-healing after appropriate care by 8 weeks in a patient without prior history of radiation to the head, face, or mouth"**. **Cases sent for adjudication** were identified by a predefined list of MedDRA terms. Consultation was obtained from the Division of Dermatology and Dental **Product's dental team, who concluded** that the search terms and adjudication process appeared adequate to identify cases of ONJ. Twenty one cases were identified to go forward with adjudication and no cases of ONJ were identified. However, it should be noted that documented cases of ONJ with denosumab use in the advanced cancer population have been identified and positively adjudicated.

Dermatologic Adverse Events: Please refer to the QSPG review for complete details of the statistical analyses performed. A significant imbalance in dermatologic adverse events (skin infections were not included) was noted in the postmenopausal osteoporosis database. A total of 501 (12.4%) placebo-treated subjects and 610 (15.1%) denosumab-treated subjects reported an adverse event related to skin and soft tissue disorders. These events did not include skin infections and were generalized, not specific to the drug injection site. This imbalance was **mainly due to imbalances observed in High Level Group Term "Dermal and Epidermal conditions", driven by dermatitis, eczema, and rashes**. Of note, dermal and epidermal adverse events including toxic skin reactions and bullous conditions occurred at approximately a 10-fold increased incidence in denosumab treated subjects. The Division of Dermatology and Dental Products was consulted to assist in the evaluation of these cases and their relationship to denosumab therapy. After review, denosumab could not be clearly implicated as the causative agent nor could it be definitively ruled out as the cause.

Hypersensitivity: With any protein product, hypersensitivity is a concern. In trial 20030216, **"drug hypersensitivity" was reported in 11 (0.3%) subjects in the placebo group and 15 (0.4%) subjects in the denosumab group**. Angioedema and urticaria adverse reactions were reported in 28 (0.7%) subjects in the placebo group and 29 (0.7%) subjects in the denosumab group. There was one report of anaphylactic shock, which occurred in a placebo-treated patient. Based on

the data provided, there is no clear evidence of significant hypersensitivity reactions in subjects treated with denosumab for up to three years.

Pancreatitis: In trial 20030216, there was an imbalance in events of pancreatitis in subjects randomized to denosumab. A total of 4 subjects in the placebo group and 8 subjects in the denosumab group reported an event of pancreatitis. Regarding the severity of the events, one placebo-treated subject had a serious adverse event of pancreatitis while all eight subjects in the denosumab group had pancreatitis events that were serious. As outlined in the primary **clinical review, pages 112 – 114, many of these** subjects had underlying risk factors for pancreatitis.

Diverticular Events: In trial 20030216, an imbalance in diverticular disorders was noted. As outlined in the primary clinical review pages **118 – 119, serious adverse events related to** diverticular disease were reported in 14 (0.3%) subjects in the placebo group and 23 (0.6%) subjects in the denosumab group. Serious adverse events of diverticulitis were reported in 7 (0.2%) subjects in the placebo group and 10 (0.2%) subjects in the denosumab group. Adverse events related to diverticular disease were reported in 68 (1.7%) subjects in the placebo group and 102 (2.5%) subjects in the denosumab group.

Ocular Adverse Events: In the preclinical studies, prolonged deposition (up to 672 hours post dose) of radiolabeled denosumab was noted in the cornea of cynomolgus monkeys. No ocular adverse effects were noted and it was concluded that the radioactivity noted in the cornea may not be a function of drug accumulation in the cornea. However, adverse events of cataracts were noted with increased frequency in the denosumab-treated subjects in the prostate cancer trial 20030138 (9 (1.2%) of the placebo group and 34 (4.7%) of the denosumab group). In the PMO database, adverse events related to the eye were reported in 537 (13%) placebo-treated subjects and 513 (12.6%) denosumab-treated subjects. Cataracts were reported in 253 (6.3%) of the placebo group and 229 (5.7%) of the denosumab group. Therefore, based on the available data, there is no clear safety signal for ocular adverse events in the PMO population.

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

The fracture healing substudy was to enroll subjects who experienced a distal radial fracture and were expected to remain in the study for at least 3 more months. A total of 190 distal radial fractures were reported in study 20030216. Of these, only 25 subjects (17 placebo, 8 denosumab) were enrolled in the fracture healing substudy. Two subjects in the placebo group and one subject in the denosumab group had delayed radiographic healing of their distal radius fracture. Healing was considered delayed if bridging at 3 of the 4 cortices was not demonstrable on x-ray at 3 months. All 3 of the fractures were radiographically considered healed by the time of the 6 month radiograph.

Laboratory Findings: A complete evaluation of the laboratory findings, including laboratories of mineral metabolism, is presented in the **primary clinical review pages 121 – 130**. No significant laboratory findings were noted.

Hypocalcemia findings are discussed in adverse Events of Special Interest above. Phosphorus is also a mineral that is impacted by bone formation and resorption. Similar to changes in calcium, greater reductions in serum phosphorus were observed in the denosumab group at month 1. Parathyroid hormone plays a key role in the regulation of mineral levels. Changes in serum calcium and phosphorus can result in compensatory changes in serum parathyroid hormone levels. as outlined in figure 13 on page 127 of the primary review, denosumab treatment resulted in an increase in serum PTH levels at month 1, and returned toward baseline at months 6 and 12.

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.

Qualitative Bone Histology

In general, there was evidence of normal lamellar bone and normal mineralization in all treatment groups. In addition, there was no evidence of osteomalacia or woven bone in these studies. 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 the table below, 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.

Denosumab Bone Histomorphometry Studies: Labeling status												
Study	20010223						20050234		20030216			
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 from denosumab group												
Source: compiled by reviewer based on respective study reports												

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 the table below.

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. 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.

Trial 20030216: 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	31	5	22	2
um ³ /um ² /yr	11.89	0.13	9.80	0.29
ES/BS, n	32	26	22	17
%	1.65	0.23	0.81	0.14
OS/BS, n	32	26	22	17
%	7.68	0.70	6.54	0.26
MAR, n	31	5	22	2
um/day,	0.730	0.300	0.755	0.400
MLT, n	31	4	22	2
days,	20	167	24	49
OTh, n	32	26	22	17
µm	9.09	5.435	8.715	5.410
OV/BV, n	32	26	22	17
%	1.16	0.08	0.72	0.03

Source: compiled by reviewer from study 20030216 study report

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 the table below.

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.

Study 20050234: Quantitative Histomorphometry Parameters		
Parameter [median]	Month 12	
	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
Source: compiled by reviewer from the 20050234 study report		

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 the figure of CTX changes on page 34 of this review, 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 the actual values that were the limit of quantitation (<0.049 ng/mL) up to read as a value of 0.049. The following table details the trabecular label status in terms of the actual month one CTX value (classified as either 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.

Trail 20030216: Comparison of Trabecular label Status and Month 1 serum CTX Status				
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. 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.

8.3 Safety update

The 4-month safety update contained safety data with a cut-off date of December 2, 2008, from multiple clinical trials. The extension studies from the two pivotal phase 3 PMO trials provided additional data regarding long-term safety. Two specific aspects of the safety of denosumab were further evaluated with these data:

1) Follow-up on the concern related to fracture efficacy in Year 3 of trial 20030216. Trial 20060289 is the extension trial of 20030216. This was an open-label study where all subjects receive denosumab (placebo treated subjects (n=2203) were begun on denosumab therapy and denosumab treated subjects (n=2346) were continued on therapy). The length of participation **in this extension trial was 6 – 15 months at the time of the safety update.** Fracture data is collected only as adverse events. Overall, 50 (2.3%) placebo/denosumab subjects and 30 (1.3%) denosumab/denosumab subjects reported a fracture. Femoral neck/femur fractures were reported in 5 (0.2%) placebo/denosumab subjects and 2 (0.08%) denosumab/denosumab subjects. Based on the very limited data available, there is no evidence of a worsening of **denosumab's fracture reduction efficacy.**

2) **The durability of denosumab's effect on incidence** of infection after discontinuation of therapy. The 48-month data from trial 20040132 was assessed with the assistance of the QSPG team. These data provide for safety analyses with subjects on 2 years of denosumab therapy, and then followed 2 additional years off denosumab therapy. As previously noted, adverse events of infection were balanced between treatment groups (101 (61.2%) placebo, 99 (60.4%) denosumab) and serious adverse events of infection were not balanced and occurred more frequently in the denosumab arm (one (0.6%) in the placebo group and 9 (4.9%) in the denosumab group) during the treatment period of the trial.

During months 25 – 48, 51 subjects in the placebo group and 54 subjects in the denosumab group reported an adverse event of infection. Only one subject in each treatment group experienced a serious adverse event of infection during months 25 – 48.

There did not appear to be a prolonged effect on serious adverse events of infection in this trial. However, there was a marked drop-off of reporting in infections even in the placebo group and under-ascertainment is a concern.

8.4 Immunogenicity, where pertinent

Denosumab is a protein product that has great potential to elicit and immune response. For evaluation of immunogenicity, the Applicant developed a three step process for the detection of antibodies. A screening immunoassay was used to detect binding antibodies. A second immunoassay was used to confirm the presence of binding antibodies. A cell-based bioassay was then used to test positive binding antibody samples for neutralizing activity against denosumab.

Screening and confirmatory immunoassays were performed in greater than >8000 subjects in studies for postmenopausal osteoporosis, cancer, and other conditions (such as rheumatoid arthritis). As outlined in the table below, 0.5% to 1.1% of subjects exposed to denosumab developed binding antibodies after therapy. However, it should also be noted that 0.1% to 0.5% of denosumab-treated subjects had pre-existing binding antibodies. When placebo or active control subjects were examined, 0.2% had pre-existing binding antibodies and 0.3% of

subjects were noted to have binding antibodies to denosumab, without being exposed to denosumab. The significance of these binding antibody assays is unclear at this time.

Denosumab Studies: Evaluation for Immunogenicity			
	N	Pre-existing Binding Ab	Binding Ab
Subjects Exposed to Denosumab			
Total	8113	12 (0.1%)	43 (0.5%)
Osteoporosis	6111	6 (0.1%)	28 (0.5%)
Cancer	1273	2 (0.2%)	7 (0.5%)
Other	729	4 (0.5%)	8 (1.1%)
Subjects Exposed to Placebo or Active Control			
Total	5320	8 (0.2%)	16 (0.3%)
Source: compiled by reviewer from the immunogenicity report			

In study 20030216, 25 denosumab-treated subjects tested positive for binding antibodies to denosumab. 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 highly immunogenic.

8.5 Special safety concerns

The safety concerns of interest are outlined in section 8.2 above.

8.6 Discussion of primary reviewer's comments and conclusions

I agree with the conclusions outlined by the primary reviewers and discussed in this document.

8.7 Discussion of notable safety issues

For treatment of postmenopausal women, the overall safety profile of denosumab is acceptable, however, there are imbalances noted that suggest the potential for serious risks with denosumab therapy. These include the risk of serious infection which was not limited to skin infection. While the overall infection rates were similar, denosumab treated subjects appeared to have infections that were more serious. This was most notable in the younger subjects from trail 20040132. There is also clear biologic plausibility related to infection, given the role of RANK ligand in B-cell, T-cell and dendritic cell functions. Hypocalcemia is a recognized adverse event with all anti-resorptive therapies and should be labeled accordingly,

which the Applicant has proposed. Osteonecrosis of the jaw has been reported with denosumab use in subjects with advanced cancer. This scenario is similar to the bisphosphonate, zoledronic acid, where the advanced cancer population was the population in whom the event was first recognized. ONJ has now been described in the osteoporosis population treated with both intravenous and oral bisphosphonates. It is expected that reports of ONJ with denosumab therapy is likely to follow a similar pattern. Dermatologic adverse events of dermatitis and eczema were significantly increased with denosumab use. While not clearly related to the timing of denosumab dosing, a concern remains on whether these findings are a function of the effects on dendritic cells in the skin, or potentially a hypersensitivity signal. These events should be included in the labeling. Similarly, the imbalance in serious pancreatitis events is concerning and should be included in the product labeling.

The questions regarding over suppression of bone turnover are unresolved and will require further monitoring. As previously discussed in the efficacy section, the degree of suppression of bone turnover markers was marked. While there was some diminution of effect toward the end of the dosing cycle, the long-term consequences of this degree of suppression is not known. Similarly, the degree of suppression of bone turnover and bone formation noted on the bone histomorphometry analyses is highly concerning and has not been noted with any other anti-resorptive drug. There is no mineralization defect noted with denosumab therapy. The question becomes, is there a point where bone turnover is suppressed such that normal microscopic-level healing mechanisms cannot function and the bone is ultimately compromised. It is somewhat reassuring that unlike bisphosphonates, denosumab very quickly loses its effect on bone turnover once treatment is discontinued. The fracture healing substudy of the main fracture trial was inadequately enrolled to allow substantive assessment of this question. Therefore, close postmarketing follow-up will be necessary. Other potential consequences of over suppression of bone turnover should also be followed closely, including osteonecrosis of the jaw and the incidence of atypical fractures.

The adverse events noted for the treatment population also apply to the prevention population, and in some ways are more concerning, given the very long-term treatment that would be required to support continued fracture reduction efficacy.

9. Advisory Committee Meeting

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

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

The following outlines the questions (in italics) and the votes and discussion of the Committee members. Questions related to the bone loss due to hormone ablation in breast and prostate cancer indications are not presented here. Please refer to the minutes of the meeting for full details.

Benefit/Risk Profile – Treatment of postmenopausal osteoporosis

Question 1a [Vote: Yes/No]: Is there a population of postmenopausal women with osteoporosis in which the benefit of treatment with denosumab is likely to outweigh the risks?

The Committee vote was unanimous 15 (yes), 0 (no) that there is a population of postmenopausal women with osteoporosis in which the benefits of denosumab therapy are likely outweigh the risks.

Question 1b [Discussion]: If yes, would this population be:

- (1) all women with postmenopausal osteoporosis,
- (2) limited to a subgroup at a high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or women who have failed or are intolerant to other osteoporosis therapies

Many committee members felt that limiting the treatment population to those at high risk of fracture may be warranted until more information is known about the long-term risks of the therapy.

Benefit/Risk Profile – Prevention of postmenopausal osteoporosis

Question 2a [Vote: Yes/No]: Is there a population of postmenopausal women with low bone mineral density who do not meet the criteria for treatment of osteoporosis in which the benefit of prevention of osteoporosis with denosumab is likely to outweigh the risks?

The Committee vote was 2 (yes) and 13 (no) that there is a population of postmenopausal women with low bone mineral density who do not meet the criteria for treatment of osteoporosis in which the benefits of denosumab therapy are likely outweigh the risks.

Risk Evaluation and Mitigation Strategies

Question 6a [Vote: Yes/No]: If approved, do you recommend that denosumab have a Risk Evaluation and Mitigation Strategy or REMS?

The Committee vote was 12 (yes), 1 (no), 3 (absent) that denosumab should have a REMS.

Question 6b [Discussion]: *If so, which elements should be included in the REMS?*

- (1) A Medication Guide to inform patients about the risks of the drug?*
- (2) A Communication Plan to disseminate information to healthcare providers?*
- (3) Other?*

The Committee members felt that a Medication Guide to inform patients about the risks of the drug and a Communication Plan to educate providers about major safety concerns were warranted. Some members also felt that given the need for providers to administer the drug, a registry was also warranted to better follow patients prospectively.

10. Pediatrics

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

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

11. Other Relevant Regulatory Issues

11.1 Financial Disclosure

Drs. Popat and Rothstein have reviewed the financial disclosure information provided by the Applicant and do not feel that the disclosures reported should compromise the data submitted.

11.2 DSI Audits

The Division of Scientific Investigation did conduct inspections for this application. Sites were chosen using the following criteria: the site enrolled a large number of subjects, the site did not have a recent history of inspections, and had a proportionally increased number of protocol violations and/or low numbers of adverse events reported compared to other trial sites. Two domestic sites and two international sites were inspected. Although isolated issues were noted

at one site, the final assessment was that the data appear acceptable in support of the application.

12. Labeling

12.1 Proprietary name

The Applicant proposed the tradename Prolia, which was found to be acceptable.

12.2 Physician labeling

Physician labeling continues to be negotiated at the time of this review. The major issue under discussion includes the language for the indication. The Applicant originally proposed **"treatment of osteoporosis in postmenopausal women"**. ~~However, the clinical team feels that~~ the population should be restricted to one at higher risk of fracture, which also appeared to be supported by the Advisory Committee. The clinical team initially proposed the same indication language used in Forteo because the clinical safety concerns are of a similar magnitude. The Applicant has proposed similar, but not identical language that is currently under review.

12.3 Carton and immediate container labels

As outlined in the review by the Division of Medication Error Prevention and Analysis, recommendations for the carton and container labels included the following:

A. General Comment for All Labels and Labeling

1. Present the established name so that the active ingredient is in parenthesis and the finished dosage form (e.g. injection) immediately follows the active ingredient as this is the customary presentation of established names.
2. Add the statement "Discard unused portion" immediately following the statement "Single use vial" or "Single use prefilled syringe".

B. Container Label - Syringe

1. If space permits, include the route of administration (i.e. For subcutaneous use) per 21 CFR 200.1 OO(b)(3) to avoid wrong route of administration errors.
2. Relocate the strength so that it immediately follows the established name and dosage form.

C. Carton Labeling - Syringe

1. Remove the line between the drug name and strength so that it does not interfere with the presentation of the drug name, dosage form and strength.
2. Relocate the strength so that it immediately follows the established name and dosage form.
3. Revise the strength unit in the green circle (i.e. 60 mg) to "60 mg/mL."

4. Per 21 CFR 208.24(d), include the Medication Guide statement (e.g. Dispense the enclosed Medication Guide to each patient or Dispense accompanying Medication Guide to each patient).

C. Syringe Topweb Labeling

1. Relocate the strength so that it immediately follows the established name and dosage form.
2. Revise the strength unit in the green circle (i.e. 60 mg) to "60 mg/mL."

D. Container Label- Vial

1. If space permits, include the route of administration (i.e. For subcutaneous use) per 21 CFR 200.1 OO(b)(3) to avoid of wrong route of administration errors.
2. Revise the strength unit in the green circle (i.e. 60 mg) to "60 mg/mL."

E. Carton Labeling - Vial

1. Remove the line between the drug name and strength so that it does not interfere with the presentation of the drug name, dosage form and strength.
2. Revise the strength unit in the green circle (i.e. 60 mg) as "60 mg/mL."
3. Increase the prominence of the route of administration (i.e. For subcutaneous use only) to avoid wrong route of administration errors.
4. Per 21 CFR 208.24(d), include the Medication Guide statement (e.g. Dispense the enclosed Medication Guide to each patient or Dispense accompanying Medication Guide to each patient).

12.4 Patient labeling/Medication guide

A medication guide (as part of the REMS) will be required for this product.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

For the indication, **Treatment of Osteoporosis in Postmenopausal Women**, I recommend a Complete Response action for this indication. Product labeling and postmarketing activities, including those outlined in the Risk Evaluation and Mitigation Strategy, are yet to be agreed upon. In addition, there are two significant issues that prevent approval of denosumab for the treatment of osteoporosis in postmenopausal women at this time: 1) the lack of an adequate feasibility assessment for the proposed postmarketing observational study and 2) the inspectional issues at the Puerto Rico drug product manufacturing site - a final decision from the Office of Compliance.

For the indication, **Prevention of Osteoporosis in Postmenopausal Women**, I recommend a Complete Response action. (b) (4)

13.2 Risk Benefit Assessment

The goal of therapy in osteoporosis is the prevention of fractures. Based on epidemiologic studies, age is an independent risk factor for fracture and women over the age of 70 years regardless of BMD would qualify for a treatment of osteoporosis indication. In the osteoporosis treatment population, denosumab, 60 mg q 6 months is effective in decreasing the incidence of new morphometric vertebral fractures (absolute reduction 4.8%, relative reduction 68%, p-value <0.0001), nonvertebral fractures (absolute reduction 1.5%, relative reduction 20%, p-value 0.0106), and hip fractures (absolute reduction 0.3%, relative reduction 40%, p-value 0.0362). Therefore, fracture reduction benefit has clearly been demonstrated in this population.

(b) (4)

Multiple safety issues have been identified, including serious infections, hypocalcemia, dermatologic adverse events, pancreatitis, and events related to over suppression of bone turnover (osteonecrosis of the jaw, delayed fracture healing and the incidence of atypical fractures). While these events can be adequately labeled to provide information to both healthcare providers and patients, they may be compounded by the chronic nature of the therapy with denosumab and will need to be closely followed in the postmarketing period.

The safety issues identified are the same in the treatment and prevention populations.

(b) (4)

13.3 Recommendation for Postmarketing Risk Evaluation and Management Strategies

The Applicant has identified the following safety risks in their development of a risk management plan: hypocalcemia, fracture healing complications, osteonecrosis of the jaw, infections, hypersensitivity, cataracts, use in pregnant or lactating women, and use in children; and proposes to use routine pharmacovigilance activities to further assess these risks.

The clinical team and the Office of Surveillance and Epidemiology are in agreement that a Risk Evaluation and Mitigation Strategy is needed to ensure that the benefits of the drug outweigh the risks of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover. Components should include a Medication Guide for patients, a communication plan for the healthcare provider, and a schedule of assessments. An information request was sent to the Applicant on October 2, 2009. The requested REMS was submitted on October 9, 2009 and is under review.

13.4 Recommendation for other Postmarketing Requirements and Commitments

To further evaluate denosumab's safety risks, the Applicant has proposed a routine pharmacovigilance plan as well as a prospective observational study using large administrative databases. The Applicant proposes a prospective observational PMO study using large administrative databases such as United Healthcare and the Medicare 5% sample, electronic medical records from closed medical systems such as Kaiser Permanente, and the Scandinavian registry database. However, the feasibility of this proposal has not been investigated. To assess the feasibility of this proposal, the Applicant proposes to partner with external experts to design appropriate studies to conduct preliminary assessments of background event rates in the relevant patient populations using these databases. These preliminary studies will assist in identifying appropriate comparator populations to reduce the impact of confounding by indication on event rates. The applicant intends that these preliminary assessments will form the basis for the study design and statistical methodologies for the proposed postmarketing observational study. They also intend to evaluate the strengths and limitations of the proposed databases in the conduct of valid postmarketing pharmacoepidemiology studies.

The Office of Surveillance and Epidemiology, Division of Epidemiology was consulted regarding the proposed observational study protocols. Their initial recommendation is that the results from Phase A (protocol 20090521), including the development and validation of the methodology and background adverse event rate assessments be acceptable before accepting Phase B as adequate and before approving the product.

Because of the difficulty with diagnosis and coding of some of the adverse events of interest, the clinical team also believes that the method of administration of denosumab (by a healthcare provider) provides a unique opportunity to collect data regarding the adverse events of concern in patients being treated with denosumab outside of the controlled clinical trial environment.

This approach would complement the observational database approaches proposed and could be dispensed as a short survey with the drug or provided to prescribers. The survey would include evaluation of the occurrence of new fractures including fracture location, fracture healing complications, osteonecrosis of the jaw, infections including skin infections, and dermatologic adverse events.

(b) (4)

Post- marketing studies/commitments recommended by the review team include:

1. Anti-cytokine antibodies such as tocilizumab, an anti-IL-6 monoclonal antibody, showed the alteration of CYP substrate drug exposure by affecting the effect of cytokine on drug metabolism. Thus, denosumab may affect the exposure to CYP substrate drugs by altering the concentration of RANKL, a cytokine that affects B- and T-cell differentiation, and dendritic cell maturation.

Therefore, the sponsor should conduct an in vitro study to assess whether RANKL modulate expression of major CYP enzymes (e.g., CYP 3A4, CYP 1A2, CYP 2C9, CYP 2C19, and CYP 2D6). If, upon review, there is no significant modulation of any of the major CYP enzyme(s) observed, further exploration would not be necessary. If the results of the in vitro study are positive, a drug interaction study or studies will be needed to further characterize the effect of denosumab on the metabolism of CYP probe drugs in PMO patients.

As an alternative to the in vitro study and the subsequent drug interaction study above, the sponsor may conduct a drug interaction study to determine the potential of denosumab to alter CYP substrate metabolism in PMO patients (e.g., using a cocktail of the major CYP probe drugs).

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

2. To perform stability testing on at least one marketed drug product lot of both the 3 cc glass vial and the 1 ml glass syringe; annually, for each year in which respective drug product is

manufactured and for each site at which it is manufactured, using the post-approval stability protocol specified in the BLA. The first update will be included in an annual report to be submitted by [Amgen to provide date]

3. To modify the acceptance criteria for the pre-filled syringe extrusion and breakloose specification. This specification was added during review and acceptance criterion is **currently listed as “report”**. **Data, analysis** and justification for a quantitative limit will be included in a prior approval supplement submitted by June 30, 2010.
4. To re-evaluate the release and shelf-life specifications and in-process limits for denosumab drug substance and drug product after 30 commercial manufacturing runs to reflect increased manufacturing experience. The revisions to the quality control system, the corresponding data from the 30 commercial manufacturing runs, and the analysis plan used to create the revisions will be provided by XXXX, 20XX. [Amgen, provide date]
5. To confirm validation of the updated SE-HPLC method (MET-001208). The method was revised to add column conditioning using material containing the high molecular weight species. The protocol and final report will be included in an annual report to be submitted by [Amgen to provide date].

In addition, the Pharmacology/Toxicology team recommends:

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

13.5 Recommended Comments to Applicant

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

For the indication **Treatment of Postmenopausal Osteoporosis**:

Clinical Deficiencies:

Because of the design and methodological challenges noted in your proposal, there is concern that the proposed postmarketing observational study using administrative databases (protocol 20090522) will not successfully capture the safety information regarding denosumab use. Therefore, it will be necessary for you to complete study 20090521, Phase A: Denosumab Global Safety Methodology and Background {AE} Rate Assessment Among Women With Postmenopausal Osteoporosis (PMO) Using Multiple Observational Databases (Denosumab

Methodology and Background Assessment [DMBA]) and submit the data for review prior to approval.

Information Needed to Address the Clinical Deficiencies:

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

For the indication **Prevention of Postmenopausal Osteoporosis:**

Clinical Deficiencies:

(b) (4)

Information Needed to Address the Clinical Deficiencies:

(b) (4)

Clinical Pharmacology Deficiencies:

(b) (4)

Information Needed to Address the Clinical Pharmacology Deficiencies:

(b) (4)

Theresa Kehoe

10/13/09

Theresa Kehoe, M.D.
Clinical Team Leader

George Benson

10/14/09

George Benson, M.D.
Deputy Director

CLINICAL REVIEW

Application Type BLA
Application Number(s) 125,320 and 125,331
Priority or Standard Standard

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Office of Drug Evaluation 3

Reviewer Name(s) Vaishali Popat, M.D., M.P.H.
Adrienne Rothstein, Pharm.D.
Review Completion Date September 14, 2009

Established Name Denosumab
(Proposed) Trade Name PROLIA™
Therapeutic Class RANK ligand (RANKL) inhibitor
Applicant Amgen, Inc.

Formulation(s) Single use prefilled syringe containing
60 mg in a 1 mL solution; Single use vial
containing 60 mg in a 1 mL solution
Dosing Regimen 60 mg SC injection Q6months
Indication(s) 125,320: Treatment of Osteoporosis
125,331: Prevention of Osteoporosis
Intended Population(s) Postmenopausal Women

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

BLA 125,320: Treatment of postmenopausal osteoporosis

From the clinical perspective, denosumab 60 mg administered subcutaneously every 6 months **should be approved** for the indication of the treatment of postmenopausal osteoporosis. This recommendation is based on the demonstration of decreased incidence of new vertebral fracture in postmenopausal women with osteoporosis with denosumab over placebo and overall risk benefit profile. However, several significant safety issues, including infections, over suppression of bone remodeling, skin hypersensitivity reactions, and a potential signal for malignancy were identified in the denosumab clinical program, which can be adequately addressed by various venues of risk management, such as labeling and phase 4 requirements and commitments.

Given these safety concerns and the fact that this is a new molecular entity and first in class, I recommend approval in postmenopausal women with osteoporosis and high risk of fracture defined as a history of osteoporotic fracture, multiple risk factors for fracture, or women who have failed or are intolerant to other osteoporosis therapies.

(b) (4)

1.2 Risk Benefit Assessment

BLA 125,320: Treatment of postmenopausal osteoporosis

Data in the denosumab BLA demonstrated the effectiveness of denosumab in decreasing the risks of new vertebral over a 36-month period in postmenopausal

women with osteoporosis. Also demonstrated were reduced risks of new non-vertebral fracture and hip fracture over the same time period of treatment with denosumab. For the primary endpoint of new vertebral fractures, treatment with denosumab resulted in a 4.8% absolute risk reduction and a 68% relative risk reduction in fracture incidence over placebo. A 1.5% absolute risk reduction and a 20% relative risk reduction of non-vertebral fractures with denosumab therapy was seen with denosumab therapy over placebo. For hip fractures, there was a 0.3% absolute risk reduction and a 40% relative risk reduction. Numbers needed to treat to prevent one new vertebral fracture is 21, non-vertebral fracture it is 70, and hip fracture is 227. The risk reduction for vertebral, non-vertebral, and hip fractures was statistically significant. The magnitude of treatment benefits with denosumab appears to be similar to bisphosphonates approved for the treatment of osteoporosis, although no head-to-head fracture trials have been conducted.

From safety perspective, there are several safety signals for denosumab, particularly serious infections, a potential signal for malignancy, skin/hypersensitivity reactions, and over suppression of bone turnover. These safety concerns will be briefly summarized below, and described in detail in Section 7 of this review.

- **Serious infections including skin infections:** There is a higher incidence of serious infections (Placebo vs. denosumab 133(3.4%) vs. 159(4.1%)) in PMO fracture trial 20030216. When looked at other 3 primary efficacy trials, there is consistent safety signal of serious infections. In trial 20040132 there were (1(0.6%) vs. 8(4.9%)), trial 20040135 (1(0.8%) vs. 3(2.3%)) and 20040138 (33(4.6%) vs. 43(5.9%)) serious infections. Numbers needed to harm for serious infections for trial 20030216 is 152 over 3 year duration. In primary efficacy fracture trial 20030216, a signal was noted in endocarditis (0 vs. 3 cases), serious skin infections such as cellulitis and erysipelas requiring hospitalization (3 vs. 14 cases) serious urinary tract infections (17 vs. 28 cases) and serious ear infections (0 vs. 5 cases).
- **Oversuppression of bone remodeling:** Denosumab at the selected clinical dose resulted in significant suppression of bone remodeling as evidenced by histomorphometry and bone biomarkers findings. Suppressed bone remodeling is suggested by the absence of tetracycline label in approximately 35% of subjects exposed to denosumab. With currently marketed antiresorptive therapies (bisphosphonates), long-term severe suppression of bone remodeling is considered a possible etiology for significant adverse outcomes such as osteonecrosis of the jaw, atypical fractures and delayed fracture healing. The observation that bone remodeling suppression was reversible upon the discontinuation of denosumab treatment ameliorates some concerns about irreversible bone suppression. However, the effect of continued long-term denosumab use on the risks of osteonecrosis of the jaw, atypical fractures, and delayed healing that have been reported with chronic bisphosphonate use (> 7 -10 years) is not known.
- **Malignancies:** There was an increased incidence of new malignancies in trial 20030216, specifically malignancies of the breast, gastrointestinal tract, and

reproductive systems. However, the information available for subjects who developed new malignancies was too limited to assess drug causality. There were early signals of a risk of malignancy in the denosumab clinical development program, with 3 subjects in a high-dose denosumab group (100 mg Q6months) in the Phase 2 dose-finding trial dying from a malignancy. The relationship between treatment with denosumab and the development of malignancy remains uncertain, but one must be cautious about this finding with its potential for mortality and long-term sequelae.

- **Dermatologic adverse events:** There are higher number of subjects in the denosumab group who developed skin conditions in PMO fracture trial 20030216, such as dermatitis, eczema and pruritus (epidermal and dermal conditions: 316(8.4%) vs. 421(11%) $p < 0.001$). However, these subjects continued receiving denosumab every 6 months and in most cases, these conditions did not recur with subsequent dosing.

There are several therapies available for treatment of postmenopausal osteoporosis. However, literature reports that over half of women who start bisphosphonates therapy, discontinue treatment based on side effects and intolerability within one year (Weycker et al. 2006; Rabenda et al. 2008; Rabenda et al. 2009). Mortality rates in the first year after a hip or vertebral fracture are significantly higher than in the general population (Hasserius et al. 2005; Ioannidis et al. 2009), and approximately 20% of women die within a year of hip fracture (Johnell and Kanis 2004). Given the magnitude of treatment benefits and the overall safety profile, this reviewer concludes that denosumab be approved for the treatment of osteoporosis in women. Since this is a first in class agent, it should be approved for women with high risk of fracture, (defined as a history of osteoporotic fracture, multiple risk factors for fracture, or women who have failed or are intolerant to other osteoporosis therapies) where benefits potentially outweigh the risks. The aforementioned safety concerns can be adequately addressed by various venues of risk management, such as labeling and phase 4 requirements and commitments.

(b) (4)



As mentioned in the risk benefit summary for the treatment of postmenopausal osteoporosis, the main safety concerns for denosumab are serious infection including skin infection, over suppression of bone remodeling and dermatologic adverse events, and a potential signal for malignancy. These safety concerns are described in detail in Section 7 of this review.

- **Serious infection including skin infection:** There is a higher incidence of serious infections in subjects receiving denosumab in trial 20040132, with 1 placebo (0.6%) vs. 8 denosumab (4.9%) subjects reporting these events. The most commonly reported serious event of infection in this trial was pneumonia (1 placebo, 3 denosumab subjects), followed by diverticulitis (2 denosumab) and sepsis (2 denosumab). There were other signals of a serious risk of infection in the denosumab clinical development program, with 3 subjects in Phase I studies requiring hospitalization for pneumonia after a single dose of denosumab. The large treatment trial 20030216 had other imbalances in serious infections, including skin infections such as cellulitis and erysipelas, urinary tract infections, ear infections, and endocarditis.
- **Oversuppression of bone remodeling:** Denosumab at the selected clinical dose resulted in significant suppression of bone remodeling as evidenced by bone biomarkers findings, with CTX levels decreased in the range of 89% at Month 1 to 62% at Month 24 for subjects receiving denosumab. Suppressed bone remodeling is suggested by the absence of tetracycline label in approximately 35% of subjects exposed to denosumab in bone histomorphometry studies. With currently marketed antiresorptive therapies (bisphosphonates), long-term severe suppression of bone remodeling is considered a possible etiology for osteonecrosis of the jaw, atypical fractures and delayed fracture healing. Although bone remodeling suppression appears to be reversible with treatment discontinuation, the effects of continuous long-term use of denosumab are unknown at this time. Bone over-suppression is of particular concern in a younger prevention population that may receive denosumab for an extended duration.
- **Dermatologic events:** Rashes were reported more often in denosumab than placebo subjects in Trial 20040132, with 5 placebo (3%) and 14 denosumab (8.5%) subjects reporting this event. In the PMO fracture trial 20030216, there were a higher number of subjects in the denosumab group who developed skin conditions in, such

as dermatitis, eczema and pruritus (epidermal and dermal conditions: 316(8.4%) vs. 421(11%) $p < 0.001$). .

- **Malignancies:** In the on-treatment period of trial 20040132, subjects receiving denosumab reported 5 neoplasms (ovarian cancer, uterine cancer, breast cancer, basal cell carcinoma, T-cell lymphoma). In the placebo group, there were 3 reported neoplasms (B-cell lymphoma, squamous cell carcinoma, skin neoplasm). In the first 12 months of the off-treatment period, there were 2 reports of neoplasms in the denosumab group (meningioma, metastatic atypical carcinoid). In the placebo group, there were 2 reported neoplasms (breast cancer, squamous cell carcinoma). There were early signals of a risk of malignancy in the denosumab clinical development program, with 3 subjects in a high-dose denosumab group (100 mg Q6months) in the Phase 2 dose-finding trial developing a fatal malignancy. Also, in trial 20030216, there was an increased incidence of new malignancies in the breast, gastrointestinal tract, and reproductive systems. At this point in time, the relationship between treatment with denosumab and the development of malignancy remains uncertain, but one must be cautious about this finding with its potential for mortality and long-term sequelae, particularly in a younger prevention population that may receive denosumab for an extended duration.

(b) (4)

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The Applicant has provided a "Risk Management Plan" in Section 1.16 of the initial submission to BLA 125,320. This document summarized their routine pharmacovigilance activities, including review of adverse event data from clinical trial and postmarketing sources as individual case reports and aggregate data and written summaries in Annual Safety, U.S. Periodic, and Periodic Safety Update Reports. The Applicant has also proposed an enhanced pharmacovigilance plan with the following attributes:

- **Targeted Surveillance** – use of standardized questionnaires to request specific, focused follow-up information on the following events of concern: Osteonecrosis of the jaw (ONJ), Infections, Fracture healing complications
- **Prospective observational trial** - using a large health claims database, the Applicant will estimate background rates, event rates and drug utilization rates to monitor and assess the following: ONJ, Infections, Fracture healing complications, Off-label use in pediatric patients
- **Adjudication of ONJ cases** – all ONJ cases from ongoing clinical trials will be adjudicated by a committee.

- **Prospective, randomized, placebo-controlled trial of cataracts** - to evaluate the incidence of cataracts in prostate cancer subjects receiving denosumab with hormone ablative therapy.
- **Pregnancy registry** – the Applicant briefly describes a pregnancy surveillance system based on spontaneous reports of pregnancy to track birth outcomes for patients who become pregnant during the use of denosumab

The Applicant provided little detail on the standardized questionnaires to be used for events of ONJ, infections, and fracture healing complications. These standardized questionnaires should also be used for dermatologic adverse events and events of malignancy. The Applicant should work closely with the Division to establish appropriate follow-up questions to ask for events of concern for this product.

The Applicant provided limited information on the observational trial in PMO using electronic health claims data to evaluate ONJ, infections, fracture healing complications and off-label use in pediatric patients. Inhibition of RANK ligand in neonatal rats was associated with inhibition of bone growth and tooth eruption. It is unclear how the Applicant would assess for the occurrence of the inhibition of bone growth and tooth eruption with its delayed onset in pediatric patients. This prospective observational trial using health claims data should also be used to provide information on the incidence of dermatologic adverse events and cancer in this population and patients exposed to denosumab. The Applicant should assess if it is possible to identify and track pregnancies and pregnancy outcomes through the prospective observational trial utilizing health claims data. The Applicant should work closely with the Agency to clearly identify the trial purpose and ensure the methodology is appropriate to achieve the trial purpose.

Denosumab has been classified as Pregnancy Category C, meaning that animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. The proposed population for denosumab is postmenopausal women and men with prostate cancer and women with breast cancer receiving hormone ablative therapy. However, there may be some women of child bearing potential who use denosumab, either because they are perimenopausal, young breast cancer patients or there is off-label use in a younger population. As such, the monitoring of reported pregnancies needs to be more vigorous. The Applicant proposed a pregnancy registry for spontaneous reports of pregnancy. The current pharmacovigilance plan does not define the period of exposure for denosumab, which is critical to a product with such a long half-life. The pharmacovigilance plan also does not define the follow-up period after birth for birth outcomes nor what outcomes are being assessed – i.e., maternal outcomes, fetal outcomes, major malformations, minor malformations, etc.

The Applicant's proposed routine and enhanced pharmacovigilance activities are insufficient to communicate and manage the risks associated with denosumab. A Medication Guide and Communication Plan are recommended for additional risk evaluation and mitigation strategies for denosumab. A Medication Guide is necessary because denosumab has serious risks relative to benefits including infection, over suppression of bone remodeling and dermatologic adverse events of which patients should be made aware. This risk information could affect a patients' decision to use or to continue to use denosumab. A Communication Plan for healthcare providers is necessary to disseminate information to relevant parties about the serious risks of infection including skin infections, dermatologic events and suppression of bone remodeling and to communicate the approved indication and population for this product.

Because denosumab is administered to the patient by a healthcare professional every 6 months, there is a unique opportunity for the healthcare professional to actively query for adverse events of concern. It is recommended that the Applicant create a patient questionnaire for health care professionals to utilize at each scheduled dose to assess for the occurrence of serious infections, dermatologic events and events related to profound suppression of bone remodeling such as atypical fractures, delayed fracture healing, adynamic bone or osteonecrosis of the jaw. This active surveillance and direct clarification with the patient will facilitate ascertaining adverse events that are difficult to classify, such as atypical fractures or delayed fracture healing.

1.4 Recommendations for Postmarket Requirements and Commitments

These reviewers recommend that the Applicant be required to conduct a trial to evaluate atypical fractures and fracture healing. This trial could be an observational trial or a large simple clinical trial. The applicant was asked to evaluate fracture healing in the premarketing development program. Bone remodeling (bone formation and resorption) is critical in fracture healing. Denosumab suppresses bone remodeling. Nonclinical trial in HuRANKL KI (knock in) mice showed delayed fracture healing. A fracture healing substudy in Study 20030216 evaluated cortical bridging by serial x-rays to determine healing progression at 3 and 6 months post wrist fracture. The number of planned subjects was 157; however, only 25 subjects were enrolled. Therefore, there is insufficient data to assess fracture healing in humans. The Applicant would have to work with the Division to define atypical fractures and delayed fracture healing and identify the proper trial design and duration to evaluate these events.

These reviewers recommend that the Applicant agree to a postmarketing commitment to conduct bone biopsies at Year 7 and Year 10 in Study 20060289. Study 20060289 is an extension trial from Study 20030216 and subjects in this trial will be exposed to denosumab 60 mg SC Q6months for up to 10 years. The trial should also evaluate off treatment effects on histology and histomorphometry of bone remodeling.

In trial 20010223 seven doses were tested: 6 mg, 14 mg and 30 mg q 3 months and 14 mg, 60 mg 100 mg and 210 mg q 6 months. There was no clear dose response observed in terms of BMD efficacy, markers of bone remodeling and histomorphometry. Only one dose, 60 mg q 6 months was taken to the phase 3 trials. This dose demonstrated fracture efficacy, however, the choice of only one dose in the phase 3 trial does not allow us to establish minimal efficacious dose. Denosumab at the selected clinical dose resulted in significant suppression of bone remodeling as suggested by the absence of tetracycline label in approximately 35% of subjects exposed to denosumab in the bone biopsy substudy at 36 months in trial 20030216. If the postmarketing data shows higher incidence of potential clinical consequences of the profound suppression of bone remodeling such as atypical fractures, delayed fracture healing, adynamic bone or osteonecrosis of the jaw, the agency should consider requiring a trial to establish minimal efficacious dose.

2 Introduction and Regulatory Background

2.1 Product Information

Denosumab is a full-length human monoclonal IgG2 against RANKL produced in a CHO (Chinese Hamster Ovary) cell line. Denosumab binds specifically and with high affinity (b) (4) to the human receptor activator of nuclear factor kappa B ligand (RANKL). The binding interaction prevents the binding of RANKL to RANK on the surface of osteoclasts and their precursor cells in the myeloid lineage. Denosumab is a biologic agent with a complex structure. This is demonstrated in Figure 1.

Figure 1: Schematic of denosumab structure.



2.2 Tables of Currently Available Treatments for Proposed Indications

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
Estrogen Agonist/Antagonist	Reclast	IV	5mg yearly		XX
	Reclast	IV	5mg every 2 years	XX	
PTH analog	Evista	oral	60 mg daily	XX	XX
	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	

Clinical Review
 Vaishali Popat, M.D., MPH.
 Adrienne M. Rothstein, Pharm.D.
 BLAs 125,320; 125,331; S-000
 PROLIA™, denosumab

Class	Drug	Route	Dose	Prevention	Treatment
	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, if approved, would be the first biologic agent available in the United States for the prevention and treatment of postmenopausal osteoporosis.

2.3 Availability of Proposed Active Ingredient in the United States

Denosumab is the first biologic product and the first monoclonal antibody agent seeking approval for the prevention and treatment of postmenopausal osteoporosis. It is currently not marketed in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

Antiresorptive medications: Bisphosphonates are commonly used antiresorptive medications approved for prevention and treatment of osteoporosis. Safety issues identified with bisphosphonate use include upper gastrointestinal disorders (with oral use), musculoskeletal pain, and renal impairment (IV zoledronic acid). Safety issues related to antiresorptive effect of the bisphosphonates include osteonecrosis of the jaw (ONJ), hypocalcemia, and atypical fractures. The findings of atypical fractures are currently under review by OSE and OND. Because of their long residence time in bone, class labeling for bisphosphonates cautions against the use of these drugs in women of child bearing age and the potential of fetal toxicity after remote exposure to the drug.

Monoclonal antibodies: There are 27 therapeutic monoclonal antibody products 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 (Appendix 1).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On 5/21/01, original IND 9837 was submitted to FDA. On 4/20/2004, pre phase 3 meeting was held for PMO indication. There was no special protocol assessment for the pivotal fracture trial (20030216). Instead, there was a lengthy discussion between FDA and Amgen about various issues, including appropriateness of the dose selection.

Pre-Phase 3 meeting:

Important issues discussed at the pre phase 3 meeting and subsequent discussions were:

- FDA did not agree that data provided from the phase 2 Study 20010223 supported 60 mg 6-month dose as the optimal dose or if the fixed-amount dosing was appropriate. One of the main concerns was that in subjects with high weight (BMI), exposure may not be optimal. FDA recommended analyzing the efficacy outcomes by body weight, and evaluating additional dose/dosing interval in the phase 3 trial. To address this concern, Amgen provided additional data including analysis of 24 month data from trial 20010223. FDA remained unconvinced. Amgen was asked to provide complete report, analysis and discussion of the effect of weight and BMI on the adequacy of the dosing regimen. This was submitted in this application and it is reviewed by the clinical pharmacology reviewers.
- FDA recommended that in addition to the proposed fracture incidence that Amgen also incorporate an analysis of the effect of denosumab on fracture repair (time to complete union, incidence of non-union, postoperative complications). This was considered especially important since paucity of preclinical bone healing quality data due to the species specific action of the drug was anticipated.
- FDA requested Amgen to analyze the complete fracture data through month 36 to adequately assess risk benefit.
- FDA recommended evaluation of the potential risk of accelerating arterial wall calcification and OPG levels be included in the protocol and requested in addition to monitoring cardiovascular events that the trial evaluate a subset of subjects with significant risk for cardiovascular disease from both treatment arms for progression of arterial calcification using imaging techniques (e.g. carotid intima-medial thickness, electronic beam computed tomography). The applicant decided to use lateral x-ray over other methods because all baseline visits in trial 20030216 would have been completed by the time these discussions were going on. There was baseline data for lateral x-ray but not for the other proposed testing methods. The applicant also formed an adjudication committee to prospectively evaluate cardiovascular serious adverse events and death.

Pre-BLA meetings:

There were 3 pre-BLA meetings; on February 5, 2008 to discuss proposed structure and format of the BLA, on July 8, 2008 to discuss CMC aspects of the denosumab Program and on October 21, 2008 to discuss clinical and nonclinical aspects of the denosumab.

program. Important issues (primarily related to clinical aspects) discussed in these meetings were:

- May 31, 2008 was accepted as primary cut-off date for the supportive trials as it is the last subject last visit date for the largest clinical trial 20030216.
- FDA requested all available safety and efficacy data be submitted for the supportive studies, noting that trial synopses would not be sufficient.
- Amgen agreed to provide additional information in the BLA including a detailed explanation of the bone biopsy data, a complete analysis of all ECG data from studies for which this information was collected, and inclusion of CRFs from all subjects with "abnormal clinically significant" ECG results, a comprehensive evaluation of infections across all studies, including phase 1 studies, and final 48-month BMD data from Study 20040132 to be included in the 120-day safety update.

The BLA was submitted on 12/19/08 with the data cut-off date of May 31, 2008 as agreed upon between the Agency and the Applicant.

2.6 Other Relevant Background Information

(b) (4)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Applicant determined that there were Good Clinical Practice (GCP) and protocol violations at one clinical site in Lithuania (Site 803) for Study 20030216, based on an inspection by the State Medicine Control Agency under the Lithuanian Health Care Ministry and a joint Amgen, (b) (4) quality assurance audit. The audit identified evidence of scientific misconduct and significant noncompliance involving record keeping, reporting of adverse events, informed consent procedures, and oversight of the conduct of the trial and of the activities of sub-investigators. This site was subsequently closed and the data from this site was excluded from all safety and efficacy analyses. This site was not inspected by the Division of Scientific Investigations (DSI) because it was not included in any trial summaries.

Sites were chosen for inspection if they enrolled a large number of subjects, did not have a recent history of inspections, and had a proportionally increased number of protocol violations and/or low numbers of adverse events reported compared to other trial sites. Based on a review of site information and inspection records, the following domestic sites were chosen: 102 (Dr. Boling, Dr. Lee), 016 (Dr. Woodson), and 102 (Dr. Bolognese). The following international sites were chosen: 0216 in Ballerup, Denmark (Dr. Riis and Dr. Teglbjaerg) and 826 in Bialystok, Poland (Dr. Supronik).

Thus, the Division of Scientific Investigations (DSI) inspected 3 individual clinical trial sites (Sites 102, 631 & 826) that participated in Study 20030216 and 1 clinical site (Site 016) that participated in Study 20010223.

The inspection report is summarized below:

1. Site 102 (Study 20030216): Eric Lee, MD at Inland Rheumatology Clinical Research Inc. in Upland, CA (previously Eugene Boling, MD)
2. Site 016 (Study 20010223): Grattan C. Woodson III, MD at Atlanta Research Center in Decatur, GA
3. Site 631 (Study 20030216): Christence Stubbe Teglbjaerg, MD at the Centre for Clinical and Basic Research in Ballerup, Denmark (formely Dr. Bente Juel Riis, MD)
4. Site 826 (Study 20030216): Jerzy Supronik, MD at the NZOZ Centrum Medyczne Artur in Bialystok, Poland

Records reviewed at various sites included, but were not limited to, consent forms, subject eligibility criteria, randomization procedures, the primary efficacy endpoint, protocol deviations, concomitant medications, early discontinuations, adverse events, laboratory reports, applicant and monitor correspondence, IRB correspondence, and test article accountability. At Site 016 (Study 20010223), a Form FDA 483 was issued for an isolated finding of a subject who was dispensed and administered test article from an incorrect box (subject did receive the correct randomized test article). This inspectional finding was unlikely to impact data integrity. Review of all other records noted above revealed no significant discrepancies/regulatory violations. DSI's final assessment was that the data appear acceptable in support of the application.

In addition, Amgen, Incorporated (Thousand Oaks, CA) was also inspected for the review of, but not limited to, the following: organizational status and assigned responsibilities, monitoring plans, drug batch records, monitor training documentation, and monitoring reports. Select CRFs from each of the four investigators noted above were reviewed. Review of these records revealed no significant discrepancies/regulatory violations. DSI's final assessment was that the data appear acceptable in support of the application.

Finally, (b) (4) was inspected, but the EIR for this inspection is pending. A Form FDA 483 was not issued for any findings related to Protocol 20010223. Any observations/commentary of significance will be noted in an addendum after review of the final EIR.

3.2 Compliance with Good Clinical Practices

Studies submitted to BLAs 125,320 and 125,331 appear to have been conducted in compliance with a) their protocols, b) Independent Ethics Committee (IEC) requirements, c) informed consent regulations and d) International Conference on Harmonization / Good Clinical Practices Guidelines, with one notable exception.

The Applicant determined that there were Good Clinical Practice (GCP) violations at one clinical site in Lithuania (Site 803) for Study 20030216, based on an inspection by the State Medicine Control Agency under the Lithuanian Health Care Ministry and a joint Amgen/ (b) (4) quality assurance audit. This site was subsequently closed and the data from this site was excluded from all safety and efficacy analyses.

3.3 Financial Disclosures

The Applicant attempted to obtain financial disclosure information from investigators and sub-investigators for the studies listed in Table 2.

Table 2. List of Denosumab Clinical Studies for Which Financial Disclosure Information Was Requested

Study Number	Phase	Study Population or Description	Total No. of Subjects Enrolled
20030216	3	Treatment of Postmenopausal Osteoporosis	7868
20050141	3	Postmenopausal women with low BMD	1189
20050179	2	Postmenopausal women with low BMD	247
20050234	3	Postmenopausal Osteoporosis	504
20040132	3	Prevention of Postmenopausal Osteoporosis	332
20040144	2	Rheumatoid Arthritis	227
20050233	3	Rollover from Study 20010223	200
20060237	3b	Rollover from Study 20050141	311
20060232	3b	Postmenopausal women with low BMD	250
20060289	3	Rollover from Study 20030216	4900-5600
20040135	3	Women with non-metastatic breast CA on aromatase inhibitor with low BMD	252
20040138	3	Men with nonmetastatic prostate CA on androgen-deprivation therapy	1468
20040113	2	Women with advanced Breast CA with bone metastases without prior IV bisphosphonate tx	255
20040114	2	Men/women with/ solid tumors (except lung) or multiple myeloma	111
20050134	2	Men/Women with relapsed or plateau-phase multiple myeloma	96
20010223	2	Dose finding trial	412

Reviewer's Comments:

The majority of investigators in the 16 studies listed above did not have financial arrangements or interests to disclose as defined in 21 CFR 54.4. A total of 103 investigators or sub-investigators did not provide financial disclosure information for the studies listed above, despite numerous attempts by the applicant to obtain this information; this total may include duplicates as some investigators or sub-investigators may have participated in several studies. Twenty-six investigators in the 16 studies listed above had financial information to disclose and are listed in Table 3.

Table 3. Investigators with Disclosable Financial Arrangements or Interests

Investigator	Study	Financial Information / Category	No. subjects enrolled
(b) (4)	20030216	2,175 shares of Amgen stock	0/7868
	20040132		1/332
	20050134	Owns Amgen stock (undisclosed amount)	0/96
	20040113	Stock valued in excess of \$50,000	2/255
	20040114		0/111
	20040135	Approx. \$35,000 in lecture honoraria in 2005	3/252
	20040138	Research grant from Amgen (undisclosed amt)	2/1468
	20040135	1,000 shares of Amgen stock	0/252
	20050134	Preceptorship	0/96
	20040113	\$50,000 to conduct preclinical studies	0/255
	20050141	Contract with Amgen to fund a trial (undisclosed amount)	6/1189
	20040144	Compensation for consultation and honoraria (undisclosed amt)	0/227
	20030216	Amgen provided research support: AUS \$56,756, AUS \$11,350, and AUS \$50,000.	17/7868
	20040138	Each of his four children own 800 shares of Amgen stock	6/1468
	20040138	Amgen stock worth \$109,400	12/1468
	20030216	Amgen provided research support in the amount of \$100,000.	51/7868
	20040114	Amgen has several grants with his institution (UPMC) (undisclosed amount)	0/111
	20040114	Owns Amgen stock (undisclosed amount)	0/111
	20050234	Undisclosed amt of stock (held for > 10 years)	5/504
	20050134	Other Amgen applicanted trials	0/96
	20040113	Research grant (undisclosed amount)	1/255
	20030216	Amgen subsidized a trial – \$85,350.	1/7868
	20060289		1/4900
	20040138	Grant or research (undisclosed amount)	5/1468
	20030216	1,200 or 5,000 shares of Amgen stock*	13/7868
	20050141		8/1189
	20040144		14/227
	20050134	Grants to support research (undisclosed amt)	0/96
	20040138	Owns equity interest exceeding \$50,000	1/1468
	20040138	Undisclosed significant equity interest	8/1468
	20040144	Funding for clinical project (undisclosed amt)	0/227

* Applicant's summary lists discrepant amounts for (b) (4)
 Source: Financial Disclosure; section 1.3.4, BLA 125,320

Reviewer's Comments:

The trial sites with investigators who had financial information to disclose had limited enrollment compared to the total enrollment for the trial (7868 subjects for Study 20030216 and 332 subjects for Study 20040132).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Important issues related to CMC aspects of this application are as follows:

- The antibody was derived using XenoMouse technology to create a fully human antibody sequence within an IgG2κ framework. The denosumab manufacturing process consists of cell culture, harvest, recovery, and purification stages. The BI Pharma and ACO sites use the same process except for facility specific differences.
- Two processes (CP1 and CP2) were used for drug substance manufacturing. CP1 material came from master cell bank and was used in phase 1 trials. CP2 material comes from working cell bank and was used during phase 2. all pivotal phase 3 clinical trials. There were minor differences (b) (4) (b) (4) seen during development between these two processes. Non Human Primate PK studies and clinical BE studies have been performed to make sure there are not clinically significant changes between the denosumab manufactured through CP1 and CP2 processes. In vitro potency was measured by the homogeneous time resolved fluorescence (HTRF) lot release, reporter gene, and tartrate-resistant acid phosphatase (TRAP) assays and is found to be comparable for all drug substance and drug product. For detailed trial evaluation, please refer to CMC review.
- Denosumab has (b) (4) There is a difference in charge variants between ACO (Amgen Colorado) and BIP (Boehringer Ingelheim Pharma) (10% increase in main peak); BIP (b) (4) are more fully processed. The variation is due to cell culture raw materials and is bounded by base media and enzymatic reaction saturation. Variants have equal *in vitro* potency. Variation in denosumab is not expected to have a clinical effect.
- Difference in reporting of the buffer:
 - The formulation buffer was (b) (4) acetate (b) (4), sorbitol.
 - Labeling in BLA is 17 mM acetate, and 4.7% sorbitol. Range of actual concentration of excipients in Drug Product is (b) (4) acetate and (b) (4) (b) (4) sorbitol. The labeling reports average of concentrations. The range is due to behavior of the concentrated protein held on one side of the filter and of the formulation buffer components that can pass through, based on the charge and the bulk of the denosumab molecules.
 - Based on a list of the actual concentrations that have been measured for denosumab Drug Product, there appear to be no differences in actual concentration ranges among processes and manufacturing sites.

- 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).
- Drug Substance and Drug Product Stability- Stability programs conform to ICH guidance and data is sufficient to establish product shelf-life according to the CMC review. For details, please refer to CMC review.

4.2 Clinical Microbiology

Sections 3.2.S of the BLA pertaining to microbial control of the drug substance manufacturing process were reviewed by the Division of Manufacturing and Product Quality (DMPQ), Biotech Manufacturing Team (BMT). There were 6 amendments (as of now) to the BLA based on information requests. The drug substance aspect of the BLA, as amended, is recommended for approval from a CMC microbiology product quality perspective. Important CMC microbiology and product quality aspects of the drug substance are summarized below:

- The ACO facility was inspected by a team of investigators (Kalavati Suvarna, Ph.D., Sarah Kennett, Ph.D, Nancy Schmidt, Kimberley Hoefen, and Maan Abdulnyaem) from June 8, 2009 to June 12, 2009. No FDA form 483 was issued at the end of inspection (No violations found). The manufacturing process is microbially controlled at the ACO site. Hold time for all in process intermediates at the ACO site has been adequately validated for microbial control.
- The BI Pharma facility was inspected by a team of investigators (Kalavati Suvarna, Ph.D., Chana Fuchs, Ph.D and Sarah Kennett, Ph.D.) from May 11, 2009 to May 19, 2009. A 1-item FDA form 483 was issued at the end of inspection. Concerning issue was that a (b) (4)
(b) (4) In response to the 483 observation, the firm indicated that (b) (4)
(b) (4). The firm's response to the observation was reviewed by the International Compliance Branch within the Office of Compliance and found to be acceptable. The Manufacturing Assessment and Pre-Approval Compliance Branch indicated in an e-mail dated August 25, 2009 that there are no pending or ongoing compliance actions to prevent approval of STN 125320/0 at this time.
- The bioburden procedure for denosumab process was adequately qualified. The endotoxin procedure for denosumab drug substance analysis was adequately validated. The applicant was asked to provide calculation of the endotoxin limit based on worst-case minimal patient weight of 50 kg and the maximum single human dose for denosumab to determine the safety margin for the proposed endotoxin specification. The endotoxin drug substance specification for the postmenopausal osteoporosis indication is (b) (4) which is well below the threshold of human pyrogenic response. The endotoxin results for batches manufactured at ACO site (b) (4) varied from that manufactured at BI Pharma (b) (4). Although the endotoxin results from the two sites varied at

the two sites, the results at both sites were within the acceptance criteria and well below the threshold of human pyrogenic response.

- Section 3.2.P of the BLA pertains to drug product manufacture and was reviewed by the Division of Manufacturing and Product Quality (DMPQ)/ Biotech Manufacturing Team. Data and information supporting drug product sterility assurance and microbiology product quality was found to be satisfactory; no major CMC issues of concern were identified that are directly related to denosumab drug product using vial or syringe. However, during a recent surveillance inspection of the Amgen drug product manufacturing facility in Juncos, Puerto Rico, it was found that several (47 so far) complaints were reported to Amgen about broken syringes for other products using prefilled syringes, especially using auto injection device. This issue is being evaluated at present by ORA district inspectors and a recommendation on the GMP compliance status of the facility is pending.

4.3 Preclinical Pharmacology/Toxicology

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

- Species specificity: 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: 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.
- Fetal toxicity: Embryofetal reproductive toxicity studies presented in this application 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 trial 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 trial is postmenopausal women, this may not be 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).

- Immune suppression: Possible signs of immune suppression were noted at denosumab doses ≥ 10 mg/kg in a 12-month toxicity trial 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) trial, 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.
- Bone growth and tooth eruptions: 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 10 times (10 mg/kg dose) the clinical exposure had abnormal growth plates.
- Ocular effects: No remarkable ocular effects were noted in the 1-month or 12-month toxicity studies with denosumab treatment in monkeys. The only histopathological finding was lymphocyte foci in the eye of 1 of 3 HD females after 6 months of dosing. In trial 104105 in the monkey, 125 I-radiolabeled denosumab was found in the cornea of the eye for up to 672 hours postdose (1 mg/kg) at levels higher than that in serum. At 1344 hrs, radioactivity could no longer be detected in the cornea. When compared to amounts in serum at similar timepoints, denosumab levels in the cornea were high, but these higher amounts of radiolabel in the cornea at 672 hours are likely not as much a function of 'drug accumulation in the cornea', but that blood levels at 672 hours were very low and close to the lower limit of quantitation, indicating that radiolabel remains in the cornea longer than in the blood as cornea is an avascular structure. No remarkable ocular effects were noted in the 1-month or 6/12-month toxicity studies with denosumab treatment in monkeys. Tissue cross reactivity studies with human, monkey, rat and rabbit tissues also did not show binding of denosumab to ocular tissues.
- Cardiovascular toxicity: Denosumab is not pharmacologically active in mice or rats and as a result, cardiovascular safety assessments were conducted in monkeys. Preclinical evaluations included a 12-month toxicology trial in cynomolgus monkey in which doses of 0, 1, 10, and 50 mg/kg were administered subcutaneously at monthly intervals (corresponding human equivalent dose of ~ 0, 20, 200 and 1000 mg). Minimal-slight focal myocarditis/pericarditis was observed in one HD male that was an unscheduled death (death proposed to be due in part to infection of GI tract). Also, slight myocardial degeneration/necrosis was observed in one HD denosumab treated male at the 6 month sacrifice, and in one HD male after recovery. Minimal to

slight inflammatory cell foci were observed in male and female treated animals at all sacrifices (6 months, 12 months and recovery), but was also observed in 3 female control animals. In examining the potential for arterial calcification in these animals, no calcification was noted by the investigator. The pharmacology toxicology reviewer did not consider these preclinical findings concerning for a potential cardiac signal. The Sponsor also conducted a safety pharmacology study that included examination of cardiovascular measurements (arterial blood pressure and heart rate) following a single dose of denosumab (0, 0.3, 3, or 30mg/kg) in male monkeys. No remarkable differences in blood pressure or heart rate were observed at any dose between the investigated timepoints of predose (-60min) to 168hrs post dose.

- Fracture Healing: Only one trial in the nonclinical package specifically examined fracture healing (Study R2006458). The purpose of this trial was to evaluate the denosumab and alendronate (ALN) on fracture healing. Knock-in mice that were created to express a chimeric form of human RANKL had transverse fractures produced in the right femora, and were treated with denosumab, ALN, or PBS (control). The animals were sacrificed at either 21 or 42 days post-fracture and both the fracture and contralateral femora were analyzed by microCT, torsion testing, and histological evaluation. The results show that although in both denosumab and ALN mice fracture healing was morphologically delayed, mechanical strength was not negatively affected. In fact, after 42 days AMG and ALN mice showed increases in strength and stiffness. Callus remodeling was, however, noticeably delayed compared to control bones. Both AMG and ALN bones had large amounts of mineralized cartilage and hypertrophic chondrocytes present at day 21, whereas control bones had almost no mineralized cartilage remaining. In addition, AMG bones showed a decreased amount of woven bone formation. Denosumab was able to virtually abolish osteoclastogenesis, while ALN did not, indicating ALN primarily works by inhibiting mature osteoclast function.
- Bone Quality (histomorphometry): 16 month toxicity trial in monkeys included histomorphometry evaluation of iliac biopsy, which showed that denosumab prevented ovariectomy(OVX)-induced bone loss in the ilia as early as 6 months, continuing (at 25 mg/kg) through 12 months as measured by BV/TV (bone volume) and trabecular number. Bone formation was significantly decreased (at both doses: 25 mg/kg and 50 mg/kg) in denosumab treated animals compared to OVX controls to levels similar to or less than sham controls. Denosumab-negative animals (due to antibody formation) demonstrated the reversal of treatment effects, with values for many of the parameters having smaller changes compared to denosumab-positive animals at 6 months, and progressing to control levels by 12 months. Percent difference of group mean for the single and double tetracycline labeled surface was -94% to -100% in the denosumab treated group at trial termination in the cancellous bone sites. This means that similar to clinical observations, very few biopsies had double tetracycline labeling present at the trial termination, indicating profound suppression of new bone formation.

- Absorption, Distribution, and Excretion in Cynomolgus Monkeys Following a Single Subcutaneous Administration of I-125 radiolabelled denosumab: The highest concentrations of radioactivity were observed in the dose site skin, dose site subcutaneous tissue, thyroid/parathyroid, axillary lymph nodes, inguinal lymph nodes, serum blood, lungs, spleen and ovaries following administration of 0.1 or 1 mg/kg of ¹²⁵I-denosumab. The major route of elimination of ¹²⁵I-denosumab and/or radioactively labeled protein fragments was in the urine, as 76-95% of the administered activity was present in the urine 672 hours postdose. Fecal elimination represented 1.1 to 3% of the administered radioactivity.
- Immunosuppression: In review of the 6/12-month monkey trial, it was noted that denosumab showed possible signs of immune suppression at doses ≥ 10 mg/kg, based on the unscheduled deaths of 2 males (50 mg/kg) due to protozoal infection, and an increased incidence of abscesses of the teeth and jaws in females treated at 10 and 50 mg/kg. In the 16-month pharmacology (bone quality) trial, there were no remarkable findings related to test article in the assay assessing T-cell dependent antibody response. However, with blood immunophenotyping, the total lymphocyte count was slightly and statistically significantly decreased at pre-necropsy for the high dose. Absolute counts of CD3+/CD8+ cytotoxic T lymphocytes were also slightly and statistically significantly decreased at the high dose compared to ovariectomized controls at pre-necropsy. The Applicant's justification for these changes is that "Similar variations were also found during the pretreatment period, thus these changes are considered to be within the normal range of the assay." While the 2 males treated at the high dose of 50 mg/kg in the 6/12-month toxicology trial that had unscheduled deaths did have a protozoal infection of the gastrointestinal tract, a number of both control and treated animals (47/64 animals) also had infections, based on frequent diarrhea and presence of giardia lamblia and/or cryptosporidium in the feces. The incidence of diarrhea was also reportedly higher in this trial than the typical incidence in this test facility, though the explanation was unknown. So the infections cannot necessarily be considered treatment-related, but it could be concluded that since the 2 deaths occurred in the high dose population, that these animals may have had an impaired ability to control the infection due to treatment with denosumab. Therefore, a healthy population may not experience these effects, but it is unclear whether effects would be seen in an immune-compromised population. The doses where immunosuppressive potential was noted (10 and 50 mg/kg) are 10-50 times the recommended human dose of 60 mg based on body weight.

4.4 Clinical Pharmacology

Clinical pharmacology of denosumab has been evaluated in 13 clinical pharmacology and biopharmaceutics studies conducted in healthy volunteers and patients performed from June 2001 to September 2008. There were 4 pharmacokinetics (PK) and tolerability studies conducted in healthy volunteers, 2 PK and tolerability studies conducted in cancer patients, 2 dose-ranging studies conducted in PMO patients, 1

intrinsic factor PK trial conducted in patients with renal impairment, and 1 extrinsic factor PK trial conducted in patients with prior exposure to bisphosphonates.

4.4.1 Mechanism of Action

RANK ligand exists as a transmembrane or soluble protein. RANK ligand is essential for the formation, function, and survival of osteoclasts, the cell type responsible for bone resorption. Denosumab binds with high affinity and specificity to RANK ligand, preventing RANK ligand from activating its receptor, RANK, on the surface of osteoclasts and their precursors. Prevention of the RANK ligand/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass in both cortical and trabecular bone.

4.4.2 Pharmacokinetics

In an open-label, randomized, single-dose, parallel-group trial (Study 20050146) in healthy men and women volunteers (n=73) having a mean age of 33.6 years (range 18 to 64 years), the mean maximum serum denosumab concentrations (C_{max}) of 6.75 µg/ml (standard deviation [SD]: 1.89 µg/ml) was reached in the median time of 10 days (range: 3 to 21 days) following a 60 mg SC dose after at least 12 hrs of fasting prior to denosumab administration. After C_{max} , serum denosumab concentrations decline over a period of 4 to 5 months with a mean half-life of 25.4 days (SD: 8.5 days; n=46; Study 20010223). No accumulation in serum denosumab concentrations was observed with repeated doses of 60 mg once every 6 month (Q6M), and denosumab PK did not appear to change with time (up to 4 years exposure). Denosumab PK was not affected by the formation of binding antibodies to denosumab and was similar in men and women.

Approximately dose-proportional increases in exposure (based on $AUC_{0-\tau}$) were observed for doses ≥ 60 mg (in the range of fixed doses of 60 to 210 mg in Study 20010223 in the PMO population). However, denosumab displayed a dose-dependent, nonlinear PK profile most pronounced where the serum denosumab concentration drops below approximately 1 µg/ml (i.e., saturable mechanism of elimination with a faster rate). Considering that denosumab is a monoclonal antibody and there is no evidence that immunogenicity affects the PK of denosumab, target-mediated disposition appears to be one of the possible mechanisms that affect the PK of denosumab administered subcutaneously.

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, considering that the effect of biologics on CYP activities is unknown, a post-marketing commitment (PMC) recommendation is being made to the Applicant to address denosumab's effect on CYP activities and drug interaction potential.

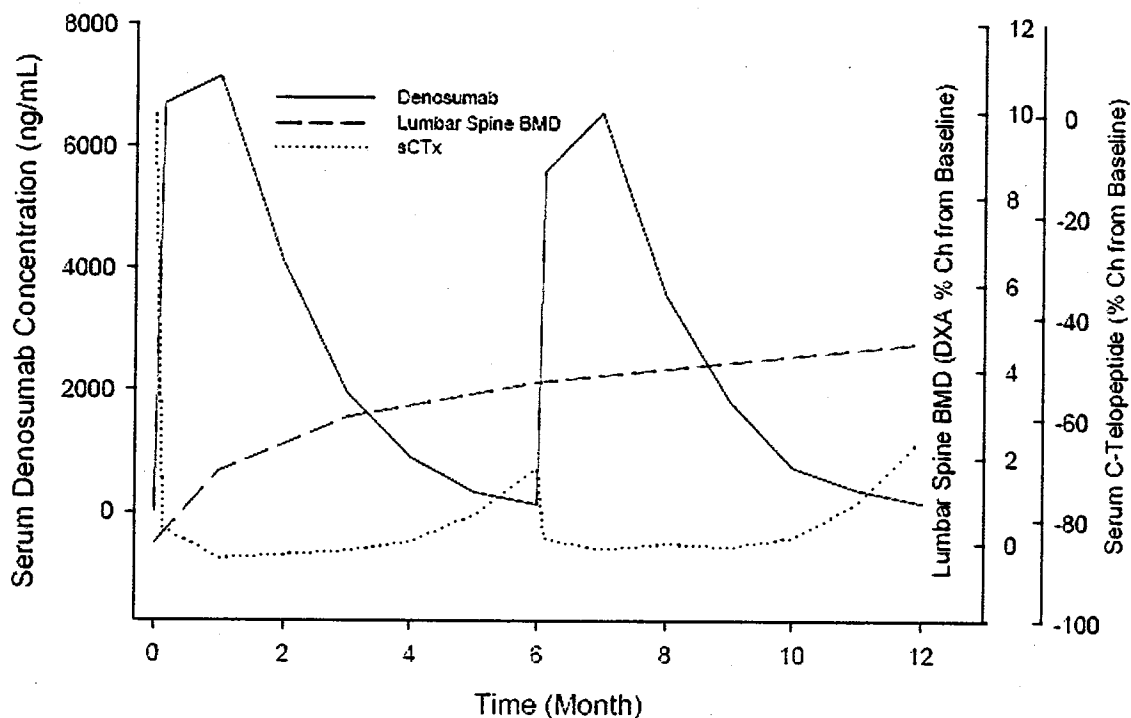
A trial including transition from a bisphosphonate to denosumab was conducted (Study 20050241) and showed that the PK of denosumab was not altered in subjects who transitioned from bisphosphonates to denosumab.

A renal impairment trial (Study 20040245) was conducted and included 55 patients with normal, mild, moderate, severe, and end-stage renal disease, defined by creatine clearance (CrCL). Overlap was observed in denosumab exposure across renal impairment cohorts, and no notable relationship was apparent between denosumab pharmacokinetics and renal impairment. No dose adjustment is necessary in patients with renal impairment from pharmacokinetic perspective.

4.4.3 Pharmacodynamics

Denosumab administration resulted in significant inhibition of bone resorption, as assessed by reductions in serum levels of Type 1 C-telopeptide (CTX). In clinical studies, treatment with 60 mg of denosumab resulted in rapid reduction in the bone resorption marker serum CTX 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 CTX 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 CTX and Lumbar Spine BMD following Two 60 mg Q6M Doses of Denosumab to Post menopausal Women with Low BMD (Study 20010223)



4.4.4 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.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

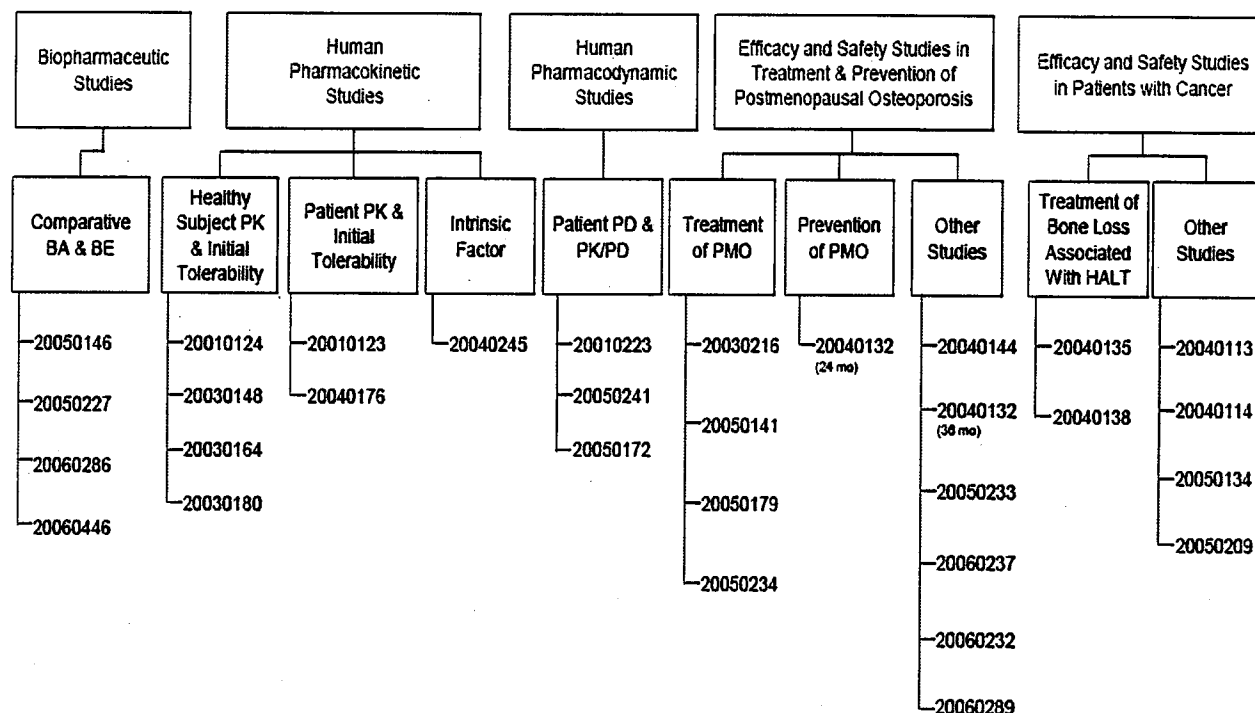
This submission contains clinical trials evaluating denosumab for the prevention and/or treatment of osteoporosis in postmenopausal women and subjects with prostate cancer or breast cancer receiving hormone ablative therapy. The Applicant seeks 4 different indications for denosumab and each of these indications was assigned a separate Biologics Licensing Application (BLA) number for administrative purposes.

Table 4. Table of Primary Studies

BLA No. (Division)	Indication	Primary Trial No.	Trial Design
125,320 (DRUP)	Treatment of osteoporosis in postmenopausal women	20030216	3-year multinational randomized, placebo-controlled, parallel group trial evaluating denosumab on the incidence of new vertebral fracture in 7,808 postmenopausal women with osteoporosis
125,331 (DRUP)	Prevention of osteoporosis in postmenopausal women	20040132	4-year multicenter randomized, placebo-controlled, parallel group trial evaluating denosumab on lumbar spine BMD loss in 332 subjects with low bone mass. I.P. administered for 2 years, then monitored for an additional 2 years ("off-treatment").
125,332 (DBOP)	Prevention and treatment of bone loss in patients undergoing hormone ablation for breast cancer	20040135	4-year multinational, multicenter, double-blind, placebo-controlled trial in 252 patients with breast cancer receiving adjuvant aromatase inhibitor therapy following definitive local therapy. I.P. administered for 2 years, then monitored for an additional 2 years ("off-treatment")
125,333 (DBOP)	Prevention and treatment of bone loss in patients undergoing hormone ablation for prostate cancer	20040138	5-year, multinational, multicenter, double-blind, placebo-controlled trial in men with prostate cancer undergoing androgen deprivation therapy (ADT) with gonadotropin-releasing hormone (GnRH) agonists or following orchiectomy. Trial enrolled 1,468 subjects who were \geq 70 years, or $<$ 70 years with low bone mass or history of fracture. I.P. administered for 3 years, then monitored for an additional 2 years ("off-treatment").

A summary of all denosumab clinical studies in the initial BLA submission is provided in Figure 3. In total the Applicant completed 12 Phase 1 trials including pharmacokinetic and pharmacodynamic trials, as well as a renal impairment trial. The Applicant completed 7 Phase 2 trials, including a dose-finding trial (20010223), and 11 Phase 3 clinical trials. Appendix 2 provides a brief summary of the trial design for the Applicant's Phase 1, Phase 2 and Phase 3 trials.

Figure 3. 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.

5.2 Review Strategy

5.2.1 Primary Review Strategy

The following approach was used to conduct the clinical review of this BLA:

- All the submitted material relevant to the use of denosumab in a postmenopausal population was analyzed.
- The focus of the efficacy review in the postmenopausal population was primary efficacy trial 20030216 for the treatment indication and primary efficacy trial 20040132 for the prevention indication. Because the prevention and treatment of osteoporosis are 2 different indications and represent two different populations of patients, the review of efficacy data is not pooled and the findings of trial 20030216 and trial 20040132 are reviewed separately under the appropriate indication.
- The focus of safety review was trial 20030216 and 20040132. In general, the safety data from these studies are pooled except for safety issues that were unique to either trial population.

- Supportive safety data included findings from bone histomorphometry studies.
- Independent analyses of datasets of the original efficacy and safety variables were conducted to verify the Applicant's findings.

The data for the postmenopausal population were primarily reviewed by two clinical reviewers in DRUP, specifically Vaishali Popat (treatment indication) and Adrienne Rothstein (prevention indication). Comments throughout the review that state "this reviewer" could represent the work of one or both reviewers because the clinical review was shared between them. The data for the cancer population were primarily reviewed by Suzanne Demko, a clinical reviewer in DBOP.

In addition, the consultation was obtained from the following divisions to assist with the analyses and interpretation of specific review questions:

- Infections – Division of Anti-Infectives and Ophthalmologic Products
- ONJ – Division of Dermatology and Dental Products
- Skin/Hypersensitivity Events – Division of Dermatology and Dental Products
- Cardiovascular Events – Division of Cardiorenal Products
- QT Review – Division of Cardiorenal Products

5.2.2 QSPG Review Strategy

The Quantitative Safety and Pharmacoepidemiology Group (QSPG) at the Agency provided Statistical Safety Analyses for this review. These Statistical Safety Analyses focused on the following Adverse Events of Interest (AEI) as defined by the applicant, specifically hypocalcemia, cardiovascular events, infections, fracture healing complications, ONJ, new primary malignancies, immunogenicity and hypersensitivity.

The basic methodology for the Statistical Safety Analyses employs categorical data analysis (see *Statistics for Epidemiology* by Nicholas P. Jewell and *Categorical Data Analysis* by Alan Agresti), supplemented by other topics from survival analysis such as time to event analysis and Kaplan Meier curves. Each AEI is associated with a number of MedDRA Preferred Terms (PTs). Starting with the list of terms identified by the applicant, each reviewer considered additional PTs from the MedDRA hierarchy derived in consultation with a clinician. Additional analyses based on High Level Term (HLT), HLGT (High Level Group Term), System Organ Class (SOC) and Standardized MedDRA Queries (SMQs) were also considered. For each AEI, the reviewer tabulated results for the double blind, randomized clinical trials for which there was a comparator, using the safety population. The starting point for the QSPG reviewers' analyses were the four 2-arm placebo controlled trials (20030216, 20040132, 20040135, and 20040138). Risk differences (RDs), risk ratios (RRs), Odds Ratios (ORs) were computed for the AEIs and associated 95% confidence intervals were found. Additionally, p-values associated with AEIs were also computed using chi-squared and Fisher's exact statistics.

The Statistical Safety Analyses provided by QSPG are exploratory in nature and the confidence intervals and p-values should not be used for statistical inference, because the trials were not designed for safety endpoints based on AE data. Instead, the confidence intervals and p-values should be interpreted as showing the magnitude and strength of the relationship between the treatment group and placebo group.

In addition to considering the four primary placebo controlled trials, QSPG reviewers expanded their review to include all double blind, randomized comparative trials. Based on this expanded group various pooling strategies of the trials were employed:

- Two placebo controlled PMO trials
- All seven controlled PMO trials
- All nine controlled trials
- Two largest placebo controlled trials (Cardiovascular events only)

The two hormone ablative studies were not pooled due to differences in the trial populations due to gender and age.

Additional analyses were performed using time to event, Kaplan Meier curves, and the distribution of AEs with respect to time were also considered. Reviewers considered laboratory data, medical history, exposure, and dispositions domain as appropriate. The results of these Statistical Safety Analyses provided by QSPG are mentioned in the review as appropriate.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Phase 2 Dose-Finding Study (20010223)

Study 20010223 was a Phase 2 dose finding trial 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 trial 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 trial. There were approximately 40 subjects per dosing cohort, for a total of 412 subjects (319 denosumab, 46 placebo, 47 alendronate). The trial design and objectives were adequate to assess dose response.

The primary endpoint for Study 20010223 was the percent change from baseline to Month 12 in the bone mineral density (BMD) of the lumbar spine (L1 through L4) for the placebo and denosumab treatment arms as measured by DXA. At Month 12, denosumab increased BMD of the lumbar spine from baseline in all denosumab cohorts (range: 3.0% to 6.7%). The differences between each denosumab cohort and placebo (- 0.8% change from baseline) were statistically significant ($p < 0.001$). Sensitivity analyses supported these findings. The dose that the Applicant chose to use in Phase 3 trials is shaded in Table 5 below.

Table 5. Lumbar Spine BMD by DXA – Percent Change From Baseline to Month 12 (ANCOVA Model, Primary Efficacy Subset, LOCF)

Treatment Arm / Dosing Cohort	Difference from Baseline		Difference from Placebo		
	n	Least Squares Mean (SEM) ^a	Least Squares Mean (SEM) ^a	95% C.I.	P-value ^b
Placebo (N = 46)	46	-0.67 (0.46)	--	--	--
Denosumab 6 mg q3m (N = 44)	40	4.14 (0.48)	4.81 (0.65)	3.53, 6.09	<0.001
Denosumab 14 mg q6m (N = 54)	53	2.92 (0.42)	3.59 (0.61)	2.39, 4.78	<0.001
Denosumab 14 mg q3m (N = 44)	43	4.51 (0.47)	5.18 (0.64)	3.92, 6.44	<0.001
Denosumab 30 mg q3m (N = 41)	40	5.99 (0.49)	6.66 (0.65)	5.38, 7.94	<0.001
Denosumab 60 mg q6m (N = 47)	46	4.29 (0.46)	4.96 (0.63)	3.73, 6.20	<0.001
Denosumab 100 mg q6m (N = 42)	41	5.33 (0.48)	6.00 (0.65)	4.72, 7.28	<0.001
Denosumab 210 mg q6m (N = 47)	46	4.85 (0.46)	5.52 (0.63)	4.29, 6.76	<0.001
Alendronate 70 mg qw (N = 47)	46	4.49 (0.45)	5.16 (0.63)	3.92, 6.40	<0.001

N = Number of subjects enrolled.

n = Number of subjects with values at baseline and 1 or more post baseline visits at or prior to month 12.

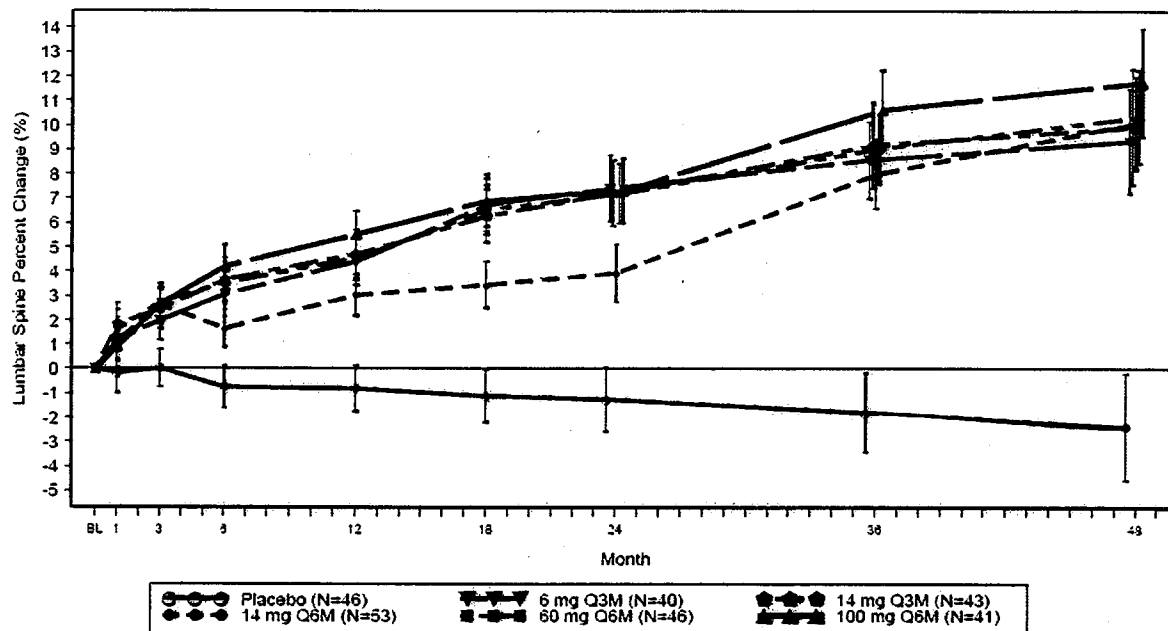
a Based on ANCOVA model adjusting for treatment, geographical location, and baseline value.

b p-values for denosumab vs. placebo are adjusted for multiple comparisons using Hochberg's procedure. Nominal p-value is reported for alendronate vs. placebo.

Source: Clinical Study Report for Study 20010223, Table 14-4.3.9.1, pages 529-531 of 9933.

Dose-response relationship data for lumbar spine BMD in the denosumab continuous treatment cohorts are shown in Figure 4. In the first 24 months of the trial, 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 trial, 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 trial; this group was classified as the continuous treatment cohort.

Figure 4. Study 20010223 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/amg182/osteo/20010223/analysis/final_48mon/graphs/program/g_bmdxa_lsm_95ci.sas
 Output: g1-01_003_002_bmdxa_lsm_95ci_bmd_spine_cont_dnaab_noaln.cgm (Date Generated: 12JUL2007: 7:59:57)
 Source Data: adamr.abmdxa

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

Table 6. Study 20010223 – Percentage Change from Baseline in Serum CTX

Visit mo #	Placebo		Den. 6 mg q3m		Den. 14 mg q3m		Den. 30 mg q3m		Den. 14 mg q6m		Den. 60 mg q6m		Den. 100 mg q6m		Den. 210 mg q6m		Alen 70 mg qw	
	n	mdn	n	mdn	n	mdn	n	mdn	n	mdn	n	mdn	n	mdn	n	mdn	n	mdn
day 4	45	-0.6	42	-68.4	44	-74.5	40	-79.3	52	-75.9	47	-81.5	41	-79.7	46	-82.9	44	-23.3
1	45	-4.0	38	-84.6	42	-86.2	39	-86.3	51	-86.3	44	-87.6	41	-86.2	44	-87.6	46	-61.8
2	42	-5.6	39	-76.5	41	-85.6	35	-85.1	53	-82.8	44	-86.9	39	-85.6	46	-86.4	45	-64.2
3	42	-2.2	37	-57.4	39	-78.0	37	-79.4	52	-75.9	45	-86.1	40	-83.9	46	-86.9	46	-64.6
4	40	1.5	39	-85.5	38	-86.3	35	-85.1	51	-61.8	45	-84.4	35	-82.6	43	-85.9	45	-66.4
5	40	1.2	36	-79.5	38	-82.1	33	-81.3	51	-45.9	44	-78.9	38	-78.5	44	-84.9	44	-68.9
6	38	-0.5	37	-64.9	38	-74.2	33	-77.9	50	-34.8	43	-69.8	38	-72.0	43	-82.9	34	-65.5
6, day 3	35	6.6	35	-78.6	35	-84.2	32	-82.8	46	-76.9	42	-83.8	34	-82.1	41	-85.5	34	-70.3
7	37	-5.3	35	-83.8	39	-80.8	34	-80.6	50	-84.1	44	-85.8	38	-81.7	42	-85.2	45	-66.3
8	39	2.6	37	-79.9	37	-80.4	30	-84.5	50	-82.1	43	-84.5	36	-82.5	42	-85.5	41	-69.1
9	39	6.7	36	-64.4	38	-75.5	32	-81.3	49	-74.8	44	-85.3	38	-81.0	42	-85.3	44	-66.5
10	39	-1.0	35	-84.0	36	-81.6	31	-85.8	49	-59.5	43	-83.5	38	-80.4	43	-84.5	42	-65.6
11	39	0.2	36	-76.9	36	-82.5	31	-85.4	47	-39.1	42	-76.8	36	-79.9	41	-82.3	44	-68.2
12	36	-0.7	35	-55.9	36	-61.9	31	-73.4	47	-13.6	41	-63.1	36	-69.4	42	-71.7	40	-67.2
15	34	3.8	34	-51.3	35	-68.0	28	-83.2	45	-74.4	40	-86.5	37	-80.5	40	-84.5	42	-64.4
18	34	14.6	34	-52.4	33	-70.5	27	-80.7	43	4.0	39	-62.5	34	-64.6	38	-73.4	37	-68.7
21	34	11.5	35	-49.6	35	-66.5	28	-71.6	41	-74.3	40	-85.4	31	-68.2	36	-86.7	37	-65.2
24	32	7.1	30	-46.6	32	-52.8	25	-68.9	38	3.6	39	-58.1	31	-57.2	33	-79.3	38	-64.7
30	28	0.6	28	-48.5	24	-55.3	21	72.3	35	-60.8	37	-47.8	27	-40.5	33	59.1	33	-40.4
36	29	-12.0	30	-50.7	24	-51.5	22	58.2	31	-49.8	36	-42.9	27	-41.7	36	81.3	32	-33.8
42	23	-6.4	27	-54.3	21	-35.2	16	-49.1	30	-49.4	35	-41.3	24	-45.0	31	42.2	27	-37.6
48	27	-8.1	29	-33.1	24	-25.5	16	-41.1	34	-38.9	37	-39.8	24	-41.1	30	9.9	29	-33.3

Mdn = median; Mo = month

Reviewer's Comments:

- *There does not appear to be a dose related effect on CTX levels*
- *CTX levels are decreased soon after denosumab administration. This percent decrease from baseline in CTX generally exceeds alendronate at most time points measured, except for the denosumab 6mg Q3months and 14 mg Q6months dosing cohorts.*
- *In the 14 mg Q6month cohort, CTX levels approach or exceed baseline prior to the next dosing interval at some later time points in the on-treatment period. This attenuation of effect is not observed with the other denosumab cohorts.*
- *In the off-treatment period, CTX levels increase in the denosumab cohort, but do not completely return to baseline at the time points assessed in this trial.*

Table 7. Study 20010223 – Percentage Change from Baseline in Bone Specific Alkaline Phosphatase

	Placebo		Den. 6 mg Q3m		Den. 14 mg Q3M		Den. 30 mg Q3m		Den. 14 mg Q6m		Deno. 60 mg Q6m		Den. 100 mg Q6m		Den. 210 mg Q6m		Alen 70 mg Qw	
Mo	n	mdn	n	mdn	n	mdn	n	mdn	n	mdn	n	mdn	n	mdn	n	mdn	n	mdn
1	44	12.6	38	-2.8	40	-7.4	39	-11.3	51	-1.6	44	-10.4	41	-2.2	44	-13.8	46	-7.4
3	41	13.4	37	-49.1	39	-52.7	36	-59.4	50	-48.0	45	-57.0	39	-48.8	45	-56.5	45	-41.1
6	38	-1.8	37	-55.6	37	-61.2	32	-67.1	49	-40.1	43	-57.7	36	-62.7	42	-61.1	44	-56.6
9	37	-2.8	36	-61.6	37	-63.5	32	-69.1	47	-60.4	44	-65.6	38	-68.2	42	-66.3	44	-60.9
12	36	10.5	35	-61.1	36	-56.1	31	-63.1	47	-35.2	40	-59.3	36	-58.7	42	-52.8	39	-56.5
15	34	14.2	34	-49.3	35	-50.4	27	-57.9	44	-43.7	40	-55.6	37	-55.2	40	-54.8	40	-45.9
18	33	27.6	34	-44.6	32	-44.7	25	-50.1	43	-18.9	39	-40.3	33	-44.4	38	-43.3	37	-39.6
21	34	24.4	34	-38.6	35	-43.8	26	-44.7	40	-42.2	39	-44.2	31	-41.3	34	-43.2	36	-42.4
24	32	23.5	30	-40.0	32	-34.3	25	-45.8	38	-14.1	37	-38.2	31	-40.5	33	-42.7	39	-40.0
30	28	18.6	27	-34.6	23	-39.6	21	13.9	34	-47.0	35	-40.5	27	-39.2	32	23.8	32	-22.6
36	29	14.8	29	-34.4	24	-40.0	22	48.1	31	-43.9	36	-36.5	26	-37.9	34	68.7	31	-11.0
42	24	14.9	27	-37.7	21	-32.3	16	-34.4	30	-45.5	35	-37.6	23	-37.5	31	47.5	27	-14.1
48	27	22.2	29	-11.5	24	-19.4	16	-36.4	34	-42.1	37	-28.7	24	-37.4	30	41.3	29	-7.1

Mdn = median; Mo = month

Reviewer Comments:

- *There does not appear to be a dose-related effect on bone-specific alkaline phosphatase (BSAP)*
- *The levels of BSAP measured in the on-treatment and off-treatment period are highly variable.*
- *The percent decrease from baseline in BSAP with denosumab is similar to that observed with alendronate in the on-treatment period, except for an attenuation of effect prior to the next dosing interval in the denosumab 14 mg Q6month cohort.*
- *In the off-treatment period, BSAP levels increase in the denosumab cohort, but do not completely return to baseline in general, except for the 210 mg Q6months cohort which had an increase over baseline in the off-treatment period.*

The Applicant selected one dose (60 mg SC Q6months) for the two Phase 3 primary efficacy trials for the postmenopausal population, including Study 20030216 for the treatment of postmenopausal osteoporosis and Study 20040132 for the prevention of postmenopausal osteoporosis. The Applicant provided the following rationale for the dose selection:

"Evaluation of markers of bone resorption (e.g., 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 \geq 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."

Reviewer Comments:

Trial 20010223 was adequate overall to determine the dose for subsequent Phase 3 trials. The Applicant's choice of a fixed denosumab dose of 60 mg Q6months for trials in the prevention and treatment of osteoporosis was considered acceptable, however, given the results, the lack of a 30mg q6 month dose does not allow a determination of whether the chosen 60 mg dose is truly the minimal effective dose.

5.3.2 Phase 3 Pivotal Studies in Postmenopausal Women

The Applicant is seeking approval for denosumab in the treatment of osteoporosis. Efficacy for this indication is primarily based on the findings from one large adequate and well controlled Phase 3 trial (Study 20030216). This 3-year trial enrolled 7,868 subjects. Note that 60 enrolled subjects from 1 clinical site (site 803 in Lithuania) were completed excluded from all safety and efficacy analyses due to GCP violations.

The Applicant is also seeking approval for denosumab in the prevention of osteoporosis. Efficacy for this indication is primarily based on the findings from one large adequate and well controlled Phase 3 trial (Study 20040132). This 4-year trial enrolled 332 subjects. Subjects received treatment with investigational product for 2 years and were then followed for an additional 2 years for trial "off-treatment" effects.

These two primary efficacy studies in the postmenopausal population are thoroughly reviewed in the appendix (section 9.4). Table 8 below briefly compares these two studies.

Table 8. Comparison of the Two Pivotal Studies in the Postmenopausal Osteoporosis Population

	Study 20030216	Study 20040132
Phase	3	3
Number of subjects	7868*	332
Countries	32	2 (U.S. & Canada)
Denosumab dose	60 mg SC Q6months	60 mg SC Q6months
Duration	3 years	4 years (2 years on-treatment, 2 years off-treatment)
Primary Endpoint	Subject incidence of new morphometric vertebral fractures at 3 years	Percent change from baseline in lumbar spine BMD at 24 months
Inclusion criteria		
Subject age	60-90 years	≤90 years
Bone Mineral Density	T-score -2.5 to -4 at lumbar spine or total hip	T-score -1.0 to -2.5 at lumbar spine
Years post menopause	Not specified	> 6 months postmenopause (confirmed by FSH if recent or uncertain); stratified as <5 years or ≥ 5 years
Exclusion criteria		
Prior fracture	Any severe or > 2 moderate vertebral fractures	None after age 25 years
T-score	< -2.5 at lumbar spine and/or total hip, but ≥ -4.0 at both locations	Lumbar spine between -1.0 and -2.5

* 60 subjects from 1 clinical site excluded due to GCP violations.

Source: Clinical Study Reports, Study 20030216 and Study 20040132

In addition, in the current application, there are two indications for denosumab currently under review in the Division of Biologic Oncology Products (DBOP). One proposed indication is the treatment and prevention of bone loss in patients undergoing hormone ablation for breast cancer. Efficacy for this indication is primarily based on the findings from one large adequate and well controlled Phase 3 trial (Trial 20040135). This 4-year trial enrolled 252 subjects. Subjects received treatment with investigational product for 2 years and were then followed for an additional 2 years. A second indication in the cancer population is the treatment and prevention of bone loss in patients undergoing hormone ablation for prostate cancer. Efficacy for this BLA is primarily based on the findings from one large adequate and well controlled Phase 3 trial (Trial 20040138). This 5-year trial enrolled 1,468 subjects. Subjects received treatment with investigational product for 3 years and were then followed for an additional 2 years.

6 Review of Efficacy

Efficacy Summary

Treatment indication: For the proposed indication “Treatment of osteoporosis in postmenopausal women”, the Applicant demonstrated in one large adequate and well-controlled trial (trial 20030216) that treatment with denosumab significantly reduced the incidence of new vertebral fracture in women with osteoporosis compared to placebo. For the primary endpoint new vertebral fractures, treatment with denosumab demonstrated a 4.8% absolute risk reduction and a 68% relative risk reduction in fracture incidence (p-value <0.0001). Efficacy results of secondary endpoints were supportive of the findings of the primary endpoint.

Prevention indication: For the proposed indication “Prevention of osteoporosis in postmenopausal women”, the Applicant demonstrated in one adequate and well-controlled trial (trial 20040132) that treatment with denosumab significantly increased lumbar spine bone mineral density (BMD) compared to placebo in postmenopausal women with low bone mass. The mean change from baseline in lumbar spine BMD was +6.5% for denosumab compared to -0.6% for placebo at month 24; the mean placebo-subtracted change in BMD for denosumab was +7% at month 24 (p<0.0001). Efficacy results of secondary endpoints were supportive of the findings of the primary endpoint.

In summary, treatment with denosumab achieved statistically significant and clinically meaningful improvements in primary endpoint and key secondary endpoints in both primary efficacy trials.

6.1 Treatment of Osteoporosis in Postmenopausal Women

6.1.1 Methods

This section of the review summarizes the results from trial 20030216, the primary efficacy Phase 3 clinical trial for treatment of osteoporosis in postmenopausal women.

Design:

Trial 20030216 was a three year, randomized, double-blind, placebo-controlled, multicenter trial of postmenopausal women with osteoporosis.

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

6.1.2 Demographics

All participants were women, a majority of whom were Caucasian (approximately 93%). The mean age at randomization was 72 years and 32% of the enrolled population was \geq 75 years old. The mean BMI was 26 kg/m² and the average number of years since menopause was 24 years. At baseline, morphometric vertebral fractures were present in 23.8% of subjects in the denosumab group and 23.4% in placebo group. The 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. Other subject demographics variables were balanced between the treatment groups at baseline (Table 9).

Table 9: Demographics and baseline disease characteristics (Trial 20030216)

	Placebo (N = 3906)	Denosumab (N = 3902)
Demographics		
Ethnic group / race, n (%)		
White or Caucasian	3629 (92.9)	3609 (92.5)
Age (years), mean (SD)	72.3 (5.2)	72.3 (5.2)
Age group, n (%)		
60 - 64 years	208 (5.3)	206 (5.3)
\geq 65 years	3698 (95)	3696 (95)
\geq 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 generated from analysis of ASLINFO dataset and combining several tables supplied by the Applicant.

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 9).

Biomarkers of bone turnover:

Mean (SD) baseline serum concentrations of biomarkers of bone turnover (CTX1 and TRAP 5b), parathyroid hormone (PTH), serum calcium, and phosphorous were similar between the 2 treatment groups. Baseline prevalence 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 use was low and similar between the two trial groups.

6.1.3 Subject Disposition

This multinational trial enrolled 7868 subjects, of which 355(4.5%) came from United States. A total of 60 subjects from site 803 in Lithuania 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 (82%) in the placebo group and 3272 subjects (84%) in the denosumab group completed the trial (Table 3).

Table 10. Subject Disposition in Trial 20030216

Subject Disposition	Placebo	Denosumab
	N = 3906 n(%)	N =3902 n(%)
Randomized	3906 (100)	3902 (100)
Discontinued trial prior to Month 36	700(17.9)	630(16.1)
Completed IP ¹	67(1.7)	79(2)
Completed trial	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 (mITT)	3691	3702
Analyzed for adverse events (safety population, subjects who received at least one dose of IP)	3876	3886
¹ IP= Investigational product. mITT= subjects who had a baseline and at least one post baseline evaluation.		

6.1.4 Analysis of Primary Endpoint(s)

This analysis subset, the primary efficacy subset, included all randomized subjects who had a non-missing baseline and at least 1 non-missing postbaseline evaluation at or prior to the time point under consideration. Subjects were analyzed according to their original randomized treatment assignment, regardless of treatment received.

Efficacy Endpoints: The primary efficacy endpoint was the incidence of new vertebral fractures at Month 36.

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.) [Grade 0 (normal); Grade 1 (mild), 20% to 25% reduction in vertebral height (anterior, middle, or posterior); Grade 2 (moderate), 25% to 40% reduction in height; Grade 3 (severe), > 40% reduction in height]. 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.

Denosumab significantly reduced the risk of new vertebral fracture compared to placebo. The crude incidence of new vertebral fracture was 7.2% in placebo and 2.3% in denosumab group at month 36. Treatment with denosumab demonstrated a 4.8% absolute risk reduction and a 68% relative risk reduction in fracture incidence (p-value <0.0001).

Table 11. Trial 20030216: Subject Incidence, Absolute Risk Reduction, and Odds Ratio for New Vertebral Fracture through Month 36 (Primary Efficacy Analysis Set, LOCF Imputation)

	No. of Events	Crude Inciden ce %	Absolute Risk Reduction* at Month % (95% C.I.)			Relative Risk Reduction ¹ at Month % (95% C.I.)			Odds Ratio ² (95% C.I.)	p- value
			12	24	36	12	24	36		
Placebo (N=3691)	264	7.2								
Denos (N=3702)	86	2.3	1.4 (0.8, 1.9)	3.5 (2.7, 4.3)	4.8 (3.9, 5.8)	61 (42, 74)	71 (61, 79)	68 (59, 74)	0.31 (0.24, 0.39)	<0.000 ¹

Source: Table 3.3 of the Statistical Review : based on Table 9-3, page 240, Trial 20030216 report and Statistical Reviewer's calculation.

¹ Absolute risk reduction and relative risk reduction based on Mantel-Haenszel method adjusting for age stratification variable.

² Odds ratio and p-value based on logistic regression model adjusting for age stratification variable.

Reviewer's comment: This reviewer concurs with the Applicant's assessment of efficacy that treatment with denosumab resulted in a statistically significant improvement in the primary endpoint (reduction of the incidence of new vertebral fracture) compared to placebo at month 36. The decreased risk of new vertebral fractures at month 36 (primary endpoint) by 68% (risk ratio: 0.31 [95% CI: 0.24, 0.39]; $p < 0.0001$). This is an acceptable endpoint in evaluating a product for the treatment of osteoporosis.

6.1.5 Analysis of Secondary Endpoints

Statistical testing for secondary endpoints was done in a step-down manner in a hierarchical testing procedure. The inferential testing was continued only if previous step was significant. These steps were 1) new vertebral fractures, 2) nonvertebral fractures, 3) hip fractures.

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 trial 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 12. 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 absolute risk reduction was 1.5% and 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 adjusted absolute risk reduction of 0.3% (95% CI: -0.1%, 0.7%). The relative risk reduction was 40%, i.e., a hazard ratio of 0.60 (95% CI: 0.37, 0.97) at month 36.

Table 12: Trial 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			
Placebo (N=3906)	293	7.5	3.1	5.8	8.0			
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
Hip fracture								
Placebo (N=3906)	43	1.1	0.6	0.9	1.2			
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

Source: Tables 3.5 and 3.6 of the Statistical Review: based on Table 9-5 and 9-6, page 251 and 254, Trial 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.

Because the 95% confidence interval for the absolute risk reduction at 36 months for hip fracture included zero, we decided to further investigate hip fracture at yearly intervals. The hip fracture data is descriptively presented as the number and percentage of hip fractures within each 1-year time interval for year 1, year 2, and year 3 (Table 13). In the denosumab group in year one and two, the hip fracture incidence is lower than the placebo. However, in year three, it is similar to the placebo group. The numbers are too small to make any inferences at this point. This finding should be evaluated further in long term studies.

Table 13: Trial 20030216: Number and Percentage of Hip Fractures within Each 1-Year Time Interval

	Year 1		Year 2		Year 3	
	Number of subjects at beginning of interval	Number of fractures in interval (%)	Number of subjects at beginning of interval	Number of fractures in interval (%)	Number of subjects at beginning of interval	Number of fractures in interval (%)
Placebo	3906	20 (0.51)	3672	14 (0.38)	3430	9 (0.26)
Denosumab	3902	10 (0.26)	3676	4 (0.12)	3477	12 (0.34)

Source: Table 3.7 of the Statistical Review: based on Figure 9-7 on page 255 of Trial 20030216 report and Statistical Reviewer's calculations.

6.1.6 Other Endpoints-Bone Mineral Density

Denosumab treatment increased BMD in the lumbar spine and total hip compared to placebo. At lumbar spine, mean difference between the treatment groups in change from baseline to Month 36 was 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 14).

Table 14: 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

Source: Table 3.10 of the Statistical Review: based on Table 14-4.5.3 on page 320 and Table 9-2 on page 138 of Trial 20030216 report ; + Based on an ANCOVA model that includes treatment, age stratification variable, baseline value, machine type, and baseline value-by-machine type interaction

6.1.7 Subpopulations

New vertebral fracture: In the overall trial population, there was a statistically significant decrease in subject incidence of new vertebral fracture. Although not pre-specified,

multiple subgroup analyses were performed including race (Caucasian vs. non-Caucasian), age (≥ 75 years, ≥ 65 years, < 75 years), geographic region, body weight, BMI, lumbar spine BMD T-score, total hip BMD T-score, fracture risk assessed by FRAX, prior use of medication for osteoporosis and serum CTX1). In all subgroups, the difference in the reduction of vertebral fracture was consistent with the results seen in the overall group. The results remain significant when analyzed by prevalent vertebral fracture or non-vertebral fracture at baseline.

Bone mineral density: 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.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Overall, the 60 mg every 6 month dose chosen by the applicant seems appropriate based on the dose finding trial 20010223. At one point in the drug development, it was questioned if the fixed dosing regimen was appropriate or should it be weight based. Review of the analysis of efficacy in relation to body weight or BMI suggests that body weight does not significantly affect the efficacy. However, the following analysis of biomarkers of bone turnover raises the question of whether the fixed dose may lead to too much suppression of bone turnover in a subgroup of subjects.

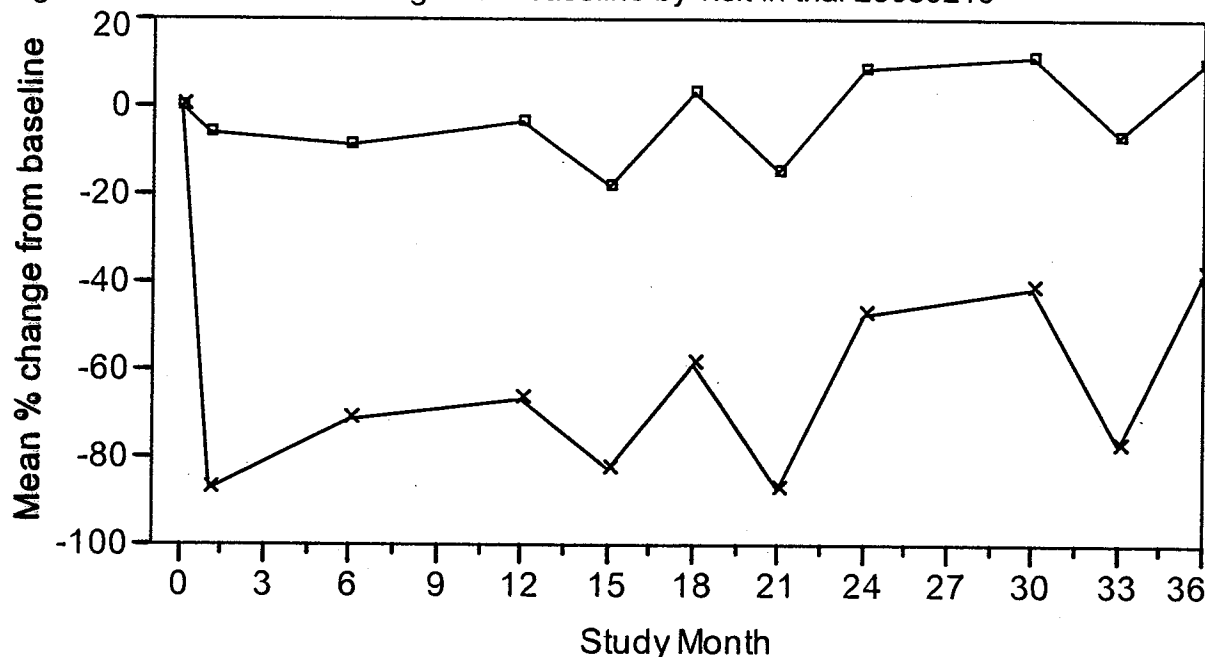
Biochemical Markers of Bone Turnover

Bone biomarkers were evaluated in trial 20030216 over 3 years. Samples taken on visits at day 1 and months 6, 12, 15, 18, 21, 24, 30, 33 and 36 were obtained before administration of investigational product. Subjects were to fast at least 10 hours before samples were taken.

Markers of bone resorption:

CTX is a product of the proteolytic process of bone resorption brought about by osteoclasts and is a marker of bone resorption. Treatment with denosumab resulted in marked suppression of serum CTX levels. The nadir in CTX appears to occur 1 – 3 months following a denosumab dose when denosumab effect is likely maximal. Before the next dose, CTX levels begin to trend back to baseline.

Figure 5: CTX levels % change from baseline by visit in trial 20030216



Source: Clinical Reviewer's analysis

The reduction in CTX level was rapid, starting at 6 hours after the dose. The degree of suppression is striking. At each visit, there were more subjects in the denosumab group who had undetectable serum CTX levels compared to placebo (Table 15).

Table 15: Subjects with undetectable CTX levels (CTX levels below the LLQ, n (%))

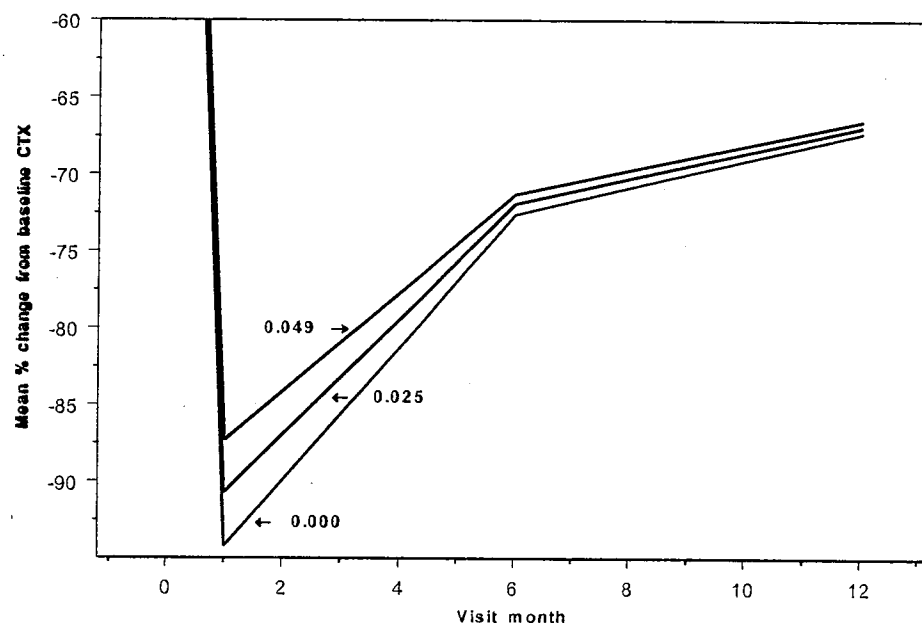
Month	1	6	12	15	18	21	24	30	33	36
Pla	0 (0)	0 (0)	1 (0.2)	0 (0)	0 (0)	3 (0.8)	3 (0.7)	0 (0)	0 (0)	5 (1)
Denos	293 (58)	46 (9)	32 (6)	161 (39)	32 (9)	266 (68)	43 (9)	15 (4)	180 (48)	38 (8)

This finding was most notable at the anticipated time of maximal denosumab effect. In this table, the bolded columns represent visits 1-3 months following denosumab dosing, a time in which the nadir of CTX occurs. At these time points, CTX was undetectable in 39 – 68% of subjects treated with denosumab. In their evaluation of the percent change in CTX, the applicant set the CTX level for subjects with undetectable levels to the lower level of quantification (0.049 mg/dL). This approach may underestimate CTX suppression in the subjects treated with denosumab. Therefore, change in CTX was evaluated based on three scenarios:

- Undetectable CTX levels set to the assay LLQ (0.049)
- Undetectable levels set to ½ the assay LLQ (0.025)

- Undetectable levels set to zero. Results are presented in Figure 6.

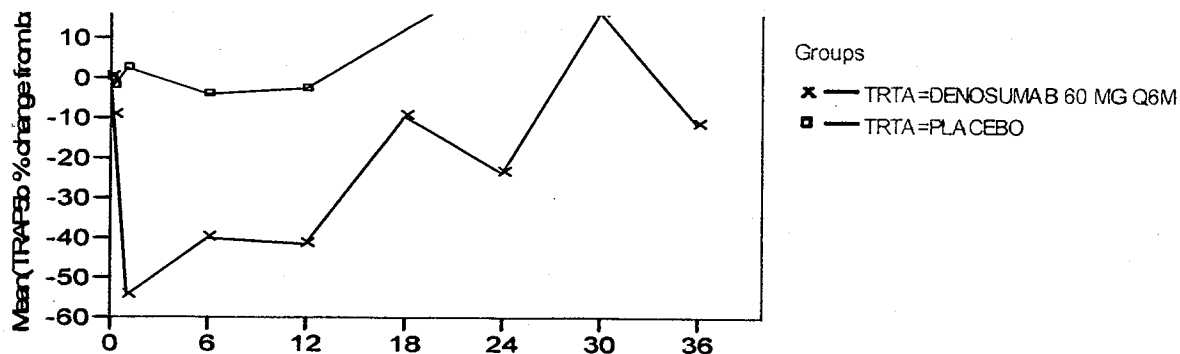
Figure 6: Percent change from baseline in serum CTX in the first year



From this analysis, we can only conclude that CTX levels one month after denosumab dosing decrease from -87 to -94%. It should be noted that this degree of suppression of bone resorption markers has not been seen before with other antiresorptive agents.

TRAP 5b is an enzyme that is secreted into the circulation by osteoclasts (Halleen et al, 2000). The synthesis and secretion of TRAP 5b increase with increased osteoclast activity; thus TRAP 5b serves as a biochemical marker of bone resorption. TRAP5b levels were suppressed in the denosumab group compared to placebo (Figure 7). However, unlike serum CTX1, these levels seem to recover towards the end of the trial, especially in the last year. This upward trend in TRAP 5b in year two and three of the trial is not expected as other markers of bone resorption (CTX) and bone histomorphometry did not show reversal of suppression. The reason or clinical significance of this finding is not clear.

Figure 7: %change from baseline TRAP 5b

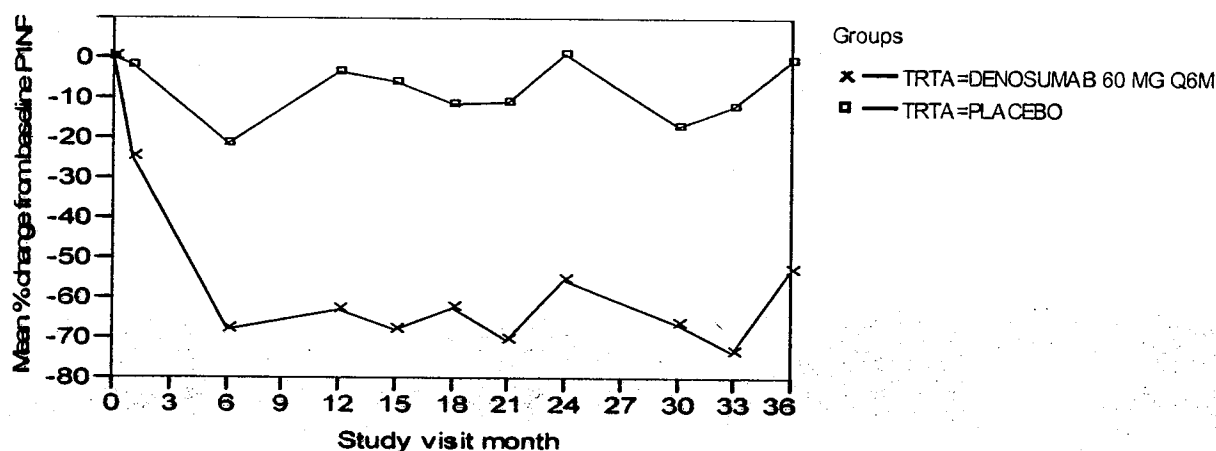


Source: Clinical Reviewer's analysis

Markers of bone formation: Bone remodeling is a coupled process. Suppression of bone formation follows approximately 6 months after suppression of bone resorption. It is expected that the markers of bone formation will follow the similar pattern as markers of bone resorption, lagging behind them by 6 months.

N-terminal Propeptide Type I Procollagen (P1NP) is the amino-terminal propeptide of type I procollagen and serves as a marker for bone formation. Similar to markers of bone resorption, treatment with denosumab resulted in suppression of P1NP (Figure 8).

Figure 8. N-terminal Propeptide Type I Procollagen % change from baseline



Source: Clinical Reviewer's analysis

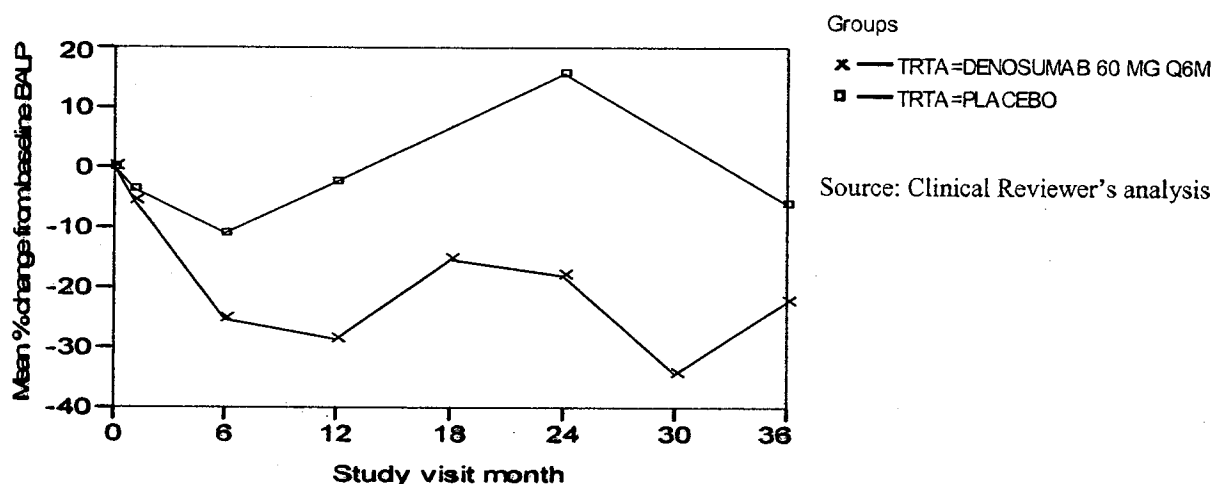
At each visit, there were significantly more number of subjects in the denosumab group who had undetectable serum P1NP levels compared to placebo (Table 16). This finding was most notable at the anticipated time of maximal denosumab effect. At 1-3 months following denosumab dosing time points (bolded columns), P1NP was undetectable in 24-36% of subjects treated with denosumab. As expected, P1NP suppression was not evident at month 1; however, month 6 onwards, suppression was clear.

Table 16: Subject incidence of undetectable P1NP levels at each visit in trial 20030216

Month	1	6	12	15	18	21	24	30	33	36
Pla	6 (1.3)	1 (0.2)	2 (0.4)	1 (0.3)	1 (0.3)	1 (0.3)	0 (0)	0 (0)	2 (0.4)	0 (0)
Denos	5 (0.9)	91 (19)	63 (12)	101 (24)	29 (8)	121 (31)	46 (9)	72 (18)	131 (36)	50 (12)

Bone specific Alkaline Phosphatase (BALP) is a major product of osteoblasts (Martin et al, 1997; Duda et al, 1988). Its measurement in serum is a marker of the rate of bone formation (Garnero and Delmas, 1996), and abnormal bone turnover in patients with many metabolic disorders (Garnero and Delmas, 1996) Treatment with denosumab resulted in reductions in concentrations of serum BALP levels.

Figure 9. Percent change from baseline in Serum bone specific alkaline phosphatase



Reviewer's comments: Treatment with denosumab resulted in suppression of markers of bone resorption followed by suppression of markers of bone formation. Since bone remodeling is a coupled process, treatment with antiresorptive agent is expected to decrease markers of bone resorption and bone formation. However, this degree of suppression is not seen with any other agent approved for treatment of osteoporosis. Significantly more subjects in the denosumab group had undetectable markers of bone remodeling compared to the placebo group. This raises concerns that if the bone remodeling is completely suppressed, it could result in complications such as osteonecrosis of the jaw, atypical fractures, etc over long term (7-10 years). This also raises a question whether the dose should be adjusted in subjects with drastic reductions in these markers or whether the applicant chose the optimal dose to take to phase 3 trials.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of Efficacy and/or Tolerance Effects related to fractures will be reviewed in detail here. The same related to BMD will be reviewed in detail in section 6.2.9.

- Effects of denosumab fracture efficacy, BMD and bone turnover markers were persistent over 3 year duration in trial 20030216. No tolerance or attenuation of efficacy was observed.
- Trial 20060289 is an ongoing, multinational, multicenter, open-label, single-arm seven-year extension trial. It enrolled 4550 subjects who completed Trial 20030216.

Data currently available for trial 20060289 are based on the database cut-off of 02 December 2008. At that time, subjects had been enrolled in Study 20060289 for durations of 6 to 15 months. These subjects completed trial 20030216, so total duration of exposure to denosumab would be 42 to 51 months for subjects in the denosumab group. This reviewer looked at the fracture incidence data with the caveat that these are based on adverse event reports, not based on radiological confirmation through central reading. All subjects are receiving denosumab 60 mg Q6M in Study 20060289. There were 50 (2.3%) clinical fractures in the placebo group (*denovo* denosumab group) and 30 (1.3%) in the continued denosumab group. Therefore, in this reviewer's opinion, fracture efficacy appears to persist up to 51 months duration, however, no definite conclusions can be made as this is an open label ongoing trial and the data has limitations described above.

- Over 5 year duration, 117 subjects received denosumab (4 years in trial 20010223 and one year in 20050233). BMD continued to increase over time in these subjects.

Effect of discontinuation of therapy:

- Trial 20040132 was randomized, double-blind placebo-controlled trial of 4 years duration; 2 years on treatment and 2 years off treatment. The off treatment phase provides important information about the effect of discontinuation of therapy. With many therapies that are used for treatment of a chronic disease such as osteoporosis, the durability of effect after cessation of the therapy is important to understand. During the first 2 years on treatment, BMD increased continuously. However, after therapy was discontinued, BMD rapidly returned toward baseline for both the lumbar spine and the total hip, so effect of discontinuation was rapid loss of gained BMD, observed mainly over first year off treatment.
- Rapid loss in BMD is an independent risk factor for osteoporotic fractures; therefore, this reviewer looked at fracture data. The Applicant determined that in the first 24 months of the trial, 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. In the follow-up phase (month 24 to 48), there were 5(3.9%) fractures in the placebo group and 9(7%) in the denosumab. Of these, 2 subjects had vertebral fractures in denosumab group and none in placebo group; 4 subjects in each group had an osteoporotic non vertebral fracture. Once again, the number of fractures is small; however, the concern of increased fracture risk upon discontinuation of therapy remains. This effect should be further evaluated in a postmarketing trial.

6.1.10 Additional Efficacy Issues/Analyses

All pertinent efficacy analyses were presented above. No additional efficacy issues were identified by this reviewer.

6.2 Prevention of Osteoporosis in Postmenopausal Women

6.2.1 Methods

This section of the review summarizes the results from Trial 20040132, the primary efficacy Phase 3 trial for the prevention of osteoporosis in postmenopausal women. This 4-year trial enrolled 332 subjects; subjects received treatment with investigational product for 2 years ("on-treatment") and then were observed for additional 2 years ("off-treatment").

Design:

Trial 20040132 was an international, multicenter (sites in the U.S. and Canada), randomized, double-blind placebo-controlled clinical trial.

Objectives:

The primary objective was to determine whether denosumab treatment can prevent lumbar spine bone loss (as measured by percent change from baseline in the lumbar spine BMD 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:

- a) BMD measured by DXA at the hip (total hip, femoral neck, and trochanter), distal radius, and total body (without head).
- b) Trabecular, cortical, and total volumetric BMD measured by quantitative computerized tomography (QCT) at the distal radius in both early and late postmenopausal women with low bone mass.

6.2.2 Demographics

All 332 subjects in the trial were female. Overall, baseline subject demographics and baseline disease characteristics were balanced between the two treatment arms. The majority of subjects were White or Caucasian (83%). The mean (SD) age of subjects at randomization was 59.4 (7.5) years with 22% of enrolled subjects ≥ 65 years of age. The age range at enrollment was 43-83 years and the median age was 58 years. The mean (SD) weight was 68.13 (12.54) kg with a mean BMI of 26.4 (4.8) kg/m².

At enrollment, subjects were stratified into 2 strata based on the number of years since menopause. Subjects who were ≤ 5 years since menopause were considered the early menopause stratum and subjects > 5 years since menopause were considered the late menopause stratum. For all enrolled subjects, the onset of menopause was ≤ 5 years for 162 subjects (48.8%) and > 5 years for 170 subjects (51.2%). The percentages for each stratum within each treatment group were similar as for the overall population.

The baseline mean (SD) BMD T-score at the lumbar spine was -1.61 (0.42) (range: -0.5 to -2.6) for the overall trial population. Mean baseline BMD T-scores were similar for the treatment groups and for the time-since-menopause strata. Mean baseline BMD T-

scores for the total hip, femoral neck, trochanter, and distal 1/3 radius also were similar for the treatment groups and for the time-since-menopause strata (see Table 17).

Using the FRAX tool and a post-hoc analysis of the trial population means for age, height, weight and BMD at the femoral neck (Hologic), the estimated 10-year risk of hip fracture was 0.8% and 10-year risk of major osteoporotic-related fracture (clinical spine, forearm, hip or shoulder) was 9.5% for the overall trial population in the primary efficacy prevention trial.

Table 17: Demographics and baseline disease characteristics for subjects in trial 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)
Baseline Total Hip BMD T-score, mean (SD)	-1.01 (0.71)	-0.98 (0.7)
Fracture risk by FRAX tool		
10-year osteoporotic fracture risk	9.5%	10%
10-year hip fracture risk	0.8%	1.0%

Source: Clinical Study Report for Trial 20040132 (24-month results), Table 8-5, pages 120-122 of 2440.

No subjects had a prior history of hip fracture and 1 subject in the denosumab group had a prior history of vertebral fracture. Based on baseline x-rays evaluated by the central imaging vendor, prevalent vertebral fractures were present in 4 subjects in the denosumab group and 6 subjects in the placebo group.

In summary, baseline subject demographics and baseline disease characteristics were balanced between the two treatment arms.

6.2.3 Subject Disposition

This trial was conducted at 21 centers in the U.S. and Canada and enrolled 332 subjects. The ITT population consisted of 329 subjects (denosumab: 164 subjects, placebo: 165 subjects). Overall, 142 subjects (86%) in the denosumab group and 144 subjects (87%) in the placebo group completed the trial (see Table 18). There were more discontinuations in the recently menopausal group, with 85% of this group completing the trial at 24 months and an 88% completion rate for subjects who were more than 5 years since menopause.

Reviewer comments: *The number of subjects in each treatment group for each menopause strata is small and these differences in discontinuation rates between the groups are not meaningful.*

Table 18. Subject disposition in the first 24 months of Trial 20040132

	≤ 5 years since menopause			> 5 years since menopause			Overall		
	Plac.	Denos.	All	Plac.	Denos.	All	Plac.	Denos.	All
	(N=81) n (%)	(N=81) n (%)	(N=162) n (%)	(N=85) n (%)	(N=85) n (%)	(N=170) n (%)	(N=166) n (%)	(N=166) n (%)	(N=332) n (%)
Randomized	81 (100)	81 (100)	162 (100)	85 (100)	85 (100)	170 (100)	166 (100)	166 (100)	332 (100)
Never got IP	0 (0)	2 (2)	2 (1)	1 (1)	0 (0)	1 (1)	1 (1)	2 (1)	3 (1)
Completed 24 Months	70 (86)	67 (83)	137 (85)	74 (87)	75 (88)	149 (88)	144 (87)	142 (86)	286 (86)
• Completed* IP	66 (81)	63 (78)	129 (80)	72 (85)	73 (86)	145 (85)	138 (83)	136 (82)	274 (83)
• Discontin. IP	4 (5)	4 (5)	8 (5)	2 (2)	2 (2)	4 (2)	6 (4)	6 (4)	12 (4)
Didn't Complete 24 Months	11 (14)	14 (17)	25 (15)	11 (13)	10 (12)	21 (12)	22 (13)	24 (14)	46 (14)
• Completed* IP	3 (4)	2 (2)	5 (3)	0 (0)	1 (1)	1 (1)	3 (2)	3 (2)	6 (2)
• Discontin. IP	8 (10)	10 (12)	18 (11)	10 (12)	9 (11)	19 (11)	18 (11)	19 (11)	37 (11)

IP = Investigational Product

* Subjects completed IP if they received all 4 planned doses.

Source: Clinical Study Report for Trial 20040132 (24-month results), Table 8-1, page 111 of 2440.

The most common reasons for trial discontinuation were withdrawal of consent and subjects lost to follow-up. Adverse events were reported as the reason for trial discontinuation in 1% of subjects, regardless of treatment randomization.

6.2.4 Analysis of Primary Endpoint(s)

The primary objective was to determine whether denosumab treatment can prevent lumbar spine bone loss (as measured by percent change from baseline in the lumbar spine BMD 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). All DXA scan data were submitted electronically to a central imaging vendor for final, blinded analysis. Study sites could be asked by the central imaging vendor to re-acquire a scan for reasons such as malpositioning or other technical reasons. The results from the central imaging vendor were used as the final dataset.

The results of the primary efficacy analyses are shown in Table 19. This analysis subset, the primary efficacy subset, included all randomized subjects who had a non-missing baseline and at least 1 non-missing post baseline evaluation at or prior to the time point under consideration. Subjects in this subset were analyzed according to their original randomized treatment assignment, regardless of treatment received. There was a statistically significant increase in lumbar spine BMD from baseline for denosumab compared to placebo at 24 months (denosumab +6.5%, placebo -0.6%) based on the least squares 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 seen in subjects ≤ 5 years since menopause. Consistent effects on lumbar spine BMD were also observed regardless of baseline age, race, weight/BMI, and BMD. The statistical reviewer Dr. Sonia Castillo concurred that the primary efficacy endpoints were met in Trial 20040132.

Table 19. Trial 20040132 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)			
Denos. (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)			
Denos. (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)			
Denos. (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

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, & baseline value-by-machine type interaction; the model (for overall assessment) adjusts for strata.

b 97.5% CI for each stratum and 95% CI for the overall assessment

Source: Clinical Study Report for Trial 20040132 (24-month results), Table 9-1, page 133 of 2440.

Reviewer Comments:

This reviewer concurs with the Applicant's assessment of efficacy for denosumab 60 mg SC Q6months in the prevention of osteoporosis in postmenopausal women with low bone mass. Statistical significance was shown in the primary efficacy endpoint for an increase in lumbar spine BMD for denosumab compared to placebo at 24 months (denosumab +6.5%, placebo -0.6%) based on the least squares mean. The overall treatment difference for denosumab was +7% (95% CI: 6.2, 7.8). This is an acceptable endpoint in evaluating a product for the prevention of osteoporosis.

6.2.5 Analysis of Secondary Endpoints(s)

The secondary objectives in Trial 20040132 were to assess the effect of denosumab on:

- BMD measured by DXA at the hip (total hip, femoral neck, and trochanter), distal radius, and total body (without head) at Month 24
- trabecular, cortical, and total volumetric BMD measured by quantitative computerized tomography (QCT) at the distal radius at Month 24

BMD measured by DXA: BMD measurements for total hip, femoral neck, trochanter, distal radius and total body are summarized in Table 20. Increases in BMD (measured by DXA) from baseline to Month 24 were greater in denosumab group than placebo for the total hip, femoral neck and trochanter, distal radius and total body. In analyses of

the least squares (LS) mean of the relative change from baseline in BMD, the treatment differences in BMD included increases of 4.5% at the total hip (95% CI: 4.0, 5.0), 3.7% at the femoral neck (95% CI: 2.9, 4.4), 6.0% at the trochanter (95% CI: 5.3, 6.6), 3.5% at the distal 1/3 radius (95% CI: 2.8, 4.3), and 3.8% at the total body (95% CI: 3.1, 4.5).

Within the denosumab group, the percent change from baseline in BMD at each of these anatomic sites was greater in women who were ≤ 5 years since menopause as compared to those subjects > 5 years since menopause. In analyses of the least squares (LS) mean of the relative change from baseline in BMD, the difference from placebo ranged from 3.5 in the distal radius to 6.0 in the trochanter ($p < 0.001$) for all locations. The difference between denosumab and placebo for the change from baseline BMD at Month 24 was statistically significant for each menopause stratum and overall subjects.

Table 20. Hip, Distal Radius and Total Body BMD by DXA – Relative Change From Baseline to Month 24 (ITT, LOCF)

Treatment Arm	Difference from Baseline ^a			Difference from Placebo ^a	
	n	Least Squares (LS) Mean	95% C.I.	LS Mean	95% C.I.
Total Hip					
Placebo (N = 163)	163	-1.1	(-1.5, -0.8)		
Denos. (N = 163)	163	3.4	(3.0, 3.7)	4.5	(4.0, 5.0)*
Femoral Neck					
Placebo (N = 163)	163	-0.9	(-1.4, -0.3)		
Denos. (N = 163)	163	2.8	(2.3, 3.3)	3.7	(2.9, 4.4)
Trochanter					
Placebo (N = 163)	163	-0.8	(-1.3, -0.3)		
Denos. (N = 163)	163	5.2	(4.7, 5.6)	6.0	(5.3, 6.6)
Distal 1/3 Radius					
Placebo (N = 163)	156	-2.1	(-2.6, -1.6)		
Denos. (N = 163)	156	1.4	(0.9, 1.9)	3.5	(2.8, 4.3)
Total Body (without head)					
Placebo (N = 163)	154	-1.4	(-1.9, -0.8)		
Denos. (N = 163)	156	2.4	(1.9, 2.9)	3.8	(3.1, 4.5)

n = No. of subjects with baseline value and at ≥ 1 postbaseline visit at or prior to the time point of interest

N = Number of subjects with values at baseline and at least ≥ 1 postbaseline visit

* P-value < 0.0001

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.

Source: Clinical Study Report for Trial 20040132 (24-month results), Table 9-2, pages 138-140 of 2440.

BMD measured by QCT: Another set of secondary endpoints involved an experimental quantitative computerized tomography (QCT) method using clinical whole body spiral

CT scanners to determine trabecular, cortical, and total volumetric BMDs of the distal radius (see Table 21). Compared to placebo, denosumab treatment resulted in an increase in cortical and total volumetric BMD at 24 months for overall subjects and for each menopause stratum and an increase in trabecular volumetric BMD for subjects overall. Based on the LS mean analyses, the difference from placebo for denosumab was 9.4 for trabecular BMD, 1.7 for cortical BMD and 2.6 for total BMD in the overall trial population.

Table 21. Trabecular, Cortical and Total Volumetric BMD at 24 months by QCT at Distal Radius – Relative Change From Baseline to Month 24 (ITT, LOCF)

Treatment	Difference from Baseline ^a			Difference from Placebo ^a	
	n	Least Sq. (LS) Mean	95% C.I.	LS Mean	95% C.I.
Trabecular BMD (QCT)					
Placebo	131	-0.7	(-6.6, 5.3)		
Denos.	144	8.7	(3.0, 14.4)	9.4	(1.1, 17.6)
Cortical BMD (QCT)					
Placebo	152	-1.4	(-1.8, -0.9)		
Denos.	156	0.3	(-0.1, 0.8)	1.7	(1.1, 2.3)
Total BMD (QCT)					
Placebo	153	-1.9	(-2.6, -1.1)		
Denos.	156	0.8	(0.0, 1.6)	2.6	(1.5, 3.8)

n = No. of subjects with values at baseline and at ≥ 1 postbaseline visit at or prior to the time point
a Based on ANCOVA models (on BMD by DXA for each stratum) that adjust for treatment, baseline value, machine type, and baseline value-by machine type interaction; and ANCOVA models (on volumetric BMD by QCT for each stratum) that adjust for treatment and baseline value; the models (for overall assessment) also adjust for strata.

Source: Clinical Study Report for Trial 20040132 (24-month results), Table 14-4.5.7, page 329 of 2440.

Reviewer's comment: The changes in BMD noted in the secondary endpoints are consistent with those of the primary endpoint.

6.2.6 Other Endpoints

Several tertiary endpoints were analyzed during the off-treatment period and included the following:

- percent change from baseline or Month 24 in BMD at various locations
- percent change from baseline or Month 24 in bone turnover markers (serum Type 1 CTX, TRAP 5b, PINP)
- percent change from baseline in biomarkers (OPG, RANKL, iPTH)
- new vertebral fractures or first clinical fractures

Within the first 12 months of the off-treatment period, any gain in BMD for subjects receiving denosumab was almost completely reversed, with BMD returning to approximately baseline levels. At month 36, BMD changes from baseline were 0.1% at the lumbar spine, 0.0% at the total hip, -0.5% at the femoral neck, 1.4% at the

trochanter, 0.8% at the distal 1/3 radius, and 0.0% at the total body. At month 36, subjects who were receiving placebo had a decline in BMD from baseline, with changes from baseline of -1.7% at the lumbar spine, -1.5% at the total hip, -1.6% at the femoral neck, -0.9% at the trochanter, -3.0% at the distal 1/3 radius, and -2.0% at the total body.

In the on-treatment period, denosumab treatment decreased serum concentrations of CTX1 relative to placebo at each assessment time point. Median changes from baseline in serum concentrations of CTX1 in the denosumab and placebo groups were -66.8% vs. -37.4% at day 1, hour 6, -89.3% vs. -3.1 at month 1, and -63.0% vs. -5.9% month 24. Serum concentrations of TRAP 5b were also decreased relative to placebo in subjects receiving denosumab, except the first assessment at day 1, hour 6. Median changes from baseline in serum concentrations of TRAP 5b in the denosumab and placebo groups were -17.1% vs. -18.4% at day 1, hour 6; -49.6% vs. -0.2% at month 1; and -39.2% vs. -8.7% at month 24. Serum concentrations of P1NP were also decreased relative to placebo in subjects receiving denosumab. Median changes from baseline in serum concentrations of P1NP in the denosumab and placebo groups were -32.0% vs. -3.5% at month 1; -73.5% vs. -14.5% at month 6; and -64.9% vs. -5.5% at month 24. P1NP was not assessed at day 1, hour 6. All 3 markers remained suppressed for the duration of the trial; however, median values appeared to be less negative by month 24. The clinical significance of this observation is unclear considering the relatively large variability in the assessments during the trial.

In the off-treatment period, the increase from baseline in serum CTX1, and TRAP 5b was greater in the denosumab group than the placebo group. For serum CTX1 levels, the percentage change from baseline at Month 27 was 0% and 26.6% for placebo and denosumab, respectively. The percentage change at Month 30 was 2.1% and 66.8% and at Month 36 was -7.3% and 34.2% for placebo and denosumab, respectively. The change in P1NP in the off-treatment period was inconsistent, with an initial decrease in both groups at Month 27 (-7.2% and -6.8% for placebo and denosumab respectively), followed by an increase over time with denosumab (increases of 42.5% and 47.7% at Month 30 and 36, respectively). The placebo group decreased from baseline by -11% at Months 30 and 36.

Reviewer's comment: The consistent increase in serum CTX1 and TRAP 5b in the denosumab group during the off-treatment period suggest the suppression of bone remodeling was also reversible.

The changes in the biomarkers OPG, RANKL, and iPTH were also measured during the trial; these biomarkers were comparable at baseline for the two treatment groups. The changes in OPG, RANKL and iPTH in the off-treatment period were not consistent for either the placebo or denosumab groups at the time points used in the trial. There was no apparent difference between the treatment groups at the time points used in the trial, similar to what was observed during the on-treatment period.

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) in the first 24 months of the trial. 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.

6.2.7 Subpopulations

Randomization in Trial 20040132 was stratified by time since onset of menopause (≤ 5 years or > 5 years). This was the only subpopulation identified *a priori* in this trial. In the overall trial population, 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 mean; this statistically significant increase in lumbar spine BMD was also seen in both menopause strata. In subjects ≤ 5 years since menopause, lumbar spine BMD increased by 6.2% for denosumab and decreased by 1.2% for placebo. In subjects > 5 years since menopause, lumbar spine BMD increased by 6.8% for denosumab and 0.1% for placebo. The treatment difference in the overall trial population was +7% (95% CI: 6.2, 7.8), with subjects ≤ 5 years since menopause having the greater treatment effect. Subjects ≤ 5 years since menopause had a treatment difference of +7.4% (95% CI: 6.1, 8.7; $p < 0.0001$), while subjects > 5 years since menopause had a treatment effect of +6.7% (95% CI: 6.2, 7.8; $p < 0.0001$).

Although not pre-specified, multiple subgroup analyses were performed, including race (Caucasian vs. non-Caucasian), baseline weight (< 55 , 55 to < 65 , 65 to < 75 and ≥ 75 kg), and baseline BMI (< 22 , 22 to < 24 , 24 to ≤ 26 and 26 to < 30 , and ≥ 30 kg/m²), age subgroup (< 65 and ≥ 65 years) for subjects ≤ 5 years since menopause and > 5 years since menopause and for overall subjects. In all subgroups, the difference in the percent change from baseline to Month 24 in lumbar spine BMD was consistent with the results seen in the overall group.

6.2.8 Analysis of Clinical Information Relevant to Dosing Recommendations

A Phase 2 dose finding trial (Trial 20010223) examined 7 different SC doses of denosumab and 1 cohort each of placebo or oral alendronate in postmenopausal women with low bone mass. The denosumab dosing cohorts were 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 trial. The dose chosen for Phase 3 trials was a fixed dose of 60 mg Q6months, based on the demonstrated efficacy, adverse event rates and a convenient dosing interval. This trial was adequate to assess dose response based on the change in lumbar spine BMD. However, the lack of a 30mg q6 month dosing regimen does not allow a determination of whether the chosen 60 mg dose is truly the minimal effective dose.

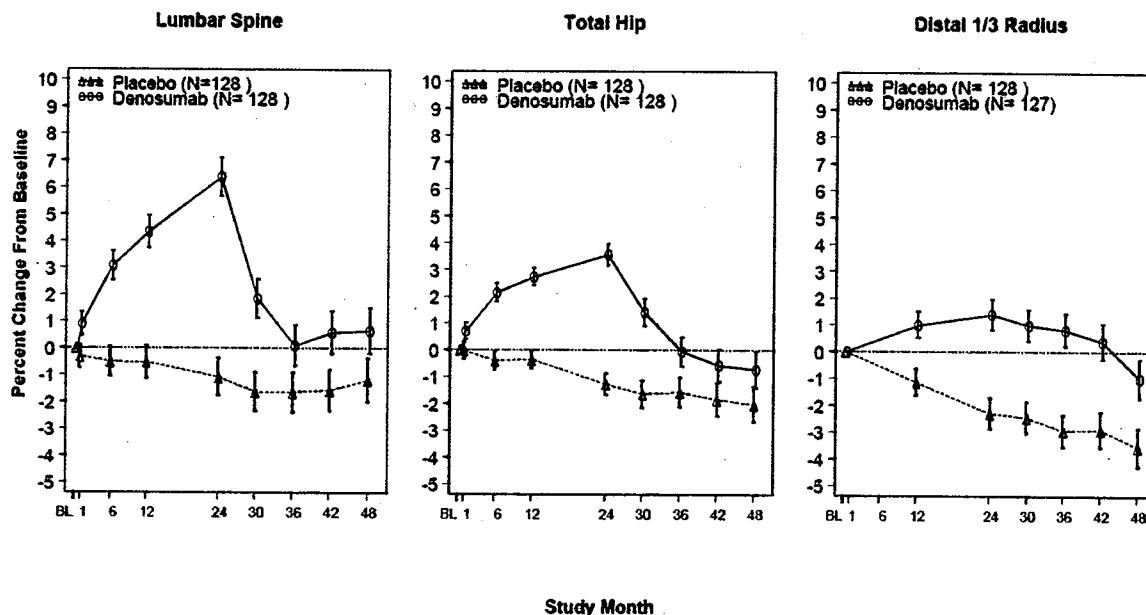
The applicant analyzed the primary endpoint by baseline weight and BMI to determine if the efficacy of a fixed 60 mg dose was affected by these parameters. In the placebo group, a higher baseline weight and BMI was correlated with maintenance of lumbar spine BMD by DXA. For the denosumab group, there was no linear correlation for either baseline weight or BMI. No linear correlations were noted for either weight or BMI with change in BMDs of the total hip, trochanter, femoral neck, or distal 1/3 radius for either the denosumab or placebo group. As such, the proposed dosing recommendation of 60 mg SC Q6months for all subjects, regardless of body weight, appears to be appropriate.

6.2.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

This trial design included 2 years of treatment with investigational product ("on-treatment") and 2 years of an observation period ("off-treatment"). These subjects received 4 doses of investigational product during the on-treatment period of the trial. There did not appear to be any evidence of tolerance to the effects of denosumab. However, this two-year treatment period did not have a sufficient duration to assess the persistence of efficacy or the development of tolerance to denosumab in subjects who may be using this product for an extended period of time.

This trial design allowed for an assessment of the persistence of effect in the off-treatment period. The effects of denosumab treatment, including increases in BMD and decreases in bone turnover markers appear to be reversible upon treatment discontinuation (see Figure 10).

Figure 10. Bone Mineral Density by DXA Percent Change From Baseline by Visit, Least Squares Means and 95% CIs From Repeated Measures Model



Source: Applicant provided figure 6-1, page 148, 120 day safety update. Includes subjects who enrolled in the off-treatment phase with values at baseline and at ≥ 1 postbaseline visit. Primary Efficacy Subset for Subjects Enrolled in the Off-treatment Phase, No Imputation, 20040132 Final Analysis, 48 Months

During the first 12 months of the off-treatment period, 6 denosumab and 3 placebo subjects had an adverse event of fracture. Though all fractures were reported as adverse events, the protocol specifically defined clinical fractures as an endpoint, which were reported by the investigators and confirmed by the central imaging vendor for 2 subjects (2%) in the denosumab group and 2 subjects (2%) in the placebo group. Fractures for 4 subjects in the denosumab group and 1 subject in the placebo group were not included in the analysis of clinical fractures because they did not meet the definition of a clinical fracture. For this trial a clinical (osteoporotic) fracture was defined as any fracture excluding skull, facial, mandible, cervical vertebrae, metacarpus, and finger and toe phalanges, all of which are typically not associated with low trauma severity. In addition, fractures with high-trauma severity and pathologic fractures were excluded.

During the entire 24-month off-treatment period, adverse events of fracture were reported in 14 subjects, 9 subjects (7.0%) who received denosumab during the treatment phase and 5 subjects (3.9%) who received placebo. Thirteen of the 14 subjects had fractures at nonvertebral sites, 8 subjects (6.3%) who had received denosumab and 5 subjects (3.9%) who had received placebo. Of the 8 denosumab subjects, 3 subjects had fractures not likely to be osteoporotic (3 phalangeal fractures) and 1 subject had a fracture for which radiographs were not provided to the central

reviewer (patella fracture). Of the 5 placebo subjects, 1 subject had a fracture not likely to be osteoporotic (metacarpal fracture) that was also not centrally confirmed. Thus, centrally confirmed osteoporotic, nonvertebral fractures occurred in 4 placebo (3.1%) and 4 denosumab (3.1%) subjects.

Reviewer's comment: The effect of denosumab on BMD is sustained with 60 mg Q6M dose while subjects remained on continuous treatment. This effect was reversible upon discontinuation. Although there were few fractures during the off-treatment period, the denosumab group had more adverse events of fracture than the placebo group. The significance of this finding is unclear at this time.

6.2.10 Additional Efficacy Issues/Analyses

All pertinent efficacy analyses were presented above. No additional efficacy issues were identified by this reviewer.

7 Review of Safety

Safety Summary

Important safety issues are summarized below and discussed in detail in the sections that follow.

- **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. In trial 20030216 (PMO treatment indication), the incidence of all-cause mortality was higher with placebo (2.3%) than denosumab (1.8%); no deaths occurred in trial 20040132 (PMO prevention indication). The number of subjects who died during the key hormone ablation studies was not higher for denosumab (45 subjects) compared to placebo (47) groups.
- **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 20040138. There were no differences in aortic calcification scores at 3 years between treatment arms.
- **Infections:** In the overall PMO clinical program, subjects exposed to denosumab group had an increased incidence of serious infections compared to placebo. 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-exposed subjects. There were 4 cases of endocarditis in the denosumab group (including 3 cases in Trial 20030216). Compared to one case in the placebo group (in Trial 20040138). Streptococcal infections, including erysipelas and cellulitis, occurred more frequently among denosumab subjects. Three denosumab-exposed subjects in Phase I studies developed

pneumonia requiring hospitalization following a single dose of denosumab. While one subject was found to have lung cancer, the other two were young, healthy males less than 35 years old. However, there did not appear to be an increase in opportunistic infections in denosumab subjects.

- ONJ: No cases of ONJ have been positively adjudicated in the PMO and hormone ablation trials under review. However, confirmed cases of ONJ in denosumab-treated patients have been reported in the Applicant's clinical development of denosumab in patients with multiple myeloma and metastatic cancer.
- 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 trial (Trial 20010223) died of a new malignancy; all subjects received denosumab 100 mg Q6 months for at least 15 months. Overall, subjects in the denosumab group in the Primary PMO safety population had an increased incidence of breast cancer, pancreatic cancer, gastrointestinal cancer and reproductive cancers. Breast cancer was the most common adverse event that led to discontinuation of investigational product in the Primary PMO safety population, with 20 denosumab (0.5%) and 10 placebo (0.25%) subjects discontinuing due to breast cancer.
- Pancreatitis: There were 8 subjects (9 events) (0.2%) with pancreatitis in the denosumab group compared to 4 subjects (0.1%) in the placebo group in the pivotal PMO studies. One subject in the denosumab group reportedly died from pancreatitis. 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. The temporal relationship between duration of denosumab exposure and the development of pancreatitis is highly variable. In addition, most cases in the denosumab group were confounded by prior episodes of pancreatitis or risk factors for the development of pancreatitis. The significance of this finding is unclear.
- 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 bone resorption and bone formation parameters. 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 trial. Outside of the controlled clinical trial environment, more patients may experience hypocalcemia. The Applicant has proposed hypocalcemia in the Contraindications and the Warnings and Precautions section of the labeling document.
- **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 impairment in renal or hepatic function.

7.1 Methods

The safety analysis population consisted of all subjects who received at least 1 dose of trial drug. Subjects were analyzed based on the actual treatment received during the trial. Clinical data from the two key denosumab studies for the PMO indication were reviewed individually and analyzed to assess overall safety in each trial. At times, clinical data from PMO and hormone ablation studies were pooled to perform additional safety analyses utilizing a larger population. These four trials were chosen in order to attempt to confirm the applicant's analyses in their Integrated Summary of Safety (ISS), and because of the homogeneity of design elements, including demographics, endpoints, dose and frequency of trial drug, and duration. The ISS data analysis datasets ASLINFO, ASLBASE, AAE, ACECV, AVS, ALBSAF, ASLSAF, and AAEFX were utilized.

For deaths, non-fatal serious adverse events and adverse events, data for trials 20030216 and 20040132 were pooled. These trial populations were similar in demographics and baseline disease characteristics, although subjects in trial 20030216 were somewhat older (mean age 75 years vs. 59 years in 20030216 and 20040132, respectively) and 24% of subjects in trial 20030216 had a vertebral fracture at baseline. These trials were similar in design and used the same dosing regimen of denosumab and measured similar outcomes.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The Applicant submitted the following key safety information:

- December 19, 2008 (000) – Original Submission – (clinical overview, summary of clinical safety)
- April 15, 2009 (017) – 4 Month Safety Update
- May 15, 2009 (023) – response to questions about dental events
- June 9, 2009 (027) – response to questions about visual events

A complete listing of the trials submitted with this BLA to support the PMO prevention and treatment indications is shown in Figure 3 and briefly summarized in Appendix 2.

The following key clinical trials were used to evaluate safety of denosumab 60 mg Q6 months:

I. Postmenopausal Osteoporosis (PMO) Studies:

- a) **Trial 20030216** - an international, multicenter, randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of denosumab in the treatment of postmenopausal osteoporosis. This 3-year trial enrolled 7808 subjects randomized to denosumab (N=3902) or placebo (N=3906).
- b) **Trial 20040132** - a randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of denosumab in the prevention of postmenopausal osteoporosis. This 4-year trial enrolled 332 women (denosumab – 166, placebo – 166); subjects received therapy for 24 months and were monitored off-treatment for an additional 24 months.

II. Hormone Ablation Therapy Studies:

- a) **Trial 20040135** - a randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of denosumab in the treatment of bone loss in subjects undergoing aromatase inhibitor therapy for nonmetastatic breast cancer. This 4-year trial enrolled 252 subjects (denosumab -127, placebo - 125); subjects received therapy for 24 months and were monitored off-treatment for an additional 24 months.
- b) **Trial 20040138** - a randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of denosumab in the treatment of bone loss in subjects undergoing androgen-deprivation therapy for nonmetastatic prostate cancer. This 5-year trial enrolled 1,468 subjects (denosumab – 734, placebo – 734); subjects received therapy for 36 months and were monitored off-treatment for an additional 24 months.

7.1.2 Categorization of Adverse Events

The Applicant collected adverse event information throughout the trial period. In addition, hematology, serum chemistry, electrocardiogram (ECG), and vital signs measurements (heart rate, systolic and diastolic blood pressure) were assessed at regular intervals. Central laboratories were used to provide uniform measurement of the key hematology and chemistry parameters. Subject safety in the pivotal trials was also scrutinized on an ongoing basis by an external Data Monitoring Committee (DMC). Cases involving specific safety issues of interest (i.e., cardiovascular safety and ONJ) were reviewed by an adjudication committee.

All adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and the submitted application was coded in MedDRA version 11.0. Adverse events were graded on a five-point intensity scale: mild, moderate, severe, life-threatening or fatal. The subject incidence of adverse events was tabulated by maximum severity. The Applicant adhered to the definition and reporting requirements for serious adverse events, as defined by the ICH guidelines. A comparison of verbatim term to MedDRA Preferred Term (PT) was performed on a random sampling of adverse event terms to verify the precision and accuracy of the medical coding of adverse

events. The coding was considered acceptable in the majority of events reviewed. In those cases where the FDA reviewers would have chosen a different PT, the differences were not clinically meaningful and would not have had a significant impact on the overall assessment of safety for the trial.

The National Cancer Institute Common Toxicity Criteria (CTCAE Criteria, version 3.0) was used to grade the severity of laboratory results. These criteria employ a grading system of 0 (laboratory values within normal limits) to 4 (severe toxicity) to classify the increase or decrease in the laboratory parameter.

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

Primary Review

Safety data have been pooled by indication (PMO and hormone ablation indications) as described in the section describing Studies/Clinical Trials Used to Evaluate Safety. Data from Studies 20030216 and 20040132 were integrated to form the "Primary PMO Safety Analysis Set", which includes 8,091 subjects in the safety population, including 4,041 subjects who were exposed to placebo and 4,050 subjects exposed to denosumab for up to 3 years (2 years in Trial 20040132, 3 years in Trial 20030216). It is important to note that the bulk of the safety data for this review were from Trial 20030216, which enrolled 7,868 subjects. In all, 71.4% and 76.4% of subjects in the placebo and denosumab groups, respectively, received all 6 scheduled doses of investigational product.

Data from Studies 20040135 and 20040138 were integrated to form the "Primary Hormone Ablation Safety Analysis Set", which includes 1,705 subjects, including 845 subjects exposed to placebo and 860 subjects exposed to denosumab for 2 years (Trial 20040135) or 3 years (20040138). For Trial 20040135, 78.3% and 80.6% of subjects in the placebo and denosumab groups, respectively, received all 4 scheduled doses of investigational product. For Trial 20040138, 62.1% and 67% of subjects in the placebo and denosumab groups, respectively, received all 6 scheduled doses of investigational product.

Pooling of Data by the QSPG Group

The Quantitative Safety and Pharmacoepidemiology Group (QSPG) provided Statistical Safety Analyses for this review. For each adverse event of interest, results were tabulated for the four primary trials (20030216, 20040132, 20040135, 20040138). The QSPG reviewers also analyzed all double blind, randomized comparative trials using various pooling strategies: 2 placebo controlled PMO trials, 7 controlled PMO trials, 9 controlled trials, 2 largest placebo controlled trials (Cardiovascular events only). The two hormone ablative studies were not pooled due to differences in the trial populations. The pooling of data is further described in Section 5.2.2.

7.2 Adequacy of Safety Assessments

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

7.2.1.1 Description of primary data sources used to evaluate safety/trial type and design

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. These studies were conducted in North and South America, Europe, Australia, and Japan. The studies that are the focus of this review are described in detail in section 7.1.1.

7.2.1.2 Demographics:

The population studied in the PMO trials is postmenopausal women with osteoporosis and low bone mass (also called osteopenia). Notable differences among the trials were mainly in age and baseline disease characteristics. Trial 20030126 population was elderly women (mean age 73 years) with postmenopausal osteoporosis (T-score ≤ -2.5). Trial 20040132 population was younger (mean age 59 years) with osteopenia (T-scores between -1 and -2.5). Most subjects were Caucasian. For the hormone ablative therapy related bone loss, denosumab was studied in both men and women. The oncology trial population had a large number of subjects with normal lumbar spine (LS) and femoral neck (FN) BMD T-scores.

Table 22. Demographics of 4 key primary efficacy trials

	PMO		hormone ablation	
Trial	20030216	20040132	20040135	20040138
N	7808	332	252	1468
Gender	Female	Female	Female	Male
Age years	72	59	59	75
BMI	26	26	28	28
Race				
Caucasian	7238 (93%)	274(82%)	235(93%)	1224(83%)
African American	57 (0.7%)	14(4%)	2 (0.8%)	68(4.6%)
Hispanic	473 (6.1)	23 (7%)	8(3%)	158(10.8)
Asian	28 (0.3%)	17(5%)	3 (0.8%)	13(0.8%)
Other	12 (0.1%)	4 (1%)	4(1.6%)	5(0.3%)
Baseline lumbar spine BMD	-2.8	-1.6	-1.1	-0.4
Baseline femoral neck BMD	-2.2	-1.5	-1.3	-1.4
Baseline prevalent vertebral fracture	23%	0%	2%	2%
T score in normal range at LS BMD	2%	12%	40%	60%
T score in normal range at Femoral neck BMD	6%	24%	33%	28.5%

Source: This table is derived from analysis of ISE database for baseline characteristics.

Baseline demographic characteristics such as age, BMI, race, baseline lumbar spine and femoral neck BMD were similar between the denosumab and placebo groups within each trial. For details, please refer to individual trial reviews.

7.2.1.3 Extent of exposure:

Safety data were examined from the phase 2/3 clinical studies relevant to the postmenopausal population. The denosumab dose in these studies ranged from 6 mg every 3 months to 210 mg every 6 months. A total of 5655 subjects received at least 1 dose of denosumab in phase 2 or 3 clinical studies, which also included matching placebo administered to 4224 subjects. Most (92.3%) of the denosumab-treated subjects in phase 2 and 3 clinical studies received ≥ 1 year of exposure; 3533 subjects (62.5%) received ≥ 3 years of exposure, and 113 subjects (2.0%) were exposed for ≥ 5 years.

Table 23: Extent of exposure

	≥ 1 Dose	≥ 1 Year	≥ 2 Years	≥ 3 Years
No. of subjects receiving denosumab				
Key phase 3 studies (20030216,20040132)	4050	3867	3656	3331
No. of subjects receiving placebo				
Key phase 3 studies (20030216,20040132)	4041	3866	3619	3250

Source: Applicant's summary of clinical safety: page 33, table 2

Within the Primary PMO studies 20030216 and 20040132, more than 70% of subjects received all 6 doses of Investigational Product (IP) as denosumab 60 mg or placebo SC Q6months. As shown in the table below, fewer subjects in the placebo group completed all 6 doses.

Table 24: 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 (5.3%)	172 (4.2%)
4	294 (7.3%)	256 (6.3%)
5	218 (5.4%)	142 (3.5%)
6	2886 (71.4%)	3093 (76.4%)
Subjects	4041	4050

Source: Integrated Summary of Clinical Safety, Table 4, pages 36-37 of 424.

7.2.2 Explorations for Dose Response

Trial 20010223 was a Phase II dose finding trial 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 trial 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 trial. There were approximately 40 subjects per dosing cohort, for a total of 412 subjects (319 denosumab, 46 placebo, 47 alendronate). This trial was adequate to assess dose response among the doses studied. However, it should be noted that this trial did not evaluate 30 mg q 6 months dose.

The Applicant chose a fixed denosumab dose of 60 mg Q6months based on evaluations of markers of bone resorption and BMD data. Denosumab doses greater than 60 mg did not result in greater gains in BMD. Denosumab doses ≥ 60 mg administered every 6 months were at least as effective as alendronate 70 mg weekly. Denosumab administered 30 mg every 3 months and 60 mg every 6 months displayed similar pharmacodynamic activity. Since denosumab was effective when dosed using

either a 3- or a 6-month dosing interval, the Applicant selected a 6-month dosing interval for convenience and potentially increased compliance.

7.2.3 Special Animal and/or In Vitro Testing

The pharmacology/toxicology program is adequate overall. However, 2 caveats should be noted:

- 1). Monkey is the only relevant species for animal testing as denosumab is not pharmacologically active in rodents (mice or rats). While the applicant has a surrogate knock-in for huRANKL mouse model, it is not an appropriate model for carcinogenicity studies. Therefore, carcinogenicity studies were not done for denosumab. Nonclinical safety evaluation programs would typically include two relevant species. However, according to the ICH S6 guidance for preclinical safety evaluation of biotechnology derived products, toxicology studies in one relevant species may suffice in special circumstances. The pharmacology/toxicology reviewer considers denosumab to be one of these special circumstances.
- 2). The embryofetal and perinatal studies did not have adequate exposure (maximum duration was 50 days, by which time the organogenesis is not complete). However, these data were not considered essential for the safety evaluation of denosumab for the PMO indication given that the target population is postmenopausal women and that the lack of embryofetal and perinatal data could be adequately labeled.

7.2.4 Routine Clinical Testing

Adequate investigations of known potential effects of monoclonal antibody such as infections, malignancy were done. Submission (denosumab) specific adverse events were also evaluated prospectively such as cardiovascular safety, ONJ, and delayed fracture healing complications. These will be described in the subsequent sections in detail.

7.2.5 Metabolic, Clearance, and Interaction Workup

Metabolism and interactions: Denosumab is a monoclonal antibody product and is not expected to be eliminated via hepatic metabolic mechanisms (e.g., CYP enzymes). Thus, no metabolism studies (hepatic impairment and drug interaction) were conducted. The clinical pharmacology reviewer recommends a postmarketing commitment, an in-vitro trial to assess whether RANKL modulates expression of major CYP enzymes and a clinical drug interaction trial in PMO patients to further study these properties.

Clearance: While denosumab displays nonlinear PK across the low dose range (< 1.0 mg/kg), denosumab displays approximately linear PK at doses at or above the proposed fixed dose of 60 mg (approximately ≥ 1.0 mg/kg). As a result, mean apparent clearance (CL/F) was approximately 8-fold higher at a dose of 0.03 mg/kg (i.e., faster rate of elimination at low serum concentrations) compared to a higher dose of 3.0 mg/kg while mean CL/F values were similar ($< 35\%$ difference), in the dose range of 1.0 and 3.0 mg/kg. Although mechanism of clearance is unclear, these data are consistent with

at least two mechanisms of elimination for denosumab: one mechanism (i.e., target mediated disposition) that predominates at low doses or serum concentrations and becomes saturated as serum levels increase; and another, nonsaturable, mechanism that governs the rate of denosumab elimination at higher doses or serum concentrations.

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

Potential safety issues were identified early in the development program for denosumab. Specifically targeted issues were hypocalcemia, cardiovascular events, malignancy, infections, ONJ, hypersensitivity, and fracture healing complications. To further assess the risk of hypocalcemia, specific searches and analyses of the data were performed in order to ensure that symptoms of hypocalcemia were identified in addition to laboratory values. With regard to ONJ, an adjudication committee was convened to evaluate suspected cases of ONJ in order to make the diagnosis based upon pre-defined criteria. Similarly, an external panel of cardiologists adjudicated all cases of cardiovascular SAEs and deaths.

The safety issues known with other monoclonal antibodies and agents having antiresorptive effects similar to denosumab's were a particular focus of this review. These analyses are discussed at length in sections to follow.

7.3 Major Safety Results

The following table summarizes the number of subjects in the safety population for each of the key PMO and hormone ablation studies. These subjects form the basis upon which safety conclusions are drawn for this review, unless a subset is used to examine a particular issue.

Table 25. Subject Totals from the Studies Comprising the Pooled Safety Data for the PMO and hormone ablation Study Populations

Study Identifier – Study Population	Placebo	Denos.	Total No. of subjects
	N (%)	N (%)	N (%)
20030216 – PMO	3876 (39.57%)	3886 (39.67%)	7762 (79.24%)
20040132 – PMO	165 (1.68%)	164 (1.67%)	329 (3.36%)
20040135 – hormone ablation	120 (1.22%)	129 (1.32%)	249 (2.54%)
20040138 - hormone ablation	725 (7.4%)	731 (7.46%)	1456 (14.86%)
Total No. of Subjects	4886 (49.88%)	4910 (50.12%)	9796 (100%)

7.3.1 Deaths

At the Division's request, the applicant provided a listing of all deaths in the denosumab clinical development program, submission sequence #23 provided on May 15, 2009. A total of 354 deaths occurred in the denosumab clinical development program. This number included 2 deaths in Phase I studies, 96 in Phase 2 trials and 256 deaths in Phase 3 trials. All deaths in Phase 2 and 3 trials were examined for subjects who were postmenopausal; deaths in Phase 2 or 3 trials in cancer patients were not examined for this review. The two deaths in subjects in Phase I studies resulted from blunt force trauma and progression of cancer in a 36-year-old breast cancer patient with bone metastases about a month after the initial dose of IP. Of the 354 total subjects who died, 185 subjects (52%) had underlying cancer and 169 subjects (48%) had osteoporosis or low bone mass as their indication for use of denosumab.

Denosumab Clinical Program

This reviewer did a hands-on review of each fatal event in the overall denosumab clinical development program to determine if the applicant's categorization of the cause of death was appropriate. Fatal events that occurred in Trial 20040216 and 20040138 were adjudicated by an independent cardiovascular adjudication committee that determined whether the death was caused by a cardiovascular event. There were no significant discrepancies between this reviewer's findings and the data summarized by the applicant. There were some disagreements between this reviewer's and the applicant's assessment as to which was the primary AE that lead to the fatal outcome in patients with multiple AEs at the time of death. An example includes the applicant's categorization of health deterioration due to metastatic cancer as an event in the General Disorders SOC, while this reviewer would have categorized the event as metastatic cancer / progression of cancer in the Neoplasms SOC as the cause of death.

This reviewer did not consider the differences in the categorization of the cause of death to be significant because the applicant captured all the AEs in the safety database. In addition, the use of a cardiovascular adjudication committee in the two largest trials (20040138 and 20040216) indicates the applicant's efforts to adequately capture the appropriate cause of death. Overall, this reviewer concurs with the applicant's conclusions regarding fatality findings in the denosumab development program.

Table 26. Cause of Death by System Organ Class for the Entire Denosumab Clinical Development Program†

	Applicant Adjudication			FDA Adjudication		
	Placebo	Denos.	Other*	Placebo	Denos.	Other*
Total No. of Fatalities	137	196	21	137	196	21
System Organ Class	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Neoplasms benign, malignant & unspec	37 (27%)	54 (27.6%)	7 (33.3%)	37 (27%)	82 (41.8%)	16 (76.2%)
Cardiac	36 (26.3%)	39 (19.9%)	3 (14.3%)	27 (19.7%)	26 (13.3%)	1 (4.8%)
General disorders & admin. site conditions	13 (9.5%)	16 (8.2%)	3 (14.3%)	25 (18.3%)	19 (9.7%)	1 (4.8%)
Nervous system	14 (10.2%)	19 (9.7%)	1 (4.8%)	15 (11%)	16 (8.2%)	1 (4.8%)
Respiratory, thoracic & mediastinal	13 (9.5%)	18 (9.2%)	2 (9.5%)	10 (7.3%)	8 (4.1%)	0
Infections & infestations	12 (8.8%)	14 (7.1%)	0	13 (9.5%)	17 (8.7%)	0
Metabolism & nutrition	1 (0.7%)	9 (4.6%)	2 (9.5%)	2 (1.5%)	2 (1%)	1 (4.8%)
Hepatobiliary	1 (0.7%)	7 (3.6%)	1 (4.8%)	1 (0.7%)	2 (1%)	0
Gastrointestinal	3 (2.2%)	5 (2.6%)	0	5 (3.7%)	6 (3.1%)	0
Injury, poisoning & proc. complications	5 (3.7%)	4 (2%)	0	1 (0.7%)	4 (2%)	0
Blood & lymphatics	0	2 (1%)	1 (4.8%)	0	2 (1%)	0
Renal and urinary	1 (0.7%)	2 (1%)	0	0	3 (1.5%)	0
Endocrine	0	1 (0.5%)	0	0	1	0
Vascular disorders	1 (0.7%)	6 (3.1%)	1 (4.8%)	1 (0.7%)	7 (3.6%)	1 (4.8%)
Social circumstances	0	0	0	0	1 (0.5%)	0

† Includes subjects with multiple myeloma, advanced breast cancer with bone metastases, and solid tumors with bone metastases.

* Other includes alendronate or an intravenous bisphosphonate

Across the entire denosumab clinical development program, the cause of death did not differ greatly between the denosumab or placebo groups by either adjudication. However, there were more fatal vascular events in the denosumab group, primarily due to hemorrhage. The majority of these patients had risk factors for the event, including myelodysplasia, thrombocytopenia, history of varices, and bleeding following a liver biopsy. The applicant adjudicated most events of cancer-associated sequelae as the cause of death, as opposed to cancer progression. For example, the applicant chose cachexia as the cause of death or liver failure, which fall under the metabolism and hepatobiliary SOCs, respectively.

Reviewer Comment:

- *This reviewer generally agrees with the categorization of cause of death, although the number of deaths due to cancer were different between the treatment groups. Many of these patients had underlying malignancies.*
- *Increased number of fatal hemorrhages in the denosumab group appears to be due to underlying risk factors.*

Osteoporosis Clinical Program:

Overall, 169 subjects died during their participation in the osteoporosis clinical development program. In Phase 1 studies, one 78-year-old subject died of blunt force trauma from a motor vehicle accident. There were 4 women in Phase 2 studies that died; all 4 women were in the dose-finding trial (Trial 20010223) and had received denosumab. A 62-year-old subject with a history of atrial fibrillation and hypercholesterolemia died of a cerebrovascular accident almost 3 years after initiating denosumab (> 5 months after the last dose). The remaining 3 deaths were due to neoplasms (2 subjects with adenocarcinoma, 1 subject with a "brain tumor"). All 3 deaths from neoplasms occurred in the denosumab 100 mg Q6 months cohort. Adenocarcinoma (primary site unknown) was diagnosed in a 74-year-old who had received denosumab for 2 years and who was an ex-smoker; lung cancer was listed as the cause of death. Another 78-year-old subject with a history of a lumpectomy died of adenocarcinoma (gastric cancer) 18 months after initiating denosumab. A 75-year-old subject 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. One 80-year-old subject from an extension of Trial 20010223 died about 4.5 years after initiating denosumab. The cause of death was not provided by family members for this subject. In addition, there was one subject who died of pancreatic carcinoma about 1 year after discontinuation from trial 20010223; this death is not reflected in the total number of fatalities for this trial. This 60-year-old subject with a history of alcohol and tobacco use was diagnosed with pancreatic carcinoma 17 days after initiating denosumab.

Fatalities in the primary PMO Safety Analysis Set (the safety population in Studies 20030216 and 20040132) were reviewed separately, as this population is most relevant for the PMO indications. No deaths occurred in the entire course of trial 20040132 (N=329), which included 24 months of treatment and an additional 24 months of an "off-treatment" observational period. Thus, all the deaths listed below (see Table 27) occurred in Trial 20030216. In the pooled PMO safety population, the overall all-cause mortality incidence was lower in the denosumab group than the control group (1.7% vs. 2.2%).

The 4 most common System Organ Classes reported as the cause of death were the Cardiac Disorders, Neoplasms, General Disorders and Nervous Systems. Within Cardiac Disorders, the majority of deaths were due to acute myocardial infarction, heart failure, and cardiogenic shock (preferred terms). Within the Neoplasms SOC, the majority of deaths 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 and sudden deaths. The Nervous System fatalities were mainly due to cerebrovascular accidents and cerebral hemorrhages. These common causes of death are common background medical conditions in a population of postmenopausal women.

Table 27. Cause of Death by System Organ Class for the Denosumab Primary PMO Safety Population (pooled data)

	Applicant Adjudication		FDA Adjudication	
	Placebo	Denos.	Placebo	Denos.
Total No. Subjects in Safety Population	4041	4050	4041	4050
Total No. of Fatalities	90	70	90	70
System Organ Class	n (%)	n (%)	n (%)	n (%)
Neoplasms benign, malignant & unspec	27 (30)	19 (27.1)	27 (30)	19 (27.1)
Cardiac	24 (26.7)	17 (24.3)	16 (17.8)	17 (24.3)
Nervous system	11 (12.2)	6 (8.6)	11 (12.2)	6 (8.6)
Respiratory disorders	9 (10)	6 (8.6)	8 (8.9)	4 (5.7)
Infections & infestations	6 (6.7)	6 (8.6)	8 (8.9)	7 (10)
General disorders	6 (6.7)	4 (5.7)	14 (15.6)	3 (4.3)
Vascular disorders	0	4 (5.7)	1 (1.1)	4 (5.7)
Injury, poisoning & proc. Complications	3 (3.3)	1 (1.4)	0	1 (1.4)
Gastrointestinal	2 (2.2)	3 (4.3)	2 (2.2)	4 (5.7)
Hepatobiliary	1 (1.1)	1 (1.4)	1 (1.1)	1 (1.4)
Metabolism & nutrition	1 (1.1)	0	2 (2.2)	0
Endocrine	0	1 (1.4)	0	1 (1.4)
Blood & lymphatic	0	1 (1.4)	0	1 (1.4)
Renal and urinary	0	1 (1.4)	0	1 (1.4)
Social circumstances	0	0	0	1 (1.4)

Reviewer Comment:

- **Based on the fatality data and analysis, this reviewer did not identify any concerning safety signal for denosumab compared to placebo in the PMO trial population.**
- **This reviewer finds the applicant's categorization of cause of death generally acceptable.**

7.3.2 Nonfatal Serious Adverse Events

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. In the primary hormone ablation Safety Population, a total of 845 subjects received placebo and 860 subjects received denosumab in the key hormone ablation studies. The total number of nonfatal serious adverse events from the ISS (pooled key PMO & hormone ablation trials) is summarized below in Table 28:

Table 28. Subjects with any Nonfatal Serious Adverse Event by Study for the Denosumab PMO and Hormone Ablation Safety Population (pooled data)

Study Identifier	Placebo N=4886 n (%)	Denos. N=4910 n (%)
20030216	939 (19.2)	973 (19.8)
20040132*	14 (0.30)	21 (0.40)
20040135	11 (0.20)	19 (0.40)
20040138	203 (4.2)	239 (4.9)

* Trial 20040132 – 36 month data

Reviewer Comment:

The incidence of nonfatal serious adverse events per trial approximately corresponds to the overall number of subjects in each of these studies.

The data for each of these studies was also examined following the removal of serious adverse events related to fractures, which may also be considered an efficacy parameter. A summary of these results are presented below.

Table 29. Subjects with any Nonfatal Serious Adverse Event (fractures excluded*) by Study for the Denosumab PMO and Hormone Ablation Safety Population (pooled data)

Study Identifier	Placebo N=4886 n (%)	Denos. N=4910 n (%)
20030216	868 (17.8)	924 (18.8)
20040132**	13 (0.3)	20 (0.4)
20040135	11 (0.2)	18 (0.4)
20040138	197 (4.0)	230 (4.7)

* Any fractures grouped under the HLTs fractures and dislocations NEC; lower limb fractures and dislocations; pelvic fractures and dislocations; spinal fractures and dislocations; thoracic cage fractures and dislocations; upper limb fractures and dislocations;

** Trial 20040132 using 36-month data

Reviewer Comment:

When fractures were excluded from the dataset, the incidence of nonfatal serious adverse events was higher in the denosumab group across each of the studies. Fractures in the safety database did not affect the safety conclusions.

All nonfatal serious adverse events in the ISS (pooled Primary PMO Studies) were reviewed by System Organ Class, including fractures. The majority of nonfatal 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.

Table 30. Nonfatal Serious Adverse Events Ordered by SOC and Treatment Group for the Denosumab Primary PMO Safety Population (pooled data)

System Organ Class	Primary PMO Safety Population	
	Placebo N=4041 n (%)	Denos. N=4050 n (%)
Injury, poisoning and procedural complications	191 (4.73)	126 (3.11)
Cardiac disorders	142 (3.51)	181 (4.47)
Infections and infestations	130 (3.22)	162 (4.30)
Musculoskeletal and connective tissue disorders	151 (3.74)	169 (4.17)
Neoplasms benign, malignant and unspec	123 (3.04)	152 (3.75)
Gastrointestinal disorders	102 (2.52)	143 (3.53)
Nervous system disorders	120 (2.97)	125 (3.09)
Respiratory, thoracic and mediastinal disorders	76 (1.88)	80 (1.98)
Vascular disorders	71 (1.76)	71 (1.75)
Eye disorders	45 (1.11)	39 (0.96)
General disorders & administration site conditions	30 (0.74)	34 (0.84)
Reproductive system and breast disorders	38 (0.94)	32 (0.79)
Hepatobiliary disorders	33 (0.82)	29 (0.72)
Ear and labyrinth disorders	15 (0.37)	24 (0.59)
Blood and lymphatic system disorders	22 (0.54)	20 (0.49)
Renal and urinary disorders	19 (0.47)	20 (0.49)
Metabolism and nutrition disorders	14 (0.35)	20 (0.49)
Psychiatric disorders	14 (0.35)	20 (0.49)
Skin and subcutaneous tissue disorders	7 (0.17)	10 (0.25)
Investigations	9 (0.22)	5 (0.12)
Endocrine disorders	6 (0.15)	5 (0.12)
Immune system disorders	1 (0.02)	1 (0.02)
Surgical and medical procedures	0 (0)	1 (0.02)
Congenital, familial and genetic disorders	1 (0.02)	0 (0)

The most common nonfatal serious adverse events in the pooled key PMO Studies are summarized below by High Level Group Term. It is noteworthy that nonfatal serious adverse events related to coronary artery disorders, unspecified infections, and urinary tract signs & symptoms occur more commonly in subjects who received denosumab.

Table 31. Nonfatal Serious Adverse Events Ordered by SOC and HLGT for the Denosumab Primary PMO Safety Population (pooled data) for MedDRA HLGT ≥ 2% or Denosumab ≥ 3 Fold

System Organ Class	High Level Group Term	Placebo N=4041 n (%)	Denos. N=4050 n (%)
Cardiac disorders	Coronary artery disorders	69 (1.71)	98 (2.42)
Eye disorders	Glaucoma and ocular hypertension	1 (0.02)	7 (0.17)
Gastrointestinal disorders	Anal and rectal conditions NEC	2 (0.05)	7 (0.17)
	Exocrine pancreas conditions	2 (0.05)	6 (0.15)
Infections & infestations	Infections - pathogen unspecified	112 (2.77)	134 (3.31)
Injury & poisoning	Bone and joint injuries	143 (3.54)	99 (2.44)
Musculoskeletal & connective tissue	Joint disorders	108 (2.67)	99 (2.44)
	Muscle disorders	0 (0)	5 (0.12)
Neoplasms benign, malignant & unspec.	Endocrine neoplasms malignant & unspec.	0 (0)	4 (0.10)
	Misc. & site unspec. neoplasms malignant and unspec.	0 (0)	5 (0.12)
	Soft tissue neoplasms benign	0 (0)	3 (0.07)
	Urinary tract signs and symptoms	1 (0.02)	9 (0.22)
Renal & urinary disorders	Cervix disorders	1 (0.02)	4 (0.10)
Skin & subcutaneous tissue disorders	Skin & subcutaneous tissue disorders	0 (0)	6 (0.15)

Reviewer Comment:

The applicant has proposed the following WARNING & PRECAUTION about skin infections:

In clinical trials in women with postmenopausal osteoporosis, skin infections leading to hospitalization were reported more frequently in the PROLIA (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 PROLIA groups. Advise patients to seek prompt medical attention if they develop signs or symptoms of cellulitis.

- *The proposed labeling should be strengthened to describe other types of serious infections that occurred more frequently in denosumab subjects, including abdominal tract infections, urinary tract infections, ear infections and infections due to streptococcus and other bacteria.*
- *Opportunistic infections did not occur at a higher incidence in denosumab subjects in the Primary PMO data reviewed. Infections are further evaluated in section 7.3.4.2.*
- *Coronary artery disorders are further evaluated in section 7.3.4.1. Glaucoma is addressed in section 7.3.4.6; skin and subcutaneous tissue disorders are addressed in section 7.3.4.8; neoplasms are addressed in section 7.3.4.5.*

7.3.3 Dropouts and/or Discontinuations

In the Primary PMO Studies, subjects could discontinue IP and remain in the trial and be monitored until trial completion or subjects choose not to complete the trial altogether (no IP or trial monitoring). Trial 20040132 had a scheduled 24-month “off-treatment” observation period.

The incidence of trial completion in the pooled data from the key PMO indication studies was 82.3% of placebo subjects and 83.9% of denosumab subjects. In subjects who did not complete the trial, the reasons for ending trial were most commonly withdrawal of consent (10.3% placebo, 8.7% denosumab), adverse events (2% placebo, 2.3% denosumab), death (1.9% placebo, 1.5% denosumab), and lost to follow-up (1.5% placebo, 1.6% denosumab). Thus, there were more subjects in the denosumab group ending trial due to adverse events and “other” reasons, but these differences were not considerable. These 2 key studies were also reviewed individually to see if Trial 20040132 differed from Trial 20030216 due to differences in the patient population studied. The only noteworthy difference between studies in the reason for ending trial is that the incidence of subjects lost to follow-up was higher in Trial 20040132, with 5 placebo subjects (3%) and 7 denosumab subjects (4.3%) lost to follow-up.

Table 32. Reason for Ending Study in Primary PMO Safety Population (pooled data)

	Placebo n (%)	Denos. n (%)
Randomized	4072	4068
Completed Study	3350 (82.3)	3414 (83.9)
Reason for Ending Study		
• Administrative decision	6 (0.1)	3 (<0.1)
• Adverse event	83 (2)	94 (2.3)
• Consent withdrawn	418 (10.3)	354 (8.7)
• Death	78 (1.9)	62 (1.5)
• Disease progression	7 (0.2)	3 (<0.1)
• Ineligibility determined	12 (0.3)	11 (0.3)
• Lost to follow-up	62 (1.5)	64 (1.6)
• Noncompliance	17 (0.4)	15 (0.4)
• Other	20 (0.5)	34 (0.8)
• Protocol deviation	12 (0.3)	10 (0.2)
• Requirement for alternative therapy	7 (0.2)	4 (<0.1)

Source: Integrated Summary of Safety, Table SP2-1.2, pages 42-43 of 5754.

In the pooled data from the key PMO indication studies, the incidence of subjects discontinuing IP was higher in subjects receiving placebo. The most common reasons for ending IP were consent withdrawn (8.3% placebo, 6.9% denosumab), adverse events (5.1% placebo, 4.8% denosumab) and subject request (2.1% placebo, 2.2%

denosumab). More subjects in the placebo group withdrew consent, had disease progression or required alternative therapy. These 2 key studies were also reviewed individually to see if Trial 20040132 differed from Trial 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 Trial 20040132 ended IP due to "subject request," which may represent adverse events in these subjects.

Table 33. Reason for Ending Investigational Product in Primary PMO Safety Population (pooled data)

	Placebo n (%)	Denos. n (%)
Randomized	4072	4068
Completed Investigational Product	3090 (75.9%)	3270 (80.4%)
Reason for Ending Invest. Product		
• Administrative decision	5 (0.1)	9 (0.2)
• Adverse event	209 (5.1)	197 (4.8)
• Consent withdrawn	336 (8.3)	281 (6.9)
• 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 (2.1)	91 (2.2)

Source: Integrated Summary of Safety, Table 5, pages 41-42 of 424.

The most common AEs occurring in at least 3 or more subjects and leading to discontinuation of IP are listed in Table 34. The most common reason for discontinuing denosumab was breast cancer, with twice as many subjects reporting this event (20 vs. 10). 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, breast cancer, thoracic vertebral fractures and increased bone resorption.

Table 34. 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 (%)
Breast cancer	10 (0.2)	20 (0.5)
Nausea	1 (<0.1)	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 (<0.1)	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)
Diarrhea	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 (<0.1)
Resorption bone increased	5 (0.1)	0 (0)

Source: Integrated Summary of Safety, Table 14, pages 72-73 of 424.

Reviewer Comment:

- **About 85% of subjects completed the Primary PMO studies, with 76% of placebo subjects and 80% of denosumab subjects completing all scheduled doses of investigational product.**
- **Adverse events were cited as the reason for discontinuing investigational product dosing in 5% of subjects in the placebo and denosumab groups.**
- **In the denosumab group, breast cancer was the adverse event with the highest incidence of subjects being removed from trial or discontinuing investigational product**

7.3.4 Significant Adverse Events

7.3.4.1 Cardiovascular Safety

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 S et al. 2004; Mikami S et al. 2008; Nybo M and Rasmussen LM 2008) and the possibility that inactivation of RANKL by denosumab could result in elevated levels of osteoprotegerin

(OPG) as it binds to the same target. To address these concerns, the Applicant established a committee to adjudicate possible cardiovascular events in two phase 3 trials, one in postmenopausal women (trial 20030216) and one in men (trial 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 subjects in trial 20030216.

Preclinical findings

Denosumab is not pharmacologically active in mice or rats and as a result, cardiovascular safety assessments were conducted in monkeys. Preclinical evaluations included a 12-month toxicology trial in cynomolgus monkey in which doses of 0, 1, 10, and 50 mg/kg were administered subcutaneously at monthly intervals (corresponding human equivalent dose of ~ 0, 20, 200 and 1000 mg). With respect to cardiovascular safety, similar histological changes (pericarditis and denegeration/necrosis) were observed in both control and denosumab-exposed animals. One animal in the high dose group that died exhibited low-grade acute focal pericarditis and minimal multifocal myocarditis. The pharmacology toxicology reviewer did not consider these preclinical findings concerning for a potential cardiac signal.

Key attributes of the adjudication process for potential cardiovascular events:

- Committee members were Cardiologists not otherwise associated with the trial.
- Identification of potential cardiovascular-related SAEs and deaths: All deaths were reviewed. Serious adverse events (SAEs) were identified for adjudication using MedDRA preferred terms (see applicant's Manual of Operations)
- The committee categorized the SAEs 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;
- Information given to the committee: SAE report, general event data collection form which contained category specific site investigator narratives, source documents and an oncologist review form if completed. This form was to be completed by the oncologist reviewer upon the request of the cardiology reviewers for subjects enrolled in trial 20040138 and was to indicate whether or not the oncologist felt the death was cancer-related.
- Source: Denosumab Event Adjudication Manual of Operations dated November 15,2007

Reviewer's comment

This medical officer reviewed the adjudication manual of procedure, the list of pre-defined MedDRA preferred term triggering the adjudication of event and

adjudication log. The adjudication process appears adequate and acceptable. The list of MedDRA preferred terms appeared comprehensive and appropriate.

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.

Cardiovascular serious event adjudication results:

Adjudication of cardiovascular SAEs 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 placebo and 247(43.2%) in 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 the 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 (Table 35).

Table 35. Adjudicated cardiovascular-related serious adverse events for trial 20030216

	20030216			20040138		
Incidence at 36 Months	Placebo (N = 3876)	Denos. (N = 3886)	Hazard ratio (95%CI)	Placebo (N = 725)	Denos. (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 trial report 20030216, page 343 and Clinical Study Report 20040138, page 196.

Unadjudicated Adverse Event analysis:

This reviewer conducted an independent analysis of cardiovascular AEs for a broader safety database which included all phase 2 and phase 3 studies in the denosumab development program to assess for any major discrepancies with the adjudicated dataset. This analysis includes a total safety population of 10,638 subjects (4738 placebo and 6329 denosumab) who received one dose of IP. Since the largest PMO clinical trial was adjudicated for cardiovascular disease AEs, all phase 2 and 3 trials were included in the unadjudicated analysis to evaluate if there was a trend in dose dependency or age dependency of these events. 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% vs. 1.7%), palpitations (1.5% vs. 1.3%), coronary artery disease (1% vs. 0.9%), and arrhythmia (1% vs. 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.

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 substudy 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 (for details, see individual trial review for trial 20030216).

Reviewer Comment:

Currently, it is unknown if elevated OPG levels in humans adversely impact cardiovascular outcomes or represent a disease-related compensatory response. The assay sensitivity, clinically meaningful change in OPG level, and power of the trial to detect this change should be considered as well while evaluating effect of OPG on adverse cardiovascular events. At this point, there was no clear increase in OPG levels and more importantly, no significant cardiovascular safety signal was observed for denosumab in the analyses of adjudicated or unadjudicated CV-related outcomes.

Aortic calcification:

Subjects were assessed for aortic calcification score if they were considered high risk according to the modified RUTH criteria (of ≥ 4 points) in trial 20030216. 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

In all, 2363 subjects were assessed for aortic calcification score. This subgroup was similar to the overall trial population with regard to subject disposition, baseline body composition and baseline BMD T-scores. Approximately 23% of subjects had baseline aortic calcification scores of 0. The distribution of baseline scores was similar in the two treatment arm and, most patients had lower baseline aortic calcification scores (mean score 7.2 in placebo and 6.8 in denosumab). The mean change from baseline in aortic calcification score was minimal and similar in both treatment groups (Table 36).

Table 36. Change from baseline in total Aortic Calcification Severity Score by Visit (Aortic Calcification Analysis Set, Observed Data)

	Number of subjects with data at all 8 aortic segments	Mean change from baseline	SD
Month 12			
Placebo (N = 1142)	664	0.1	0.6
Denosumab 60 mg Q6M (N = 1221)	713	0.1	0.4
Month 24			
Placebo (N = 1142)	583	0.2	0.7
Denosumab 60 mg Q6M (N = 1221)	648	0.2	0.8
Month 36			
Placebo (N = 1142)	501	0.4	1
Denosumab 60 mg Q6M (N = 1221)	544	0.4	1.1

Source: Applicant table 14-6.7.7 (page 922 of CSR 20030216)

Reviewer's comment: *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 if they exist.*

Reviewer's summary for cardiovascular disease:

The cardiovascular adjudication process was comprehensive and appropriate in this medical officer's opinion. The findings of adjudicated and unadjudicated analyses of adverse CV outcomes, osteoprotegerin levels, aortic calcification, and the preclinical monkey trial consistently indicated a lack of adverse cardiovascular outcomes for denosumab compared to placebo.

7.3.4.2 Infections

RANKL is expressed on activated T and B lymphocytes and in the lymph nodes. It is thus biologically plausible that the RANKL inhibitor denosumab could possibly increase the risk of infection as T and B lymphocytes are responsible for foreign antigen recognition.

Preclinical Findings

Possible signs of immune suppression with denosumab were noted during the 6/12-month toxicity trial. There were unexplained deaths at doses 50 times the proposed clinical dose, potential impairment of the ability to control infection, and teeth/jaw abscesses at doses 10 times the proposed clinical dose. Changes in lymphocytes were also noted following denosumab exposure in 16-month pharmacology (bone quality trial). At the end of the trial, the total lymphocyte count was statistically significantly decreased in the high-dose denosumab group. Absolute counts of CD3+/CD8+ cytotoxic T lymphocytes were also statistically significantly decreased at the high dose

compared to controls. The applicant considered this normal variation, but the significance of this finding is not clear. Based on the available data, disruption of RANKL/RANK signaling in immunologically intact patients would be of negligible clinical significance, but it is unclear whether disruption in signaling would be of clinical significance in immune-compromised patients as a result of concurrent therapy or age-related immunosenescence. The Pharmacology/Toxicology reviewer noted that denosumab is primarily distributed to the lymph nodes and spleen, among other sites.

Clinical Findings

A Phase 1 trial (Study 20010124) conducted T & B cell enumeration on Study Day 1, 2, 8, 85 and 169 in 37 subjects who received single-dose and multi-dose subcutaneous denosumab. There was no evidence of a clinically significant effect of denosumab on T & B cell counts measured in this trial, but this was a very small sample with limited numbers of samples at later time points.

Table 37. CD4 Shifts from Baseline in Common Toxicity Criteria (Study 20010124)

Dose Group	Baseline Grade*	Most Extreme On-Study Decrease in Grade		
		0	1	2
Placebo (N = 12)	n/a	1		
	0	10		
	2			1
Denos. 0.01 mg/kg SC (N = 6)	0	6		
Denos. 0.03 mg/kg SC (N = 6)	0	5		
	2	1		
Denos. 0.10 mg/kg SC (N = 6)	n/a	3		
	0	3		
Denos. 0.30 mg/kg SC (N = 6)	0	5	1	
Denos. 1.00 mg/kg SC (N = 6)	0	4		2
Denos. 3.00 mg/kg SC (N = 7)	0	7		

* only columns or rows with a value are depicted

Source: Final Study Report 20010124, Table 14-23.1.5, pages 1904-1906 of 4278.

Reviewer Comments:

- **No denosumab subjects had a grade 3 or 4 decrease in CD4 counts.**

Table 38. Lymphocyte Shifts from Baseline in Common Toxicity Criteria (Study 20010124)

Dose Group	Baseline Grade*	Most Extreme On-Study Decrease in Grade			
		0	1	2	3
Placebo (N = 12)	0	10			1
	2			1	
Denos. 0.01 mg/kg SC (N = 6)	0	5	1		
Denos. 0.03 mg/kg SC (N = 6)	0	6			
Denos. 0.10 mg/kg SC (N = 6)	0	4	1		
	2	1			
Denos. 0.30 mg/kg SC (N = 6)	0	5	1		
Denos. 1.00 mg/kg SC (N = 6)	0	5	1		
Denos. 3.00 mg/kg SC (N = 7)	0	6	1		

* only columns or rows with a value are depicted

Source: Final Study Report 20010124, Table 14-23.1.12, pages 1925-1927 of 4278.

Reviewer Comments:

- **No denosumab subjects had a grade 3 or 4 decrease in lymphocyte counts.**

A Phase 2 trial (Trial 20010223) had an immune cell assessment substudy which enrolled 91 subjects from 5 centers. These subjects underwent enumeration of T- and B-cells by flow cytometry and WBC and lymphocyte cell counts. Blood samples used for this substudy were from baseline and 3, 6, 12, 18 and 24 months after multiple doses of denosumab. The following analyses were performed:

- Enumeration of T and B cells (CD3, CD4, CD8, and CD19) and natural killer (NK) cells (CD16/CD56) by flow cytometry
- WBC and lymphocytes counts

Two subjects receiving denosumab 210 mg Q6months had a grade 3 decrease in lymphocyte counts; one subject had a normal lymphocyte count at baseline and the other subject had an unknown baseline value. No denosumab subjects had a grade 3 or 4 decrease in white blood cell, neutrophil, or CD4 counts in this substudy. Thus, there was no evidence of a clinically significant effect of denosumab on the cell counts measured in this substudy.

In two Phase I studies, three subjects were hospitalized for pneumonia. 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 these cases were not well documented, it is concerning that healthy volunteers appeared to have serious events of pneumonia after a single dose of denosumab. In addition, three denosumab subjects in Study 20030216 developed endocarditis and 7 denosumab subjects developed SAEs of erysipelas; no placebo subjects developed endocarditis or SAEs of erysipelas in Study 20030216. As such, serious adverse events of infection in the ISS PMO pooled data were closely examined. Denosumab subjects had a higher incidence of serious infections due to bacteria or unspecified pathogens.

Table 39. SAEs in the Infections SOC in ISS pooled data (Primary PMO Studies) by HLG

High Level Group Term	Placebo N=4041 n (%)	Denos. N=4050 n (%)
Bacterial infectious disorders	15 (0.37)	25 (0.62)
Fungal infectious disorders	1 (0.02)	2 (0.05)
Infections - pathogen unspecified	115 (2.85)	138 (3.41)
Mycobacterial infectious disorders	3 (0.07)	2 (0.05)
Rickettsial infectious disorders	1 (0.02)	0 (0)
Viral infectious disorders	5 (0.12)	6 (0.15)

When these events were examined based by High Level Term, denosumab subjects appeared to have a higher incidence of bacterial, streptococcal, abdominal, ear, and urinary tract infections, as shown below in grey. These serious adverse events were reviewed across the key PMO studies as the subjects in Trial 20040132 were younger than subjects in Trial 20030216. The incidence of SAEs was much lower in Trial 20040132. The highest reported incidence was 3 denosumab subjects (1.8%) each developed serious abdominal infections and lower respiratory tract infections; only 1 placebo subject (0.06%) each developed these events.

Table 40. SAEs in the Infections SOC in Primary PMO Safety Population (ISS pooled data) by HLG and HLT

High Level Group Term	High Level Term	Placebo N = 4041 n (%)	Denos. N = 4050 n (%)
Bacterial infections	Bacterial infections NEC	4 (0.10)	12 (0.32)
	Borrelial infections	2 (0.05)	1 (0.02)
	Clostridia infections	2 (0.05)	1 (0.02)
	Escherichia infections	2 (0.05)	1 (0.02)
	Helicobacter infections	0 (0)	2 (0.05)
	Pseudomonal infections	0 (0)	2 (0.05)
	Salmonella infections	2 (0.05)	0 (0)
	Staphylococcal infections	2 (0.05)	1 (0.02)
	Streptococcal infections	2 (0.05)	7 (0.17)
Fungal infections	Aspergillus infections	0 (0)	1 (0.02)
	Fungal infections NEC	1 (0.02)	1 (0.02)
Infections - pathogen unspec.	Abdominal & gastrointestinal infections	25 (0.62)	31 (0.77)
	Bone and joint infections	1 (0.02)	0 (0)
	Cardiac infections	0 (0)	1 (0.02)
	Central nervous system & spinal	1 (0.02)	0 (0)
	Ear infections	0 (0)	5 (0.12)
	Female reproductive tract infections	1 (0.02)	3 (0.07)
	Hepatobiliary and spleen infections	2 (0.05)	2 (0.05)
	Infections NEC	5 (0.12)	7 (0.17)
	Lower respiratory tract & lung infections	63 (1.56)	60 (1.48)
	Sepsis, bacteraemia, viraemia & fungaemia	8 (0.20)	7 (0.17)
	Skin structures and soft tissue infections	2 (0.05)	3 (0.07)
	Upper respiratory tract infections	3 (0.07)	5 (0.12)
	Urinary tract infections	17 (0.42)	31 (0.77)
	Vascular infections	0 (0)	2 (0.05)
Mycobacterial infectious disorders	Tuberculous infections	3 (0.07)	2 (0.05)
Rickettsial infections	Typhus infections	1 (0.02)	0 (0)
Viral infections	Herpes viral infections	2 (0.05)	2 (0.05)
	Influenza viral infections	1 (0.02)	0 (0)
	Rotaviral infections	0 (0)	1 (0.02)
	Viral infections NEC	2 (0.05)	3 (0.07)

The incidence of all adverse events (serious and non-serious) of infection was reviewed by HLG. The incidence of infection was almost the same between the two treatment groups. These events were reviewed across each of the Primary PMO studies. There was no difference between treatment groups in the incidence of adverse events of infection for either trial.

Table 41. AEs in the Infections SOC in ISS pooled data (Primary PMO Studies) by HLGT

High Level Group Term	Placebo N=4041 n (%)	Denos. N=4050 n (%)
Bacterial infectious disorders	124 (3.07)	124 (3.06)
Chlamydial infectious disorders	3 (0.07)	1 (0.02)
Ectoparasitic disorders	3 (0.07)	5 (0.12)
Fungal infectious disorders	102 (2.52)	107 (2.64%)
Helminthic disorders	3 (0.07)	5 (0.12)
Infections - pathogen unspecified	2847 (70.45)	2803 (69.21)
Mycobacterial infectious disorders	7 (0.17)	3 (0.74)
Protozoal infectious disorders	3 (0.07)	3 (0.74)
Rickettsial infectious disorders	2 (0.05)	1 (0.02)
Viral infectious disorders	629 (15.57)	634 (15.65)

When serious and non-serious infections are reviewed by PT, there was not a significant difference in adverse events between treatment groups. However, there were a few uncommon events that occurred almost exclusively in denosumab subjects, including infective arthritis and infected skin ulcer.

Table 42. All Infections (serious + non-serious) in Primary PMO Studies (ISS pooled data) occurring in $\geq 1\%$ of subjects in either treatment group or > 3 -fold with denosumab

Preferred Term	Placebo N=4041 n (%)	Denos. N=4050 n (%)
Nasopharyngitis	637 (15.76)	607 (14.99)
Influenza	356 (8.81)	346 (8.54)
Bronchitis	313 (7.75)	308 (7.60)
Urinary tract infection	272 (6.73)	265 (6.54)
Cystitis	230 (5.69)	233 (5.75)
Upper respiratory tract infection	189 (4.68)	213 (5.26)
Pneumonia	151 (3.74)	160 (3.95)
Sinusitis	139 (3.44)	113 (2.79)
Pharyngitis	83 (2.05)	94 (2.32)
Gastroenteritis	97 (2.40)	84 (2.07)
Herpes zoster	76 (1.88)	83 (2.05)
Lower respiratory tract infection	89 (2.20)	71 (1.75)
Viral infection	76 (1.88)	70 (1.73)
Rhinitis	84 (2.08)	63 (1.56)
Respiratory tract infection	69 (1.71)	56 (1.38)
Ear infection	25 (0.62)	43 (1.06)
Tooth infection	43 (1.06)	29 (0.72)
Arthritis infective	0 (0)	8 (0.20)

As this product 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 concerns in regards to infection.

Reviewer Comments:

- ***Three volunteers in 2 Phase I studies were hospitalized for pneumonia after a single dose of denosumab; one was subsequently diagnosed with lung cancer.***
- ***Unusual serious infections occurred in denosumab subjects, such as endocarditis, erysipelas and infective arthritis. However, opportunistic infections did not occur more frequently in denosumab subjects as compared to placebo.***
- ***Elderly subjects did not appear to have a higher incidence of infection or more opportunistic infections when compared to the overall PMO safety population.***
- ***Serious infections of cellulitis, gastrointestinal infections and urinary tract infections occurred at a higher incidence in denosumab subjects compared to placebo.***

A consult was requested of the Division of Anti-Infective and Ophthalmology Products (DAIOP) to further evaluate events of infection. It was noted that although denosumab subjects may have had somewhat more frequent infections, there was no specific signal for infections due to opportunistic pathogens. An adult with a fully functioning immune system may not be at increased risk of infection because of redundancies in immune signaling. However individuals with underlying defects in the immune system (e.g. elderly patients with waning immunologic function, those on concomitant immunosuppressant medications or patients with uncontrolled diabetes) may be at increased risk of infection.

Recommendations were made regarding labeling and further information to be collected postmarketing. If denosumab is approved the applicant should collect information on all infection-related adverse events in the indefinite future during the postmarketing period, perhaps as a postmarketing requirement. Regarding labeling, the product label should include language that denosumab may cause serious infections that are not limited to specific pathogens. Similar labeling to that of HUMIRA was recommended, including:

- a) Patients on concomitant immunosuppressive therapy may be at increased risk of infections
- b) Infections, sometimes serious, have been noted in multiple organ systems, that is, not solely cellulitis
- c) If a patient develops a serious infection while on therapy, denosumab should probably be discontinued.

- d) Physicians should exercise caution when considering the use of denosumab patients with a history of recurrent infection or underlying conditions which may predispose them to infections.

The applicant has proposed the following WARNING & PRECAUTION about skin infections:

(b) (4)
[Redacted text block]

Reviewer Comments:

- ***The currently proposed product labeling does not adequately convey the risk of serious infections. It seems reasonable to note that patients on concomitant immunosuppressive therapy may be at increased risk of infections.***
- ***It also seems reasonable to have the labeling note that infections, sometimes serious, have been noted in multiple organ systems.***
- ***The recommendation to discontinue denosumab if a patient develops a serious infection does not seem warranted at this time; there was not an excess of deaths due to infections in denosumab subjects. This reviewer would recommend that the labeling contain language to prompt the physician to reassess the use of therapy in subjects who develop serious infections.***
- ***The recommendation to physicians to exercise caution in patients with a history of recurrent infection or underlying conditions that predispose patients to infections also seems reasonable.***
- ***The recommendation for the applicant to conduct enhanced safety monitoring of infectious events is a possible mechanism to closely monitor these serious events after product approval.***
- ***In the benefit-risk assessment of this product, careful consideration will be given to this issue and steps to mitigate this risk.***

7.3.4.3 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. 2009). The mechanism by which osteonecrosis develops in relationship to treatment with bisphosphonates is not well understood.

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.

The applicant pre-defined ONJ as:

- 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.

Reviewer comment: This definition is accurate and consistent with the current medical literature and American Dental Association and American Society of Bone Mineral research (Ruggiero and Mehrotra 2008).

The applicant identified events to be adjudicated by using a pre-defined list of MedDRA preferred terms (Table 43). In addition, oral or orofacial fistulas suspicious for underlying ONJ and any clinical trial adverse events reported by the investigator as possible ONJ were sent to the adjudication committee.

Table 43: Predefined list of MedDRA terms to identify potential cases of ONJ

Abscess jaw	Abscess oral
Alveolar osteitis	Bone debridement
Bone erosion	Bone fistula
Bone infarction	Dental fistula
Dental necrosis	Gingival abscess
Gingival erosion	Gingival ulceration
Jaw lesion excision	Jaw operation
Loose tooth	Maxillofacial operation
Necrosis	Oral cavity fistula
Oral surgery	Oroantral fistula
Osteitis	Osteomyelitis
Osteomyelitis acute	Osteomyelitis chronic
Osteomyelitis drainage	Osteonecrosis
Pain in jaw	Periodontal destruction
Periodontal infection	Periodontal Operation
Primary sequestrum	Secondary sequestrum
Sequestrectomy	Tertiary sequestrum

Source: ONJ manual of procedures

In order to expand the search, the applicant included terms that were not contained in the table above, but could potentially represent ONJ events (Table 44). These events were assessed on a case by case basis and queries were sent to the site to assess if the event was in fact suspected ONJ.

Table 44 Expanded MedDRA Terms for Possible ONJ Signal (PTs in bold italic)

• Ischemic necrosis
• <i>Aseptic necrosis bone</i> , aseptic necrosis, aseptic necrosis of bone, aseptic necrosis of bone (site unspecified), avascular necrosis of bone,
• <i>Osteonecrosis, necrosis</i> , bone necrosis, necrosis bone
• <i>Bone infarction</i>
• <i>Osteomyelitis, osteomyelitis acute, osteomyelitis drainage, osteomyelitis chronic</i> , osteomyelitis chemotherapy related
• <i>Primary sequestrum, secondary sequestrum, tertiary sequestrum, sequestrum</i>
• <i>Jaw lesion excision, jaw operation, mandibulectomy, maxillofacial operation, oral surgery, bone debridement, sequestrectomy</i>
• <i>Osteopetrosis</i>

Source: ONJ manual of procedures

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. Table 45 shows number of subjects sent for adjudication in each clinical trial. Even though the search criteria listed above seems comprehensive, very few cases were adjudicated.

Table 45. Listing by Study of All Oral Adverse Events Sent to the Adjudication Committee

Study	Subject Enrollment	Number of subjects in each trial adjudicated
20030216	7868	12
20040132	332	6
20040138	1468	1
20050233	200	0
20050234	504	0
20050179	247	0
20060237	311	2
Total	10930	21

The adjudication committee did not consider any of the 21 cases sent for adjudication to be a bona fide case of ONJ. The meeting minutes of the adjudication committee indicated that one of the adjudicator raised concerns about the under-reporting of potential ONJ cases and lack of information on which to base a decision. He subsequently resigned. However, even in light of this criticism, it appears that the conduct of the ONJAC was appropriate.

Reviewer's comment:

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. Therefore, a search of the adverse events database was performed utilizing the expanded search criteria by looking at the verbatim terms. 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.

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 by agency experts, however, that a more detailed search utilizing these terms would not likely yield new cases for adjudication.

The Quantitative Safety and Pharmacovigilance group (QSPG) also widened the search for potential ONJ cases by adding 30 additional PTs to the list of PTs provided by the applicant. This analysis also showed no difference in the two treatment groups.

It should be noted that while no cases of ONJ have been confirmed in the PMO 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 receiving higher doses.

7.3.4.4 Delayed Fracture Healing

Reason for concern:

Fracture healing involves the production of a callus of cartilage and woven bone that stabilizes the fracture (Barnes et al. 1999). The fracture callus gradually mineralizes and is remodeled over time to form lamellar bone and complete the fracture repair. Bone remodeling (bone formation and resorption) is critical in fracture healing. Patients with bone loss are at increased risk and incidence of fracture. Denosumab is primarily an antiresorptive agent. Bone resorption and formation are coupled processes, and therefore denosumab suppresses bone formation as well.

Preclinical findings:

HuRANKL KI (knock in) mice were used in studies to compare the effects of alendronate and denosumab on murine fracture healing, with denosumab doses roughly equivalent to the proposed clinical dose of 60 mg. At either 21 or 42 days post femur fracture, the fracture and contralateral femora were analyzed by microCT, torsion testing and histology. The results showed that both alendronate and denosumab treatment delayed the removal of cartilage, remodeling of the fracture callus, and induced changes in the morphology and time course of tissue remodeling of the fractured femur, as compared to the control mice with fractured femur. Mechanical strength was not negatively affected. Treatment with either denosumab or alendronate also induced increases in strength and stiffness relative to the nonfractured control or vehicle control group. Overall, fractures took greater time to repair when the huRANKL mice were treated with denosumab or alendronate, as compared to the vehicle control.

To address this concern, fracture healing was assessed for all nonvertebral fractures in Trial 20030216 using specific case report forms. Such assessments were not performed in Trial 20040132. In addition, a fracture healing substudy in Trial 20030216 was conducted to further evaluate cortical bridging by serial x-rays to determine healing progression at 3 and 6 months post **wrist fracture** (For details, see individual trial review for trial 20030216).

Results:

In trial 20030216, a total of 386 nonvertebral fractures occurred in 303 subjects in the denosumab group and a total of 465 nonvertebral fractures occurred in 364 subjects in the placebo group. As shown in Table 46, fracture healing complications were few and balanced between the two groups. 2 subjects in the each group experienced delayed healing and one subject in the placebo had non-union. Mean time to fracture was 468 days in the placebo and 465 days in the denosumab group.

Table 46: Non vertebral fracture healing complications

	Placebo N=3876	Denosumab N=3886
Total number of non vertebral fractures	465	386
Fracture Healing Time abnormal	3	2
Fracture that require More Than One Reduction	15	7
Fracture that require Surgical Intervention	100	66
Fx Healing Complications incidence		
Chronic Pain	11	7
Delayed Healing	2	2
Malunion	3	3
Nonunion	1	0
Osteomyelitis	0	0
Other	7	10

Fracture healing substudy results: Only twenty-five subjects were enrolled in the Fracture Healing Substudy, 8 in the denosumab group and 17 in the placebo group. There were 197 subjects eligible for enrollment in the substudy (107 in placebo and 90 in denosumab group) with wrist fracture. The applicant reasons that it was difficult to enroll patients in the fracture healing substudy following an acute fracture where regular scheduled visits occurred every 6 months. The mean age of the women enrolled was 72 years of age; 9 subjects were 75 years of age or older. One subject in the denosumab group and 2 subjects in the placebo group had delayed radiographic healing of a distal radius fracture. Healing was considered delayed if bridging was not demonstrable in any visible cortex at 3 months by radiography. The fractures of all 3 subjects were healed by the time of the 6 month radiograph.

Reviewer's Comment:

- *Overall, fracture healing complications were few and balanced between the treatment groups. It is likely that even though healing is delayed subclinically, due to increased mechanical strength of the callus subjects did not report clinical complications.*

- ***Only 25 subjects were enrolled in the fracture healing substudy. 157 subjects were planned to enroll. The applicant reasons that it was difficult to enroll patients in the fracture healing substudy following an acute fracture where regular scheduled visits occurred every 6 months. No conclusions can be made regarding fracture healing complications based on this substudy due to insufficient enrollment.***
- ***Given findings in nonclinical studies, and inadequate clinical radiographic data, concern remains. These reviewers recommend a long term trial to evaluate this potential adverse effect.***

7.3.4.5 Malignancy

Preclinical Findings

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 for 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 trial 20010223 in the denosumab 100 mg Q6 months cohort (N=41) died of a new malignancy. The Neoplasms SOC contains both benign and malignant conditions and both types of events are presented, but malignancies are the focus of this summary. As the subjects in the hormone ablation studies had an underlying malignancy, the review of new onset of malignancy will focus on the key PMO studies.

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 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), which was due to pancreatic carcinoma. 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 was malignant respiratory neoplasms, with events reported in 16 denosumab and 25 placebo subjects.

Table 47. All Adverse Events in the Neoplasms SOC in Primary PMO studies (pooled data) by HLGT

High Level Group Term	Placebo N=4041 n (%)	Denos. N=4050 n (%)
Breast neoplasms benign (incl nipple)	14 (0.35)	19 (0.47)
Breast neoplasms malignant and unspecified (incl nipple)	30 (0.74)	35 (0.86)
Cancer-related morbidities	0 (0)	2 (0.05)
Cutaneous neoplasms benign	38 (0.94)	31 (0.77)
Endocrine neoplasms benign	13 (0.32)	19 (0.47)
Endocrine neoplasms malignant and unspecified	2 (0.05)	7 (0.17)
Gastrointestinal neoplasms benign	9 (0.22)	3 (0.07)
Gastrointestinal neoplasms malignant and unspecified	24 (0.59)	35 (0.86)
Haematopoietic neoplasms (excl leukaemias and lymphomas)	0 (0)	3 (0.07)
Hepatic and biliary neoplasms benign	2 (0.05)	4 (0.10)
Hepatobiliary neoplasms malignant and unspecified	3 (0.07)	1 (0.02)
Leukaemias	2 (0.05)	2 (0.05)
Lymphomas NEC	2 (0.05)	2 (0.05)
Lymphomas non-Hodgkin's B-cell	4 (0.10)	2 (0.05)
Lymphomas non-Hodgkin's T-cell	0 (0)	1 (0.02)
Lymphomas non-Hodgkin's unspecified histology	1 (0.02)	1 (0.02)
Mesotheliomas	0 (0)	1 (0.02)
Metastases	11 (0.27)	9 (0.22)
Miscellaneous and site unspecified neoplasms benign	9 (0.22)	14 (0.35)
Miscellaneous and site unspec. neoplasms malignant & unspec.	5 (0.12)	8 (0.20)
Nervous system neoplasms benign	2 (0.05)	4 (0.10)
Nervous system neoplasms malignant and unspecified NEC	8 (0.20)	6 (0.15)
Ocular neoplasms	1 (0.02)	1 (0.02)
Plasma cell neoplasms	4 (0.10)	6 (0.15)
Renal and urinary tract neoplasms benign	1 (0.02)	3 (0.07)
Renal and urinary tract neoplasms malignant and unspecified	8 (0.20)	6 (0.15)
Reproductive neoplasms female benign	20 (0.49)	22 (0.54)
Reproductive neoplasms female malignant and unspecified	9 (0.22)	21 (0.52)
Respiratory and mediastinal neoplasms benign	10 (0.25)	6 (0.15)
Respiratory and mediastinal neoplasms malignant & unspec.	25 (0.62)	16 (0.40)
Skeletal neoplasms benign	2 (0.05)	0 (0)
Skeletal neoplasms malignant and unspecified	0	1 (0.02)
Skin neoplasms malignant and unspecified	51 (1.26)	47 (1.16)
Soft tissue neoplasms benign	22 (0.54)	15 (0.37)
Soft tissue sarcomas	1 (0.02)	0 (0)

Reviewer Comments:

- *The higher incidence of several types of malignancies in denosumab subjects is concerning, particularly in light of 3 deaths in the dose-finding*

trial when higher doses of denosumab were used. The significance of this finding in these studies of moderate duration is unclear due to the long latency for malignancies.

- ***No carcinogenicity studies were performed due to the lack of an appropriate animal model.***
- ***The Pharmacology/Toxicology reviewer noted that denosumab is primarily distributed to the thyroid/parathyroid, serum, lymph nodes, blood, spleen, and ovaries.***
- ***This finding of an increased incidence of certain gastrointestinal, reproductive and endocrine malignancies is essential to the benefit-risk assessment for this product, particularly for the osteoporosis prevention indication.***

7.3.4.6 Ocular Adverse Events

Bisphosphonates (antiresorptive agents) are associated with rare adverse events of eye inflammation including uveitis (Tan et al. 2009). In trial 20040138 (prostate cancer), a signal for cataract (9 vs. 34 cases in placebo vs. denosumab group) was noted.

Preclinical findings:

In trial 104105 in the monkey, ¹²⁵I-radiolabeled denosumab was found in the cornea of the eye for up to 672 hours postdose (1 mg/kg) at levels higher than that in serum. At 1344 hrs, radioactivity could no longer be detected in the cornea. When compared to amounts in serum at similar timepoints, denosumab levels in the cornea were high, but these higher amounts of radiolabel in the cornea at 672 hours are likely not as much a function of 'drug accumulation in the cornea', but that blood levels at 672 hours were very low and close to the lower limit of quantitation, indicating that radiolabel remains in the cornea longer than in the blood. No remarkable ocular effects were noted in the 1-month or 6/12-month toxicity studies with denosumab treatment in monkeys. Tissue cross reactivity studies with human, monkey, rat and rabbit tissues also did not show binding of denosumab to ocular tissues.

The Applicant was asked to address the nonclinical cornea findings. The Applicant's response appears to be a valid argument that due to the avascular structure of the cornea, denosumab would likely be found in the tears, causing a subsequent interaction with corneal tissue. In addition, since the human lacrimal glands secrete very low levels of IgG, only relatively little denosumab would be available in tears to bind to the cornea. Furthermore, in mRNA expression studies, RANKL mRNA expression was not found to be present in retina, iris, ciliary bodies, eyecup, lens or cornea. Hence, the argument is that biodegradation of the radiolabeled denosumab protein occurred prior to reaching the eye, and what is observed as preferential distribution of denosumab to the cornea, is actually the presence of free radiolabel in the cornea due to low level secretion of iodine into tears. Since the presence of denosumab in the cornea does not correlate

with any remarkable toxicological finding in longer term studies in monkeys with higher doses, this argument appears reasonable.

Clinical: Overall, in the PMO population, in the placebo group, 537 (13 % of 4041) subjects reported adverse events in the eye disorders SOC compared to 513 (12.6% of 4050) subjects in the denosumab group. There was a small increase in incidence of blurred vision and retinal pathology in denosumab group in trial 20030216. More information was requested from the applicant on these cases. More denosumab subjects (11, 0.3%) than placebo subjects (2, 0.1%) reported adverse events of blurred vision. However, in related MedDRA hierarchy, the eye disorders SOC and in the vision disorders high level group term; adverse events were balanced between denosumab and placebo subjects. Alternative etiologies were identified in 9 of 11 reported events. Medical conditions included cerebrovascular accident (2), benign neoplasms of the eye (1), ophthalmic artery vasculitis (1), worsening hypertension (2) and cataracts (3). Most events were monocular versus binocular blurred vision, which is less likely to be drug-induced and more likely to be related to underlying medical conditions. There was no relationship between longer duration of denosumab exposure and the incidence of blurred vision.

Reviewer's Comment: Time to event onset, time to event resolution, and individual cases submitted by the applicant in response to information request were reviewed. No concerning trends were found. There is no clear safety signal of eye disorders with denosumab treatment in PMO population.

7.3.4.7 Pancreatitis

In trial 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 48. All the events that occurred in the denosumab group were categorized as serious, while only one event in the placebo group was serious.

Table 48. Events of Pancreatitis in Primary PMO Studies (pooled data)

Preferred Term	Placebo N = 4041 n (%)	Denos. N=4050 n (%)
Total No. of Unique Subjects	4	8
Pancreatitis	1 (0.02)	2 (0.05)
Pancreatitis acute	1 (0.02)	5 (0.12)
Pancreatitis chronic	1 (0.02)	1 (0.02)
Pancreatic pseudocyst	1 (0.02)	1 (0.02)

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 denosumab. However, this subject had been receiving denosumab for more than 2 years. The majority of the remaining cases were confounded by a prior history of pancreatitis or hypercholesterolemia (unknown triglyceride levels). There was one subject who died about 4 months after receipt of the initial dose of trial drug, but the family refused to provide further information about the subject's death.

Table 49. Line Listing of Pancreatitis Events in Subjects Receiving Denosumab in Primary PMO Studies (pooled data)

Study / SID	Inv Prod	Days from 1st dose (days from last dose)	Preferred Term	Medical History & Risk Factors	Reviewer Comments
20030216 6136012	Denos	293 (99)	pancreatitis acute	h/o cholelithiasis & biliary 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 (refused any more info)	Unable to assess due to limited information
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 since initial dose). Subject diagnosed with biliary acute pancreatitis and underwent cholecystectomy.
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 initial dose of trial drug.
20030216	Denos	1095 (104)	pancreatitis acute	h/o HTN, DM (req. insulin),	Event occurred ~3 months after last dose

Study / SID	Inv Prod	Days from 1st dose (days from last dose)	Preferred Term	Medical History & Risk Factors	Reviewer Comments
6754032				diverticular disease of sigmoid colon, cholecystectomy, cerebral atherosclerosis, GERD. Conmed: perindopril.	(~ 3years since initial dose). Diagnosis: acute pancreatitis (hemorrhagic, necrotic) – unk etiology. CT scan also showed liver steatosis & diverticular disease (sigmoid colon).
20030216 6835096	Denos	87 (87) 95 (95) 572 (26) 584 (38)	pancreatitis chronic (4 episodes)	h/o acute pancreatitis & chronic pancreatitis.	Diagnosis: exacerbation of chronic pancreatitis, initial episode ~87 days after initial dose in subject with history of acute & chronic pancreatitis. U/S: cyst on head of pancreas. CT scan: pancreatic calcifications & dilated biliary tracts. Event recurred. Subject continued to receive trial drug.

No subjects withdrew from trial in any of the Primary PMO studies due to pancreatitis. One placebo subject discontinued IP due to pancreatitis.

Reviewer Comments:

There does not appear to be a strong causal relationship between the use of denosumab and the development of pancreatitis. The temporal relationship between use of denosumab and the start date for these events is highly variable. In addition, the cases reviewed herein were confounded by prior episodes of pancreatitis or risk factors for the development of pancreatitis. However, one cannot exclude the possibility that perhaps denosumab precipitates episodes of acute pancreatitis in subjects who have a prior history of pancreatitis.

7.3.4.8 Skin and soft tissue disorders

Analysis for skin and soft tissue disorder includes data from 2 pivotal studies (20030216 and 20040132) for postmenopausal women. There were 8091 total subjects (4041 in placebo and 4050 in denosumab) in combined PMO safety population of subjects who received ≥ 1 dose of an IP 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 (501, 12.4%). This imbalance was mainly due to imbalance observed in HLGT “Dermal and Epidermal conditions”.

Table 50. Adverse Event High Level Group Term in Skin and Soft tissue disorders SOC

Adverse Event High Level Group Term	Placebo N=4041	Denosumab N=4050
Angioedema and urticaria	32	31
Cornification and dystrophic skin disorders	22	22
Cutaneous neoplasms benign	5	8
Epidermal and dermal conditions	340	447
Pigmentation disorders	6	4
Skin and subcutaneous tissue disorders NEC	38	44
Skin appendage conditions	96	88
Skin vascular abnormalities	12	12
Subjects Total	501	610

Source: This table is generated using ISS AAE dataset, including studies 20030216 and 20040132.

This imbalance was mainly due to an imbalance observed in HLGT "Dermal and Epidermal conditions" (340 vs. 447 events in placebo vs. denosumab). Table 51 shows the number of subjects in imbalanced AE high level terms (MedDRA) in placebo vs. denosumab group. These events are not specific to injection site.

Table 51: Imbalanced Adverse Event High Level Terms in HLGT Epidermal and dermal conditions

Adverse Event High Level Term	Placebo N=4041	Denosumab N=4050
Bullous conditions	3	9
Dermal and epidermal conditions NEC	56	69
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

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 in an exploratory analysis by Quantitative Safety and Pharmacoepidemiology Group (QSPG) [Epidermal and dermal conditions HLGT [p-value < 0.001, relative risk 1.8, 95% CI (1.34, 2.36) and risk difference of 0.014, 95% CI (0.007, 0.021)]. Rashes, eruptions and exanthems were also found to be statistically significantly different.

SAEs and IP discontinuation: There were 7/501 (1.4%) subjects in the placebo group and 10/610 (1.6%) subjects in the denosumab group with serious skin adverse events, not an appreciable difference. There were also 7 subjects in the placebo group who discontinued because of skin event and 12 who discontinued because of a skin event in the denosumab group. The reasons for discontinuations in the placebo group included dermal and epidermal conditions (1), dermatitis and eczema (1), psoriatic conditions (2), and rashes, eruptions and exanthems (3). The reasons for discontinuation in the denosumab group included bullous condition (1), dermatitis and eczema (3), papulosquamous condition (1), pruritus (5), and rashes, eruptions, and exanthems (2). Again, there is not an appreciable difference between placebo and denosumab for events that lead to discontinuation, the difference being driven by the event of pruritus rather than a specific dermatosis.

Bullous and Photosensitivity conditions and toxic skin reactions: Given that the bullous conditions and photosensitivity conditions, although rare, had an increased incidence in the denosumab group and it was noted that there were 4 subjects in the denosumab group with "toxic skin reactions" vs. none in the placebo group, an dermatology consultation was requested. This reviewer also asked for a narrative of each event and the CRF to determine, if possible, the characterization of these events in terms of severity and seriousness and causality of denosumab. It should be noted that while reviewing the CRFs of these subjects, most were from foreign sites and very little, if any, information was given describing the exact characterization of the lesions of the various skin eruptions.

For the 4 cases of toxin skin eruption, the data does not make a convincing case for these eruptions to be secondary to denosumab. Only one case was classified as a serious event, where the sequence of events described suggested that it was a drug eruption likely due to oral nystatin and not denosumab. Subject 6412063 was a 68 y/o female who experienced the event on trial day 970, approximately 212 days (7 months) from the previous dose of denosumab. The subject had discontinued denosumab because of worsening autoimmune hepatitis. The subject was treated with oral nystatin, from 8/23/07 – 9/1/07. On (b) (4), the subject was hospitalized with a generalized skin eruption and had a skin biopsy which, was characterized as a "toxic dermatitis". The nystatin was withheld and the subject was treated with steroids and paracetamol. The event resolved in 12 days. The $t_{1/2}$ of denosumab is 25 days. The subject was 212 ($>8 t_{1/2}$) days out from her last dose of denosumab when the eruptions occurred, which likely were not causally related to denosumab. Other 3 cases were mild to moderate in severity. All 3 subjects remained on denosumab therapy and tolerated subsequent rechallenges without recurrence of the symptoms.

For the photosensitivity conditions, 5 out of the 6 events has a reasonable alternative etiology for the adverse event other than denosumab and the subjects did well despite continuing the drug product. In only one subject is there a lack of another agent as the cause of the photosensitivity. This makes photosensitivity conditions in the denosumab

group no more common than in the placebo group (0.02%) where one subject had a photosensitive allergic reaction (verbatim term: solar allergy).

In the bullous conditions, there are only 3 out of 9 cases in which denosumab may have been causally related to the event. These 9 cases are discussed here briefly, for more detail discussions; please refer to the dermatology consult. In 2 cases, that of oral pemphigus and dermatitis herpatiformis (probably linear IgA dermatosis), the etiology was most probably due to another drug known to cause the drug induced variant of each disease. In a case of worsening pemphogoid, the subject remained on denosumab and completed all subsequent scheduled doses without further worsening of the event. Therefore, it is not clear that denosumab caused worsening of the disease; it could have been due to the natural course. Remaining were 6 cases of blister on the denosumab arm, of which 5 had isolated blisters that occurred either as a solitary one or two lesions or in the case of one subject, as a cluster on the buttock. This latter subject most likely had pressure bullae, secondary to hospitalization for multiple traumas after a fall. All of these events either resolved spontaneously or with treatment such as Neosporin or occlusive dressings. All subjects had subsequent doses of denosumab without reoccurrence of a blister event. The 6th case of blister was a 81 year old woman, who reported mild blisters on approximately trial day 936, approximately 24 days from the previous dose of denosumab. She also complained of red itchy legs on the same day. The investigator considered these 2 separate events. The site of the blisters is not documented. Other dermatologic conditions of the subject included a history of oral lichen planus. The subject had had 2 episodes of rash throughout the trial, but each resolved without discontinuing denosumab. In the case of the blisters and pruritus, they were ongoing at the end of the trial following treatment with aqueous cream. As the subject had received her last dose of denosumab, worsening or reoccurrence of the event could not be assessed. In summary, there were more subjects in the denosumab group with aforementioned skin conditions; however, there were alternate etiologies present in most cases to explain these events.

Reviewer comment:

- ***Overall, subjects in the denosumab group were more likely to develop skin and soft tissue related adverse events. There were more bullous conditions, pruritic conditions, skin rashes, dermatitis and eczema related adverse events in the denosumab group compared to placebo. This increase is clinically significant and should be included in the labeling document.***
- ***There were more cases of photosensitivity and bullous conditions in the denosumab group; however it appears that clear cut cases that implement denosumab are tenuous, at best. Since there is no way to know for certain, it should be mentioned in the adverse event section of labeling document that bullous eruptions, including one case each of oral pemphigus, worsening of pemphigoid, DH, and EM occurred in the trial. The relationship to denosumab is unclear as some subjects were on concomitant***

medications and that most subjects with cutaneous events were able to remain on drug with appropriate treatment and that some events spontaneously resolved.

7.3.4.9 Diverticular Disorders and Diverticulitis

Events of diverticular disorders were closely examined because there seemed to be an imbalance between denosumab and placebo when individual studies were reviewed. When the pooled data were examined, there were more serious events of diverticulum and diverticulum intestinal with denosumab; all other serious events of diverticular disorders were about equally distributed between the treatment groups.

Table 52. Serious Adverse Events of Diverticular Disorders in Primary PMO Studies (pooled data) by HLT and PT

High Level Term	Preferred Term	Placebo N=4041 n (%)	Denos. N=4050 n (%)
Diverticula	Diverticulum	3 (0.07)	7 (0.17)
	Diverticulum intestinal	2 (0.05)	8 (0.20)
	Pharyngoesophageal diverticulum	1 (0.02)	0 (0)
Diverticulum inflammations	Diverticulitis intestinal haemorrhagic	0 (0)	1 (0.02)

When both serious and non-serious events of diverticular disorders were reviewed, denosumab subjects had almost 2 times the incidence of the event diverticulum and 1.5 times the incidence of the event diverticulum intestinal than placebo subjects.

Table 53. All Adverse Events (Serious + Non-Serious) of Diverticular Disorders in Primary PMO studies (pooled data) by HLT and PT

High Level Term	Preferred Term	Placebo N=4041 n (%)	Denos. N=4050 n (%)
Diverticula	Diverticulum	21 (0.52)	39 (0.96)
	Diverticulum intestinal	20 (0.49)	33 (0.81)
	Diverticulum oesophageal	1 (0.02)	2 (0.05%)
	Pharyngoesophageal diverticulum	1 (0.02)	0 (0)
Diverticulum inflammations	Diverticulitis intestinal haemorrhagic	0 (0)	1 (0.02)

In the MedDRA hierarchy, the PT diverticulitis maps to the Infections SOC. Infections have previously been described, but events of diverticulitis are relevant to this section as well. There was an increased incidence of serious abdominal and gastrointestinal infections in the denosumab group, with 25 placebo and 31 denosumab subjects

reporting these types of serious events. There were 7 placebo and 10 denosumab subjects who reported serious events of diverticulitis.

Reviewer Comment

Events of diverticular disorders and diverticulitis are not listed in the proposed labeling. These events should be added to the labeling under Adverse Reactions.

7.3.5 Submission Specific Primary Safety Concerns

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.

Hormone ablation trials were not designed to evaluate cancer related outcomes e.g., progression-free survival (PFS), overall survival (OS). In the breast cancer trial 20040135, there was an imbalance in metastatic events [placebo 5 (4.2%), denosumab 9 (7.0%)]. In the prostate cancer trial 20040138, similar imbalance was noted [placebo 40 (5.5%), denosumab 60 (8.2%)]. All cause mortality included 2 deaths for each treatment group at 24 months for trial 20040135 (breast cancer). All cause mortality in trial 20040138 was 5.9% for both treatment groups at 36 months. Other safety issues identified in the hormone ablation trials were similar to postmenopausal osteoporosis trials with an exception of ocular adverse events. An imbalance in incidence of cataract in prostate cancer trial was noted (9 (1.2%) in placebo vs. 34 (4.7%) in denosumab). In PMO trials, this imbalance was not observed. Ocular adverse events are discussed in detail in section 7.3.4.6.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

7.4.1.1 Eliciting adverse events data in the development program:

Adverse events were assessed continuously during the trial at each visit with directed questions and recorded in the case report form. The investigator was to provide the patient with his/her recommendation concerning stopping or modifying treatment. Events were to be followed up until they returned to baseline status or stabilized.

7.4.1.2 Appropriateness of adverse event categorization and preferred terms:

An adverse event (AE) was appropriately defined as any untoward medical occurrence in a patient administered a pharmaceutical product and which did not necessarily have

to have a causal relationship with the treatment. Worsening of a pre-existing condition was also reported as adverse events. The intensity of adverse events was graded on a five-point scale (mild, moderate, severe, life threatening and fatal). Serious adverse events were appropriately defined. Adverse events listings utilized MedDRA preferred terms. The AEs were coded in MedDRA version 11.0.

7.4.1.3 Incidence of common adverse events:

As outlined in the section below, the overall incidence of AEs in PMO population was comparable across the treatment groups (93% in both groups) and across studies 20030216 and 20040132. The most commonly noted disorders were musculoskeletal, infections, and GI disorders. The 3 MedDRA system organ classes with the highest subject incidence of adverse events were (placebo, denosumab) musculoskeletal and connective disorders (64.4%, 64.5%), infections and infestations (54.7%, 53.2%), and gastrointestinal disorder (36.7%, 37.6%). The most frequent adverse events were back pain, arthralgia, hypertension, nasopharyngitis, pain in the extremity, osteoarthritis, constipation, influenza and bronchitis for trial 20030216. The most frequent adverse events were arthralgia, back pain, nasopharyngitis, pain in the extremity, influenza and constipation for trial 20040132. The largest differences in rates of AE reporting between denosumab and placebo-treated patients were for pain in the extremity (11.2% vs. 11.8% in placebo vs. denosumab), hypercholesterolemia (5.9% vs. 7%), and upper respiratory infections (4.7% vs. 5.2%).

Table 54. Common adverse events in 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)

	Placebo N=4041		Denosumab N=4050	
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)

Source: This table is generated by medical officer, using AAE dataset for ISS safety population, including studies 20030216 and 20040132.

COMMENT: Overall adverse events rates were comparable between studies 20030216 and 20040132 and treatment groups.

Quantitative Safety and Pharmacoepidemiology Group (QSPG) analyzed preferred terms in trial 20030216 of the adverse events analysis dataset and reported exploratory p-values for each PT. PTs with p value ≤ 0.1 are presented in the Appendix 3. PTs related to fractures are not presented in this table, as fractures are efficacy endpoints in this trial and discussed earlier. It should be noted that this p value is exploratory and not adjusted for multiplicity or not meant to be inferential.

7.4.2 Laboratory Findings

Hypocalcaemia: 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 higher incidence of hypocalcemia. The applicant evaluated hypocalcemia in several clinical trials.

Phase 1 Study:

Study 245 was a Phase I, single dose, open label trial to assess PK, safety and tolerability in patients with both normal and abnormal renal function. Patients with renal dysfunction were stratified into mild, moderate, severe, and end stage renal disease (ESRD) cohorts and standard PK parameters were analyzed.

This trial was halted during enrollment of severe Chronic Kidney disease (CKD: CrCL < 30 mL/min), as subjects developed hypocalcemia (ie, albumin-adjusted serum calcium concentration < 7.5 mg/dL or symptomatic). The hypocalcemia was thought to be due to lack of calcium and vitamin D supplementation in subjects with significant renal dysfunction. The protocol was subsequently amended to require that all subjects with CKD receive daily supplementation with calcium and vitamin D starting at enrollment.

Among subjects enrolled before this amendment, the severe CKD and ESRD groups had the lowest median nadir albumin-adjusted serum calcium concentrations (7.1 mg/dL and 8.1 mg/dL respectively). After the amendment, the median nadir albumin-adjusted serum calcium concentration (8.8 mg/dL) in the severe CKD group was similar to that of the normal, mild CKD, and moderate CKD groups. The ESRD group still had a lower median nadir albumin-adjusted serum concentration (7.9 mg/dL). In the normal renal function group, the median times to nadir was 8-11 days.

Reviewer's comment: Subjects with severe CKD and ESRD were more likely to develop hypocalcemia compared with subjects with mild or moderate CKD and subjects with normal renal function. This is likely due to the fact that subjects with severe CKD or ESRD rely more heavily on the bone to provide a source of calcium due to their impaired ability to reabsorb calcium from the urine and to absorb calcium in the gastrointestinal tract. Therefore, with antiresorptive therapy, these subjects may be more susceptible to reductions in serum calcium. As a result, it is important to ensure that patients with impaired renal function, particularly patients with severe kidney disease or ESRD, are adequately supplemented with calcium and vitamin D.

Phase 3 Trials:

In trial 20030216, serum calcium levels were measured at screening; trial day 1, Study month 1, 6, 12, 18, 24, 30 and 36 months. Mean serum calcium levels were balanced 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. An analysis of outliers showed that at month 1, there were more subjects with hypocalcemia (S. ca <8.5 mg/dl) in the denosumab group (33) group vs. placebo (3) (see Table 55).

Table 55 Outlier analysis: Number patients with Hypocalcemia (Corrected Calcium <8.5 mg/dl)

Number of subjects with outlier value of calcium	Placebo N=3876		Denosumab N=3886	
	N	Mean	N	Mean
Visit				
BASELINE	2	8.1	5	8.0
MONTH 1	3	7.4	33	8.3
MONTH 6	0	.	2	8.2
MONTH 12	7	8.2	12	8.2
MONTH 18	1	8.4	3	8.4
MONTH 24	1	8.2	5	8.4
MONTH 30	1	8.4	7	8.1
MONTH 36	0	.	4	8.4
Total	15		66	

Source: reviewer's analysis of safety lab data for trial 20030216.

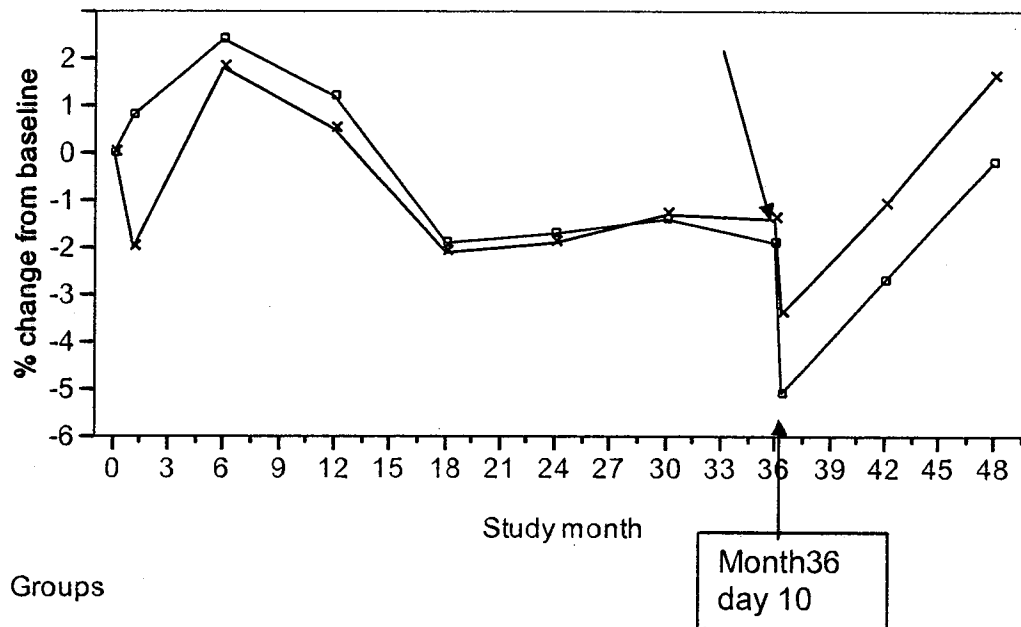
Four subjects in the denosumab group had multiple events of mild hypocalcemia (S. Ca <8.5 but ≥ 8.3) and none in the placebo group.

Of the 15 subjects in the placebo group and 66 subjects in the denosumab group who experienced hypocalcemia, 9 subjects in the denosumab group and 1 in the placebo group did not complete the trial. The Quantitative safety and Pharmacoepidemiology Group (QSPG) group performed AE event analysis by MedDRA hierarchy (Preferred Term, High level term, High level group term, and System Organ Class). The analysis did show any difference between the treatment groups. Events of hypocalcemia were analyzed in different strata of Vitamin D (in ng/ml <12, 12-20, 20-32 and >32) and renal function (Cr clearance in ml/min <30, 30-60, 60-90 and >90). No significant differences were detected in any of these groups.

Trial 20060289 : Since trial 20040245 showed that nadir in serum calcium levels occurs in first two weeks (day 8-11) after administration, trial 20060289 measured s. calcium levels at day 10 \pm 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 trial of trial 20030216. shows that there was 3-5% decrease in S. calcium levels at day 10 in both groups. In subjects who received placebo in trial 20030216 (de novo), and started receiving denosumab in trial 289, this decrease was observed in more subjects and slightly more pronounced.

This reviewer looked at S. calcium level of these subjects with hypocalcemia at each visit and their reported adverse events. These reductions were transient and not associated with AEs (hypoesthesia, oral hypoesthesia, paresthesia, oral paresthesia, and tetany) related to hypocalcemia.

Figure 11: Serum Calcium (corrected) % change from baseline in Trial 20030216 rolling over to 20060289



Groups

- × — Treatment=DENOSUMAB 60 MG Q6M
- — Treatment=PLACEBO

There were 100 subjects in the *de novo* denosumab group who developed hypocalcemia (serum calcium < 8.5) 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 56). This table also demonstrates that day 10 is more sensitive to measure changes in serum calcium compared to month 1, as seen in trial 20030216.

Table 56: 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 <8.5	2	33	100	48
Serum calcium ≤ 8.0	2	0	7	5
Serum calcium ≤ 7.5	2	0	2	1

In trial 289 there were 2 subjects in the *de novo* denosumab group who developed serum calcium level of <7.5 mg/dl at day 10. Subject 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.

Subjects with impaired renal function were more likely to have greater reductions in the S. Ca compared to subjects with normal renal function as shown in Table 57. Mean % change from baseline was -5.5% in de novo subjects and -3.6% in continuous denosumab subjects with creatinine clearance <30 mL/min. This change from baseline was more pronounced compared to subjects with creatinine clearance ≥30 mL/min.

Table 57: % change from baseline in S.Ca levels in subjects with varying degrees of renal function in trial 20060289

Creatinine clearance	placebo to denosumab			denosumab		
	n	mean	SD	n	mean	sd
15 - < 30 mL/min	20	-5.5	3.7	23	-3.6	5.8
30 - < 60 mL/min	806	-3.1	4.4	930	-1.7	4.8
60 - < 90 mL/min	1050	-3.1	4.2	1068	-1.9	4.5
>90mL/min	198	-3.1	4.4	178	-2.3	5.2

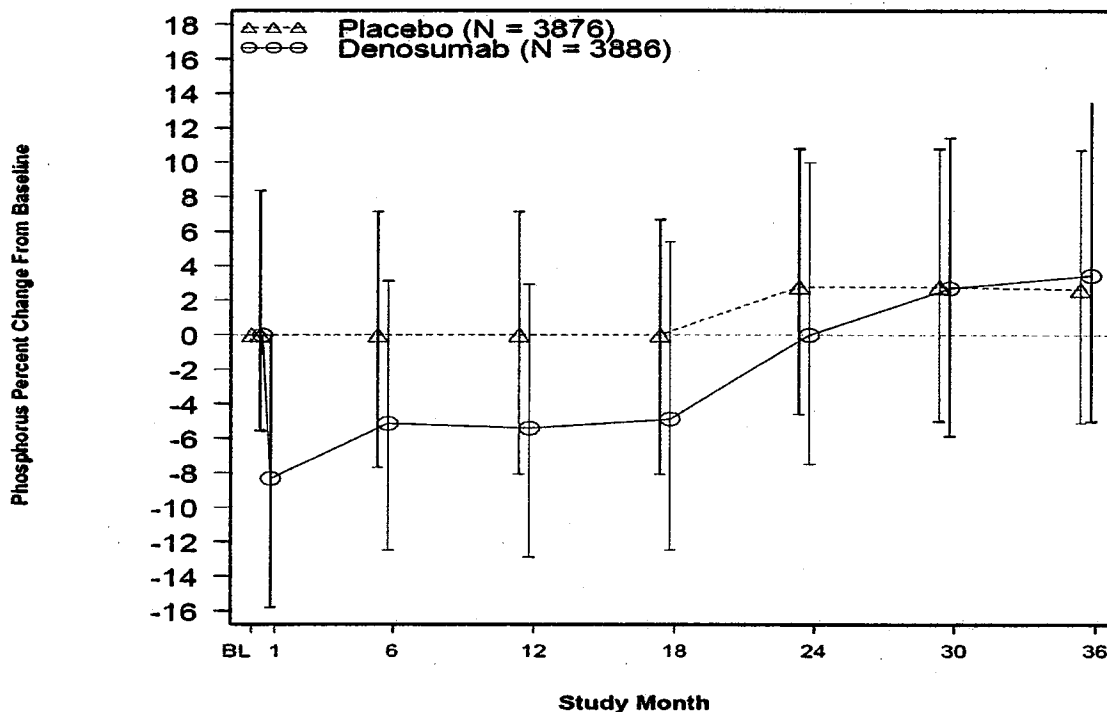
Reviewer's comments: Hypocalcemia is a known class effect of antiresorptive drugs. However, denosumab induced hypocalcemia appears to be transient (in first month after dosing, nadir at day 8-11) with spontaneous resolution without any serious sequelae observed in this trial. In this clinical trial setting, hypocalcemia was an exclusion criterion. Subjects were given 1 gm calcium as a concomitant medication. In the real world setting, more patients may experience hypocalcemia. The applicant proposed labeling hypocalcemia in Contraindication and Warnings and Precautions sections, this reviewer agrees with it. In subjects with renal dysfunction (Creatinine clearance <30 mL/min) change in serum calcium was more pronounced, I recommend monitoring calcium closely in this population.

Hypophosphatemia: When looked at analysis of central tendency (mean and SD) for trial 20030216 and trial 20040132, greater reductions in serum phosphorus were observed in the denosumab group at 1 month compared to placebo. Median (interquartile range) changes from baseline in serum phosphorus concentration at month 1 were -8.3% (-15.8% to 0%) in the denosumab group and 0% (-5.6% to 8.3%) in the placebo group (Figure 12). Median changes from baseline in the denosumab group were approximately -5% through month 18; at month 36, median changes from baseline in the denosumab group (3.4% [-5.0%, 13.5%]) were similar to those in the placebo group (2.6% [-5.1%, 10.7%]).

When looked at outlier analysis, there was higher incidence of grade 3 (<0.6 mmol/L) decreases in serum phosphorus were observed in the denosumab-treated group (7

subjects [0.2%]) compared with the placebo group (0 subjects). One subject (< 0.1%) in the placebo group had a grade 4 (<0.3mmol/L) decrease in phosphorus. This reviewer looked at S. Phos level of these subjects with hypophosphatemia at each visit and their reported adverse events. These reductions were transient and not associated with AEs related to hypophosphatemia.

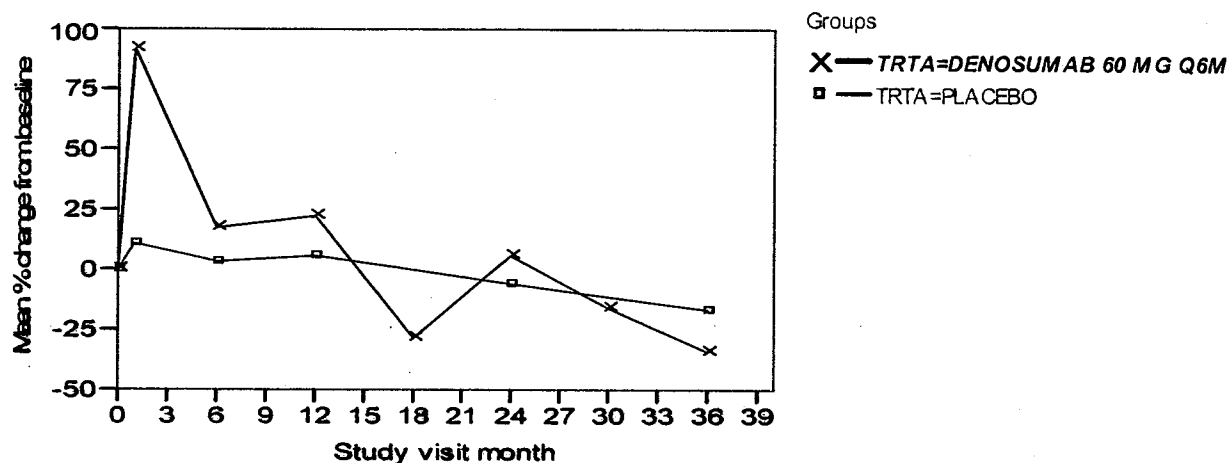
Figure 12 Serum Phosphorus: mean % change from baseline in Trial 20030216



Reviewer's comment: Similar to mechanism for hypocalcemia, decreased bone remodeling may explain the hypophosphatemia. Subjects were not given oral phosphorous supplements in this trial. Trial 289 did not measure serum phosphorous at day 10 after dosing. Phosphorous levels are dependent on dietary phosphorous intake. Hypophosphatemia effect should be in the labeling document.

Parathyroid Hormone: Treatment with antiresorptive agents can lead to decreases in serum calcium with resultant compensatory increases in parathyroid hormone (PTH). Compared to placebo, denosumab treatment resulted in an increase in serum PTH levels at month 1, but not at any other time points.

Figure 13: % change from baseline in Intact Parathyroid Hormone levels



Reviewer's comment:

It is reassuring to see this rise and subsequent normalization of both, PTH and serum calcium levels at the later time points. This suggests that normal compensatory mechanisms for calcium regulation are not impaired on continued denosumab therapy.

Clinical Laboratory evaluations among subjects with PMO:

When looked at analysis of central tendency, 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 58.

Table 58. Subject Incidence of Laboratory CTC Grade ≥ 3 during the Trial 20030216 and 20040132

Laboratory Parameters	Relationship to Normal	Grade	Placebo (N = 4041) n (%)	Denosumab (N = 4050) n (%)
Sodium	Above	Grade 3 >155 mmol/L	1 (<0.1)	0 (0.0)
	Below	Grade 3 <130 mmol/L	42 (1.0)	38 (0.9)
		Grade 4 <120 mmol/L	2 (<0.1)	0 (0.0)
Potassium	Above	Grade 3 >6 mmol/L	10 (0.2)	4 (<0.1)
	Below	Grade 4 >7 mmol/L	0 (0.0)	3 (<0.1)
		Grade 3 <3 mmol/L	6 (0.1)	5 (0.1)
Magnesium	Above	Grade 3 >1.23 mmol/L	5 (0.1)	2 (<0.1)
	Below	Grade 4 <0.3 mmol/L	1 (<0.1)	0 (0.0)
Creatinine	Above	Grade 3 >3xULN	0 (0.0)	1 (<0.1)
Glucose	Above	Grade 3 >250mg/dl	41 (1.0)	40 (1.0)
	Below	Grade 3 <40 mg/dl	1 (<0.1)	1 (<0.1)
Glucose	Below	Grade 4 <30 mg/dl	0 (0.0)	1 (<0.1)
Hemoglobin	Below	Grade 3 <8 mmol/l	7 (0.2)	9 (0.2)
		Grade 4 <6.4 mmol/l	0 (0.0)	1 (<0.1)
Platelets	Below	Grade 3 <50,000	4 (<0.1)	1 (<0.1)
		Grade 4 <25,000	2 (<0.1)	4 (<0.1)
White Blood Cells	Below	Grade 3 <2000	9 (0.2)	5 (0.1)
		Grade 4 <1000	0 (0.0)	1 (<0.1)

Source: This table includes data from trial 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 standard deviation of SGOT, SGPT and total bilirubin in each group. When looked at outlier analysis, Subjects were balanced with respect to the incidence of grade 3 or 4 transaminase elevations (Table 59). Five denosumab-treated subjects (0.1%) and 0 placebo subjects had grade 3 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. The elevations were temporally related to events described above. Remaining one subject had PE, cardiac failure and multiple co-morbid conditions.

Table 59. Subject Incidence of LFT Laboratory abnormality during the Trial 20030216 and 20040132

LFT Laboratory Parameters	Grade	Relationship to Normal	Placebo (N = 4041) n (%)	Denosumab (N = 4050) n (%)
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 trial 20030216 and 20040132 and generated from Applicant table 42, summary of clinical safety. ULN=upper limit of normal

In the largest PMO fracture trial (20030216), among subjects with normal baseline, there were 20 subjects on the placebo group and 31 subjects in the denosumab with Alanine amino transferase (ALT)>3 times normal at any visit. There were 7 subjects in the placebo and 6 subjects in the denosumab group with ALT>5 times normal at any visit. Similar results were found for Aspartate Amino transferase (AST) were 21 and 23 subjects in placebo and denosumab group with AST>3times normal and 6 and 8 subjects respectively, with AST >5 times normal at any visit among subjects with normal baseline. There were 21 subjects in denosumab and 18 in placebo with total bilirubin >1.5 xULN among subjects with normal baseline at any visit. No trends in the shifts of liver function tests were noted.

AE review related to liver disorders:

There were 128 subjects in the placebo and 123 subjects in the denosumab group with AE related to liver disorders, of which there were 17 placebo and 14 denosumab subjects with bile duct disorders, 82 placebo and 63 denosumab subjects with gall bladder disorders and 42 placebo and 55 denosumab subjects with hepatic and hepatobiliary disorders. There was one imbalanced PT, liver disorder with 11 subjects in the denosumab group and 3 subjects in the placebo group. Detail review of these 11 subjects revealed that 2 subjects had drug induced hepatopathy (other than denosumab), 3 subjects had a baseline elevation of liver enzymes, 5 subjects had normal baseline and mild transient elevation with subsequent normal values. One subject died with chronic decompensated hepatopathy. This subject had hepatic neoplasm and ascites, cholecystectomy, lower limb varices, inguinal hernia, thrombocytopenia as well as baseline liver enzyme elevation.

Reviewer's Comment:

Because denosumab is a monoclonal antibody and is not eliminated via hepatic metabolic mechanisms (e.g., by cytochrome P450 [CYP] enzymes), and there are alternate etiologies to explain hepatic impairment in above noted subjects with liver function test abnormality or adverse events, this reviewer does not believe that there is a safety concern.

Renal Function:

Among subjects with normal creatinine (<1.5) at baseline, 6 in placebo vs. 5 in the denosumab group had S.Cr >2.25 (1.5xULN) at any visit, and 30 in placebo vs. 30 in denosumab had S.Cr >1.8 at any visit in trial 20030216.

7.4.3 Vital Signs

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

In trial 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. For details, please refer to individual trial reviews.

QSPG group performed an independent exploratory statistical analysis of cardiovascular system and found that there was an increased risk of bradycardia in subjects treated with denosumab. This reviewer looked at vital sign data in trial 20030216 for measurement of pulse. Subjects with bradycardia were balanced between the two groups (Table 60). Of the 7 subjects with pulse rate <40, only one subject had documented adverse event of bradycardia. Adverse event dataset was queried for the preferred terms in the Cardiovascular SOC that contained word "brady" in the safety population. There were 19 subjects in the placebo group and 22 in the denosumab group that meet these criteria.

Table 60: Trial 20030216, number of subjects with bradycardia

	Placebo N=3876	Denosumab N=3886
Pulse rate <60	831	808
Pulse rate <50	91	111
Pulse rate <40	4	3

Source: reviewer's analysis of avs dataset for trial 20030216.

It is likely that before each dosing visit, which would be approximately 6 months from the previous dose, potential effect of the drug on heart rate may not be seen. Therefore, a phase trial 20010223 vital sign data were reviewed for the first 12 months, where measurements of vital signs were performed at baseline, at day 4 and then monthly thereafter. Monthly measurements would show a difference between the effect of denosumab at times between the doses and before the next dose. This analysis did not show a difference in number of subjects or events with bradycardia between the two

groups at any timepoint. This analysis included 7 denosumab doses, however, only one dose, 60 mg q6 months (to be marketed) is included in the table below for simplicity.

Table 61: Number of Subjects with Heart Rate <60 in Trial 20010223

Visit	PLACEBO	DENOSUMAB 60 mg q6 month
BASELINE	0	1
DAY 4	3	1
MONTH 1	4	2
MONTH 2	2	2
MONTH 3	2	4
MONTH 4	1	2
MONTH 5	1	1
MONTH 6	4	1
MONTH 7	3	1
MONTH 8	5	0
MONTH 9	5	1
MONTH 10	1	1
MONTH 11	3	1
MONTH 12	0	4

Source: This reviewer's analysis of dataset AVS for trial 20010223

The QSPG report includes analysis using the standardized MedDRA Query (SMQ) for bradycardia. The SMQ includes preferred terms such as conduction defects, accessory pathway, agonal rhythm, AV conduction time shortened, asystole, PR shortened, prolonged QT, and sinus arrhythmia. While it is important to look at a broad range of possible terms that may identify subjects with a disorder that may span many organ systems, false positive rate may be high when using a broad search criteria. Looking at the opinion of agency experts in cardiovascular disease, which concluded no concerning signal for arrhythmia and more detailed vital sign data, it does not appear that denosumab treatment leads to changes in the heart rate.

7.4.4 Electrocardiograms (ECGs)

Denosumab, a fully human monoclonal antibody, with a molecular weight of approximately 144 kDaltons, is not anticipated to have a direct effect on ion channels. Therefore, a thorough QT trial was not required.

ECG Procedures:

The clinical development program included an intensive assessment of the effects of denosumab on electrocardiograms, with particular emphasis on the QTc interval. ECGs were obtained at baseline, around Cmax and at several time points during the follow-up period in most clinical studies (Table 62). In all studies, ECG assessments were based on automated readings using machines provided by the investigative sites. Paper copies of ECGs were collected and manually read (semi-automated) in a blinded

fashion for Studies 20010223 and 20040132. The remaining studies did not have ECGs centrally read.

Table 62: EKG evaluation in clinical development program of denosumab

	20010124 (Phase 1)	20030180 (Phase 1)	20030148 (Phase 1)	20030164 (Phase 1)	20050146 (Phase 1)	20050227 (Phase 1)	20050241 (Phase 1)
Study Population/	Healthy PM women N= 49 single dose SC 48 single dose IV 8 multi-dose SC	Healthy PM women N=46	Healthy men N=40	Healthy PM Japanese women N=40	Healthy Volunteers N=148	Healthy vol. N=122	PM* women with low BMD* N=20
route of administration/ dose	Single doses of .01, .03, .1, .3, 1, and 3 mg/kg SC and IV/ multiple doses of 0.1 mg/kg SC 84 days apart	Single dose/ .03, .1, .3, 1, and 3 mg/kg SC	Single dose/ .03, .1, .3, 1, and 3 mg/kg SC	Single dose/ .03, .1, .3, 1, and 3 mg/kg SC	Single dose/ 60mg SC	Single dose/ 1 mg/kg SC	Single dose/ 15 and 60 mg SC
ECG time points	Baseline, predose, days 2, 5, 85, and 169	Screening, day -1, predose, days 15, 113, 169 and 253	Screening, day -1, predose, days 2, 5, 11, 15, 22, 85, 113, 141, 169, 197, 225 and 253	Screening, day -1, predose, days 2, 5, 8, 11, 15, 22, 85, 113, 141, 169, 197, 225 and 253	Screening, day -1, pre-dose and end of trial	Screening, day -1, pre-dose and end of trial	Screening, day 1, predose, and days 2, 3, 4, 15, and 107.
	20060446 (Phase 1)	20060286 (Phase 1)	20040245 (Phase 1)	20010223 (Phase 2)	20040144 (Phase 2)	20050172 (Phase 2)	20040132 (Phase 3)
Study Population/ Status	Healthy Volunteers N=116	Healthy Volunteers N=116	Subjects with various degrees of renal function N=55	PM* women with low BMD N=412	RA* patients N=227	Japanese PM women with osteoporosis N=226	Osteopenia N=332

	20010124 (Phase 1)	20030180 (Phase 1)	20030148 (Phase 1)	20030164 (Phase 1)	20050146 (Phase 1)	20050227 (Phase 1)	20050241 (Phase 1)
route of administration/ dose	Single dose/ 120mg SC	Single dose/ 60mg SC	Single dose/ 60 mg SC	Placebo, 6, 14, and 30 mg q 3 months; 14, 60, 100, 210 mg q 6 months; alendronate 70 mg weekly.	Placebo, 60, 180 mg SC Q6M; 2 doses. Study duration 18 mo	Placebo, 14, 60 and 100 mg SC at day 1 and month 6	60 mg q 6 months SC/ 24 months
ECG time points	Screening, day -1 and end of trial	Screening, day -1 and end of trial	Screening, and days -1, 15, 43, 85 and end of trial (113)	Screening, months 1, 12, 36 and 48	Baseline, month 1 and 12	Baseline and months 1, 6, and 12	Predose, months 1, 12, 18 and 24.

Effect of Denosumab on QT prolongation:

In preclinical studies, no effect of denosumab on QTc interval was observed.

Clinical: In the above studies, there were no significant differences in the changes from baseline in QTcF across the denosumab and placebo treatment groups, however, several outliers with QTcF value > 500 ms and QTcF change from baseline >60 ms were noted more frequently in the denosumab group. A QT consult was requested from IRQT team to evaluate effect of denosumab on QT interval. The consultant's opinion is that the applicant's ECG evaluations appear adequate and there are no large effects on the QT interval due to denosumab. Outliers (patients with absolute post-dose QTcF over 500 ms or over 60 ms change from baseline) have been noted in several studies although underlying ECG abnormalities were noted in several of the studies except Study 20050172 and Study 20040114. It is important to note that subjects were not excluded because of baseline QTc prolongation. There was no imbalance in the reports of sudden death between the denosumab and comparator groups.

Denosumab administration was associated with mild transient decreases in serum calcium as described above in the section 7.4.2. No relationship was observed between change from baseline in QTc and change from baseline in serum calcium concentration. There is no discernible relationship between denosumab pharmacokinetic exposure and changes in serum calcium. There was no relationship between denosumab serum concentration and change in QTcF.

Conclusion: Denosumab does not appear to have either a direct or indirect (i.e., hypocalcemia) effect on QTc interval duration.

7.4.5 Special Safety Studies/Clinical Trials

Bone biopsy evaluation was performed in 3 clinical trials.

- Trial 20030216 was the randomized, double-blind, placebo-controlled fracture trial in postmenopausal women. One hundred-three subjects consented to participate in the substudy, 92 subjects (45 placebo, 47 denosumab) received ≥ 1 dose of IP and had ≥ 1 evaluable biopsy, and 23 subjects (17 placebo, 6 denosumab) underwent sequential biopsy evaluation. The mean age of enrollees in this bone biopsy substudy was 71 years. It should be noted that one subject in the month 36 denosumab group was excluded from the Agency's analysis because the patient had discontinued trial drug after month 12.
- Trial 20010223 was the randomized, placebo and active-controlled, dose-finding trial in postmenopausal women with low bone mineral density. At baseline, biopsies were obtained from 39 subjects, of which 37 were evaluable (31 denosumab, 5 placebo, and 1 alendronate). At 12 months, biopsies were obtained from 51 subjects, 49 of which were evaluable (41 denosumab, 4 placebo, and 4 alendronate). The mean age of enrollees in the bone biopsy substudy was 60 years.
- Trial 20050234 was a double-blind, double-dummy, active-controlled, parallel-group trial 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 trial entry. At trial entry, subjects were randomized to either continue on alendronate 70 mg once weekly or switch to denosumab 60 mg q 6 months. Bone biopsies were obtained from 36 subjects (21 alendronate, 15 denosumab) at month 12. The mean age of enrollees in the bone biopsy substudy was 67.6 years.

Histology

In general, there was evidence of normal lamellar bone and normal mineralization in all treatment groups. In addition, there was no evidence of osteomalacia or woven bone in these studies. In trial 20030216, Normal osteoid was seen in all placebo (62/62) subjects and (48/53, 91%) of subjects in denosumab group. 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 turnover. One denosumab treated subject (6613015), who received all doses of denosumab, was determined to have normal histology at month 24 and cortical trabecularization at month 36. Cortical-endosteal resorption ("trabecularization" of the cortical bone) is one of the major determinants of reduced bone strength. In trial 20050234, one subject treated with alendronate had evidence of marrow fibrosis on biopsy.

Histomorphometry

Bone histomorphometry is the only method that allows the measurement of mineralization rate and the trial of bone formation at cell, remodeling unit and tissue levels. In order to assess ongoing bone remodeling, subjects participating in the bone biopsy substudies were treated with two courses of either demeclocycline or tetracycline with 10-14 day interval between the two courses. Tetracycline is incorporated into mineralizing bone and fluoresces under ultraviolet light. Therefore, in active bone, the time-spaced lines of tetracycline can be used for calculation of new bone formation and mineralization rates and absence of label means that during the tetracycline dosing period there was no new bone mineralization.

The presence of double tetracycline labeling in a biopsy specimen provides an indication of active bone remodeling and formation. Trabecular bone, the most active site of bone remodeling, is the usual site of evaluation of tetracycline labeling. Across all studies, all subjects in the placebo had double label, however, only 31-60% subjects in the denosumab group had any double label. Absence of label suggests suppressed bone formation. In subjects treated with denosumab, 21% had no tetracycline label present at a month 12 biopsy, 35% had no label present at month 24 biopsy and 38% had no label present at month 36 biopsy. One subject treated with alendronate had no label present at month 12 biopsy. While a sporadic biopsy specimen with absence of double label is not unusual, the number of patients treated with 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.

Table 63: Labeling status in 3 trials with bone biopsy substudy

	223 (12 months)			234 (12 months)		216 (24 months)		216 (36 months)	
	Placebo n (%)	Alen	Denosn (%)	Alen	Denos	Placebo n (%)	Denos* n (%)	Placebo n (%)	Denos* n (%)
Number of biopsies evaluable	4	4	41	21	15	37	31	25	21
Any double label	4 (100%)	2	13 (31%)	21 (100%)	9 (60%)	37 (100%)	11 (35%)	25 (100%)	9 (43%)
Only single label	0	1	11 (27%)	0	3 (20%)	0	9 (29%)	0	4 (19%)
No label	0	1	14 (34%)	0	3 (20%)	0	11 (35%)	0	8 (38%)

*subject with only 12 months of treatment and biopsy at 36 months is excluded

In subsequent sections, placebo controlled trials (20030216 and 20010223) are discussed separately from active control trial (20050234).

In trial 20030216, the number of biopsies evaluable for analysis of all histomorphometry parameters at month 24 was 31 placebo, 5 denosumab; and at month 36 was 22 placebo and 2 denosumab (one subject who only received denosumab for 1 year and had biopsy at month 36 was excluded, since effect of denosumab is expected to reverse in one year based on BMD data from trial 20040132). To be able to evaluate all histomorphometric parameters, a double label in the trabecular bone is necessary. There were 23 subjects (17 placebo, 6 denosumab) underwent sequential biopsy evaluation. Paired evaluation can provide insight into progressive effect of denosumab on bone with increasing duration. However, due to limited number of evaluable biopsies, this evaluation could not be performed.

Activation frequency is the most important regulator of bone turnover. It is defined as the rate at which the bone remodeling units are formed. Suppression is evident at month 12 and by month 36 it was severely suppressed and virtually zero in the denosumab group.

Bone formation rate per bone surface: Bone formation rate per bone surface represents the volume of bone formed per unit of trabecular surface. Treatment with denosumab decreased bone formation rate.

Eroded surface/Bone surface and Osteoid surface / Bone surface: Eroded surface represents the fraction of trabecular bone surface where osteoclasts have eroded or are eroding bone. Denosumab inhibits osteoclast recruitment. Treatment with denosumab resulted in decreased number of osteoclast sites. The osteoid surface presents the fraction of trabecular bone surface where osteoid is present. Osteoblast lays down the osteoid matrix. Treatment with denosumab resulted in decrease in osteoid surface suggesting suppression of new bone formation.

Mineral apposition rate: Mineral Apposition Rate (MAR) is an important parameter assessing mineralized bone accrual at remodeling sites. No change or small increases in MAR during treatment with trial 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. Treatment with denosumab decreased MAR.

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

Osteoid thickness and Osteoid volume: Increases in osteoid thickness and osteoid volume would be expected in the setting of a mineralization defect. Treatment with denosumab did not result in increased osteoid thickness or volume. However, in this case, no increase in osteoid thickness could be a result of severely suppressed bone formation.

Table 64. Placebo controlled trials: Dynamic bone formation parameters

Parameter(Median)	Trial 20010223		Trial 20030216			
	MONTH 12		MONTH 24		MONTH 36	
	Placebo (n=4)	Denosumab (n=14)	Placebo (n=37)	Denosumab (n=31)	Placebo (n=25)	Denosumab (n=21)
Biopsy with evaluable parameters	4	13	31	5	22	2
Activation frequency (/year)	0.81	0.08	0.27	0.001	0.2	0.003
Bone formation rate/ BS (μm^3 / μm^2 /year)	22.7	2.2	11.89	0.13	9.8	0.29
Mineral apposition rate ($\mu\text{m}/\text{day}$)	0.77	0.52	0.73	0.3	0.75	0.4
Mineralization lag time	17.94	41.8	20	167	24	49
Eroded surface/ bone surface (%)	1.98	0.51	1.65	0.23	0.81	0.14
Osteoid surface/Bone surface (%)	12.4	3.4	7.68	0.7	6.54	0.26
Osteoid Volume/bone volume (%)	2.09	0.33	1.16	0.08	0.72	0.03
Osteoid Thickness μm	6.8	4.9	9.09	5.43	8.7	5.4

This table is generated using ABMHMR dataset for trial 20030216 and 20010223, excluding data from subject 6412687 in trial 20030216. This subject was excluded because she stopped IP product at month 12 and the biopsy was done at month 36, by which time, the effect of denosumab is expected to reverse.

In trial 20010223, 7 doses of denosumab were evaluated. Evaluation of dose response relationship suggested no clear relationship to histomorphometric parameters, however, number of subjects with evaluable biopsies in each dose group were too few to reach any conclusions.

Trial 234 (subjects switched from alendronate to denosumab or continued on alendronate) provides comparison to active control (alendronate) and offers important safety information for patients who may be switched from bisphosphonate to denosumab. The results demonstrated further decreases in bone turnover with denosumab compared with continued alendronate, as noted in Table 65. Activation frequency, eroded surfaces and osteoid volume were further suppressed with initiation of denosumab treatment, compared to continued alendronate therapy. Mineralization lag time and osteoid thickness were not appreciably increased with denosumab therapy, as compared to alendronate by month 12.

Table 65: Histomorphometry parameters in active controlled trial, 20050234

	Alendronate, n=21	Denosumab n=6
Median (95% CI)	MONTH 12	MONTH 12
Activation frequency (per year)	0.04 (0.0, 0.07)	0.015 (0,0.3)
Bone formation rate- surface based (u3 /u2 /year)	1.97 (0.2,3.9)	2.7 (0.29,3.3)
Formation period (day)	353 (263,1111)	378 (178,773)
Mineral apposition rate (u/day)	0.6 (0.4,0.8)	0.3 (0.3,0.5)
Mineralization lag time (days)	54 (36,108)	38 (36,55)
Osteoid Volume/bone volume (%)	0.3 (0.1,0.6)	0.08 (0.02,0.3)
Eroded surface/ bone surface (%)	1.9 (0.75,2.7)	0.34 (0.09,1.5)
Osteoid surface (%)	2.9 (1.3,4.1)	1.07 (0.4,3.9)

This table is generated from applicant table 11-8, page 153, clinical summary of efficacy.

Correlation to clinical findings and reversibility:

The relationship between percent change in BMD at month 36, incident fractures, and degree of reduced remodeling, as reflected by label status, was explored in trial 20030216. Those subjects with less prominent tetracycline labeling showed the greatest gains in BMD at the total hip and lumbar spine at month 36. There were 3 fractures in subjects enrolled in the denosumab. Among subjects with no label, 2 sustained fractures, 1 of which was a patellar fracture that occurred less than 6 months after the first dose of denosumab (6128038 and 6413231) (Listing 1-8.1.512). One subject with single label sustained both a radial and ulnar fracture 6.5 months after first dose of denosumab (6304188), and 6 subjects with double label, all of whom received placebo, sustained a fracture (6412183, 6612018, 6612024, 6613025, 6613025, 6613031).

Reviewer's comment: Applicant argues that long-term reduction in bone remodeling, as reflected by the small number of tetracycline labels in bone biopsy samples, did not translate into an increase in fracture risk in these subjects. However, decrease in bone remodeling is expected to increase BMD in a relatively short term use (upto 3 years). The risk of complications related to continuously suppressed bone remodeling is expected to increase after a long term use (7-10 years).

Bone histology evaluation did not identify any major concerns.

Bone histomorphometry results raise significant concerns about the degree of bone remodeling suppression. Denosumab group had markedly suppressed bone remodeling compared to placebo and alendronate. Absence of label suggests suppressed bone remodeling. Dynamic bone formation parameters such as activation frequency, bone formation rate and mineralizing surface were markedly suppressed.

I recommend that applicant conduct additional bone biopsy trial to evaluate effect of long term denosumab therapy on bone biopsy as well as reversibility of the effect of denosumab on suppression of bone remodeling as a post marketing requirement.

7.4.6 Immunogenicity and Hypersensitivity

Any therapeutic protein has the potential to elicit an immune response and hypersensitivity. In a preclinical 12 month monkey trial, 25/32 (~78%) monkeys developed anti-drug antibodies (ADA). In the monkeys positive for ADA, 7/32 tested positive for neutralizing antibodies. The development of ADA corresponded with approximately 30- 50% reduction in denosumab exposure based on AUC as compared to animals that were antibody negative. Since denosumab is a fully humanized monoclonal antibody, it is expected that majority of animals would develop antibodies. However, it was not clear if significant number of human subjects would develop antibodies against denosumab.

To evaluate 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 trial 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.

Reviewer's comment: In conclusion, denosumab does not appear to be immunogenic in humans.

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 7.3.4.8. 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.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The dose-finding trial (Trial 20010223) for the osteoporosis indications examined 7 different SC doses of denosumab, including 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 trial. There was a greater reduction in corrected calcium from baseline at higher doses of denosumab. There was no clear dose response observed in terms of markers of bone remodeling and bone histomorphometry. There were no other noteworthy trends in dose-related adverse events when the adverse event, laboratory parameters and physical findings were examined by cumulative yearly denosumab dose.

7.5.2 Time Dependency for Adverse Events

There was no apparent exposure-based signal for specific adverse events. As outlined in section 7.4.5, a trend of progressive suppression of bone remodeling was noted at 12, 24 and 36 months.

When adverse events of infection were reviewed in Trial 20040132 during the off-treatment period, there was no difference in the incidence of events of infection and serious infection between subjects who had received denosumab or placebo during the on-treatment period. However, it should be noted that number of events of infection reported during this off-treatment trial period was much lower than during the on-treatment period for a similar number of trial visits.

7.5.3 Drug-Demographic Interactions

Adequate safety and efficacy was reported in the pivotal trial for patients <75 and ≥ 75 years of age. No clinical studies in pediatric patients were submitted in this application. The overall incidences of adverse events were balanced across geographic regions and

between treatment groups within each regional subgroup. Denosumab is intended for the treatment and prevention of postmenopausal women with osteoporosis. Studies predominantly enrolled women; however, trial 20040138 was conducted in men and denosumab was found to be efficacious. Since most patients in the osteoporosis trials were Caucasian, the effects of race/ethnicity on the safety and efficacy of denosumab are not known. Thus, the PMO and hormone ablative studies reviewed herein do not suggest a need for dose adjustments based on demographic parameters.

7.5.4 Drug-Disease Interactions

Degree of bone loss: Efficacy findings were similar in subjects with prevalent vertebral fractures vs. none and subjects with lumbar spine and femoral neck BMD in osteoporosis vs. low bone mass (osteopenia) range.

Renal Impairment: Trial 20040245 investigated PK, PD and safety of denosumab in subjects with renal impairment. The PK and PD profile of denosumab was not notably different between subjects with normal renal function and those with renal impairment. However, there was a difference in the hypocalcemia laboratory observations in patients with severe kidney disease (i.e., CrCL < 30 mL/min) and ESRD compared with those with mild or moderate renal impairment and normal renal function. Similarly, Trial 20060289 (the ongoing extension trial for Trial 20030216), showed a trend towards larger reductions in day-10 serum calcium in subjects with severe renal impairment compared with subjects with normal renal function and mild or moderate renal impairment. Calcium and vitamin D supplementation is particularly important in patients who have severe renal impairment or renal failure requiring dialysis. Serum calcium should be monitored closely in subjects with renal failure or in subjects with severe CKD (CrCL 30 mL/min).

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

Rheumatoid arthritis: Study 20040144 was a phase 2 placebo-controlled trial that evaluated denosumab administered Q6M SC at doses of 60 and 180 mg in subjects with mild to moderately active rheumatoid arthritis on stable doses of methotrexate. The difference between the 60-mg group and placebo was not statistically significant in reducing the rheumatoid arthritis erosion score as measured by MRI. Infection events led to hospitalization in 4% of denosumab-treated subjects and 1% of subjects who received placebo.

Breast cancer related metastasis: Study 20040113 is a phase 2 trial that evaluated denosumab SC (30-, 120-, and 180-mg Q4W and 60- and 180-mg Q12W) or IV bisphosphonate in subjects with breast cancer-related bone metastasis who had not previously been treated with bisphosphonate therapy (n = 254 treated subjects; 211 denosumab, 43 IV bisphosphonate). Decreases in albumin-adjusted serum calcium

concentration to < 2 mmol/L (8 mg/dL) were observed in 16 subjects (8%) who received denosumab and 3 subjects (7%) who received IV bisphosphonate. The subject incidence of serum calcium values < 2 mmol/L was higher in the denosumab 180-mg Q4W and Q12W groups than in the other dose groups.

Multiple Myeloma: Study 20050134 is an ongoing, phase 2, open-label, non-comparative, 2-cohort, proof-of-concept trial in heavily pretreated subjects with relapsed (n = 53) or plateau-phase myeloma (n = 43) receiving denosumab (120 mg SC on days 1, 8 and 15, then on trial day 29, then Q4W thereafter). ONJ was confirmed in a subject (134111010) with a history of exposure to zoledronic acid plus chemotherapy, radiotherapy, multiple dental restorations, spinal compression fractures, vertebroplasty, and autologous stem cell transplant.

7.5.5 Drug-Drug Interactions

No drug/drug interaction studies have been conducted with denosumab to date.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

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. In the two long term studies (12-month toxicity and 16-month pharmacology studies), there were no incidences of tumor formation indicated. The only noteworthy finding was in the 12-month trial, one low dose and one high dose female exhibited squamous metaplasia (benign) in the uterus. In the 16-month trial, there were no noted findings from gross pathology or general observations, but general organ histopathology was not conducted. Due to the lack of an appropriate animal model, formal carcinogenicity studies would not be recommended.

7.6.2 Human Reproduction and Pregnancy Data

Preclinical Findings:

Reports in the literature suggest that RANK-RANKL signaling during pregnancy is involved in a crucial step in breast development and lactation. In mice that are RANK/RANKL KO mice, there is impaired lymph node formation, absence of lactation due to inhibition of mammary gland maturation. The Applicant's embryofetal trial showed no effect on prenatal loss or maternal clinical signs or weight, and there were no teratogenic effects of denosumab. Nonsignificant trends in delayed ossification and increased incidence of shortened, isolated, rudimentary and/or vestigial ribs were observed, along with slight decreases in adrenal, heart and fetal body weight, and a

slight increase in ovary weight. While both studies were adequate, and dosing during the embryofetal trial covered the period of primate organogenesis, antibodies do not typically cross the placenta until later in fetal primate development. Therefore, the trial likely only assessed potential secondary effects of denosumab on the fetus resulting from maternal exposure. In addition, the embryofetal trial only evaluated limited organs by histopathology; fetal lymph nodes were not examined, even though signaling via RANK has been shown to be required for lymph node development in mice.

No human pregnancy data are available for denosumab. The proposed indication is for use in postmenopausal women. A total of four subjects became pregnant while participating in denosumab trials. The outcomes of these 4 pregnancies were as follows: healthy infant – 1, ongoing pregnancy - 1, lost to follow-up – 2. In trial 20050227, a healthy volunteer who received a single dose of 60 mg became pregnant within 3 months of receiving denosumab. The infant appeared to be healthy at birth. The father of the infant was enrolled in the same trial and had received a single 78 mg dose. In trial 20060286, a healthy volunteer became pregnant within 2 months of receiving a single 60 mg dose of denosumab. The pregnancy was ongoing at the time of the BLA submission. In trial 20050146, two healthy volunteers became pregnant within 6 months of receiving a single 60 mg dose of denosumab. Both of these women were reported by the applicant to be lost to follow-up.

The proposed pregnancy category is C. The Applicant has proposed a pregnancy registry, which is described in section 1.3.

Reviewer Comments:

The pregnancy category is acceptable. A pregnancy registry is necessary to monitor for potential adverse outcomes in women who become pregnant. Suggestions to improve this registry and overall monitoring for pregnancy outcomes are provided in section 1.3

7.6.3 Pediatrics and Assessment of Effects on Growth

Denosumab studies were not conducted in pediatric patients and as such there is no data for this population or its effects on human growth. However, toxicology studies showed deleterious changes in epiphyseal growth plates that were not closed prior to treatment in addition to delayed molar eruption, decreased upper/lower incisor length, and 'flared' morphometry in femoral metaphysis (club-like femur). Thus, denosumab should not be administered to pediatric patients and will be labeled as such.

Reviewer Comment:

The applicant's proposed labeling appears to be adequate in regards to use in pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose was not reported during the denosumab PMO and hormone ablation studies. In the dose-finding trial (Trial 20010223), subjects received repeated fixed SC doses of denosumab up to 210 mg every 6 months for up to 24 months. Also, cumulative doses up to 1080 mg over 6 months have been evaluated in subjects with advanced cancer in Study 20040114 without dose-limiting toxicity.

There is no suggestion of drug abuse potential at this time.

The "off-treatment" effects of denosumab were evaluated for a year following treatment (18 months from last dose) in Trial 20040132 (full analysis on second year pending) and for up to 2 years following treatment (18 to 30 months from last dose) in Trial 20010223 ("dose-finding" trial). Within 12 months of discontinuing denosumab, BMD returned to approximately baseline levels in these subjects.

7.7 Additional Submissions / Safety Issues

A four month safety update report was submitted 15 April 2009 and covers events through 02 December 2008. The data in this update were not integrated with the data in the original BLA or across studies in this Safety Update because the individual trial designs and objectives are significantly different. The data described in this summary fall into 4 categories, which will be the organization for the update: 1) long-term safety of denosumab treatment, 2) safety of commercial drug substance/drug product, 3) off-treatment effects, and 4) ongoing studies.

A brief summary of the individual studies included in each of the four categories is provided below:

7.7.1 120-Day Safety Update on Long-Term Safety

Long-Term Safety of Denosumab Treatment:

Two studies provide additional information on the long-term safety of denosumab treatment:

- a) Trial 20050233 – women with low BMD
- b) Trial 20060289 – women with PMO

Trial 20050233 was a Phase 3, open-label, single-arm extension trial from Trial 20010223 (dose-finding trial). The trial enrolled 200 women who completed Trial 20010223 (age \leq 80 years) who were postmenopausal and had low BMD. Subjects received denosumab 60 mg SC Q6months for 8 doses (48 month duration). As such, safety data will be available on subjects receiving continuous treatment with denosumab for up to 8 years and subjects in the parent trial who received placebo or alendronate may provide safety information for up to 4 years of treatment. The continuous treatment cohort included subjects who had received denosumab 6 mg Q3M, 14 mg Q3M, 14 mg

Q6M, 60 mg Q6M, or 100 mg Q6M for 2 years, followed by 2 years of denosumab 60mg Q6M in Trial 20010223.

There were a total of 5 deaths from trial start until data cut-off (02 December 2008). Since 2 deaths were reported in the initial BLA, 3 new deaths had been reported. Subject 307006 unexpectedly died at home 6 months after initiation of trial drug (3 weeks after last dose); the only relevant history was that the subject had a history of hypertension. Subject 309093 was a 72-year-old female with a family history of colon cancer. She was diagnosed with metastatic adenocarcinoma of the colon 11 months after the initial dose of trial drug (5 months after last dose). Three additional subjects died during the period of this update. Subject 309030 died of an exacerbation of COPD 23 months after initiation of trial drug (5 months from last dose). The subject had a history of COPD, emphysema, 35-year history of smoking 1.5 packs per day and required home oxygen. Subject 209097 died of stage IV lung cancer (non small cell lung carcinoma) which was diagnosed 25 months after initiation of trial drug. The subject had more than a fifty-pack year history of smoking, bronchitis, chronic cough, and COPD. Subject 321004 was diagnosed with liver cancer, bone cancer and lung cancer (primary site unknown) about 13 months after the first dose of trial drug. No medical history was provided for the subject, who subsequently died in hospice.

A total of 25 subjects (12.5% of enrollees) experienced SAEs from the trial start until data cutoff (02 December 2008). The applicant provided data on subjects in the placebo group (N=23), alendronate group (N=22) and denosumab 210 mg Q6months (N=17), 30 mg Q3months (N=14) and continuous treatment (N=124). The continuous treatment cohort included subjects who had received denosumab 6 mg Q3M, 14 mg Q3M, 14 mg Q6M, 60 mg Q6M, and 100 mg Q6M in Trial 20010223. The majority of SAEs occurred only once during the trial period, so no further conclusions can be made about SAEs in the period of update. However, noteworthy events of endocarditis and malignancies will be described in detail.

Endocarditis occurred in a denosumab subject in the continuous treatment cohort. This is the fourth case of endocarditis in subjects receiving denosumab. This 83-year-old subject (307082) had a history hyperlipidemia, overactive bladder, hypertension, and heartburn and had received denosumab 100 mg SC Q6months in Trial 20010223. She was hospitalized 1 month earlier for *Staphylococcus aureus* bacteremia and was being treated with ceftriaxone 2 g IV daily. The subject initiated denosumab in Trial 20050233 on (b) (4). About 8 months later, on (b) (4), the subject had symptoms of heart failure and an echocardiogram showed mitral valve leaflets heavily calcified; mitral annular calcification; moderate mitral regurgitation; and mild tricuspid regurgitation. Chest x-ray revealed pulmonary vascular congestion consistent with fluid overload/CHF. Treatment for the event included IV furosemide and continued ceftriaxone. The event resolved on (b) (4) and the subject was discharged. On (b) (4), subject was rehospitalized with exacerbation of symptoms. A transesophageal echocardiogram revealed endocarditis of mitral valve leaflet with calcified vegetation noted at leaflet tip;

posterior leaflet also with small perforation with regurgitation jet and aneurysm near the commissure. Treatment for the event included mitral valve replacement with bioprosthesis. The event resolved on (b) (4) and the subject was discharged from the hospital. Denosumab was continued in this subject at last report.

Reviewer Comments on Long-Term Safety Studies:

The endocarditis case occurred in a subject who had received a high dose of denosumab in the parent trial. This case of bacteremia progressed to endocarditis despite seemingly adequate intravenous antibiotic therapy.

The following malignancies were reported from the trial start until data cutoff (02 December 2008). Nine subjects (6%) reported malignancies, including 2 cases of basal cell carcinoma and 1 case each of the following: basal cell carcinoma/squamous cell carcinoma of skin, lung neoplasm malignant/malignant bone neoplasm/hepatic neoplasm malignant, lung neoplasm malignant, lung carcinoma cell type unspecified Stage IV, breast cancer, breast cancer *in situ*, and colon cancer metastatic.

Reviewer comments on Long-Term Safety Studies:

All malignancies occurred in the continuous treatment cohort, except for 1 subject who had Stage IV lung cancer diagnosed that had received placebo in the parent trial. Two subjects in the continuous treatment cohort developed lung cancer.

Adverse events were reported in 78% of subjects, with the most frequent adverse events of upper respiratory tract infection (24 subjects, 12.0%) and arthralgia (22 subjects, 11.0%). During the reporting period, 25 subjects withdrew from the trial, including 6 subjects for adverse events and 20 for other reasons. Twenty-seven subjects discontinued denosumab, including 6 subjects for adverse events and 21 for other reasons. The adverse events that resulted in denosumab discontinuation in 6 subjects were injection site reaction, non-cardiac chest pain, muscle spasms, musculoskeletal pain, breast cancer, breast cancer *in situ*, and paresthesia.

Trial 20060289 – Trial 20060289 is an ongoing multicenter, open-label, single-arm extension trial to evaluate the long-term safety and sustained efficacy of denosumab in the treatment of PMO. To enter this trial, subjects had to have successfully completed Trial 20030216 (the parent trial), a 3-year placebo-controlled trial in women with PMO. In Trial 20060289, all subjects will receive denosumab 60 mg SC Q6M for 7 years (for a total of 10 years in subjects who received denosumab in Trial 20030216). 120-day Safety Update provided an interim analysis of safety data from trial start through 02 December 2008 and included a full dataset of changes in serum calcium measured 10 days after the first dose. The calcium results are reviewed in the section evaluating hypocalcemia. Main safety findings will be reviewed in this section.

Subject Demographics and Disposition

A total of 4550 subjects enrolled in the current trial, 2343 subjects who are continuing treatment with denosumab (long-term treated subjects) and 2207 subjects who received placebo in the parent trial and are receiving denosumab for the first time in the current trial (*de novo* treated subjects). In both prior-treatment groups, all subjects are women and most (> 90%) are white. Mean age is 75 years in both groups. Thus far, no subject has completed the trial. Overall, 172 subjects have withdrawn from the trial, 82 long-term treated subjects (3.5%) and 90 *de novo* treated subjects (4.1%). The most common reason for trial withdrawal was consent withdrawn (117 subjects, 2.6%) followed by adverse events (24 subjects, 0.5%).

From enrollment of the first subject through 02 December 2008, at which time about 79% of subjects in each prior-treatment group had received 2 denosumab doses adverse events were reported for 53.5% of long-term treated subjects and 54.4% of *de novo* treated subjects (The most frequent adverse events were back pain (4.4% of long-term treated subjects, 4.8% of *de novo* treated subjects) and arthralgia (4.3%, 4.4%).

Table 66. Summary of Subject Incidence of Adverse Events 20060289 (120-day Safety Update)*

Adverse events	Placebo (N=2206) n (%)	Denos. 60 mg Q6M (N=2343) n (%)
All	1200 (54.4)	1253 (53.5)
Serious	176 (8.0)	165 (7.0)
Fatal	16 (0.7)	5 (0.2)
Leading to trial discontinuation	12 (0.5)	15 (0.6)
Leading to investigational product discontinuation	19 (0.9)	22 (0.9)

For subjects who received at least 1 dose of investigational product.

*Treatment groups are the original randomized assignments in the 20030216 trial; All subjects in the 20060289 trial received denosumab 60 mg Q6M.

Deaths: From trial start through 02 December 2008, 21 subjects died, 5 long-term denosumab treated subjects (0.2%) and 16 subjects begun on denosumab treatment of completion of placebo (0.7%). It should be noted that an additional fatal adverse event, the death of Subject 633094 due to metastatic ovarian cancer, is not included, because the onset date of this adverse event is prior to the start of the reporting period. Of these, 5 deaths were due to malignancies (4 in *denovo* group and 1 in long-term group). These included peritoneal carcinoma, large intestine carcinoma, lung neoplasm malignant, metastasis, and metastatic renal cell carcinoma. Three subjects died with cardiac disorders (cardiac failure (1), cardiopulmonary failure (2)). Two subjects died with cerebrovascular disease (one subject in *de novo* group had CVA and in long term

treatment group had cerebral hemorrhage). There were 6 subjects in general disorders SOC; 2 subjects reported as death, 2 reported as sudden death and 2 subjects had multi organ failure.

Adverse events:

AE leading to IP discontinuation: Twenty-two long-term treated subjects (0.9%) and 19 *de novo* treated subjects (0.9%) were withdrawn from IP due to adverse events. Two subjects in the long-term treated group were withdrawn from IP due to lung neoplasm malignant (1 smoker and 1 nonsmoker). Four long-term treated subjects (0.2%) and 3 *de novo* treated subjects (0.1%) withdrew from IP due to adverse events considered related to IP; these events were drug eruption, erythema, mantle cell lymphoma, and rash pruritic in the long-term treated group, and fatigue, international normalized ratio fluctuation, and rash in the *de novo* treated group.

Infections: 397 long-term treated subjects (16.9%) and 372 *de novo* treated subjects (16.9%) reported adverse events in the infections SOC. The most common infections were (long-term, *de novo*) nasopharyngitis (2.6%, 3.1%) and cystitis (2.0%, 1.9%). Serious adverse events of infection were reported in 22 long-term treated subjects (0.9%) and 25 *de novo* treated subjects (1.1%). The most common serious adverse event of infection (> 0.1%) was pneumonia, reported in 6 long-term treated subjects (0.3%) and 7 *de novo* treated subjects (0.3%). One subject reported a serious adverse event of erysipelas and one subject reported a serious adverse event of erysipelas co-reported with necrotizing fasciitis; both were long-term treated subjects. These 2 cases are described below.

Subject 6652012, an 81-year-old woman who received denosumab for 3 years in Trial 20030216, was reported to have erysipelas of the right leg 8 days after receiving the first dose of denosumab in the current trial and was treated with amoxicillin. Thirteen days later, the subject was noted to have a bullous rash with increased pain and erythema. The subject was hospitalized with an admission diagnosis of necrotizing fasciitis and erysipelas of the right leg. Cutaneous exam revealed external and internal right leg ulceration that was clean and without signs of infection. Wound culture revealed *Pseudomonas aeruginosa*, *Enterobacter cloacae*, and *Enterococcus faecalis*. The ulcer was incised and the subject was treated with intravenous antibiotics. The subject clinically improved, and antibiotics were switched to oral therapy. The subject was eventually discharged from the hospital on oral antibiotics. Investigational product was discontinued. Subject 6631051, an 82-year-old woman who received 3 years of placebo in Trial 20030216, developed erysipelas (left leg) approximately 2 months after initiating treatment with denosumab in the current trial. The subject was hospitalized. Treatment included antibiotic therapy, and the subject was discharged 6 days later.

Malignancy: There were 30(1.4%) subjects in *de novo* and 33 (1.4%) subjects in long term group developed malignancy. Of these, basal cell carcinoma (8 vs. 6), breast cancer (1 vs. 4) and lung neoplasm malignant (1 vs. 3) were most common.

Reviewer comment:

Since this is an open label extension trial, it is more difficult to interpret differences between the long-term and de novo groups. When looked at different system organ class, similar trends were observed as the parent trial, 20030216. No major concern was identified in this extension phase.

7.7.2 120-Day Safety Update on Commercial Drug Substance/Drug Product

Safety of Commercial Drug Substance/Drug Product

Three studies provide additional information on the immunogenicity and safety of commercial drug substance/drug product.

- a) Study 20060237, in which women with low BMD received denosumab manufactured at Amgen, Colorado (ACO) from either a vial or a prefilled syringe (PFS). The final clinical trial report was provided in the submission.
- b) Study 20060289, in which a subset of women with PMO received denosumab manufactured at Boehringer Ingelheim Pharma (BIP) given using a PFS
- c) Study 20050233, in which women with low BMD were given denosumab from a vial manufactured at ACO.

Studies 20060289 and 20050233 were described previously. No noteworthy trends were identified in the safety update that relate to the safety of commercial drug substance/drug product. These studies will not be discussed further in this section.

Study 20060237 - was a multicenter, randomized, open-label trial designed to evaluate the safety of denosumab in a pre-filled syringe (PFS) compared with denosumab in a vial commercially manufactured at Amgen Colorado (ACO). All subjects enrolled had to have successfully completed Study 20050141, which compared the efficacy of denosumab 60 mg SC Q6M (vial) with alendronate 70 mg PO QW for changes in BMD in postmenopausal women with osteoporosis. In Study 20060237, subjects were randomized in a 1:1 ratio to receive denosumab 60 mg SC Q6M using either a PFS or a vial. Subjects received 2 injections during the 1-year of the trial. A total of 310 subjects (154 subjects on denosumab-vial and 156 subjects on denosumab-PFS) were evaluable for safety.

Twenty-eight subjects (14 denosumab-vial, 14 denosumab-PFS) did not complete the trial. The reason for discontinuing trial was adverse events in 1 subject receiving denosumab-vial and 2 subjects receiving denosumab-PFS; the remaining subjects discontinued trial for other reasons such as consent withdrawn or lost-to-follow-up. In the denosumab-vial group, 104 subjects (67.5%) reported adverse events, while the incidence rate was higher in the denosumab-PFS group, as 121 subjects (77.6%) reported adverse events. The most frequent adverse events were (vial, PFS) arthralgia

(7.1%, 8.3%), back pain (5.8%, 7.1%), and upper respiratory tract infection (3.2%, 6.4%).

No subjects died during the trial. Serious adverse events were reported for 7 subjects (4.5%) who received denosumab-vial and 12 subjects (7.7%) who received denosumab-PFS. In the denosumab-vial group, 3 subjects developed cancer (breast, endometrial and vaginal cancer). In the denosumab-PFS group, one subject each developed lung cancer, ovarian adenoma, and pancreatic carcinoma. There was 1 serious event of hypocalcemia in the denosumab-PFS group, with a reported calcium level of "less than 7." The subject received calcium gluconate and calcium chloride for the event.

Reviewer comments on Commercial Drug Substance/Drug Product Studies: Subjects who received denosumab PFS had more adverse events and serious adverse events than subjects who received denosumab vial. It is possible that the slight differences in these incidence rates were due to the small number of subjects enrolled in the trial and the small number of subjects who reported adverse events.

7.7.3 120-Day Safety Update on Off-treatment Effects

Follow-up safety data in subjects who are no longer receiving denosumab was provided for the following studies:

- a) Trial 20040132 – postmenopausal women with low BMD.
- b) Trial 20040135 – bone loss associated with hormone ablation therapy in women undergoing aromatase inhibitor therapy for nonmetastatic breast cancer
- c) Trial 20040138 – bone loss associated with hormone ablation therapy in men receiving androgen deprivation therapy for prostate cancer.

Trial 20040132 – was one of the Pivotal Primary PMO studies. Subjects received IP for 2 years (4 doses), followed by a 2-year off-treatment phase after administration of IP was withdrawn. The 120-day safety update provided information on the 2-year-off-treatment period. Overall, 332 subjects were enrolled in the treatment phase of the trial and 256 subjects participated in the off-treatment phase, including 128 subjects each who had been exposed to denosumab or placebo during the treatment phase. The interim trial report for this trial for the treatment phase and the first 12 months of the off-treatment phase were submitted with the BLA and summarized previously. The 120-day safety update described the last 12 months of the off-treatment phase.

Within the first 12 months of the off-treatment period, any gain in BMD for subjects receiving denosumab was lost, with BMD returning to approximately baseline levels. Subjects who had received placebo during the treatment period had an even greater decline in BMD because the mean BMD value had decreased relative to baseline. During the 24 months of the off-treatment period, adverse event and serious adverse events occurred at the same incidence for subjects who had received denosumab or

placebo in the on-treatment period. Four subjects in each treatment group experienced osteoporotic, nonvertebral fractures that were centrally confirmed during the off-treatment period. Two denosumab subjects and no placebo subjects were diagnosed with a vertebral fracture in the off-treatment period.

Trial 20040135 – was one of the Pivotal Primary hormone ablation studies. It was a randomized, double-blind, placebo-controlled trial to evaluate denosumab in the treatment of bone loss in subjects undergoing aromatase inhibitor therapy for nonmetastatic breast cancer. This 4-year trial enrolled 252 subjects (denosumab -127, placebo - 125); subjects received therapy for 24 months and were monitored for an additional 24 months. Supportive safety information was available through 6 to 12 months after treatment. In the off-treatment period, generally adverse event and serious adverse events occurred at the same incidence for subjects who had received denosumab or placebo in the on-treatment period. However, there were more fractures in the denosumab group, specifically 12 denosumab subjects (12.5%) who had received and 5 placebo subjects reported a fracture during the off-treatment period, including 3 denosumab subjects who had a vertebral fracture and 9 denosumab subjects and 5 placebo subjects who had fractures at nonvertebral sites that were likely to have been osteoporotic. Three subjects in each group died during the follow-up period, based on data provided in the 120-day safety update.

Trial 20040138 – was one of the Pivotal Primary hormone ablation studies. It was a randomized, double-blind, placebo-controlled trial to evaluate denosumab in the treatment of bone loss in subjects undergoing androgen-deprivation therapy for nonmetastatic prostate cancer. This 5-year trial enrolled 1,468 subjects (denosumab – 734, placebo – 734); subjects received therapy for 36 months and were monitored for an additional 24 months. In the off-treatment period, adverse event, serious adverse event, and fatal adverse events occurred at the same incidence for subjects who had received denosumab or placebo in the on-treatment period. Fractures were reported in 3 denosumab subjects and 6 placebo subjects, including 1 subject in each treatment group that developed a vertebral fracture in the off-treatment period and 2 denosumab and 4 placebo subjects that were diagnosed with nonvertebral fractures that were likely to be osteoporotic.

Reviewer Comments on Off-Treatment Effects:

It is unclear why the incidence of fracture during the off-treatment period was higher in subjects who had been exposed to denosumab in Trial 20040135, but not 20040138. Trial 20040135 enrolled fewer subjects (252), which makes it difficult to interpret slight differences in the occurrence of fractures in this trial.

7.7.4 120-Day Safety Update on Ongoing Studies

The four clinical ongoing studies in the 120-day safety update are as follows:

- a) Trial 20060232
- b) Trial 20040114

- c) Study 20050134
- d) Trial 20050209

Trial 20060232 – is an ongoing multicenter, randomized, open-label, crossover trial in postmenopausal women with low BMD evaluating denosumab and alendronate. Subjects were randomized (1:1) to either denosumab 60 mg SC Q6m x 1 year followed by alendronate 70 mg PO QW x 1 year or vice versa. The 120-day safety update provided safety information on 250 subjects, including 126 subjects randomized to denosumab followed by alendronate treatment and 124 subjects randomized to alendronate followed by denosumab treatment.

A total of 7 subjects experienced SAEs thus far; 4 subjects were receiving denosumab and 3 subjects were receiving alendronate. For the denosumab group, there was 1 subject each who experienced chest pain, diverticulitis, back pain and osteoarthritis. For the alendronate group, there was 1 subject each who experienced atrial fibrillation, pain and lumbar spinal stenosis. Two subjects, one in each treatment group, discontinued IP due to adverse events, including dyspepsia in an alendronate subject and warm skin in a denosumab subject. There were no deaths at the time of the safety update.

Trial 20040114 – is an ongoing multicenter, randomized, open-label, active-controlled, parallel group, multidose trial of denosumab in subjects with advanced cancer and bone metastases who were being treated with IV bisphosphonates at the time of entry into the trial. Subjects were randomized in a 1:1:1 ratio to receive denosumab 180 mg SC every 4 weeks (Q4W), denosumab 180 mg SC every 12 weeks (Q12W), or to continue receiving IV bisphosphonate therapy for 25 weeks, after which they could opt to be treated with denosumab in a 2-year, open-label extension phase. The 120-day safety update provided data collected thus far as part of the 2-year open-label extension phase. Nineteen subjects participated in the extension phase, 12 subjects had received denosumab 180 mg Q4weeks and 7 subjects had received denosumab 180 mg Q12weeks.

Three subjects died, all related to malignancy. Adverse events led to the withdrawal of IP in 2 subjects. One subject receiving denosumab 180 mg Q4weeks discontinued denosumab due to metastatic colon cancer. One subject receiving denosumab 180 mg Q12weeks discontinued denosumab due to osteonecrosis. A detailed narrative is provided for this case of osteonecrosis of the jaw (ONJ) in a subject who had received IV bisphosphonates for almost 2 years prior to entering Trial 20040114. Subject 114358016 was an 83-year-old woman with breast cancer who developed jaw pain suspicious for ONJ after receiving denosumab 180 mg Q12W for approximately 28 months; IP was discontinued. About 2 weeks after the diagnosis of osteonecrosis, the subject died due to progression of metastatic breast cancer. The event of ONJ was ongoing at the time of death. The investigator considered the event of ONJ possibly related to denosumab. The investigator did not report the presence of exposed bone or

the treatment provided for the event. Although the independent expert committee adjudicated this case as an event of ONJ, the case is confounded by long-term IV bisphosphonate therapy.

Study 20050134 – is an ongoing multicenter, open-label, 2-cohort trial to evaluate denosumab 120 mg SC on days 1, 8, 15, 29 and every 28 days thereafter in subjects with relapsed (cohort 1) or plateau-phase (cohort 2) multiple myeloma. Safety data is available for 53 subjects in the relapsed cohort and 43 subjects in the plateau-phase cohort. Twenty subjects were still enrolled in the trial; safety data for these subjects was provided in the update. No deaths occurred during the period of the safety update. Three subjects experienced serious adverse events, including 1 case each of renal impairment, colostomy/perirectal abscess, and cellulitis. Subject 134205008, an 80-year-old woman diagnosed with stage IA myeloma 8 years earlier and received a stem cell transplant 6 years prior to trial entry. The subject developed cellulitis of the left leg 29 months after initiating denosumab 120 mg Q4weeks; the subject was hospitalized twice over several weeks for the event. The WBC was normal throughout and the subject was treated with antibiotics. The event resolved with unspecified sequelae. Denosumab was discontinued due to the event of cellulitis. No other subjects discontinued denosumab due to adverse events.

Trial 20050209 – is an ongoing multicenter, randomized, double-blind, placebo-controlled, trial of denosumab in postmenopausal women with nonmetastatic breast cancer undergoing aromatase inhibitor therapy. Subjects are randomized (1:1) to receive either placebo or denosumab 60 mg SC Q6months. Subjects are followed for survival every 12 months for up to 5 years after the first dose of IP. An interim synopsis of the 535 subjects enrolled in the trial was provided in the initial BLA submission. Data for this trial is still blinded. For the 120-day safety update, safety data was provided on a total of 598 subjects (some previously described in the initial BLA submission).

From the trial start through the data cut-off, 3 subjects died; 1 case each due to metastases to lymph nodes, cardiac failure and diabetes mellitus, and sepsis and shock. Six subjects discontinued IP due to adverse events, specifically breast cancer, metastasis, cardiac failure/diabetes mellitus, gastroesophageal reflux disease, pneumonia, dizziness, and tibia fracture.

A total of 72 subjects experienced serious adverse events (SAEs). The most common SAEs were cholelithiasis (3 subjects), erysipelas (3), and radius fracture (3). The treatment for this trial is still blinded at this time. The 3 cases of erysipelas summarized herein. A 57-year-old woman (SID 209087025) experienced erysipelas of the breast following radiation therapy approximately 6 months after starting blinded IP. The event resolved after 1 week following antibiotic treatment. A woman (SID 209070007) was hospitalized with erysipelas postoperative with subcutaneous fistula in the breast about 5 months after the first dose of IP. Her medical history was significant for ablation and axillary dissection for breast cancer 1 month before the initial dose of IP, followed by

radiotherapy 6 weeks later. Five months after the first dose of IP, the subject was hospitalized with a *Staphylococcus aureus* wound infection and received IV antibiotics. A 62-year-old woman (SID 209903001) experienced erysipelas of the breast and arm with erythema and pain about 11 months after starting blinded IP. The event resolved after 10 days following antibiotic treatment. The subject was receiving concomitant immunosuppressive medication (azathioprine, prednisolone) and pyridostigmine bromide for myasthenia gravis.

There was one serious case of hypocalcemia in a 50-year-old woman (SID 209001021). She experienced paresthesia, hypotonia, and calf cramps and was hospitalized due to hypocalcemia 8 days after initial exposure to blinded IP. The subject was not receiving calcium and vitamin D supplementation. The subject received calcium glutamate and the hypocalcemia resolved the next day. The subject's calcium level was 2.34 mmol/L at baseline, 1.26 mmol/L at hospitalization and increased to 1.52 mmol/L the following day. This subject was receiving peritoneal dialysis due to renal failure and had a history of parathyroidectomy due to persistent reactive renal autonomous hyperparathyroidism. The subject was subsequently withdrawn from the trial when it was determined that her medical history made her ineligible.

There were two subjects who developed hypersensitivity and a swollen tongue. A 67-year-old woman (SID 209052007) was hospitalized due to an allergic reaction after receiving the second dose of blinded IP. About 30 minutes after administration of IP, the subject developed shivering and fever. She was treated with prednisolone and paracetamol and recovered that day. Investigational product was continued. A 77-year-old woman (SID 209001027) developed tongue swelling and had difficulties swallowing (dysphagia) 1 day after the first dose of blinded IP. The subject was treated with diphenhydramine and the event resolved that same day. Investigational product was continued.

Reviewer Comment on Ongoing Studies:

- ***Trial 20040114 in subjects with advanced cancer and bone metastasis is noteworthy for a positively adjudicated case of ONJ in a subject receiving denosumab 180 mg Q12W for approximately 28 months, following almost 2 years of IV bisphosphonate therapy.***
- ***Study 20050134 in subjects with relapsed or plateau-phase multiple myeloma is noteworthy for a case of serious cellulitis in a subject receiving denosumab 120 mg SC Q28 days for 29 months.***
- ***Trial 20050209 in postmenopausal women with nonmetastatic breast cancer undergoing aromatase inhibitor therapy is noteworthy for a subject developing a serious case of hypocalcemia 8 days after receiving either IP (denosumab 60 mg SC or placebo). The subject should not have been enrolled in the trial due to a history of parathyroidectomy, which put her at risk for hypocalcemia. Also, the subject was not supplemented with***

calcium and vitamin D. In this trial, 3 subjects developed erysipelas and 2 subjects experienced tongue swelling.

8 Postmarket Experience

Denosumab has not been approved for use in other countries and there is no postmarket experience for this product.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

See separate document.

9.3 Advisory Committee Meeting

Introduction

Denosumab is the first biologic agent seeking indication for postmenopausal osteoporosis and low bone mass. As required by section 505(s) of the Federal Food, Drug, and Cosmetic Act, (before approving a drug no active ingredient of which has been approved, FDA must either refer that drug to an advisory committee or provide in the action letter for the drug a summary of the reasons why FDA did not refer the drug to an advisory committee before approval) an advisory committee was held on August 13, 2009 at the Hilton Washington DC North/Gaithersburg, 620 Perry Parkway, Gaithersburg, MD, 20877. Prior to the meeting, the members and the invited consultants had been provided with background material from the FDA and from the Applicant. This was a voting meeting. There were approximately two hundred and fifty (250) persons in attendance.

At the time of this review, the transcripts were not available, so the following is this medical officer's interpretation of the meeting. This review will focus on issues pertaining to postmenopausal osteoporosis indications.

The participants of the meeting were the following:

Advisory Committee for Reproductive Health Drugs (Voting):

Sandra Carson, M.D. (OB/GYN), Chair, Julia Johnson, MD (OB/GYN)

Industry Representative Member Present:

Robert Gut, M.D., Ph.D.

Special Government Employee Consultants (Voting):

Michael T. Collins, M.D. (Endocrinology), Clifford J. Rosen, M.D.
(Endocrinology), Lawrence M. Nelson, M.D.(Reproductive Endocrinologist), Scott Emerson, MD, PhD, (Biostatistics), John Bennett, MD (Infectious Disease), Gulba Uzel, MD (Infectious Disease), Merrill Goozner (consumer representative), Martha Solonche (patient representative).

Oncology members:

Joanne E. Mortimer, MD (Breast cancer), James L. Gulley, MD, PhD (Prostate cancer), Aman Buzdar MD, (Breast cancer), Ronald Richardson, MD (Prostate cancer)

FDA Participants (Non-Voting):

Julie Bietz, M.D., George Benson, MD, Theresa Kehoe, MD, Richard Pazdur, MD, Suzanne Demko, PA-C

Designated Federal Official:

Kalyani Bhatt, BS, MS

Open Public Hearing Speakers:

Kathleen Cody (Foundation for Osteoporosis Research and Education dba American Bone Health); Roberta Biegal (National Osteoporosis Foundation); Marilyn Brown (Retired Microbiologist); Gladys Quinterro; Laurel Glassman (Attorney), Seth D. Ginsberg (President Global Healthy Living Foundation), and Cynthia A. Pearson (Executive Director National Women's Health Network).

Presentations

Introduction: Dr. George Benson, MD

The Applicant's presentations included the following:

- Introduction (Paul Eisenberg, MD, MPH)
- Burden of Disease and Need for Improved Therapy in Postmenopausal Osteoporosis (PMO) and Hormone Ablation Therapy (HALT) (Ethel Siris, MD)
- Discovery of RANK Ligand and Development of Denosumab (David Lacey, MD)
- Denosumab Clinical Efficacy and Safety Assessments: PMO & HALT (Catherine Stehman-Breen, MS, MD)
- Denosumab Pharmacovigilance Plan: PMO & HALT (Paul Eisenberg, MD, MPH)

The FDA presentation was given by

- FDA analysis on denosumab efficacy (Vaishali Popat, MD, MPH)
- FDA analysis on denosumab safety (Adrienne Rothstein, PharmD)
- Bone histomorphometry, discussion of FDA's risk benefit assessment (Theresa Kehoe, MD)

Pertinent Points from Applicant's Presentation related to PMO indications

- FRAX tool for fracture risk assessment was discussed in detail
- Denosumab reduces bone reabsorption, as reflected in reduced bone turnover and increased bone mass in both non-clinical and clinical studies. Denosumab 60 mg Q6M reduced the rate of vertebral and non-vertebral and hip fractures and increased BMD in postmenopausal women.
- The Applicant emphasized that there were fewer deaths in the denosumab group and all adverse events occurred at a similar rate in both groups. For infections, the applicant stated that skin infections resulting in hospitalizations were observed more frequently in the denosumab group (0.4% denosumab vs. 0.2% placebo). There was no increased risk of opportunistic infections, recurrent infections, sepsis or death.
- For neoplasms and malignancy related adverse events, the applicant argued that the imbalances noted were most likely due to chance.
- Long term additional safety studies and a pharmacovigilance plan (postmarketing surveillance) were proposed for further assessment of risks identified in the review process. These included an open label extension of the trial 20030216 trial 20060289 , 10 year total duration, phase 2 trial 20010223 extension with 200 subjects, total 8 year duration, and phase 3 1200 subject osteoporosis fracture trial, total 3 year duration. The pharmacovigilance plan included collaborations with large database systems such as Kaiser, United Healthcare, and Medicare databases in the USA and Nordic National Health Registry in E.U.

Pertinent Summary Points from DRUP Presentation

1. In conclusion, for efficacy, the Applicant achieved the primary objective in the primary efficacy trials for fracture (20030216) and prevention (20040132) indications. Treatment with denosumab for three years reduced the risk of fractures in postmenopausal women with osteoporosis and increased lumbar spine BMD in postmenopausal women with low bone mass. However, It was noted that the incidence of hip fracture was lower than placebo in the first and second year, but became similar to placebo in the third year of the primary fracture trial.
2. There was profound suppression of markers of bone remodeling. Bone biopsy and histomorphometry showed suppression of both, bone resorption and bone formation parameters. It was noted that the degree of suppression of bone remodeling was not seen with any other antiresorptive agent. Long term consequences of these findings are unclear.
3. In summary, the principal safety concerns that we have identified for denosumab include risk of serious infections(skin, ear, urinary tract,

endocarditis), new malignancies, dermatological conditions and over suppression of bone turnover.

The following questions asked for the Committee's overall assessment of the benefit/risk profile for denosumab for the indications sought, and whether a Risk Evaluation and Mitigation Strategy (REMS) is needed if denosumab were approved.

The questions for the committee and quick minutes are included verbatim in this section:

Benefit/Risk Profile – Treatment of postmenopausal osteoporosis

Question 1a [Vote: Yes/No]: Is there a population of postmenopausal women with osteoporosis in which the benefit of treatment with denosumab is likely to outweigh the risks?

Result: Yes: 15 No: 0 Abstain: 0

Question 1b [Discussion]: If yes, would this population be:

- (1) All women with postmenopausal osteoporosis,
- (2) Limited to a subgroup at a high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or women who have failed or are intolerant to other osteoporosis therapies

Medical officer's comment: The committee voted unanimously in favor of having favorable risk benefit ratio for denosumab in the treatment of osteoporosis in postmenopausal women. A few members expressed their concerns about the long term safety and recommended considering approval as "almost" second line therapy to other available agents (for subjects described in option 2 of question 1b) as well as long term follow-up to further characterize associated risks.

Benefit/Risk Profile – Prevention of postmenopausal osteoporosis

Question 2a [Vote: Yes/No]: Is there a population of postmenopausal women with low bone mineral density who do not meet the criteria for treatment of osteoporosis in which the benefit of prevention of osteoporosis with denosumab is likely to outweigh the risks?

Question 2b [Discussion]: If yes, which population?

Result: Yes: 3 No: 12 Abstain: 0

Medical officer's comment: Most members felt that the benefits of the drug in preventing osteoporosis are not likely to outweigh risks for women with

low bone mass.

(b) (4)

(b) (4)

Questions 3, 4 and 5 are related to hormone ablation therapy related bone loss in cancer indication population. Question 6 relates to both PMO and hormone ablation populations.

Risk Evaluation and Mitigation Strategies

Question 6a [Vote: Yes/No]: If approved, do you recommend that denosumab have a Risk Evaluation and Mitigation Strategy or REMS?

Result: Yes: 12 No: 1 Abstain: 0

Question 6b [Discussion]: If so, which elements should be included in the REMS?

- (1) A Medication Guide to inform patients about the risks of the drug?
- (2) A Communication Plan to disseminate information to healthcare providers?
- (3) Other?

Medical officer comment: *The committee voted in favor of REMS, specifically a medication guide to inform patients about the risks of the drug and a communication plan to educate providers about major safety concerns. One member brought up an idea that since denosumab is administered by a health care provider, it is relatively easy to make a registry and follow patients prospectively. However, a concern was raised in terms of time and cost involved in REMS implementation. This medical officer sensed that after discussion, it was felt that since this is a first in class drug, at least a medication guide and a communication plan is recommended.*

9.4 Review of Individual Studies

9.4.1 Trial 20030216

Title: "A Study to Evaluate Denosumab in the Treatment of Postmenopausal Osteoporosis: Fracture reduction evaluation of denosumab in osteoporosis every 6 months."

Original protocol date: March 15, 2004.

Amendments:

- 19 December 2005
- 25 October 2006

Objectives:

Primary: 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 + calcium).

Secondary:

To assess the effect of denosumab on

- Time to first non-vertebral fracture
- Time to first hip fracture
- Characterization of the safety and tolerability profile in postmenopausal women.

Substudies

Within the overall trial, 7 substudies were conducted to evaluate the treatment effect on the following:

- 1) DXA: BMD measured at the lumbar spine, proximal femur, distal 1/3 radius, and total body
- 2) QCT Spine/Hip: trabecular and cortical bone parameters as assessed by QCT of the lumbar spine and hip
- 3) QCT Distal Radius: trabecular and cortical bone parameters as assessed by QCT of the distal radius
- 4) Bone Marker: bone turnover (measured by serum type I C-telopeptide [CTX1], tartrate-resistant acid phosphatase 5b [TRAP-5b], bone-specific alkaline phosphatase [BALP], and procollagen type I N-terminal peptide [P1NP]) and on levels of osteoprotegerin (OPG), and intact parathyroid hormone (iPTH), Receptor Activator of Nuclear Factor- κ B Ligand (RANKL),
- 5) Pharmacokinetics: the pharmacokinetics of denosumab using population pharmacokinetic

- 6) Fracture Healing: healing of distal radius fractures
- 7) Bone Biopsy bone histology, histomorphometry, and micro-architecture (micro-CT) of transiliac bone biopsies

Study Design:

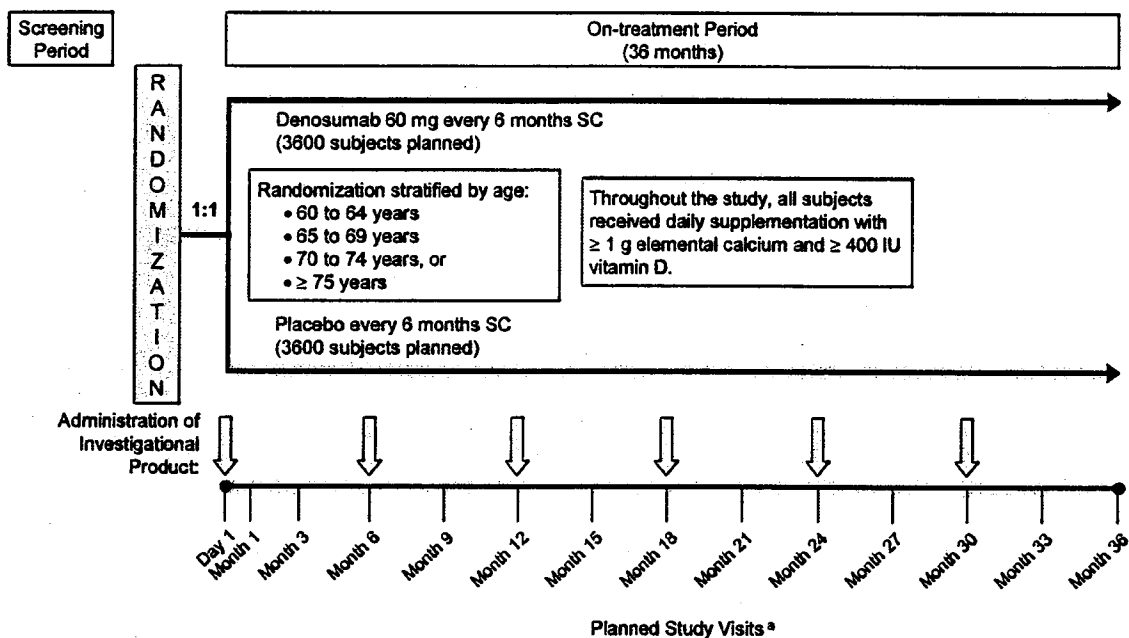
Study 20030216 was an international, multicenter, randomized, double-blind placebo-controlled trial to investigate the safety and efficacy of denosumab on the reduction of new vertebral fractures in postmenopausal women with osteoporosis after 3 years of treatment. Subjects were randomized (1:1) to receive 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 trial.

The Amgen Central randomization group generated the randomization schedule. Randomization was stratified by age at trial 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 trial scheme is presented in Figure 14.

Figure 14: Study Schema



Study visits occurred every 6 months, for a total of 7 visits over 3 years. Telephone contacts were conducted every 3 months in between scheduled visits. The last scheduled dose of IP 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 trial 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 trial 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.

A summary of the trial schedule is presented in Table 67.

Table 67: Schedule of Events for Study 20030216 (Primary Study) through Year 3

Study procedures	Screening	Day 1 ³	M1	M6	M12	M18	M24	M30	M36
Medical, medication, & fracture history; height and 25(OH) D level	X								
Physical examination & weight	X	X		X		X		X	
Vital signs	X	X	X	X	X	X	X	X	X
Lateral spine X-rays (lumbar and thoracic)	X			X ¹	X		X		X
DXA of spine	X						²		X
DXA of hip	X			X		X		X	
VFA of spine by DXA	-			X					
Serum chemistry and hematology panels	X	X	X	X	X	X	X	X	X
Administration of IP	-	X		X	X	X	X	X	
Denosumab antibody assay		X	X	X	X	X	X	X	X
Serum denosumab level		X	X	X					
CTX1 and TRAP 5b		X							
Patient reported outcomes assessments (OPAQ-SV and EQ-5D)		X		X	X	X	X	X	X

M=month, CTX1 = serum type I C-telopeptide; DXA = dual energy x-ray absorptiometry; EQ-5D = EuroQol-5 Dimensions; OPAQ-SV = Osteoporosis Assessment Questionnaire Short Version; PRO = Patient reported outcomes; PRWE = Patient-rated Wrist Evaluation; QCT = quantitative computerized tomography; TRAP 5b = tartrate-resistant acid phosphatase 5b; VFA = Vertebral Fracture Assessment.

¹conduct only if subject has a suspected vertebral fracture based on VFA or if VFA technology is not available at trial center, ²For subjects that discontinue trial medication, an additional lumbar spine DXA was obtained at month 24 or as soon as possible after the month 24 visit. ³Day 1 procedures completed before dosing.

Adverse events, clinical fracture recording, concomitant medications recording and disability back pain questionnaires were assessed at every 3 months. For this, telephone contact was sufficient, visit was not required.

In addition to the primary trial in which all subjects participated, several sub-studies also were conducted within the main trial. The Schedules of Events for these sub-studies are provided in Table 68.

Table 68: Schedules of Events for Sub-studies within Study 20030216

Substudy	Planned N	Assessments	Visits for Assessments
DXA Substudy b	300	BMD by DXA of the lumbar spine, total hip, femoral neck, and trochanter BMD by DXA of the distal 1/3 radius, ultradistal radius, total radius and total body HSA of the narrow neck, intertrochanter, and shaft	Months 1, 6, 12, 24, and 36 Day 1 and months 12, 24, and 36 Months 6, 12, 24, and 36
QCT Spine/Hip Substudy	100	BMD of the spine and hip by QCT	Day 1 and months 12, 24, and 36
QCT Distal Radius Substudy	100	BMD of the distal radius as assessed by QCT	Day 1 and months 1, 6, 12, 24, and 36
Bone Marker Substudy	200	Serum concentrations of CTX1, TRAP 5b, BALP, P1NP, OPG, and iPTH	Screening, day 1 (predose) d, and months 1, 6, 12, 24, 36
PK Substudy c	500	Serum denosumab concentrations (sparse sampling for population PK analysis)	Months 12, 18, 24, 30 and 36; also between months 15.5 to 17.5, 19.5 to 21.5, and 33.5 to 35.5
Bone Biopsy Substudy	120	Histology, histomorphometry, and micro-CT assessment of transiliac bone biopsies	Months 24 and 36
Fracture Healing Substudy	157	Radiographic healing of distal radius fractures; PRWE	6 weeks and 3 and 6 months (\pm 2 weeks) after the fracture event

Eligibility criteria

Inclusion Criteria

The target population was postmenopausal, ambulatory women, between 60 and 90 years old and BMD T-score < -2.5 at the lumbar spine or total hip.

Exclusion Criteria (Including, but not limited to)

- BMD T-score < -4.0 at Lumbar spine or total hip

- Any medication affecting bone metabolism:
 - Oral bisphosphonate treatment for osteoporosis: Ineligible if used for 3 or more years cumulatively, If used for >3 months, but \leq 3 years, at least a one year period since last dose was necessary for eligibility. If used \leq 3 months, subject was eligible.
 - Administration of intravenous bisphosphonate, fluoride or strontium for osteoporosis within the last 5 years
 - Administration of any of the following treatments 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, Therapy with 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 below 2.13 mmol/L [8.5 mg/dL])
 - Vitamin D deficiency (25-hydroxy Vitamin D level < 12 ng/mL)
 - 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
- Known sensitivity to mammalian cell derived drug products
- Evidence of alcohol or substance-abuse within the last 12 months
- For biopsy substudy subjects only: known or suspected sensitivity or contraindication to tetracycline derivatives

Reviewer's Comment:

Eligibility criteria are acceptable and are appropriate for the target population. Exclusion criteria includes BMD T score <-4. For a placebo controlled trial, it would be unethical to leave these subjects untreated for 3 years.

If the subject's screening 25(OH) vitamin D was < 12 ng/mL, the subject failed screening but could be repleted with vitamin D and reassessed for eligibility. If the repeat vitamin D levels were <12ng/ml, the subject was ineligible; if the repeat Vitamin D level was between 12 and 20 ng/ml, then the subject was eligible for the trial and was given 800 IU vitamin D supplementation per day. The treatment regimen for repletion of vitamin D was 50, 000 IU three times a week for 2 weeks. This regimen has potential to cause transient hypercalcemia.

Study Medication:

Denosumab was presented as a sterile, clear, colorless, preservative-free liquid in glass vials containing 1.0 mL of liquid. The formulation was 60 mg denosumab per mL of 10 mM sodium acetate, 5% Sorbitol in Water for Injection with pH = 5.2.

Placebo was presented in identical containers, and the formulation was identical to denosumab with the exception of the protein content. Denosumab and placebo were stored at investigational sites at 2° to 8°C.

Investigational product was administered as a subcutaneous injection during scheduled visits every 6 months *by a health care professional* after all other procedures at that trial visit had been completed.

Reviewer's Comment: The selected denosumab dose was based on the results of the dose finding trial 20010223, which demonstrated that denosumab 60 mg every 6 months was at least as effective as alendronate 70 mg once a week. There was an extensive discussion between FDA and Amgen regarding dose selection, especially in subjects with higher body mass index (BMI). According to previous communications, the applicant explained that, although the 12-month data demonstrated a significant dose by-body weight interaction at the femoral neck, this interaction was no longer observed after 24 months of treatment. The rationale for the selected dose for trial 20030216 is acceptable for the doses studied.

Concomitant Medications:

Subjects were provided daily supplementations of calcium and vitamin D throughout the trial. The dosage of elemental calcium was ≥ 1 g-daily. The dosage of vitamin D was either ≥ 400 IU vitamin D daily (if screening 25[OH] vitamin D was > 20 ng/mL) or ≥ 800 IU vitamin D daily (if screening 25[OH] vitamin D was ≥ 12 to ≤ 20 ng/mL). Throughout the trial, investigators could prescribe any concomitant medications or treatments deemed necessary to according to standard of care except for those that might affect bone mass or bone metabolism.

Proscribed/disallowed medications: The following were disallowed medications while subject was on the trial.

- a) Bisphosphonates (IV any use and *oral cumulative use* > 30 days on trial)
- b) Fluoride (for osteoporosis) aluminum, lithium
- c) Cinacalcet, strontium, tibolone, calcitonin,
- d) Systemic estrogen (cumulative use > 30 days per dose interval) , androgens
- e) Selective estrogen receptor modulators (SERMs), anabolic steroids, aromatase inhibitors,
- f) Protease inhibitors, methotrexate, chemotherapeutics
- g) Systemic glucocorticoids (> 5 mg/day for > 10 days),
- h) Chronic heparin use (> 7 days),
- i) Parathyroid hormone (or a derivative), calcitriol
- j) Anticonvulsants (benzodiazepines are allowed),
- k) Adrenocorticotrophic hormone, gonadotropin-releasing hormone agonists
- l) Other experimental/investigational products,
- m) Growth hormones

Efficacy Measures

Efficacy Endpoints

The primary efficacy endpoint is subject incidence of new vertebral fractures (Yes/No) at Month 36/ET

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.

Other efficacy endpoints include the following:

- The number of subjects with new vertebral fractures (Yes/No) at Months 6, 12 and 24
- The number of subjects with incident (new or worsening) vertebral fractures at Months 12, 24 and 36.
- The number of subjects with multiple incident vertebral fractures at Months 12, 24 and 36.
- The time to first clinical fracture (vertebral or non-vertebral).
- Percent change from baseline in lumbar spine BMD at Month 36.
- Percent change from baseline in total hip, femoral neck, and trochanter BMD at Months 12, 24, and 36.

- Percent change from baseline in lumbar spine, total hip, femoral neck, and trochanter BMD in a subset of subjects at Months 1, 6, 12, 24, and 36.
- Percent change from baseline in distal 1/3 radius and total body BMD in a subset of subjects at Months 12, 24, and 36.
- Percent change from baseline in volumetric BMD of trabecular bone region of lumbar spine and trabecular and cortical bone regions of total hip, femoral neck and trochanter assessed by QCT in a subset of subjects at Months 12, 24, and 36.
- Percent change from baseline in volumetric BMD of trabecular and cortical bone regions of the distal radius assessed by QCT in a subset of subjects at 1, 6, 12, 24, and 36 months.
- Percent change from baseline in bone markers (serum Type I CTX, PINP, and BALP), iPTH, TRAP 5b, RANKL and OPG in a subset of subjects at Months 6, 12, 24, and 36.
- Bone histomorphometric parameters in a subset of subjects at Months 24 and 36.
- Bone histology (qualitative assessment of bone) in a subset of subjects at Months 24 and 36.
- Three-dimensional structural parameters based on micro-CT of transiliac bone biopsy samples in a subset of subjects at Months 24 and 36.
- Changes in hip structural analysis based on hip DXA in a subset of subjects at Months 12, 24, and 36.
- The number of subjects with incident breast cancer during 36 months of treatment.
- Change from baseline in Patient Reported Outcomes (OPAQ SV physical function, emotional status and back pain scores, and EQ-5D questionnaire) at Months 6, 12, 18, 24, 30, and 36.
- Change from baseline in Disability/Back Pain Questionnaire responses at Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, and 36.

Reviewer's Comment:

Approval of therapies for the indication of treatment of osteoporosis in postmenopausal women in USA is based on fracture efficacy at 3 years. The primary endpoint, incidence of new vertebral fractures after 3 years of treatment, is commensurate with current Food and Drug Administration (FDA) guidance for osteoporosis.

Definitions of key issues:

All fractures reported by the investigators were considered adverse events. Asymptomatic, or morphometric, vertebral fractures noted only by the imaging vendor were not reported as adverse events.

- For assessment of prevalent vertebral fractures at baseline and new vertebral fractures on trial by an expert radiologist at the central imaging center, the Genant Semiquantitative Scoring Method was used: Grade 0 (normal); Grade 1 (mild), 20% to 25% reduction in vertebral height (anterior, middle, or posterior); Grade 2 (moderate), 25% to 40% reduction in height; Grade 3 (severe), > 40% reduction in height (Genant et al, 1993). *Fractures associated with high trauma severity or any pathologic (i.e., metastatic) fractures were excluded from these definitions.*
- Prevalent vertebral fracture: A vertebral fracture detected at baseline by Genant grade ≥ 1 (i.e., pre-existing).
- New vertebral fracture: an increase of ≥ 1 grade in any vertebra from T4 to L4 from the previous grade of 0 (includes morphometric and clinical vertebral fractures)
- Worsening vertebral fracture: an increase of ≥ 1 grade from the previous grade of ≥ 1 in any vertebra from T4 to L4.
- New and worsening vertebral fracture: an increase of ≥ 1 grade from the previous grade in any vertebra from T4 to L4.
- Clinical vertebral fracture: a new vertebral fracture assessed at either a scheduled or unscheduled visit and associated with any signs and/or symptoms indicative of a fracture.
- Multiple new vertebral fractures: New vertebral fractures observed in ≥ 2 vertebrae from T4 to L4.
- Nonvertebral fractures (osteoporotic) were those occurring on trial excluding those of the vertebrae (cervical, thoracic, and lumbar), skull, facial, mandible, metacarpus, finger phalanges, and toe phalanges.
- Major nonvertebral fractures: a subset of nonvertebral fractures comprising the pelvis, distal femur (i.e., femur excluding hip), proximal tibia (i.e., tibia excluding ankle), ribs, proximal humerus (i.e., humerus excluding elbow), forearm, and hip
- Major osteoporotic fractures: clinical vertebral, hip, forearm, and humerus fractures not associated with a pathologic fracture, *regardless of trauma severity.*
- Any osteoporotic fracture included any new vertebral fractures or osteoporotic nonvertebral fractures
- Hip fracture: femur neck, femur intertrochanter, and femur subtrochanter fractures
- Clinical fracture: clinical vertebral and nonvertebral (osteoporotic) fractures

Reviewer's Comment: The category of major osteoporotic fractures includes fractures regardless of trauma severity. Severe trauma can result in fracture of a healthy bone; therefore, major osteoporotic fractures

should exclude high trauma severity. When the fracture datasets (AAEFX and ASLEFF) were reviewed, it appeared that no subjects with major osteoporotic fractures had fracture from high trauma severity. Therefore, this is not a concerning issue.

Study Methods:

Before any subject participated in the trial or in a substudy, the investigator obtained written informed consent from the subject or legally acceptable representative. All screening procedures were completed within 56 days before randomization, with the exception of the screening hematology and chemistry measurements which were completed within 1 month before day 1. The screening date was defined as the date the first trial-related procedure was performed, and day 1 was defined as the day that the initial dose of IP was administered to the subject.

Administration of IP occurred after all trial visit procedures had been completed. Imaging procedures (DXA, x-ray, QCT) could be performed on different days than the other visit procedures but were required to be within 7 days before administration of IP.

Vertebral fractures

Vertebral fractures were determined from X-rays of the lateral thoracic and lumbar spine (T4-L4). Two lateral spine x-rays were acquired during the screening period and at months 12, 24, and 36 or unscheduled visit. If a subject presented with acute back pain at a time point before the month 36 spinal x-ray, and occurrence of a vertebral fracture was suspected, the investigator was to obtain a lateral spinal x-ray and submit it to the central imaging vendor. A trained and validated radiologist with experience in vertebral fracture assessment read each radiograph to identify prevalent and incident fractures in all assessable vertebrae from T4 to L4.

All films were forwarded to a Central Reading Facility for semi-quantitative analysis using the methodology described by Genant (ref). A repeat assessment by an independent reviewer was performed on those subjects identified by primary reviewer. If the second radiologist agreed with the first radiologist on the presence, level and severity of the incident fracture no additional reading was necessary. If there was disagreement, a third radiologist adjudicated the films independently.

In addition, vertebral fracture assessment (VFA), a software analysis of DXA data (Olenginski et al, 2006; Vokes et al, 2003), was done at baseline and at 6 months. The trial center acquired the scans for VFA, and the central imaging vendor conducted the analyses. If a suspected vertebral fracture was noted at 6 months based on central evaluation of the VFA scan, a lateral spine X-ray was

acquired to confirm the presence of a vertebral fracture. For those trial sites without access to VFA technology, a lateral spine X-ray was required at 6 months in lieu of the VFA scan.

Dual X-ray Absorptiometry (DXA) Assessment

For all subjects in the trial, BMD assessments were performed at baseline and at month 36 for the lumbar spine and at baseline and at months 12, 24, and 36 for the hip.

The same DXA machine was used for all trial procedures for an individual subject. The left side was to be used for the hip and distal radius scans (unless prohibited by, e.g., left hip replacement). Lumbar spine scans included L1 through L4.

The absolute BMD values (g/cm²) that correspond to the entry criteria T-scores for GE Lunar and Hologic densitometers are shown in Table 7-10. Eligibility was established using the T-score obtained using the site's DXA local machine software and based on the manufacturer's databases.

Table 69: Densitometer-specific Bone Mineral Density Values (g/cm²)

	GE Lunar		Hologic	
T-score	-4	-2.5	-4	-2.5
Lumbar Spine	0.7	0.88	0.607	0.772
Total hip	0.520	0.7	0.454	0.637

Investigators were to be notified by the central imaging vendor for the following scenarios:

- Any subjects with > 7% BMD and/or ≥ 10% BMD reduction at the total hip within any 12-month period of the trial.
- Any subjects with ≥ 10% BMD reduction at the total hip from baseline at any point during the course of the trial.
- Any subjects with a T-score < -4 at the total hip at any point during the course of the trial.

Blood Laboratory assessments:

The central laboratory was responsible for all screening and on-trial serum chemistry, hematology, and serum 25(OH) Vitamin D tests as shown in the table below. Amgen was responsible for denosumab serum levels, denosumab antibody assessments, and selected bone marker substudy assessments, and a specialty lab was responsible for the remaining bone marker substudy assessments. Biomarker assay and pharmacogenetic samples were archived for possible future analysis.

To minimize the risk of bias, all on-trial lab results for serum calcium or albumin-adjusted calcium, alkaline phosphatase and phosphorus were not reported to the sites after randomization.

Table 70: Assay panels

Panel	Analytes
Serum chemistry	albumin, albumin-adjusted calcium a, alkaline phosphatase a, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), calcium a, chloride, creatinine, glucose, magnesium, potassium, phosphorus a, sodium, total bilirubin, total protein
Hematology	red blood cell (RBC) count, hemoglobin concentration, reticulocyte count, platelet count, white blood cell (WBC) count with differential count (neutrophils, bands, eosinophils, basophils, lymphocytes, and monocytes)
Bone markers	CTX1, TRAP 5b, BALP, P1NP, OPG, iPTH

Results remained blinded to investigative site (except for panic values, which were provided to the site by phone or fax). BALP = bone-specific alkaline phosphatase; CTX1 = serum type I C-telopeptide; iPTH = intact parathyroid hormone; OPG = osteoprotegerin; P1NP = procollagen type I N-terminal peptide; TRAP 5b = tartrate-resistant acid phosphatase 5b

Withdrawal criteria were as follows:

- Withdrawal of consent, investigator or Amgen's decision, significant protocol violation, patient noncompliance
- Ineligibility
- Osteoporosis-related fracture
- Significant decrease in BMD (reduction in BMD of the total hip > 7% or ≥ 10% within any 12-month period, reduction in BMD of the total hip from baseline ≥ 10% at any point during the trial; or t-score < -4.0 at the total hip at any point during the trial)
- New malignancy (except basal cell carcinoma, cervical or breast ductal carcinoma *in situ*)
- Non-vertebral fracture that has not healed by six months

The early termination visit was to include all the procedures of the Month 36 visit. Subjects who discontinued drug treatment prematurely were encouraged to continue the schedule of trial observations, provided the subject has not withdrawn full consent.

Ethics and informed consent

Study 20030216 was conducted in compliance with 1) protocol, 2) independent ethics committee requirements, 3) informed consent regulations and 4) appropriate country regulations and 5) the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines.

Reviewer's Comment: One of the international trial sites (site 803, Lithuania) was found to have significant GCP violations, such as enrolling patients without informed consent, enrolling patients not meeting eligibility criteria, under reporting of serious adverse events and trial conduct violations. All subjects (N=60) were excluded from efficacy and safety analysis prior to unblinding and the exclusion of these data was articulated in the SAP. For these reasons, this reviewer agrees that no bias was introduced into the analyses of the trial data. The results presented here exclude site 803 data.

Unblinding

A subject's treatment assignment was to be unblinded only when knowledge of the treatment was essential for the further management of the subject.

Unblinding at the trial site for any other reason was considered a protocol deviation.

To maintain the integrity of the blind, the following parameters were not reported to investigators after randomization: serum calcium, albumin-adjusted calcium, phosphorus, alkaline phosphatase, BMD by DXA and by QCT, bone histology and histomorphometry, and HSA. To ensure adequate safety oversight, the investigative site and the applicant were to be notified of absolute analyte values if there were significant changes to predefined panic values for laboratory assessments or alert values for BMD.

Statistical Analyses:

Treatment Comparison: The primary comparison of interest at month 36 was denosumab therapy versus placebo therapy for the incidence of new vertebral fracture. The 36-month analysis was conducted when all subjects have had the opportunity to complete the 36-month assessment.

Sample size calculations: assumptions for estimating a sample size are described below:

Background fracture rates (calcium and vitamin D treatment only (Black et al; 1996; Harris et al, 1999) :

- Vertebral fracture rate in the placebo arm assumed to be 4% per year,
- Non-vertebral fracture rate in the placebo arm assumed to be 3.3% per year
- Hip fracture rate (subset of the non-vertebral) in the placebo arm assumed to be 1.0% per year
- The loss-to-follow-up vertebral radiograph rate: 5% per year.
- Rate of censoring for non-vertebral fracture assessment, including hip: 4% per year.

The total sample size of 7200 subjects (3600:3600 equally allocated between the treatment groups) determined by EAST v3 statistical software for this trial was driven by the hip fracture endpoint, due to the low expected rate of this event. This number of subjects is also anticipated to provide >99% power using a log-rank test at the 36-month analysis ($\alpha = 0.05$) to detect:

- A 45% reduction in the incidence of new vertebral fracture
- A 40% decrease in the risk of non-vertebral fracture
- A 40% decrease in the risk of hip fracture

Primary Efficacy Outcome

Vertebral Fracture

Vertebral fracture subject incidence was calculated as the ratio of the number of subjects experiencing at least one treatment-emergent vertebral fracture to the number of subjects at risk for vertebral fracture at the time of each analysis. Whether or not a subject experienced a vertebral fracture (Yes/No) was compared between treatment groups using a logistic regression model adjusting for the age strata.

Analysis Population: The intent-to-treat (ITT) was the primary population for analysis as described below.

Primary Efficacy Analysis Subset for Vertebral Fracture

Subjects in this subset were analyzed according to their original treatment assignment, regardless of treatment received. This analysis subset included all randomized subjects who had a baseline and ≥ 1 post baseline evaluation of vertebral fracture at or before the time point under consideration. This analysis subset additionally included subjects who had vertebrae with missing Genant semiquantitative scores at baseline and whose first post baseline spinal radiograph shows no fracture on the same vertebrae (because it can be inferred that the baseline scores would have also shown no fracture had they been available). In addition, for month-6 vertebral fracture evaluation, the analysis subset further included subjects whose month-6 spinal radiograph was not available but the month-6 VFA by DXA showed no fracture (i.e., all available scores are 0 based on Genant semiquantitative scoring) because a spinal radiograph at month 6 was not required for such subjects. For subjects whose month-6 VFA showed fractures, only fractures confirmed by radiographic assessment were included in the analysis.

Primary Efficacy Analysis Subset for BMD, QCT, OPAQ-SV, and EQ-5

This analysis subset included all randomized subjects who had a baseline and ≥ 1 post baseline evaluation at or before the time point under consideration. This subset could differ from endpoint to endpoint due to missing data. Subjects in this

subset were analyzed according to their original treatment assignment, regardless of treatment received.

Full Analysis Subset

This subset included all randomized subjects. Subjects in the full analysis subset were analyzed according to their original randomized treatment assignment, regardless of treatment received. The full analysis subset was used as the primary analysis subset for time-to-fracture efficacy endpoints and as a sensitivity analysis subset for the primary efficacy endpoint.

Statistical Methods:

For the primary efficacy endpoint (subject incidence of new vertebral fractures during the entire 36-month treatment period) and the secondary efficacy endpoints (time to first nonvertebral fracture and time to first hip fracture), a fixed sequence testing procedure was employed among these 3 endpoints in the order mentioned above. Subjects were analyzed as randomized, and analyses followed intent to- treat principles.

The significance of the treatment comparisons between denosumab and placebo for the primary efficacy as well as for other binary endpoints, were assessed using the score test from a logistic regression model with treatment as the main effect and age strata as a covariate. In addition to the estimate of the odds ratio from the logistic regression model, point estimates of absolute risk reduction (difference in proportions, placebo – denosumab) and risk ratio (ratio of proportions, denosumab over placebo) as well as the corresponding 95% confidence intervals were calculated using Mantel-Haenszel methodology adjusting for age strata.

The significance of the treatment effect between denosumab and placebo on time-to-event endpoints was assessed using the score test from a stratified Cox proportional hazards model controlling for age strata with treatment as the independent variable. Time-to-event endpoints were summarized descriptively using the Kaplan-Meier estimates at time point(s) of interest

Changes in Statistical Methods

The Statistical Analysis Plan (SAP) was amended twice during the trial. Substantive changes included in these amendments were:

- Removed the planned 24-month analysis in accordance with FDA recommendations for phase 3 clinical trials in the treatment of PMO
- Incorporated additional safety assessments which included adjudication of potential cardiovascular-related serious adverse events by an external cardiovascular adjudication committee, assessment of aortic calcification using lateral spine x-rays, and a fracture healing substudy;

- Added a pharmacokinetic substudy for the purposes of obtaining serum concentration data of denosumab throughout the 6-month dosing interval for use in a population pharmacokinetic analysis;
- Excluded subjects from site 803 (N = 60) from all efficacy and safety analyses due to GCP noncompliance and the potential for confounding of safety and efficacy analyses (see Section 8.2). Key safety data were summarized from this site
- Because the protocol allowed a ± 28 -day visit window around the scheduled target day, subjects who had their month-36 visit during the first half of the visit window would have been excluded from the risk set at trial day 1096, the scheduled target day for month-36 visit. The definition of the risk set at month 36 on the Kaplan-Meier figures was revised to include subjects whose month-36 visits were on or after the beginning of the month-36 visit window.

Reviewer's Comment: The changes to the Statistical analysis plan were made before database lock and unblinding for the data. The statistical team at FDA reviewed the amendments and found them acceptable.

Protocol Amendments:

There were 2 major amendments to the protocol.

In the first amendment on 19 December 2005, major changes were, 1) an external cardiovascular adjudication committee was formed to adjudicate all deaths and potential cardiovascular related SAEs. 2) Assessment of aortic calcification was conducted using lateral spine x-rays in a subset of patients. 3) A fracture healing substudy was incorporated. 4) A PK substudy was conducted.

Second Amendment on October 25, 2006 included following major changes. 1) the trial endpoints were modified to reflect 3-year efficacy analyses of fracture reduction. Therefore, the interim analysis at 24 months was removed. 2) To minimize bias, it was decided that 2 independent central readers evaluated radiologic films to assess fracture healing. If there was disagreement between readers, a third reader was to adjudicate the film. 3) The endpoint for aortic calcification was modified to absolute change in severity score from baseline to month 36. 4) Lumbar spine BMD at month 36 and/or early termination visit was added for all subjects to provide more complete information on changes in BMD as a consequence of treatment. 5) Collection of Serious adverse events was changed from 30 days to 6 months after discontinuation of IP or End of Study, whichever was longer.

STUDY RESULTS

The trial was conducted from 03 August 2004 (first subject enrolled) to 17 June 2008 (last subject's end-of-trial visit). The trial was conducted by 217 investigators at 214 centers in 32 countries, most of which were in Europe. Denmark (1254), Poland (955) and United Kingdom (790) enrolled the most number of subjects. A total of 582 of enrolled subjects (7.4%) were from North America, 355 of whom (4.9%) were from the USA.

Reviewer's comment: Overall, population of Europe (especially Caucasian) is similar to US population in terms of osteoporosis disease process, however, there might be environmental risk factors and factors like vitamin D status, calcium intake and exercise level may be different. Since the trial included vitamin D and calcium as concomitant medications, generally speaking results are applicable to US population.

Patient Disposition: A total of 20,949 subjects were screened. 13,081 were excluded prior to randomization. The trial enrolled 7868 subjects. However, 60 subjects from site 803 were excluded from all efficacy and safety analysis before unblinding, due to 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.

Table 71 Subject disposition by treatment arm

	Placebo	Denosumab
Randomized to treatment group	3906 (100%)	3902 (100%)
Completed trial	3206 (82.1%)	3272 (83.9%)
Completed IP	2882 (73.8%)	3052 (78.2%)
Discontinued IP	324 (8.3%)	220 (5.6 %)
Discontinued trial	700(17.9%)	630(16.1%)
Completed IP	67(1.7%)	79(2%)
Discontinued IP	610(15.6%)	528 (13.5%)
Never received IP	23 (0.6%)	23 (0.6%)

IP= Investigational product. Source: from CSR 20030216 page 216

Reviewer's Comment:

Given the three year duration of the trial, approximately 83% trial completion rate is adequate. Subjects >75 years of age had a lower trial completion rate (76% in placebo and 78% in denosumab).

The intention to treat population consists of total 7808 patients (3906 in placebo and 3902 in denosumab group).

Withdrawals: Study and/or investigational product discontinuations:

A similar proportion of subjects in each treatment group discontinued prematurely overall and for specific reasons, with the exception of consent withdrawal, disease progression, and requirement for alternative therapy, where there was a higher incidence of withdrawals from the placebo group. The most common reasons for discontinuation of the trial and investigational product were consent withdrawal and adverse events (Table 72).

Table 72: Reason for investigational product and trial discontinuation

Reason for discontinuation	Reason for ending investigational product use		Reason for ending Study	
	PLACEBO N=3906	DENOSUMAB N=3902	PLACEBO N=3906	DENOSUMA B N=3902
Completed	2949 (75.5%)	3131 (80.2%)	3206 (82.1%)	3272 (83.8%)
Consent withdrawn	334 (8.6%)	287 (7.4%)	403 (10.3%)	344 (8.8%)
Adverse event	202 (5.2%)	192 (4.9%)	81 (2.1%)	93 (2.4%)
Requirement for alternative therapy	69 (1.8%)	30 (0.8%)	7 (0.2%)	4 (0.1%)
Death	58 (1.5%)	38 (1%)	78 (2.0%)	62 (1.6%)
Other	38 (1%)	36 (0.9%)	20 (0.5%)	32 (0.8%)
Disease progression	63 (1.6%)	10 (0.3%)	7 (0.2%)	3 (0.1%)
Lost to follow-up	38 (1%)	34 (0.8%)	57 (1.5%)	57 (1.5%)
Protocol deviation	28 (0.7%)	22 (0.6%)	12 (0.3%)	10 (0.3%)
Noncompliance	17 (0.4%)	14 (0.4%)	17 (0.4%)	13 (0.3%)
Ineligibility determined	17 (0.4%)	13 (0.3%)	12 (0.3%)	9 (0.2%)
Administrative decision	5 (0.1%)	9 (0.2%)	6 (0.2%)	3 (0.1%)

Source: This table is generated using ASLINFO dataset for trial 20030216 after excluding site 803 data.

Reviewer's Comments:

- Adverse events were the reason for trial discontinuation in about 2% of patients with and did not appear to differ by treatment group. This expected and acceptable in a clinical trial of subjects with mean age 72 years over 3 years duration. Adverse events leading to withdrawal of the IP was 4.9% in the denosumab group and 5.2% in the placebo group.***

- *There were more subjects with IP discontinuation compared to subjects with trial discontinuation in both groups.*
- *Line listings of consent withdrawn and lost to follow-up were evaluated and no concerns were noted.*
- *There were more subjects in the placebo group (8.3%) who discontinued IP but stayed on the trial compared to denosumab group (5.6%). This was mainly due to disease progression in the placebo group requiring alternative therapy such as bisphosphonates.*
- *Among subjects who discontinued the trial after completing IP, 3 subjects were in the denosumab group and 49 in placebo group due to disease progression.*
- *An analysis of reasons for trial and IP discontinuation conducted for subjects > 75 years old indicated the same reasons as those listed in Table 3.*
- *Study and IP discontinuation was analyzed by year of treatment (Year 1, Year 2, and Year 3) and no significant differences in the incidence of withdrawals by year of treatment were observed between treatment groups.*
- *In summary, this reviewer does not find any concerning reasons or trends among treatment groups in trial discontinuation and IP discontinuation.*

Protocol Violations: A subject was considered to have had an important protocol deviation if she did not meet eligibility criteria, received certain pre-specified proscribed medications, had baseline x-rays done outside of the prescribed window, received the incorrect treatment, missed > 25% of planned doses of IP, received IP that had not been stored at the correct temperature, did not have a spine x-ray at month 36 or end-of-treatment visit for subjects who completed treatment or trial (for primary endpoint), or had an important GCP violation.

Overall, 683 subjects in the denosumab group (17.5%) and 830 in the placebo group (21.2%) had a major protocol violation.

Eligibility related protocol violations:

The incidence of subjects with important eligibility protocol deviations was similar between the treatment groups (9.0% in the placebo group and 9.2% in the denosumab group).

Non-eligibility protocol violations:

Non-eligibility protocol violations:

More subjects in the placebo group than the denosumab group had trial conduct deviations (535 [13.7%] placebo vs. 367 [9.4%] denosumab). This imbalance was mainly due to exclusionary medication taken, 7.8% in the placebo vs. 4.1% in the denosumab group. See Table 73.

Table 73 Protocol violations

	Placebo (N = 3906) n (%)	Denosumab (N = 3902) n (%)
Any major protocol violation	830 (21.2)	683 (17.5)
Eligibility Deviations	351(9)	358(9.2)
Key Non-eligibility Deviations	535 (13.7)	367 (9.4)
Exclusionary medication taken on trial	304 (7.8)	161 (4.1)
Bisphosphonates	231 (5.9)	97 (2.5)
Other medications affecting bone metabolism	53 (1.4)	50 (1.3)
SERMs / systemic estrogen	31 (0.8)	16 (0.4)
Other approved therapies for osteoporosis	16 (0.4)	13 (0.3)

Reviewer's Comment: The higher incidence of major protocol deviations in the placebo group was primarily due to the concomitant administration of bisphosphonates (5.9% placebo vs. 2.5% denosumab). The use of bisphosphonates is expected to improve fracture and BMD outcomes in placebo group and therefore, should not bias efficacy results in favor of denosumab.

Demographics:

All participants were females, a majority of whom were Caucasian (approximately 92%). The mean age (\pm SD) at randomization was 72 years (\pm 5) with 32% being > 75 years old. The mean (\pm SD) BMI was 26 kg/m² (\pm 4) and the average number of years since menopause was 24 years. Baseline subject demographics were balanced between the treatment groups. See Table 9.

Table 74: Demographics

	Placebo (N = 3906)	Denosumab (N = 3902)
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 Other 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)	25.95(4.2)	26(4.1)
Years since menopause		
n	3891	3891
Mean (SD)	24.2(7.5)	24.2(7.4)

Source: MO generated table by using ASLINFO dataset.

Reviewer's Comment:

Because trial subjects were predominantly Caucasian, it is unclear if the results are generalizable to other ethnic groups, especially Black and Asian. Epidemiological data suggest that Hispanic women are similar to Caucasian women with regards to osteoporosis and osteoporosis-related risk factors(Looker et al. 1997) and thus, the trial results may be generalizable to the Hispanic population, Given that a majority of women in the U.S. are Caucasian or Hispanic, there is adequate representation of the target population in the U.S.

Baseline disease characteristics:

Fracture history

A similar proportion of subjects in placebo and denosumab groups reported a medical history of at least 1 fracture (53% in both treatment groups) or a medical history that included at least 1 non-vertebral fracture (39% for both treatment groups). (Table 75).

Baseline spine radiographs evaluated by the central imaging vendor showed prevalent vertebral fractures at baseline in 23.8% of subjects in the denosumab group and 23.4% subjects in placebo group.

Baseline BMD: Baseline mean BMD T-scores at the lumbar spine, total hip, femoral neck, and trochanter were -2.8, -1.9, -2.16, and -1.52 (0.84), respectively, for both treatment groups.

Table 75: Baseline disease characteristics

	Placebo (N = 3906)	Denosumab (N = 3902)
Baseline Fracture History		
Baseline prevalent vertebral fracture	23.4%	23.8%
Nonvertebral fracture	38.6%	39.1%
Baseline BMD		
Mean Lumbar spine BMD	-2.84	-2.82
Mean Total hip BMD	-1.91	-1.89
Mean Femoral neck BMD	-2.17	-2.15
Fracture risk by FRAX tool		
10-year osteoporotic fracture risk with BMD	18.7%	18.5%
10-year hip fracture risk with BMD	7.19%	7.24%

Source: This table is generated from several tables supplied by the applicant in the CSR.

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.

Reviewer's comment: The 10-year fracture risk calculated from the FRAX tool is used to guide treatment decisions for osteoporosis. According to the 2008 National osteoporosis foundation guideline, treatment is recommended in postmenopausal women or men age 50 and older with low bone mass (T score -1 to -2.5) at the femoral neck, total hip, or spine and 10 year hip fracture risk probability >3% or a 10-year all major osteoporosis related fracture probability of >20% based on the U.S. adapted WHO absolute fracture risk model. Although FRAX tool has its limitations, it is widely used in clinical practice.

Baseline Bone Turn over markers and laboratory parameters:

Mean (SD) baseline serum concentrations of CTX1 and TRAP 5b, PTH, S. calcium, and phosphorous were similar between the 2 treatment groups.

Table 76: Baseline bone turnover markers and laboratory parameters

	Placebo (N = 3906)	Denosumab (N = 3902)
	Mean (SD)	Mean (SD)
S. calcium mg/dl (corrected for albumin)	9.75(0.43)	9.76(0.42)
s. Phosphorous	3.59(0.43)	3.58(0.42)
25 (OH) Vitamin D (ng/mL)	24.00(36.42)	23.13(12.39)
iPTH (N=150)	50.17(21.8)	47.87 (27.32)
Serum CTX I (ng/mL) (N=150)	0.582 (0.36)	0.573 (0.28)
TRAP 5b (U/L) (N=150)	4.58 (1.64)	4.58 (1.64)

Source: This table is generated from several tables supplied by the applicant in the CSR.

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 trial groups.

Reviewer's Comment: Baseline disease characteristics were well balanced between the two treatment groups.

Primary efficacy endpoint:

The primary efficacy endpoint in trial 20030216 was subject incidence of new vertebral fractures during the entire 36-month treatment period. Denosumab significantly reduced the risk of new vertebral fracture compared to placebo. The crude incidence of new vertebral fracture was 7.2% in placebo and 2.3% in denosumab group at month 36. Treatment with denosumab demonstrated a 4.8% adjusted absolute risk reduction and a 68% relative risk reduction in fracture incidence (p-value <0.0001). Based on the analysis by year of treatment, the relative risk of developing a new radiographic vertebral fracture through each of Year 1, 2, and 3 was statistically significantly in favor of Denosumab 60mg sq 6M treatment.

Table 77: Study 20030216: Subject Incidence, Absolute Risk Reduction, and Odds Ratio for New Vertebral Fracture Through Month 36 (Primary Efficacy Analysis Set*, LOCF Imputation)

	No. of Events	Crude Incidence %	Absolute Risk Reduction* at Month % (95% C.I.)			Relative Risk Reduction ¹ at Month % (95% C.I.)			Odds Ratio ² (95% C.I.)	p-value
			12	24	36	12	24	36		
Denosumab (N=3702)	86	2.3	1.4 (0.8, 1.9)	3.5 (2.7, 4.3)	4.8 (3.9, 5.8)	61 (42, 74)	71 (61, 79)	68 (59, 74)	0.31 (0.24, 0.39)	<0.000 ¹
Placebo (N=3691)	264	7.2								

Source: Table 9-3, page 240, Study 20030216 report and Statistical Reviewer's calculation.

* The primary efficacy analysis set includes all randomized subjects with a baseline and at least one post-baseline evaluation.

¹ Absolute risk reduction and relative risk reduction based on Mantel-Haenszel method adjusting for age stratification variable.

² Odds ratio and p-value based on logistic regression model 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 (≥ 75 years, >65 years, <75 years), geographic region, body weight, BMI, lumbar spine BMD T-score, total hip BMD T-score, fracture risk assessed by 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.

Generalizability:

Geographic Location: Study 20030216 was conducted in 32 countries, most of which were in Europe. The efficacy results were consistent across the continents. See Table 78,

Table 78: Generalizability risk comparison estimates:

	n/N (%)	% of subjects with fracture	Absolute Risk Reduction (%), 95% CI	Risk Ratio, 95% CI	p-value
Western EU, Australia, and New Zealand					
Placebo (N = 1821)	138/1730	8			
Denosumab (N = 1805)	32/1721	1.9	6.1 (4.7, 7.6)	0.23 (0.16,0.34)	<0.0001
Eastern EU					
Placebo (N = 1326)	88/1248	7.1			
Denosumab (N = 1343)	36/1270	2.8	4.2 (2.5, 5.9)	0.4 (0.28,0.59)	<0.0001
Latin America					
Placebo (N = 462)	23/436	5.3			
Denosumab (N = 472)	12/447	2.7	2.6 (0.0, 5.2)	0.51 (0.26,1.01)	0.0488
North America					
Placebo (N = 297)	15/277	5.4			
Denosumab (N = 282)	6/264	2.3	3.2 (0.0, 6.4)	0.41 (0.16,1.04)	0.0529

Reviewer's comment:

Although the results from North America did not reach statistical significance (p=0.529), the number of subjects and the number of fractures in the North America group are too low to be statistically significant. Furthermore, the efficacy results from the other continents, especially from Europe/New Zealand/Australia where the population would be generalizable to those in the U.S., are consistent and statistically robust.

Vitamin D status:

25-OH Vitamin D deficiency is common and may result in compensatory increase in 1-25 di hydroxy vitamin D, which has osteoclastogenic effect on the bone. Increased 1, 25 (OH)₂ vitamin D could theoretically negate the action of denosumab. This effect is described in literature through mechanisms of target gene expressions that are regulated by 1,25(OH)₂D₃ in skeletal cells. That is an independent mechanism from RANK/RANKL pathway. So, Differential vitamin D status can potentially affect the results. However, as seen in Table 79, effect of denosumab was consistent in lowering fracture incidence in subgroups of vitamin D.

Table 79: Subject Incidence of New Vertebral Fracture through Month 36 by Serum 25 (OH) Vitamin D Level

	N	%	Absolute Risk Reduction (%)	Risk Ratio 95% CI	p-value
Vitamin D < 20 ng/mL					
Placebo (N = 2001)	134/1882	7.1			
Denosumab (N = 1993)	37/1887	2	5.2 (3.9, 6.5)	0.27 (0.19, 0.39)	<0.0001
Vitamin D ≥ 20 ng/mL					
Placebo (N = 1903)	130/1808	7.2			
Denosumab (N = 1908)	49/1814	2.7	4.5 (3.1, 5.9)	0.37 (0.27, 0.52)	<0.0001

Secondary Efficacy Endpoint: Time to First Nonvertebral Fracture

Statistical testing for secondary endpoints was done in a step-down manner in a hierarchical testing procedure. The inferential testing was continued only if previous step was significant. These steps were 1) new vertebral fractures, 2) nonvertebral fractures, 3) hip fractures.

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 trial 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 80. The incidence of nonvertebral fractures at Month 36 (based on Kaplan-Meier estimates) was 8.0% 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 80: 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.

Important tertiary end points:

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 6.6% (**Table 14**)

Table 81: 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	3608	-1.4		
Placebo	3624	5.0	6.4 (6.2, 6.6)	< 0.0001
Denosumab				

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

Sensitivity analysis:

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.

Tertiary fracture related end points :

The applicant explored the following types of fractures in denosumab compared to placebo as seen in Table 82.

Major osteoporotic fractures were defined as clinical vertebral, hip, forearm, and humerus fractures not associated with a pathologic fracture. 7.5% of the subjects in the placebo group vs. 5% in the denosumab group had major osteoporotic fractures.

Major nonvertebral fractures were fractures comprising the pelvis, distal femur (i.e., femur excluding hip), proximal tibia (i.e., tibia excluding ankle), ribs, proximal humerus (i.e., humerus excluding elbow), forearm, and hip. 6% of the subjects in the placebo group vs. 4.9% in the denosumab group had major osteoporotic fractures. Clinical fracture was defined as vertebral and nonvertebral (osteoporotic) fractures associated with signs and symptoms. Denosumab treatment was associated with reduction in clinical fractures at 3 years (9.5% in placebo vs. 6.8% in denosumab). Any osteoporotic fracture included any new vertebral fractures or osteoporotic nonvertebral fractures. Denosumab treatment was associated with reduction in any osteoporotic fracture at 3 years (13.3% in placebo vs. 8.0% in denosumab).

Table 82: Fracture related tertiary endpoints

Number (%) of subjects with the event	Placebo	Denosumab	Risk Ratio (95% CI)	P value
Major Osteoporotic fracture	294 (7.5%)	196(5%)	0.65 (0.55, 0.78)	<0.0001
Major Nonvertebral Fracture	235 (6.0%)	191 (4.9%)	0.80 (0.66, 0.97)	0.0224
Clinical Fracture	373 (9.5%)	265 (6.8%)	0.70 (0.59, 0.81)	<0.0001
Any Osteoporotic Fracture	518 (13.3%)	312 (8.0%)	0.57 (0.49, 0.66)	<0.0001

Efficacy Conclusions:

Study 20030216 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.

Safety Results

The safety analysis subset included all randomized subjects who received ≥ 1 dose of IP. Subjects were analyzed according to their actual treatment received; subjects randomized to placebo who incorrectly received ≥ 1 dose of denosumab

were analyzed as receiving denosumab, and subjects randomized to denosumab who received no actual denosumab doses were analyzed as receiving placebo. AE's were coded by MedDRA coding dictionary version 11.

Extent of Exposure and Compliance

A total of 6 doses of IP were planned. In the denosumab group, 79.6% of subjects received all 6 doses, and in the placebo group, 74.5% of subjects received all 6 doses.

Investigational product was administered by a health care provider. Compliance with the schedule of administration of investigational product was assessed by regularly reviewing the IP administration case report form.

Table 83: Extent of exposure

	Placebo	Denosumab
Number of subjects randomized	3906	3902
Number of subjects receiving 1 dose of investigational product	3876	3886
Number of injections		
0	23 (0.6%)	23 (0.6%)
1	214 (5.5%)	204 (5.2%)
2	194 (5%)	165 (4%)
3	211 (5%)	165 (4%)
4	153 (4%)	117 (3%)
5	220 (6%)	140 (4%)
6	2891 (75.0%)	3088 (79%)

Source: This table is generated using ASLINFO dataset from trial 20030216, excluding data from site 803, and applicant table 11-2, page 326, CSR 20030216 .

Reviewer's Comment: *The number of subjects completing all 6 doses was higher in denosumab group, however, number of subjects receiving 5 or 6 doses were similar between the two treatment groups.*

Event rates

A total of 7762 subjects (3886 who received denosumab, 3876 who received placebo only) received at least 1 dose of IP and were evaluated for safety. As shown in the Table 15, approximately 93% of patients reported at least adverse event (AE) and 25% experienced serious adverse events (SAEs).

Table 84: Adverse Event rates

Adverse events	Placebo	Denosumab
	n (%)	n (%)
N, enrolled	3906	3902
N, safety	3876	3886
Deaths	90 (2.3)	70 (1.8)
Nonfatal Serious	972 (25.1)	1004 (25.8)
Leading to trial discontinuation	81 (2.1)	93 (2.4)
Leading to investigational product discontinuation	202 (5.2)	192 (4.9)
At least one adverse event	3607 (93.1)	3605 (92.8)

Deaths

Fatal adverse events occurred in 70 subjects (1.8%) in the denosumab group and 90 subjects (2.3%) in the placebo group (**Table 85**). The most common cause of death by MedDRA SOC was neoplasms (approximately 29% in both treatment groups) and cardiac disorders (26% in both treatment groups). Denosumab group had a higher incidence of death reported in the SOC infections (8.6% vs. 6.7%); see more detailed discussions on infections later in this review.

All deaths were sent for adjudication to the cardiovascular adjudication committee. Death was classified as a Cardiovascular death (at any certainty level) or a Non-Cardiovascular Death. All deaths were assumed Cardiovascular in nature unless a Non-Cardiovascular cause can be clearly shown (e.g. metastatic death, accidental death).

San Francisco co-coordinating center adjudicated all reports of death to determine the most likely cause of death. The cause of death recorded was the underlying cause, not the immediate mode of death.

Table 85: Incidence of Death by body/system/organ class

Body System or Organ Class	PLACEBO N=3876	DENOSUMAB N=3886
Neoplasms benign, malignant	26 (28.89%)	20 (28.57%)
Cardiac disorders	23 (25.56%)	18 (25.71%)
Respiratory, thoracic and mediastinal disorders	11 (12.22%)	6 (8.57%)
Nervous system disorders	11 (12.22%)	6 (8.57%)
Infections and infestations	6 (6.67%)	6 (8.57%)
General disorders and administration site conditions	6 (6.67%)	4 (5.71%)
Gastrointestinal disorders	2 (2.22%)	4 (5.71%)
Injury, poisoning and procedural complications	3 (3.33%)	1 (1.43%)
Vascular disorders	0 (0.00%)	3 (4.29%)
Hepatobiliary disorders	1 (1.11%)	1 (1.43%)
Social circumstances	0 (0.00%)	1 (1.43%)
Renal and urinary disorders	0 (0.00%)	1 (1.43%)
Metabolism and nutrition disorders	1 (1.11%)	0 (0.00%)
Endocrine disorders	0 (0.00%)	1 (1.43%)
Total deaths	90 (100.00%)	70 (100.00%)

This table is MO analysis of AAE dataset for trial 20030216 for safety population.

Reviewer's comment: No safety concerns were identified in the fatality data for the denosumab group over placebo. There were no differences between treatment groups with regards to the time of death.

Non fatal Serious Adverse Events:

As outlined in Table 86, Overall, 973 subjects in the denosumab group (51.5%) reported 1798 SAEs and 939 subjects in the placebo group (48.8%) reported 1666 SAEs. The most common SAE's by MedDRA SOC were: cardiac disorder, musculoskeletal disorder infections and infestations, neoplasms, GI disorders, and nervous system disorders.

Table 86: Nonfatal serious adverse events and subject incidence

System/Organ/Class (MedDRA v11-0)	Placebo N=3876		Denosumab N=3886	
	SAE	n, subjects	SAE	n, subjects
Cardiac disorders	195	141	265	181
Musculoskeletal and connective tissue disorders	181	148	198	165
Infections and infestations	148	128	186	154
Neoplasms benign, malignant and unspecified	129	120	161	146
Gastrointestinal disorders	131	101	181	141
Nervous system disorders	142	119	151	125
Injury, poisoning and procedural complications	269	189	179	124
Respiratory, thoracic and mediastinal disorders	88	76	92	80
Vascular disorders	79	71	82	71
Eye disorders	61	45	54	39
General disorders and administration site conditions	38	30	37	34
Reproductive system and breast disorders	42	38	34	31
Hepatobiliary disorders	35	32	33	29
Ear and labyrinth disorders	16	15	27	24
Blood and lymphatic system disorders	28	22	22	20
Metabolism and nutrition disorders	17	14	26	20
Psychiatric disorders	17	13	23	20
Renal and urinary disorders	20	19	23	20
Skin and subcutaneous tissue disorders	12	7	11	10
Endocrine disorders	6	6	6	5
Investigations	10	9	5	5
Immune system disorders	1	1	1	1
Surgical and medical procedures	0	0	1	1
Congenital, familial and genetic disorders	1	1	0	0
Total	1666	939	1798	973

Source: This table is generated using from AAE dataset for trial 20030216 for safety population, excluding site 803.

Among subjects with nonfatal serious adverse events, 207 in placebo and 215 in denosumab group did not complete the trial. The SAEs were similarly distributed among body class of the both treatment groups among those who did not complete the trial.

Adverse events leading to withdrawal of investigational product:

There were more subjects in the placebo (202) group discontinuing the IP compared to denosumab group (192). However, more subjects in denosumab group discontinued IP in the body system of neoplasms, skin and subcutaneous

tissue disorders, general disorders, cardiac disorders and hepatobiliary disorders as seen in Table 87.

Table 87: Adverse events leading to withdrawal of investigational product by body system

System Organ Class	PLACEBO N=3876	DENOSUMAB N=3886
Neoplasms benign, malignant and unspecified	42	58
Musculoskeletal and connective tissue disorders	37	29
Nervous system disorders	25	27
Injury, poisoning and procedural complications	37	11
Gastrointestinal disorders	18	20
Skin and subcutaneous tissue disorders	9	13
General disorders and administration site conditions	7	14
Cardiac disorders	3	14
Respiratory, thoracic and mediastinal disorders	8	9
Infections and infestations	6	7
Blood and lymphatic system disorders	2	5
Psychiatric disorders	3	4
Renal and urinary disorders	5	2
Vascular disorders	5	2
Hepatobiliary disorders	5	1
Reproductive system and breast disorders	3	1
Investigations	2	1
Eye disorders	2	1
Ear and labyrinth disorders	1	2
Metabolism and nutrition disorders	1	2
Immune system disorders	2	0
Endocrine disorders	1	0
Total subjects	202	192

This table is generated using AAE dataset for trial 20030216, excluding site 803 data in safety population.

The most common AEs leading to IP discontinuations by MedDRA PTs in the placebo vs. denosumab group are shown in Table 88. Important differences between the treatment groups (where # denosumab > # placebo) in the less common AE's (by PT's) include: neoplasm (1 placebo vs. 4 denosumab), lung adenocarcinoma (0 vs. 2), abdominal pain (0 vs. 4), pancreatic cancer (1 vs. 3), pruritus (0 vs. 3), pruritic rash (0 vs. 2)

Table 88: Most common AE preferred term leading to IP discontinuation in ≥5 subjects in either group.

Preferred Term	PLACEBO N=3876	DENOSUMAB N=3886
Breast cancer	10	20
Back pain	10	6
Lumbar vertebral fracture	12	2
Constipation	6	6
Headache	4	6
Diarrhea	4	5
Thoracic vertebral fracture	8	1
Colon cancer	4	5
Cerebrovascular accident	3	5
Femur fracture	5	2
Fatigue	2	5
Nausea	1	5
Gastric cancer	1	5
Resorption bone increased	5	0

Source: This table is generated using AAE dataset for trial 20030216, excluding site 803 data.

As seen in Table 89, there were no concerning trends in IP discontinuation by year of trial duration.

Table 89: IP discontinuation rate due to AE by trial period

Study Period of IP discontinuation	PLACEBO N=3876	DENOSUMAB N=3886
BASELINE TO MONTH 12	181	183
MONTH 13 TO MONTH 24	160	136
MONTH 25 TO MONTH 36	116	95
Subjects total	202	192

This table is generated using AAE dataset for trial 20030216, excluding site 803 data.

Reviewer's comments:

Overall, more subjects in placebo discontinued IP compared to denosumab group, which is reassuring. This was evenly distributed by year of trial duration. IP discontinuation in placebo arm was mainly due to lack of efficacy such as an event of fracture or increased bone resorption. However, it is noteworthy that there were more subjects in the denosumab group discontinuing IP due to an AE of malignancy, cardiovascular disease or skin and subcutaneous disorder. These issues will be further explored in the "AE's of special interest" section below.

Common Adverse events:

Overall proportion of subjects reporting at least one adverse event was comparable between the two treatment groups (Placebo 92.6% vs. Denosumab 92.2%). Most frequently reported AEs by SOC are Musculoskeletal (~64%) infections and infestations (~52%), GI disorders (~37%) and nervous system disorders (~27%) See Table 90.

Table 90: Common Adverse Event by System Organ Class

Organ Class	PLACEBO (N=3876)		DENOSUMAB (N=3886)	
	n	%	n	%
Musculoskeletal and connective tissue disorders	2505	64.6	2507	64.5
Infections and infestations	2111	54.5	2052	52.8
Gastrointestinal disorders	1427	36.8	1444	37.2
Nervous system disorders	1031	26.6	1072	27.6
Injury, poisoning and procedural complications	1103	28.5	924	23.8
Vascular disorders	944	24.4	914	23.5
Respiratory, thoracic and mediastinal disorders	661	17.1	649	16.7
General disorders and administration site conditions	640	16.5	669	17.2
Metabolism and nutrition disorders	522	13.5	589	15.2
Skin and subcutaneous tissue disorders	464	12.0	576	14.8
Eye disorders	526	13.6	495	12.7
Cardiac disorders	496	12.8	513	13.2
Psychiatric disorders	490	12.6	507	13.0
Ear and labyrinth disorders	316	8.2	294	7.6
Neoplasms benign, malignant and unspecified	275	7.1	306	7.9
Renal and urinary disorders	279	7.2	258	6.6
Reproductive system and breast disorders	247	6.4	211	5.4
Blood and lymphatic system disorders	194	5.0	222	5.7
Investigations	214	5.5	176	4.5
Hepatobiliary disorders	128	3.3	123	3.2
Endocrine disorders	119	3.1	118	3.0
Immune system disorders	80	2.1	74	1.9
Surgical and medical procedures	33	0.9	44	1.1
Congenital, familial and genetic disorders	12	0.3	10	0.3
Social circumstances	4	0.1	3	0.1
At least one event	3615	93.3	3598	92.6

Source: This table is generated using JMP program AAE dataset for trial 20030216 after excluding site 803 data

The most common adverse events reported by Preferred Terms (>10% in either treatment group) are back pain (34.7% denosumab, 34.6% placebo), arthralgia (20.2%, 20.2%), hypertension (15.8%, 16.4%), nasopharyngitis (14.5%, 15.5%),

pain in extremity (11.7%, 11.1%), and osteoarthritis (11.2%, 11.4%) . These were similarly distributed between the treatment groups.

Adverse events of special interest

Hypocalcemia:

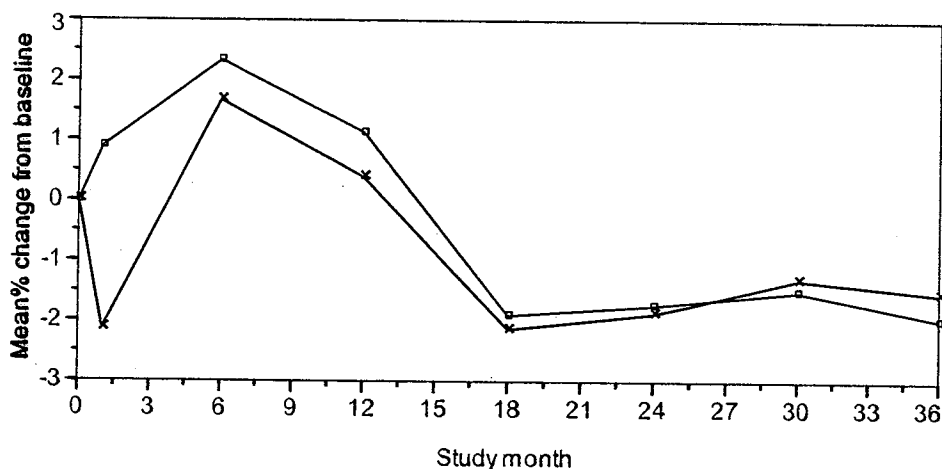
Denosumab decreases bone resorption. Bone resorption plays an important role in calcium homeostasis. Hypocalcemia triggers increase in PTH secretion, which in turn increases bone resorption. It is physiologically plausible that denosumab administration maybe associated with higher incidence of hypocalcemia; therefore, hypocalcemia is an adverse event of special interest.

In trial 20030216, serum calcium levels were measured at screening; trial day 1, Study month 1, 6, 12, 18, 24, 30 and 36 months. As seen in Table 91, serum calcium levels were balanced 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.

Table 91: Serum calcium (corrected) levels by treatment group per visit

	Placebo (N= 3876)			Denosumab (N=3886)		
	N	Mean	SD	N	Mean	SD
DAY 1	3879	9.75	0.43	3873	9.76	0.42
MONTH 1	3842	9.83	0.43	3825	9.54	0.47
MONTH 6	3735	9.97	0.42	3724	9.91	0.43
MONTH 12	3605	9.85	0.44	3616	9.78	0.47
MONTH 24	3369	9.57	0.39	3425	9.56	0.41
MONTH 36	3191	9.54	0.37	3255	9.59	0.41

Figure 15: % change from baseline in Serum calcium (corrected)



Groups

- x — TRTA=DENOSUMAB 60 MG Q6M
- — TRTA=PLACEBO

An analysis of outliers showed that at month 1, there were more subjects with hypocalcemia (S. ca <8.5 mg/dl) in the placebo (3) vs.denosumab group (33) group Table 92.

Table 92: Outlier analysis: Number patients with Hypocalcemia (Corrected S.Ca<8.5 mg/dl)

Number of subjects with outlier value of calcium	Placebo N=3876		Denosumab N=3886	
	N	Mean	N	Mean
BASELINE	2	8.1	5	8.0
MONTH 1	3	7.4	33	8.3
MONTH 6	0	.	2	8.2
MONTH 12	7	8.2	12	8.2
MONTH 18	1	8.4	3	8.4
MONTH 24	1	8.2	5	8.4
MONTH 30	1	8.4	7	8.1
MONTH 36	0	.	4	8.4
Total	15		66	

Four subjects in the denosumab group had multiple events of mild hypocalcemia (S. Ca <8.5 but \geq 8.3) and none in the placebo group.

Of the 15 subjects in the placebo group and 66 subjects in the denosumab group who experienced an outlier value of hypocalcemia, 9 subjects in the denosumab group and 1 in the placebo group did not complete the trial. The Quantitative

safety and pharmaco epidemiology group (QSPG) group performed AE event analysis by MedDRA hierarchy (Preferred Term, High level term, High level group term, and System Organ Class). The analysis did show any difference between the treatment groups. Events of hypocalcemia were analyzed in different strata of Vitamin D (in ng/ml <12, 12-20, 20-32 and >32) and renal function (Creatinine clearance in ml/min <30, 30-60, 60-90 and >90). No significant differences were detected in any of these groups.

Reviewer's comment: Hypocalcemia is a known class effect of antiresorptive drugs. Denosumab-induced hypocalcemia appears to be transient (Month 1) with spontaneous resolution and without any serious sequelae. In this clinical trial setting, however, hypocalcemia was an exclusion criterion and enrolled subjects were given supplemental calcium (1 gm calcium/day). In the uncontrolled real world setting, however, more patients may experience hypocalcemia with unknown consequences. Therefore, this reviewer recommends labeling hypocalcemia in contraindication and Warnings and Precautions sections.

Osteonecrosis of the Jaw (ONJ):

Postmarketing experience with intravenous and, to a much lesser extent, oral bisphosphonates has raised concerns about the potential for profound bone remodeling inhibition and osteonecrosis isolated to the jaws. Although their exact mechanism of action differs, both denosumab and bisphosphonates are antiresorptive medications. Therefore, ONJ is an AE of special interest.

The applicant adjudicated all potential ONJ events identified during trial 20060216. 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.

Reviewer's comment: This definition is adopted from definition developed by American Dental Association and American Society of Bone Mineral research and is acceptable (Ruggiero and Mehrotra 2008).

The applicant identified events to be adjudicated by using a pre-defined list of MedDRA preferred terms (details in the dental consult report). In addition, oral or orofacial fistulas suspicious for underlying ONJ and any clinical trial adverse events reported by the investigator as possible ONJ were sent to the adjudication committee. The adjudication committee did not consider any of the 12 cases sent for adjudication to be a bona fide case of ONJ.

Reviewer's comment:

Since there were no cases of adjudicated ONJ were found in trial 20030216, ONJ is discussed in more detail in section 7.2, the main review document.

Malignancy

There were total 581 subjects who developed malignancy during the 3 year duration of the clinical trial (274 (7% of 3876) in placebo and 307(7.9% of 3886) in the denosumab group). There were more subjects in the denosumab group with benign and malignant breast neoplasms, GI neoplasms, endocrine and reproductive neoplasms Table 93. Average trial day of the malignancy related adverse event was 484 days for placebo group and 522 days for the denosumab group.

Table 93: Number of subjects in the neoplasms SOC by HLGT (Most frequent (> 9 or a difference of 3 subjects between the placebo and denosumab group)

HLGT	PLACEBO N=3876	DENOSUMAB N=3886
Skin neoplasms malignant and unspecified	49	46
Breast neoplasms malignant and unspecified (incl nipple)	29	34
Breast neoplasms benign (incl nipple)	12	16
Cutaneous neoplasms benign	33	29
Gastrointestinal neoplasms malignant & unspec	24	35
Reproductive neoplasms female benign	18	21
Respiratory and mediastinal neoplasms malignant and unspecified	24	15
Soft tissue neoplasms benign	21	14
Endocrine neoplasms benign	12	19
Reproductive neoplasms female malignant and unspecified	9	19
Miscellaneous and site unspecified neoplasms benign	8	14
Metastases	9	9
Respiratory and mediastinal neoplasms benign (excl mesotheliomas)	9	6
Renal & urinary tract neoplasms malig & unspec	8	5
Gastrointestinal neoplasms benign	8	3
Miscellaneous and site unspecified neoplasms malignant and unspecified	3	7
Endocrine neoplasms malignant and unspecified	2	7
Haematopoietic neoplasms (excl leukaemias and lymphomas)	0	3

Source: This reviewer's analysis of AAE dataset, safety population. This is subject level data.

Malignancy related serious adverse events:

Malignancy-related SAEs were observed more frequently in denosumab group compared to placebo, especially in the SOC Breast and nipple neoplasms (34 vs. 27 events), GI and hepatobiliary neoplasms (34 vs. 27 events), Reproductive system neoplasms (24 vs. 14 events), and endocrine neoplasms (9 vs. 4 events). On the other hand, less frequent neoplastic events in Denosumab were observed in respiratory tract neoplasms, placebo (23) compared to denosumab group (15); Renal and Urinary tract neoplasms placebo (11) compared to denosumab group (6); and nervous system neoplasms placebo(8) vs. Denosumab (4). There were 26 subjects in the placebo group and 20 in the denosumab group who died with an AE of malignancy.

Noteworthy is one case of Schofflers tumor was observed in one subject (20030216-759), in the denosumab arm in Czech Republic. To date, only 6 such cases are described in the literature (3 in Germany and 3 in Japan). Schofflers tumor is a rare inflammatory pseudotumour of the abdominal wall with aggressive connective tissue proliferation which frequently infiltrates neighbouring abdominal organs. Usually this tumor occurs several years after abdominal surgery or trauma, thus posing substantial problems in the interpretation of the clinical and morphological findings. In one of male patients for instance, a sarcoma of the abdominal wall was suspected pre- and intraoperatively. Another female patient was falsely considered to have a carcinoma of the urinary bladder. The lesion belongs to the reactive tumor-like fibromatoses. Since RANKL was originally found in dendritic cells of the skin, and this very rare condition occurred in denosumab group, this one case raises concerns about increased possibility of such events. However, it is not possible to assess the risk of this very rare tumor base on one case.

Reviewer's comment: Because malignancies are a serious safety issue and trial 20030216 is a well-controlled trial with a placebo arm, this reviewer is concerned (even though numbers are small) about the increased incidence of malignancies in the denosumab group for the breast neoplasms, GI, endocrine, and reproductive system.

Infections:

AEs:

Overall, infection-related AEs appear to be fairly balanced between denosumab and placebo subjects. There were 2108 subjects (4307 events) in the placebo group and 2055 subjects (4316 events) in the denosumab group. When viewing all infection-related AEs the following epithelial/mucosal infections occurred more frequently among denosumab subjects: "Bacterial infections NEC", "Streptococcal infections", "Candida infections", "Tinea infections", and "Ear

infections". It is also interesting to note that there were two "Giardia infections" in the denosumab group and none in the placebo group. "Tuberculous infections" occurred less frequently among denosumab subjects.

SAEs

There were more serious infectious adverse events in the denosumab group compared to placebo as shown in Table 94. There were more subjects with multiple serious infections in denosumab group. There were total 6 subjects in the placebo group and 10 subjects in the denosumab group with multiple infections. One subject in the denosumab group had 4 episodes of bronchiectasis, 5 episodes of "lower respiratory tract infection", and two pseudomonal infections. However, incidence of infections leading to death was similar between the two groups (6 in the placebo and 6 in the denosumab group).

Table 94: Serious Adverse Events in the Infections SOC by High Level Group Term

High Level Group Term	PLACEBO N=3876	DENOSUMAB N=3886
Bacterial infectious disorders	15	25
Fungal infectious disorders	1	2
Infections - pathogen unspecified	119	144
Mycobacterial infectious disorders	3	2
Rickettsial infectious disorders	1	0
Viral infectious disorders	5	6

Table 95: Serious Adverse Events in the Infections SOC by High Level Term (within the two imbalanced HLGs: bacterial infections and unspecified pathogen).

AEHLT	PLACEBO N=3876	DENOSUMAB N=3886
Bacterial infectious disorders		
Bacterial infections NEC	4	11
Borrelial infections	2	1
Clostridia infections	2	1
Escherichia infections	2	1
Helicobacter infections	0	2
Pseudomonal infections	0	1
Salmonella infections	2	0
Staphylococcal infections	2	1
Streptococcal infections	1	7

AEHLT	PLACEBO N=3876	DENOSUMAB N=3886
Infections - pathogen unspecified		
Abdominal and gastrointestinal infections	22	28
Bone and joint infections	1	0
Cardiac infections	0	1
Central nervous system and spinal infections	1	0
Ear infections	0	5
Female reproductive tract infections	1	3
Hepatobiliary and spleen infections	2	2
Infections NEC	5	7
Lower respiratory tract and lung infections	58	55
Sepsis, bacteraemia, viraemia and fungaemia NEC	7	5
Skin structures and soft tissue infections	2	3
Upper respiratory tract infections	3	5
Urinary tract infections	17	28
Vascular infections	0	2

Source: This MO's analysis of AAE dataset, safety population.

Looking at the preferred terms, there were seven subjects on denosumab who developed a serious erysipelas infection with none reported in the placebo group. In addition, there were several events of concern, including one subject with aspergillosis (SID6652020), three subjects with endocarditis, and one subject with a liver abscess (SID 6718019).

Reviewer's Comment:

- *Among the HLGT "Bacterial Infectious Disorders", there were three times as many "Bacterial infections NEC [Not Elsewhere Classified]" in the denosumab group (11) as compared to placebo (3). "Streptococcal infections", which tend to occur through a epithelial or mucosal surface, occurred more frequently among denosumab subjects (7) vs. 1 in the placebo group.*
- *Mycobacterial, Rickettsial, and viral infectious disorders were similarly distributed between the 2 groups.*
- *There were more subjects in the denosumab group compared to placebo group with multiple infections.*

Review of endocarditis cases:

SID 20030216-762526: The subject was a 75 year old female from Estonia who experienced a serious AE of endocarditis on (b) (4). The subject had a history of hypertension, ischemic heart disease, arrhythmia, chronic pyelonephritis,

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, CRP=81 mg/dL and transesophageal echocardiography confirmed the diagnosis of "septic endocarditis". The patient received cefuroxime and gentamicin with resolution of the endocarditis on (b) (6). No causative organism identified.

SID 20030216-430063: The subject was an 82 year old female from Brazil who experienced a serious AE of endocarditis on 4/27/05. 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 [cefalexin 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. The Applicant reported that 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 trial). 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 (b) (6). The investigator reported that an echocardiogram was performed; however the Applicant did not have the results. Amgen also reported that, "A check-up in December 2007 indicated "no changes". The event did not resolve and was ongoing."

Reviewer's comment: *All 3 subjects who experienced endocarditis were treated with denosumab. It is concerning that the Applicant was unable to provide explicit information on the causative pathogens for any of the cases, and in most cases Amgen had no medical records for the patients' hospitalizations related to the endocarditis episodes.*

Consultant opinion:

Denosumab has the potential to interact with multiple layers and processes within the immune system. An Infectious Disease consult was requested to evaluate safety profile of denosumab in terms of infections. The consulting M.O. recommends that, if denosumab is approved, Amgen should continue collecting information on all infection-related adverse events for the indefinite future during the postmarketing period. This may take the form of a postmarketing requirement. In addition, the consulting M.O.

recommends that the product label include language that denosumab may cause serious infections that are not limited to specific pathogens. This medical officer agrees with the recommendation.

Eye Disorders

A preclinical trial with denosumab in primates (Study 104105) showed that denosumab was concentrated in cornea. In trial 20040138 (prostate cancer), a signal for cataract (9 placebo vs. 34 denosumab) was noted. However, in trial 20030216, overall events and incidence of eye disorders was less in denosumab compared to the placebo group including cataracts and glaucoma. There was increased incidence of blurred vision and retinal pathology in denosumab group. Overall, in the placebo group, 525 (13.5%) subjects reported adverse events in the eye disorders SOC compared to 496 (12.8%) subjects in the denosumab group. However, there was a small increase in incidence of blurred vision and retinal pathology in denosumab group (Table 96).

Table 96: Eye disorders, selected Preferred Terms

Eye disorders	SAE		AE	
	Placebo N=3876	Denosumab N=3886	Placebo N=3876	Denosumab N=3886
n, subjects	45	39	525	496
Events	61	54	806	727
Cataract	38	29	354	320
Glaucoma	2	7	74	70
Macular degeneration	5	3	26	11
Macular hole	2	0	2	0
Retinal pathology	6	5	50	63
Vision blurred	0	1	2	11

Source: This table is generated from AAE dataset for trial 20030216, excluding site 803 data.

As seen in Table 96, adverse events were balanced in the High Level Group Term of "vision disorders", which includes the Preferred Term "vision blurred". In the placebo group, 44 (1.1%) subjects reported adverse events related to vision disorders compared to 52 (1.3%) denosumab subjects. Further, the preferred terms "visual acuity reduced" and "visual disturbance" were balanced between placebo and denosumab groups.

Table 97 Preferred terms within HLGT "Vision disorders"

Preferred Term	Placebo N=3876	Denosumab N=388
Amblyopia	0	1
Amaurosis fugax	0	1
Blindness	1	2
Blindness transient	0	1
Visual acuity reduced	17	16
Astigmatism	0	1
Hypermetropia	4	1
Myopia	2	0
Presbyopia	1	1
Diplopia	3	4
Phosphenes	0	1
Photopsia	2	1
Vision blurred	2	11
Visual disturbance	12	12
Scotoma	1	0
Optic neuropathy	1	0
Total subjects	44	52

Source: This table is generated from AAE dataset for trial 20030216, excluding site 803 data.

The applicant conducted time to event onset, time to event resolution, severity of vision blurred events and case level review. The majority of subjects remained on treatment. One placebo subject, with a mild event of blurring of vision on trial day 1, discontinued placebo. Two subjects with blurred vision discontinued denosumab but this was a result of cerebrovascular accidents. One subject discontinued denosumab at a later time point. All other subjects remained on denosumab. In subjects continuing on denosumab, there were no subjects with repeat events of blurred vision following further doses. This medical officer reviewed time to event onset, time to event resolution, and case level review submitted by the applicant in response to information request and agrees that no concerning trends were found.

Reviewer's comments:

- *More denosumab subjects (11, 0.3%) than placebo subjects (2, 0.1%) reported adverse events of blurred vision. Overall, in the eye disorders SOC and in the vision disorders high level group term, adverse events were balanced between denosumab and placebo subjects.*
- *Alternative etiologies were identified in 9 of 11 reported events. Medical conditions included cerebrovascular accident (2), benign*

neoplasms of the eye (1), ophthalmic artery vasculitis (1), worsening hypertension (2) and cataracts (3).

- ***Most events were monocular versus binocular blurred vision, which is less likely to be drug-induced and more likely to be related to underlying medical conditions.***
- ***There was no relationship between longer duration of denosumab exposure and the incidence of blurred vision.***
- ***This reviewer agrees that there is no clear safety signal of eye disorders with denosumab treatment.***

Cardiovascular System:

Reason for concern:

During denosumab's development program, the Division of Metabolism and Endocrinology Products expressed concern for the potential for denosumab to cause atherosclerosis. This was based on the theoretical concern that inactivation of RANKL by denosumab could result in elevated levels of osteoprotegerin (OPG) via an unopposed feedback mechanism, as well as reports in the published literature regarding a possible association between OPG levels and arterial (aortic) wall calcification, cardiovascular disease and mortality (Kiechl S et al. 2004; Mikami S et al. 2008; Nybo M and Rasmussen LM 2008). To aid in the assessment of cardiovascular risk, the applicant established a committee to adjudicate possible cardiovascular events. In addition, an analysis of changes in abdominal aortic calcification (as assessed using lateral lumbar spine radiographs) was also conducted in a subset of trial subjects in trial 20030216.

Reviewer's comment

This medical officer reviewed the adjudication manual of procedure, the list of pre-defined MedDRA preferred term triggering the adjudication of event and adjudication log. The adjudication process appears adequate and acceptable. The list of MedDRA preferred terms appeared comprehensive and appropriate.

Baseline cardiovascular disease characteristics

The distribution of baseline cardiovascular risk factors was similar between treatment groups overall as shown in Table 98. The denosumab group included more subjects with a history of myocardial infarction (132 [3.4%] vs. 106 [2.7%] in the placebo group) and a history of coronary procedures (coronary artery bypass graft surgery 44 [1.1%] vs. 28 [0.7%]; percutaneous coronary intervention: 42 [1.1%] vs. 30 [0.8%]).

Table 98: Baseline cardiovascular risk level

	Placebo (N=3906)	Denosumab (3902)
Cardiovascular risk level	n,(%)	n,(%)
Low	2757 (70.6)	2676 (68.6)
High	1149 (29.4)	1226 (31.4)
Risk factor for cardiovascular events		
Myocardial infarction	106 (2.7)	132 (3.4)
Percutaneous coronary intervention	30 (0.8)	42 (1.1)
Coronary artery bypass graft surgery	28 (0.7)	44 (1.1)
Diabetes mellitus	293 (7.5)	303 (7.8)
Age ≥ 70 years	2878 (73.7)	2872 (73.6)
Age 65 to 69 years	820 (21.0)	824 (21.1)
Former / current smoker	1105 (28.3)	1120 (28.7)
Hypertension	1957 (50.1)	1980 (50.7)
High cholesterol	1137 (29.1)	1155 (29.6)

Source: This table is applicant generated (table 14.2.6.1), clinical trial report 20030216, page 449

Unadjudicated Adverse event analysis:

Overall, 494 (12.7%) subjects in the placebo group and 515 (13.3%) in the denosumab group had a cardiovascular-related adverse event. The most common adverse events (placebo vs. denosumab) were angina pectoris (2.2% vs. 2.6%), atrial fibrillation (both groups 2.0%), palpitations (both groups 1.5%), cardiac failure (1% vs. 1.4%), and arrhythmia (both groups 1.1%). The subject incidence of SAEs was 5.0% in the denosumab group and 4.1% in the placebo group. The most frequent of these events were atrial fibrillation (0.9%, 0.9%), angina pectoris (0.5%, 0.8%), and myocardial infarction (0.6%, 0.6%).

Table 99: Cardiovascular adverse events (all AEs) by treatment group

Adverse Event High Level Group Term	Placebo N= 3876	Denosumab N= 3886
N, Subjects	494	515
Events	616	661
Coronary artery disorders	171	195
Cardiac arrhythmias	238	253
Heart failures	69	82
Cardiac disorder signs and symptoms	76	65
Cardiac valve disorders	43	38
Myocardial disorders	18	25
Pericardial disorders	1	3

Source: This table is generated by medical officer using jreview program, AAE dataset for trial 20030216, excluding site 803 data.

Cardiovascular serious event adjudication results:

The number of events submitted for adjudication was 526 in the placebo and 572 in the denosumab group. The number of events adjudicated as CV related was 233(44.3%) in placebo and 247(43.2%) in denosumab group.

The point estimate for the hazard ratio for the cardiovascular death was 0.7 (0.4, 1.2) and any adjudicated event was 1.02(0.8, 1.3). 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 below).

Table 100: Adjudicated cardiovascular-related serious adverse events

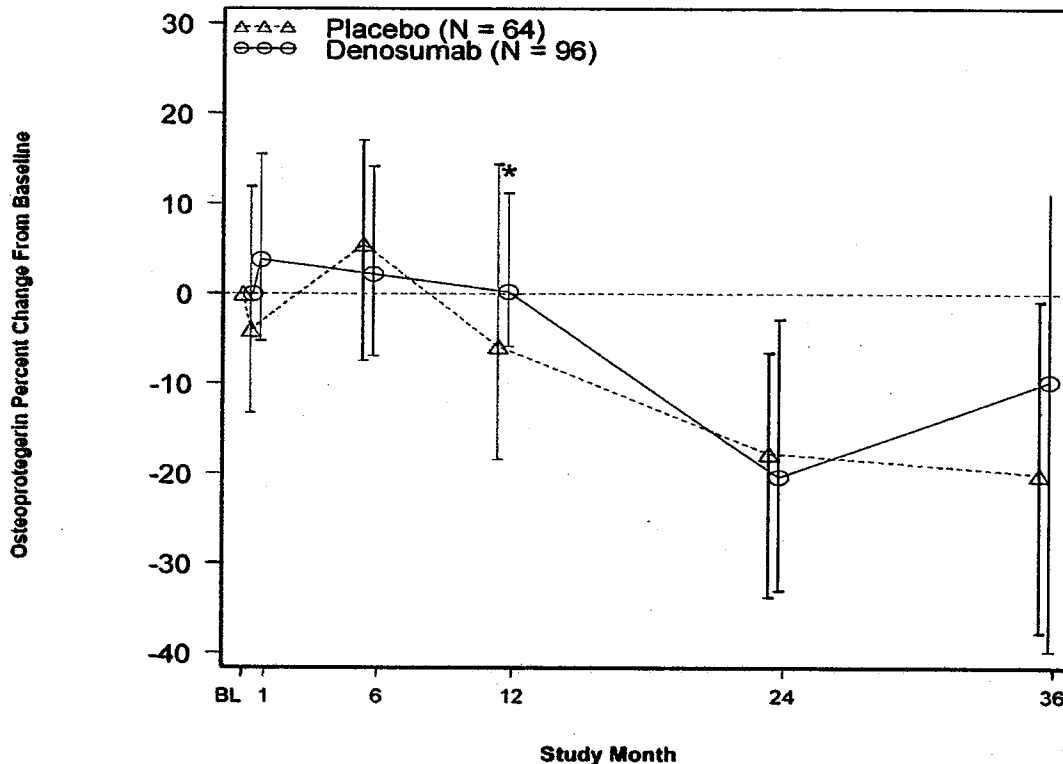
Incidence at 36 Months	Placebo (N = 3876)	Denosumab (N = 3886)	Hazard ratio (95%CI)
	n (%)	n (%)	
Any adjudicated positive CV SAE	178 (4.6)	186 (4.8)	1.02 (0.83,1.25)
CV death	31 (0.8)	23 (0.6)	0.72(0.42,1.24)
Stroke / transient ischemic attack	54 (1.4)	56 (1.4)	1.17(0.77,1.79)
Acute coronary syndrome	39 (1.0)	47 (1.2)	1.02(0.7,1.48)
Congestive heart failure	22 (0.6)	27 (0.7)	1.19(0.68,2.09)
Other vascular event	30 (0.8)	31 (0.8)	1 (0.6,1.65)
Arrhythmia	45 (1.2)	52 (1.3)	1.13(0.76,1.69)

This table is applicant generated from table 11-8, clinical trial report 20030216, page 343

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 substudy of protocol 20030216 (N=64 placebo and N=96 denosumab). As shown in the applicant's figure below, there was no clear increase in osteoprotegerin levels in denosumab compared to placebo-treated subjects.

Figure 1. Percent change from baseline and median and inter-quartile ranges by treatment arm and trial visit for osteoprotegerin



N = Number of randomized subjects enrolled in the bone marker substudy
 * statistically significant (p-value ≤ 0.05); ** statistically significant (p-value ≤ 0.025);
 *** statistically significant (p-value ≤ 0.01)

(Source: Figure 14-9.1.5, Clinical Study Report 20030216, page 2665)

Reviewer's Comment:

Whether elevated OPG levels in humans play a causative role in adverse cardiovascular outcomes or simply represent a compensatory response to disease is not known (colln-Osdoby, 2004, Montecucco et al, 2007; Van campenhout et al, 2009). The assay sensitivity, clinically meaningful change in OPG level, and power of the trial to detect this change should be considered as well while evaluating effect of OPG on adverse cardiovascular events. This medical officer is reassured by this finding that OPG levels did not change significantly between the two groups.

Aortic calcification:

The Applicant used a radiographic scoring method for lateral x-ray calcification (Tanko 2005a, Wilson 2001, Kauppila 1997). A central reading facility blinded to treatment analyzed the digital films obtained at baseline and years 1, 2, and 3.

Eight individual anterior and posterior aortic segments (each bounded by the midpoint of the intervertebral space above and below the vertebrae) from L1-L4 were analyzed. Each segment was scored from 0 to 3 (total aortic calcific [AC] score of 0-24) where:

0: No aortic calcific deposits

1: Small, scattered deposits filling $<1/3$ of the longitudinal wall

2: $\geq 1/3$ but $<2/3$ of the longitudinal wall involved

3: $\geq 2/3$ of the longitudinal wall involved

The severity score in denosumab vs. placebo-treated patients was compared in a subset of patients at high risk for cardiovascular events. "High risk" was defined using baseline risk factors and a modified classification scheme from the RUTH (Raloxifene Use for the Heart) trial. Subjects were assigned points based on the following baseline data (a total of ≥ 4 points signifies high risk).

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

1 point: Current smoker

1 point: Hypertension (systolic >160 mmHg, diastolic >95 mmHg or medicated)

1 point: Hyperlipidemia (LDL-C >160 mg/dL, or HDL-C <45 mg/dL with triglycerides

>250 mg/dL, or receiving lipid-lowering therapy)

Extra point if current smoker + hypertension + hyperlipidemia

The power to detect a 0.2 difference (using the standard deviation of 0.84) in AC units was 96% if there were ~500 high-risk subjects in each group.

The 2363 subjects assessed for aortic calcification score were similar to the overall trial population with regard to subject disposition, baseline body composition and baseline BMD T-scores. Approximately 23% of subjects had baseline aortic calcification scores of 0. The distribution of baseline scores was similar in the two treatment arm and, most patients had lower baseline aortic calcification scores (7.2(6.5) in placebo and 6.8(6.6) in denosumab).

Table 101: Total Aortic Calcification Severity Score Change From Baseline by Visit (Descriptive Statistics)(Aortic Calcification Analysis Set, Observed Data)

	N, subjects with data at all 8 aortic segments	Mean	SD
Month 12			
Placebo (N = 1142)	664	0.1	0.6
Denosumab 60 mg Q6M (N = 1221)	713	0.1	0.4
Month 24			
Placebo (N = 1142)	583	0.2	0.7
Denosumab 60 mg Q6M (N = 1221)	648	0.2	0.8
Month 36			
Placebo (N = 1142)	501	0.4	1
Denosumab 60 mg Q6M (N = 1221)	544	0.4	1.1

Source: Applicant table 14-6.7.7 (page 922 of CSR)

Reviewer's comment for cardiovascular disease:

- *There was an increase in unadjudicated all cardiovascular events in the denosumab group however, at a baseline, denosumab group had more subjects with risk factors for cardiovascular disease. The denosumab group included more subjects with a history of myocardial infarction (132 [3.4%] vs. 106 [2.7%] in the placebo group) and a history of coronary procedures (coronary artery bypass graft surgery 44 [1.1%] vs. 28 [0.7%]; percutaneous coronary intervention: 42 [1.1%] vs. 30 [0.86%]).*
- *The cardiovascular adjudication process was comprehensive and appropriate in this medical officer's opinion.*
- *Adjudicated serious cardiovascular events were similar between the two treatment groups*
- *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 if they exist.*

Musculoskeletal system:

Adverse events related to musculoskeletal system were noted most frequent of all body systems in both treatment groups. Most subjects had more than one adverse event. As shown in Table 102, the denosumab group had a higher number of subjects, 2513 with 6314 events, while placebo group had 2499 subjects with 6294 events.

Table 102. Adverse events in musculoskeletal SOC by Preferred Terms

	PLACEBO N=3876	DENOSUMAB N= 3886
n, subjects	2499	2513
events	6294	6314
Adverse Event PT		
Back pain	1340 (53.39%)	1347 (53.37%)
Arthralgia	782 (31.16%)	785 (31.10%)
Osteoarthritis	450 (17.93%)	445 (17.63%)
Pain in extremity	430 (17.13%)	453 (17.95%)
Musculoskeletal pain	291 (11.59%)	297 (11.77%)
Muscle spasms	182 (7.25%)	167 (6.62%)
Neck pain	136 (5.42%)	129 (5.11%)
Bone pain	117 (4.66%)	142 (5.63%)
Myalgia	94 (3.75%)	114 (4.52%)
Spinal osteoarthritis	64 (2.55%)	82 (3.25%)
Musculoskeletal chest pain	63 (2.51%)	61 (2.42%)
Joint swelling	66 (2.63%)	55 (2.18%)
Tendonitis	47 (1.87%)	56 (2.22%)
Arthritis	53 (2.11%)	48 (1.90%)
Musculoskeletal stiffness	36 (1.43%)	30 (1.19%)
Bursitis	32 (1.27%)	34 (1.35%)
Intervertebral disc protrusion	24 (0.96%)	37 (1.47%)
Exostosis	22 (0.88%)	31 (1.23%)
Muscular weakness	29 (1.16%)	23 (0.91%)

Source: This table is generated by medical officer, using AAE dataset for trial 20030216, excluding site 803 data.

Nervous system:

1073 subjects in denosumab and 1030 subjects in placebo had any AE in the Nervous system SOC. The AEs in all HLGTS are balanced except “mental impairment disorders” “Spinal cord and nerve root disorders” and “movement disorders”. Within these imbalanced HLGTS, HLTs and selected imbalanced PTs are shown to emphasize that higher number of subjects in the denosumab group had memory impairment, Parkinson’s disease and spinal cord and nerve root compression disorders. Number of subjects with serious adverse events was similar between the two groups (131 (3.4%) in the denosumab group and 125 (3.2%) in the placebo group).

Table 103: Imbalanced HLGT, HLT and PTs by treatment group in the Nervous system disorders SOC

HLGT HLT	PT	Pla N=3876	Denos N=3886
Mental impairment disorders			
Alzheimer's disease (incl subtypes)	Dementia Alzheimer's type	7	10
	Presenile dementia	0	1
Dementia (excl Alzheimer's type)	Dementia	6	7
	Senile dementia	2	4
	Vascular dementia	2	1
Memory loss (excl dementia)	Amnesia	16	18
	Amnesic disorder	0	1
	Memory impairment	37	52
Spinal cord and nerve root disorders			
Cervical spinal cord and nerve root disorders	Cervical root pain	3	7
	Cervicobrachial syndrome	8	9
	Radiculitis cervical	1	1
Lumbar spinal cord and nerve root disorders	Lumbar radiculopathy	2	4
	Radiculitis lumbosacral	0	3
	Sciatica	149	178
Spinal cord and nerve root disorders NEC	Cauda equina syndrome	0	3*
	Nerve root compression	0	1
	Nerve root lesion	1	0
	Spinal claudication	1	0
	Spinal cord compression	1	0
Movement disorders			
Parkinson's disease and parkinsonism	Freezing phenomenon	0	1
	Parkinsonian rest tremor	0	1
	Parkinsonism	7	4
	Parkinson's disease	7	17

Source: This table is generated using AAE dataset for trial 20030216, excluding site 803 data.*
Subject narratives were reviewed, not considered to be clinically consistent with cauda equina syndrome.

Reviewer's Comment:

For spinal cord and nerve root disorders, it is plausible that due to suppression of bone remodeling the area of bone that may have been removed normally by osteoclasts still persists or increased bone mass may impinge upon nerves and may be responsible for nerve root compression disorders. However, when looked at the data in totality, and at the PT level,

these differences are small. Nonetheless, postmarketing surveillance may help to further characterize these potential adverse events.

GI Disorders:

1450 subjects in denosumab and 1421 subjects in placebo had any AE in the GI SOC. The AEs in all HLT were balanced except "diverticular disorders" and "Gastrointestinal vascular disorders". Within these HLTs, main imbalances were found in "rectal haemorrhage" (15 in placebo vs. 24 in denosumab) and non site specific haemorrhages (Table 104). Higher number of subjects had diverticulum disorder in the denosumab group. When looked at preferred terms within GI disorders SOC, flatulence was noted in higher number of subjects in the denosumab (84) compared to the placebo (53) group.

Table 104: Imbalanced HLT and PTs in the GI disorders SOC

High Level Group Term	Preferred Term	Placebo N=3876	Denos. N=3886
Intestinal haemorrhages	Anal haemorrhage	3	3
	Colonic haematoma	1	
	Intestinal haemorrhage	2	1
	Large intestinal haemorrhage		1
	Rectal haemorrhage	15	24
Non-site specific GI haemorrhages	Gastrointestinal haemorrhage	7	5
	Haematemesis	1	4
	Haematochezia	5	12
	Lower GI haemorrhage		3
	Melaena	4	6
	Upper GI haemorrhage	3	1
Diverticula	Diverticulum	21	37
	Diverticulum intestinal	20	33
	Diverticulum oesophageal	1	2
	Pharyngoesophageal diverticulum	1	

Source: This table is generated by medical officer, using AAE dataset for trial 20030216, excluding site 803 data.

SAE:

There were 145 subjects with a SAE in GI disorders SOC vs. 103 in the placebo group. The main imbalances were in the diverticular disorders (6 in placebo vs. 15 in denosumab), Exocrine pancreas disorders (2 in placebo vs. 8 in denosumab) and in GI ulcerations and perforations (9 in placebo vs. 15 in denosumab).

Pancreatitis was noted in 8 subjects in the denosumab compared to 3 in the placebo group. Among subjects with Pancreatitis, all 8 subjects in the

denosumab had a serious event, vs. none in the placebo group. One subject, SID 20030216-835096 had 4 episodes of Pancreatitis. IP product was not discontinued for this subject. These cases are described in detail in section 7.3.4.7, table 49.

Reviewer's comment:

- ***Denosumab use was associated with small but higher incidence in GI haemorrhages and diverticular disease. Diverticular disease is common in elderly population; however, since this is a placebo controlled trial, this issue will be further explored in the total safety database.***
- ***Although mechanism is not clear, it is concerning that all 8 cases of Pancreatitis were serious events in the denosumab group while placebo group had no case of serious pancreatitis. This imbalance is concerning. It should be further characterized in the postmarketing studies and included in the labeling document.***

Metabolism and nutrition disorders

There were more subjects with hypercholesterolemia (383, 9.8%) in the denosumab group compared to placebo (325, 8.3%). Applicant did not collect any lab data related to lipid metabolism. This analysis is from the AAE dataset.

Table 105: Metabolism and nutrition disorders

Categories of interest	Placebo N=3876	Denosumab N=3886
Elevated cholesterol	245	291
Hyperlipidaemias NEC	35	46
dyslipidemia	38	29
Elevated triglycerides	7	17
Diabetes mellitus (incl subtypes)	96	96
Hyperglycaemic conditions NEC	41	47
Hypoglycemic conditions NEC	8	12
Calcium metabolism disorders	14	10
Food malabsorption and lactose intolerance	0	5

Source: This table is generated AAE dataset for trial 20030216, excluding site 803 data.

Of the subjects with lipid metabolism disorders, 74(19.3%of 291) in the denosumab and 62(19%of 245) in the placebo had history of lipid metabolism disorders. Incidence of statin initiation during the trial was 11.5% for denosumab and 10.6% for placebo.

There were 5 subjects in denosumab compared to none in placebo group with food allergies. All 5 patients in denosumab developed mild lactose and other sugar intolerance on trial day ranging from 89-842.

Reviewer's Comment: The applicant did not measure lipids in a prospective manner in the trial. There was no reason to suspect that denosumab use would be associated with hypercholesterolemia. However, now that this effect is seen in a phase 3 clinical trial, this potential adverse effect should be in the labeling document. The applicant should consider measuring lipid levels in one of their post marketing studies.

Skin and Soft tissue disorders

There were more subjects in the denosumab group (576, 15%) with adverse events related to skin and soft tissue disorders compared to placebo (464, 13%).

Table 106 Adverse Event High group Level Term in skin and soft tissue disorders SOC.

Adverse Event High Level Group Term	PLACEBO	DENOSUMAB
Angioedema and urticaria	28	29
Cornification and dystrophic skin disorders	21	21
Cutaneous neoplasms benign	3	7
Epidermal and dermal conditions	316	421
Pigmentation disorders	5	4
Skin and subcutaneous tissue disorders NEC	37	42
Skin appendage conditions	89	83
Skin vascular abnormalities	11	12
Total Subjects	464	576

Source: This table is generated using AAE dataset for trial 20030216, excluding site 803 data.

This imbalance was mainly due to imbalance observed in HLGT "Dermal and Epidermal conditions" (316 vs. 412 events in placebo vs. denosumab). Table 107 shows number of subjects in AE high level terms (MedDRA) in placebo vs. denosumab group. The imbalances are bolded. These events are not specific to injection site

Table 107 Adverse Event High Level Term in HLGT Epidermal and dermal conditions

Adverse Event High Level Term	PLACEBO	DENOSUMA B
Bullous conditions	3	9
Connective tissue disorders	1	1
Erythemas	14	18
Exfoliative conditions	3	1
Granulomatous and deep cutaneous inflammatory conditions	1	2
Papulosquamous conditions	12	5
Photosensitivity conditions	1	6
Pruritus NEC	92	107
Psoriatic conditions	13	14
Rashes, eruptions and exanthems NEC	84	102
Dermal and epidermal conditions NEC	47	62
Dermatitis and eczema	77	141
Dermatitis ascribed to specific agent	1	6
Skin injuries and mechanical dermatoses	3	2

Source: This table is generated using AAE dataset for trial 20030216, excluding site 803 data.

Reviewer's Comment:

- **Bullous conditions were observed 3 times more frequently in denosumab (3 vs. 9 in placebo vs. denosumab) group.**
- **Photosensitivity is an immune reaction triggered by sunlight. Several drugs are related to photosensitivity. Photosensitivity was observed in 6 times more subjects in the denosumab group (1 vs. 6 in placebo vs. denosumab).**
- **There were 4 subjects with "toxic skin eruptions" in the denosumab group vs. none in the placebo group.**
- **Pruritus and rashes were observed more frequently in the denosumab group. Dermatitis and eczema were observed in twice the number of subjects with denosumab group vs. placebo.**

Bullous and Photosensitivity conditions and toxic skin reactions: Given that the incidence of bullous conditions and photosensitivity conditions, although rare, had an increased incidence in the denosumab group and it was noted that there were 4 subjects in the denosumab group with "toxic skin reactions" vs. none in the placebo group, an dermatology consultation was requested. This reviewer also asked for a narrative of each event and the CRF to review to determine, if possible, the characterization of these events in terms of severity and seriousness and to determine what level of certainty can be ascertained that denosumab caused these events. It should be noted that while reviewing the CRFs of these subjects, most were from foreign sites and very little, if any,

information was given describing the exact characterization of the lesions of the various skin eruptions.

For the 4 cases of toxin skin eruption, the data does not make a convincing case for these eruptions to be secondary to denosumab. For the photosensitivity conditions, all but one of the 6 events has a reasonable alternative etiology for the adverse event other than denosumab and the subjects did well despite continuing the drug product. In the bullous conditions, there are only 3 out of 9 cases in which denosumab as a possible culprit cannot be fully discounted. These cases are described in detail in section 7.3.4.8. In summary, although unlikely, completely ruling out denosumab in these cases is not possible; however there does not seem to be a safety signal.

Reviewer's Comments:

- **Overall, subjects in the denosumab group were more likely to develop skin and soft tissue related adverse events.**
- **There were more subjects with pruritic conditions, skin rashes, dermatitis and eczema related adverse events in the denosumab group compared to placebo. This increase is clinically significant and should be included in the labeling document.**
- **There were more subjects in the denosumab group with bullous conditions, photosensitivity and skin conditions compared to placebo group. However, detail review of each case identified other confounding medications and no reappearance of these conditions upon rechallenge. The agency experts in dermatology do not feel that denosumab is a causative agent in these conditions and this MO agrees with it.**

Clinical Laboratory Abnormalities:

Liver Function tests: Among subjects with normal baseline, there were 20 subjects on the placebo group and 31 subjects in the denosumab with Alanine amino transferase (ALT)>3 times normal at any visit. There were 7 subjects in the placebo and 6 subjects in the denosumab group with ALT>5 times normal at any visit. Similar results were found for Aspartate Amino transferase (AST) were 21 and 23 subjects in placebo and denosumab group with AST>3times normal and 6 and 8 subjects respectively, with AST >5 times normal at any visit among subjects with normal baseline. There were 21 subjects in denosumab and 18 in placebo with total bilirubin >1.5 xULN among subjects with normal baseline at any visit. No trends in the shifts of liver function tests were noted.

Renal Function:

Among subjects with normal creatinine (<1.5) at baseline, 6 in placebo vs. 5 in the denosumab group had S.Cr >2.25 (1.5xULN) at any visit, and 30 in placebo vs. 30 in denosumab had S.Cr >1.8 at any visit.

Vital Signs:

Among subjects with normal systolic BP (<120) at baseline, 92 in placebo vs. 99 in the denosumab group had SBP>160 at any visit, and 5 in placebo vs. 7 in denosumab had SBP>190 at any visit.

Among subjects with normal diastolic BP (<90) at baseline, 42 in placebo vs. 40 in the denosumab group had DBP>110 at any visit, and 4 in placebo vs. 5 in denosumab had DBP>120, and 5 in placebo vs. 7 in denosumab had DBP<40 at any visit.

Among subjects with pulse rate (60-100) at baseline, 9 in placebo vs. 4 in the denosumab group had pulse>120 at any visit, and 3 in placebo vs. 5 in denosumab had pulse<40 at any visit.

Reviewer's Comment: No significant differences or trends were noted in the denosumab group compared to placebo in vital signs or safety laboratory data.

Bone biopsy substudy

The applicant conducted a transiliac bone biopsy trial (a cross-sectional design) at 10 selected trial sites to evaluate effect of denosumab on bone histology and histomorphometry. A total of 115 biopsies were obtained (62 placebo, 53 denosumab). One hundred-three subjects consented to participate in the substudy, 92 subjects (45 placebo, 47 denosumab) received ≥1 dose of investigational product and had ≥1 evaluable biopsy, and 23 subjects (17 placebo, 6 denosumab) underwent sequential biopsy evaluation.

Subjects were anticipated to undergo a biopsy within 56 days before their 24 and/or 36 month visit(s). All subjects scheduled for biopsy followed a double tetracycline labeling procedure before undergoing the biopsy. The subjects took 3-day of tetracycline 250 mg (or demeclocycline 150 mg) 4 times a day, did not to take any tetracycline derivatives for 14 days, and then took another 3-day of tetracycline. Urine samples were collected for tetracycline measurements to confirm compliance.

Reviewer's comment:

The compliance to tetracycline was acceptable, as 95-100% of subjects in both groups had confirmed compliance by urinary measurements.

Baseline characteristics:

The 92 subjects in the bone biopsy substudy were similar to the overall trial population with regard to subject disposition, demographics, baseline body composition, baseline BMD T-scores, baseline CTX1, and baseline selected laboratory analytes. These parameters were balanced across treatment groups within the substudy.

Bone Histology Evaluation

All 115 biopsies (53 denosumab, 62 placebo) were evaluable for histology in 92 subjects. After 24 or 36 months of treatment with either denosumab or placebo, there was evidence of normal lamellar bone, normal mineralization, and normal osteoid in both treatment groups. There was no evidence of osteomalacia, marrow fibrosis, woven bone, or abnormal osteoid.

Normal osteoid was seen in all placebo (62/62) subjects and (48/53, 91%) of subjects in denosumab group. Five subjects in the denosumab-treated group at month 24 did not have osteoid that could be visualized.

One denosumab treated subject (6613015), who received all doses of denosumab, was determined to have normal histology at month 24 and cortical trabecularization at month 36.

Marrow Dyscrasia: There was one case of marrow dyscrasia in denosumab group and none in placebo group (T 14-17.2.6) In an initial review, the hematopathologist noted lymphoid aggregates in the assessment of marrow dyscrasia for 4 subjects (2 denosumab, 2 placebo); 1 of the denosumab subjects had enrolled in the sequential biopsy procedure, and the month 36 biopsy findings were reported as normal. Since marrow dyscrasia is not typically observed when evaluating bone quality, and since this had not been reported in other bone biopsy substudies (20010223 or 20050234), a second evaluation by a blinded hematopathologist was conducted. The second hematopathologist did not find any evidence of marrow abnormality and therefore did not confirm the previous observations. In addition, none of these 4 subjects had any evidence of clinical or hematologic abnormalities at the time of biopsy or in follow-up.

Reviewer's comment:

Mineralization impairment: The applicant claims that denosumab did not impair mineralization. However, when looked at detail line listings (listing 1-

8.1.2. Page 20270-20304 of the clinical trial report), in most cases, the applicant reports that although no label was identified, there was secondary evidence of normal mineralization assuming there was unmineralized osteoid at trial initiation and this osteoid had normally mineralized. No label was observed in most cases; therefore, no conclusions can be made about normal mineralization.

Marrow dyscrasia: Based upon the lack of confirmation of this finding by a second hematologist, the lack of abnormalities upon re-biopsy of 1 subject, and the lack of clinical evidence suggesting a hematologic disorder, the initial observations were felt to be erroneous by the applicant. This explanation is acceptable.

Cortical trabecularization: The subject who showed evidence of cortical trabecularization on histology (subject 6613015) also showed evidence of extensive remodeling with double label in the cortical compartment, but no label was observed in the trabecular compartment. Cortical-endosteal resorption ("trabecularization" of the cortical bone) is one of the major determinants of reduced bone strength. This subject was 65 years old, had gonarthrosis of the knee as a co-morbid condition and did not sustain a fracture.

Bone Histomorphometry: Bone histomorphometry is the only method that allows the measurement of mineralization rate and the rate of bone formation at cell, remodeling unit and tissue levels. The applicant obtained 115 biopsies, of which 98 were evaluable for histomorphometry and 17 biopsies were evaluable only for cortical width due to crushing or fragmentation artifacts in the trabecular compartment.

A small number of subjects underwent sequential biopsy evaluation at both 24 and 36 months. To avoid double-counting biopsy specimens for histomorphometric measurements in these subjects, only 36-month data were included in the analysis since the total number of biopsies at that time point was less than at 24 months.

Two types of parameters are reviewed in evaluation of bone histomorphometry; Static parameters and dynamic parameters. For dynamic parameters, tetracycline double label in the cortical bone is necessary. Since there were very few biopsies with tetracycline double label in the denosumab group, in this review, the static parameters and dynamic parameters are reviewed separately.

Static parameters:

Static formation parameters: Significant decreases were observed with denosumab compared with placebo with lower osteoblast-osteoid interface, osteoid surface, and osteoid width (Table 108).

Static resorption parameters: Subjects in the denosumab group had lower osteoclast cell counts compared with placebo, as indicated by significantly decreased surface- and length based osteoclast numbers (Table 108).

Table 108: Static bone formation and resorption parameters

	Month 24		Month 36	
	Placebo (N = 37)	Denosumab (N = 31)	Placebo (N = 25)	Denosumab (N = 22)
	Median (Q1,Q3)	Median(Q1,Q3)	Median (Q1,Q3)	Median (Q1,Q3)
Number of evaluable biopsies	N=32	n =26	N=22	N=18
Static formation parameters				
Osteoblast – osteoid interface (%)	37.81 (8.1,55.8)	1.15 (0.0,18.3)	25.29 (6.7,37.9)	0 (0,0)
Osteoid surface (%)	7.68 (4.2,10.2)	0.69 (0.11,1.6)	6.54 (4.1,10.4)	0.305 (0.2,1.2)
Osteoid width (µm)	9.09 (6.8,10.7)	5.44 (4.4,6.6)	8.72 (6.6,13.1)	5.56 (4.5,8.1)
Static resorption parameters				
Eroded surface/bone surface (%)	1.6 (0.7,2.8)	0.23 (0.07,1.4)	0.8 (0.6,1.3)	0.16 (0,0.4)
Osteoclast number – length based (1/mm)	0.09 (0.05, 0.1)	0 (0,0)	0.07 (0.04,0.12)	0(0,0.06)
Osteoclast number – surface based (1/100 mm)	9 (5.5,13.5)	0 (0,3)	7 (4,12)	0 (0,6)

Reviewer's Comment:

Subjects in the denosumab group had markedly suppressed osteoclast numbers. The osteoclast numbers were zero in the denosumab group at month 24 and 36. This is unusual given 25 and 22 biopsies in each group. Osteoclast and osteoblast play important role in bone remodeling. This raises a concern that over long term use, suppression of bone remodeling may lead to complications such as delayed fracture healing, ONJ, or atypical fracture.

Dynamic parameters: Dynamic bone formation parameters provide information about bone formation during the labeling interval (between 2 dosing periods of

tetracycline). Tetracycline gets deposited in the newly mineralized bone, so absence of label means that during the tetracycline dosing period there was no new bone mineralization. To identify bone biopsy sections with label, standard operating procedures at the Bone Histomorphometry Laboratory at Mayo Clinic (Rochester, MN) were followed.

Labeling status (no label, single label, and/or double label) is summarized for trabecular and cortical bone in Table 109.

Table 109: Labeling Status at 3 years

	Trabecular		cortical		Trabecular or cortical	
	Placebo n (%)	Denosumab n (%)	Placebo n (%)	Denosumab n (%)	Placebo n (%)	Denosumab n (%)
Number of biopsies evaluable at month 36	25	22	25	22	25	22
Any label	25 (100)	10 (45)	25 (100)	11 (50)	25 (100)	14 (64)
Any double label	24 (96)	7 (32)	24 (96)	7 (32)	25 (100)	10 (45)
Only single label	1 (4)	3 (14)	1 (4)	4 (18)	0 (0)	4 (18)
No label	0 (0)	12 (55)	0 (0)	11 (50)	0 (0)	8 (36)

Reviewer's Comment: Absence of label suggests suppressed bone formation. No biopsy samples in the placebo group showed no label while 50% (cortical) and 55% (trabecular) of samples showed no label in denosumab group. This severely suppressed bone formation could potentially lead to complications such as delayed healing, ONJ, atypical fracture. The expected duration of treatment is several years.

Dynamic parameters:

Activation frequency, bone formation rate and mineralizing surface were markedly decreased in the denosumab group compared to placebo as shown in Table 110. Activation frequency is the most important regulator of bone turnover. It is defined as the rate at which the bone remodeling units are formed.

There were only 3 biopsies available for dynamic bone parameters in the denosumab group at 36 months. Of these, one subject (6412687) discontinued therapy at month 12 and underwent a biopsy at month 36. Applicant included data from this subject in analysis. Denosumab effect on bone remodeling is

expected to be reversed in 2 years, so this medical officer does not think it is appropriate to include her in this analysis.

Table 110: Dynamic bone formation parameters

	MONTH 24		MONTH 36	
Mean (SD)	Placebo (n=37)	Denosumab (n=31)	Placebo (n=25)	Denosumab (n=21)
Biopsy with evaluable parameters	31	4	22	2
Activation frequency (/year)	0.36(0.3)	0.05(0.1)	0.22(0.1)	0(0)
Bone formation rate - surface based ($\mu\text{m}^3/\mu\text{m}^2/\text{year}$)	16(12.6)	1.7(3.5)	10.94(7.6)	0.29(0.1)
Bone formation rate - volume based (%/year)	21.8(15.6)	2.9(5.8)	14.51(9.1)	0.38(0.02)
Formation period (day)	360.4(1406.8)	1180.2(1376.1)	163.5(169)	344.2(162.6)
Mineralizing surface (%)	5.8(4.3)	0.49(0.8)	4.1(2.9)	0.2(0.1)
Mineral apposition rate ($\mu\text{m}/\text{day}$)	0.7(0.2)	0.47(0.4)	0.77(0.2)	0.4(0.1)
Mineralization lag time	61.2(214)	172.8(148)	31.5(33)	48.6(34)

This table is generated using ABMHMR dataset, excluding data from subject 6412687.

Mineral apposition rate was imputed for 4 biopsies at month 24 and 1 biopsy at month 36, due to the presence of single label. For subjects who had single labels in trabecular bone within the measurement field of 20mm², a value of 0.3 $\mu\text{m}/\text{day}$ was imputed for mineral apposition rate and used to derive other dynamic histomorphometric parameters.

Reviewer's comment:

It is concerning that there were no bone remodeling units being formed (activation frequency) in the denosumab group at month 36. However, there were only 2 subjects in the denosumab group at month 36. So, the numbers are not enough to make conclusions. More data is necessary to evaluate dynamic parameters in the denosumab group.

Bone formation period and mineralization lag time were prolonged significantly in the denosumab group. This again, suggests suppression of bone remodeling.

Correlation to clinical findings and reversibility:

The relationship between percent change in BMD at month 36, incident fractures, and degree of reduced remodeling, as reflected by label status, was explored. Those subjects with less prominent tetracycline labeling showed the greatest gains in BMD at the total hip and lumbar spine at month 36. There were 3 fractures in subjects enrolled in the denosumab. Among subjects with no label, 2 sustained fractures, 1 of which was a patellar fracture that occurred less than 6 months after the first dose of denosumab (6128038 and 6413231) (Listing 1-8.1.512). One subject with single label sustained both a radial and ulnar fracture 6.5 months after first dose of denosumab (6304188), and 6 subjects with double label, all of whom received placebo, sustained a fracture (6412183, 6612018, 6612024, 6613025, 6613025, 6613031).

In the subject who discontinued therapy 24 months before bone biopsy (subject 6412687), evidence of the reversibility of denosumab was demonstrated since this subject had extensive double label and several dynamic parameters, including mineral apposition rate, approaching values of the placebo group.

Reviewer's comment: Applicant argues that long-term reduction in bone remodeling, as reflected by the small number of tetracycline labels in bone biopsy samples, did not translate into an increase in fracture risk in these subjects. However, decrease in bone labeling is expected to increase BMD in a relatively short term use (upto3 years). The risk of complications related to continuously suppressed bone remodeling is expected to increase after a long term use (7-10 years).

Applicant notes that the suppression of bone biomarkers was not worse at 36 months compared to 24 months. That means that the bone remodeling suppression does not get worse with time. Applicant also argues that bone biomarkers are not different if there was single label, double label or no label. In my opinion, the numbers are too small to make these judgments and labeling status of tetracycline remains a concern.

Conclusion:

- Important information on bone remodeling at the cellular level was obtained in the bone biopsy substudy.***
- Baseline characteristics were similar between the groups and similar to the overall trial population.***
- Bone histology evaluation did not identify any major concerns.***
- Bone histomorphometry results raise concerns about the degree of bone remodeling suppression. Denosumab group had markedly suppressed osteoclast and osteoblast counts at both, 24 and 36***

months. Absence of label suggests suppressed bone remodeling. Dynamic bone formation parameters such as activation frequency, bone formation rate and mineralizing surface were markedly suppressed.

- I recommend that applicant conduct additional bone biopsy trial to evaluate effect of long term denosumab therapy on bone biopsy as well as reversibility of the effect of denosumab on suppression of bone remodeling as a post marketing requirement.***

DXA substudy:

The applicant conducted a substudy within trail 20030216 to measure BMD at more frequent time points for a subset of 441 subjects. For all subjects in the study, BMD assessments were performed at baseline and at month 36 for the lumbar spine and at baseline and at months 12, 24, and 36 for the hip (i.e., total hip, femoral neck and trochanter). For subjects enrolled in the DXA substudy, BMD assessments of the lumbar spine and hip were performed at baseline and at months 1, 6, 12, 24, and 36 (including those planned for all subjects); in addition, BMD assessments of distal 1/3 radius and total body were performed at baseline and at months 12, 24, and 36. DXA scan data were sent to the central imaging vendor for final, blinded analysis.

The 441 subjects enrolled in the DXA Substudy were similar to the overall study population with regard to subject disposition, demographics, baseline BMD T-scores, baseline BMD. Denosumab increased BMD at all anatomic sites assessed at months 12, 24, and 36 ($p < 0.005$ for all). These results for the two most important sites, lumbar spine and total hip are shown in Figure 16 and Figure 17. These increases are similar in magnitude as the entire trial population (7808 subjects).

Figure 16: Lumbar Spine BMD (by DXA) Percent Change From Baseline by Visit, Least-squares Mean and 95% CIs From ANCOVA (Primary Efficacy Analysis Set in the DXA Substudy, LOCF)

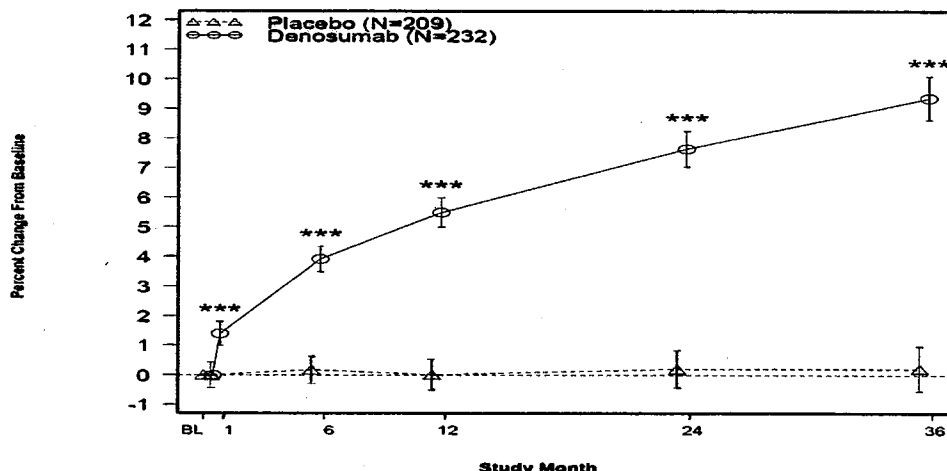
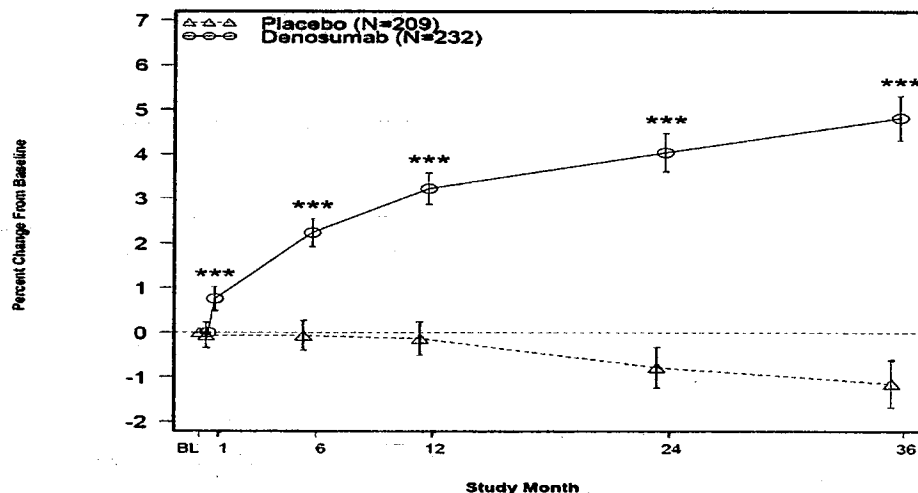


Figure 17 Total Hip BMD (by DXA) Percent Change From Baseline by Visit Least-squares Mean and 95% CIs From ANCOVA (Primary Efficacy Analysis Set in the DXA Substudy, LOCF)



Point estimates and nominal 95% confidence intervals are based on an ANCOVA model adjusting for treatment, baseline value, machine type, and baseline value-by-machine type interaction* statistically significant (p-value <= 0.05); ** statistically significant (p-value <= 0.025). *** statistically significant (p-value <= 0.01)

Reviewer's comment: Denosumab increased BMD at all anatomic sites assessed at months 12, 24, and 36. These sites include lumbar spine, total hip, total body and 1/3rd radius. The results of the substudy are similar to the entire trial population.

Fracture Healing Substudy

Reason for concern:

Fracture healing involves the production of a callus of cartilage and woven bone that stabilizes the fracture (Barnes et al. 1999). The fracture callus gradually mineralizes and is remodeled over time to form lamellar bone and complete the fracture repair. Bone remodeling (bone formation and resorption) is critical in fracture healing. Patients with bone loss are at increased risk and incidence of fracture. Denosumab is primarily an antiresorptive agent. Bone resorption and formation are coupled processes, and therefore denosumab suppresses bone formation as well. To address this concern, information on fracture healing complications was collected for all nonvertebral fractures occurring during Study 20030216. In addition, a fracture healing substudy evaluated cortical bridging by serial x-rays to determine healing progression at 3 and 6 months post **wrist fracture**.

Subjects who experienced a fracture of the distal radius (traumatic or nontraumatic) and were expected to have at least 3 more months on trial were asked to participate in a substudy to compare the incidence of radiographic healing in denosumab-treated versus placebo-treated subjects. Fracture healing was assessed using standard anteroposterior (AP) and lateral radiographs. Radiographs were taken at 6 weeks and 3 and 6 months after the fracture event. Radiographic assessments to evaluate fracture healing were conducted at a central imaging facility by 2 independent reviewers blinded to treatment assignment. If there was disagreement between the 2 reviewers, a third reviewer was to evaluate and independently adjudicate the radiograph.

Definitions: Fractures were considered healed radiographically when all 4 cortices (dorsal, volar, radial, and ulnar surfaces) were bridged in cases where all 4 could be visualized, or when all 3 visible cortices were bridged in cases where only 3 could be visualized. If < 3 cortices could be seen, the healing status was considered "unknown" for the film.

Results:

A total of 386 nonvertebral fractures occurred in 303 subjects in the denosumab group and a total of 465 nonvertebral fractures occurred in 364 subjects in the placebo group.

As shown in Table 46, fracture healing complications were few and balanced between the two groups. 2 subjects in the each group experienced delayed healing and one subject in the placebo had non-union. Mean time to fracture was 468 days in the placebo and 465 days in the denosumab group.

Table 111: Non vertebral fracture healing complications

	PLACEBO N=3876	DENOSUMAB N=3886
Total number of non vertebral fractures	465	386
Fracture Healing Time abnormal	3	2
Fracture that require More Than One Reduction	15	7
Fracture that require Surgical Intervention	100	66
Fx Healing Complications incidence		
Chronic Pain	11	7
Delayed Healing	2	2
Malunion	3	3
Nonunion	1	0
Osteomyelitis	0	0
Other	7	10

Fracture healing substudy results: Only twenty-five subjects were enrolled in the Fracture Healing Substudy, 8 in the denosumab group and 17 in the placebo group. There were 197 subjects (107 in placebo and 90 in denosumab group) with wrist fracture. The applicant reasons that it was difficult to enroll patients in the fracture healing substudy following an acute fracture where regular scheduled visits occurred every 6 months. The mean age of the women enrolled was 72 years of age; 9 subjects were 75 years of age or older. One subject in the denosumab group and 2 subjects in the placebo group had delayed radiographic healing of a distal radius fracture. The fractures of all 3 subjects were healed by the time of the 6 month radiograph.

Reviewer's Comment:

- ***Overall, fracture healing complications were few and balanced between the treatment groups.***
- ***Only 25 subjects were enrolled in the fracture healing substudy. While applicant's justification for enrolling few subjects in the trial is reasonable, no conclusions can be made regarding fracture healing complications can be made based on the substudy.***
- ***Long term trial might be necessary to evaluate this potential adverse effect.***

Safety Conclusions:

- ***The number of subjects died during the trial was not higher in denosumab (70) compared to placebo (90) groups.***
- ***Serious adverse events were slightly higher in the denosumab group compared to placebo.***

- ***Clinical osteoporotic fractures (osteoporotic fractures with clinical signs and symptoms) were recorded as adverse events. Placebo group had more clinical fractures compared to denosumab group.***
- ***Subjects in the denosumab group developed hypocalcemia at month 1 at a higher frequency than placebo. However numbers of subjects were low and hypocalcemia was mild, transient and not accompanied by hypocalcemia related adverse events. This reviewer agrees hypocalcemia being a contraindication and in the warnings and precautions section of the label as the applicant proposed.***
- ***Even though the applicant did not find any positively adjudicated events of osteo necrosis of the jaw (ONJ) in this trial, it has been observed in other trials (in patients with malignancy). This reviewer agrees with the applicant to include ONJ in the warnings and precautions section of the labeling document.***
- ***Subjects in the denosumab group were more likely to have serious AE related to infections, and be hospitalized with infections (cellulitis) compared to placebo. There were 3 cases of endocarditis in denosumab group vs. none in placebo. "Streptococcal infections", which tend to occur through a epithelial or mucosal surface, occurred more frequently among denosumab subjects.***
- ***There were slightly higher numbers of subjects with malignancy in the denosumab group compared to placebo. However, baseline risk of these subjects was not available and numbers being small, it is difficult to interpret these numbers. Given experience with other monoclonal antibodies and the fact that denosumab has the potential to interact with multiple layers and processes within the immune system, this MO recommends postmarketing trial to assess effect of denosumab on infections, especially in high risk populations.***
- ***Overall, subjects in the denosumab group were more likely to develop skin and soft tissue related adverse events. There were more bullous conditions, pruritic conditions, skin rashes, dermatitis and eczema related adverse events in the denosumab group compared to placebo. This increase is clinically significant and should be included in the labeling document. There were 4 cases of toxic skin reactions in the denosumab group, while none in placebo.***
- ***Bone biopsy substudy showed that denosumab severely suppressed bone remodeling. This medical officer recommends postmarketing long-term trial to evaluate effect of denosumab on bone formation and resorption parameters to identify potential complications early.***
- ***There were no other 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.

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9.4.2 Trial 20040132

The title of the trial is "A Randomized Double-Blind Trial to Evaluate Denosumab in the Prevention of Postmenopausal Osteoporosis." The trial was conducted at 21 centers in North America (16 in the United States and 5 in Canada).

Objectives:

Primary

The primary objective of this trial 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 osteopenia (lumbar spine BMD T-score between -1.0 and -2.5).

The primary safety objective was to characterize the safety and tolerability of denosumab in this population based on adverse event incidences, changes in laboratory profiles, electrocardiograms (ECGs), and immunogenicity to denosumab.

Secondary

The secondary objectives were to assess the effect of denosumab on:

- a) BMD measured by DXA at the hip (total hip, femoral neck, and trochanter), distal radius, and total body (without head).
- b) trabecular, cortical, and total volumetric BMD measured by quantitative computerized tomography (QCT) at the distal radius in both early and late postmenopausal women with osteopenia.

Reviewer Comments:

- *These secondary efficacy endpoints listed in the trial report at Month 24 differ slightly from the secondary objectives listed in the protocol.*
- *The initial protocol lists BMD measurements at the proximal femur, distal radius, and total body as a secondary efficacy endpoint.*
- *Amendment 1 added trochanter to the list of anatomical sites of interest for BMD. This secondary efficacy endpoint is ultimately listed as: percent change in BMD of the total hip, femoral neck, trochanter, distal 1/3 radius, and total body after 24 months.*

Exploratory

Exploratory/Tertiary objectives were to evaluate the effect of denosumab on:

- a) changes in other QCT parameters measured at the distal radius;
- b) bone turnover, measured by serum concentrations of type 1 C-telopeptide (CTX1), tartrate-resistant acid phosphatase (TRAP) 5b, and intact N-terminal propeptide of type 1 procollagen (P1NP);

- c) currently available or newly developed bone markers that may become available;
- d) hip structural analysis (HSA) based on hip DXA.
- e) investigate the effects of genetic variation in drug metabolism genes, osteoporosis genes, and drug target genes on subject response to denosumab (optional procedure).

Off-treatment exploratory

Off-treatment exploratory objectives, which will be reported separately, are to evaluate:

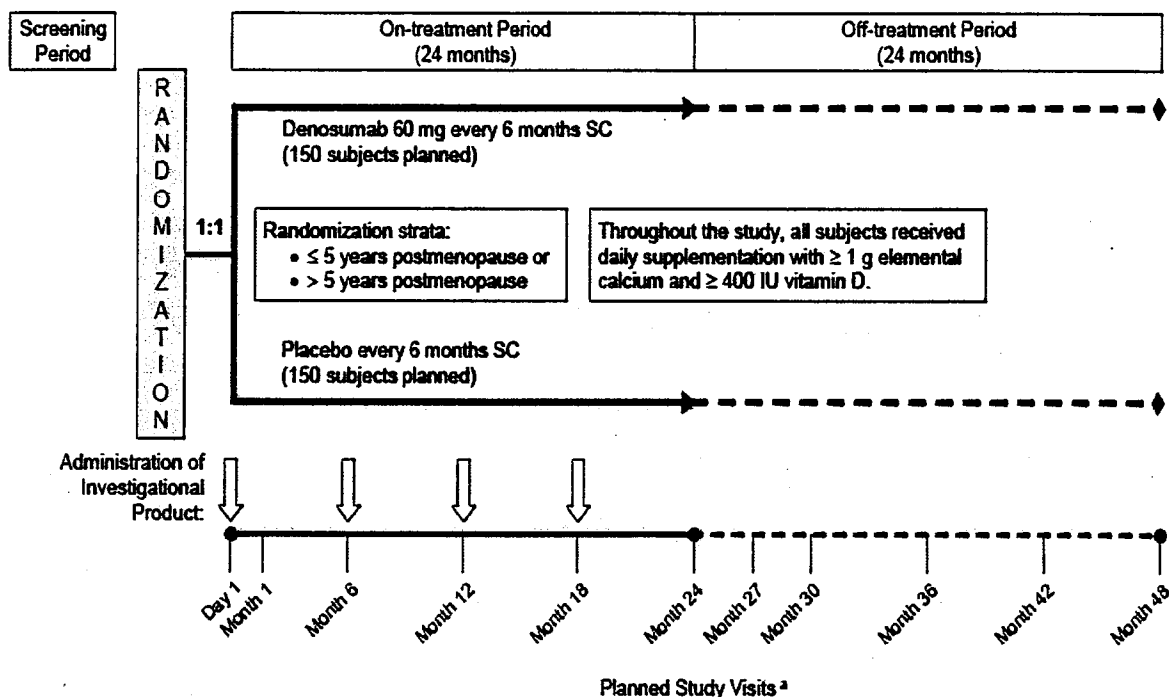
- a) changes in BMD and bone turnovers markers during the off-treatment period, and
- b) the safety profile of denosumab during the off-treatment period.

Trial Design:

This multicenter, randomized, double-blind, 2-period (on-treatment, off-treatment), parallel-group trial enrolled postmenopausal women with lumbar spine BMD T-score between -1.0 and -2.5. 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 1 g) and vitamin D (at least 400 IU) through month 48.

During the on-treatment period (baseline to month 24), subjects received blinded investigational product (60 mg denosumab or placebo) every 6 months (Q6M) subcutaneously (SC) (last dose at month 18). During the off-treatment period (months 25 to 48), administration of investigational product was discontinued. The trial is design is summarized below in Figure 18 below.

Figure 18. Schema for Trial 20040132



^a BMD of the lumbar spine was assessed at screening and at all planned study visits except day 1 and month 27; the assessment obtained during screening was used as the baseline assessment of the BMD of the lumbar spine.

Source: Clinical Trial Report for Trial 20040132 (24-month results), Figure 7-1 Trial Schema, page 53 of 2440.

The first 24 month part of the trial was conducted from 27 August 2004, when the first subject was enrolled, to 20 February 2007, when the last subject ended the on-treatment period. This is followed by 24 months of observation in the off-treatment period.

Population:

The trial population included ambulatory postmenopausal women with low bone mineral density as noted by a lumbar spine BMD T-score between -1.0 and -2.5 that had no history of bone fracture after 25 years of age. These subjects were not receiving medication that affected bone metabolism (other than calcium and vitamin D) and were free from any underlying condition that might have resulted in abnormal bone metabolism. See below for additional inclusion and exclusion criteria.

Inclusion Criteria

Subjects were eligible for this trial if they met all of the criteria listed below:

- Postmenopausal women

- If the subject was 6 to 12 months postmenopause, or if the subject's menopausal status was uncertain, the subject's menopausal status was confirmed by high serum follicle-stimulating hormone (FSH) (≥ 50 mIU/mL) or low serum estradiol (≤ 20 pg/mL).
- If the subject was > 12 months postmenopause based on medical history, an assessment of the subject's hormonal status was not required.
- Not more than 90 years of age
- Lumbar spine BMD T-score between -1.0 and -2.5 (ie, $-2.5 < \text{T-score} < -1.0$)
- Appropriate written informed consent provided before any trial-specific Procedure

Exclusion Criteria

Subjects were not eligible for this trial if they met any of the criteria listed below:

- Oral bisphosphonate administration
 - If used for ≥ 3 years cumulatively, subject was ineligible.
 - If used for > 3 months but ≤ 3 years cumulatively:
 - If the last dose was < 1 year before enrollment, subject was ineligible.
 - If the last dose was ≥ 1 year before enrollment, subject was eligible.
 - If used ≤ 3 months, subject was eligible.
- Administration of intravenous (IV) bisphosphonate, fluoride (for osteoporosis) or strontium within the last 5 years
- Administration of any of the following treatments within the last 6 weeks:
 - parathyroid hormone (PTH) or PTH derivatives, eg, teriparatide
 - anabolic steroids or testosterone
 - glucocorticosteroids (> 5 mg prednisone equivalent per day for more than 10 days)
 - systemic hormone replacement therapy
 - selective estrogen receptor modulators (SERMs), eg, raloxifene
 - tibolone
 - calcitonin
 - calcitriol
- Evidence of any of the following per subject report, chart review, DXA, or x-ray review:
 - Hyperthyroidism or hypothyroidism; subjects on stable thyroid treatment with a normal thyroid-stimulating hormone (TSH) were eligible
 - Current hyperparathyroidism or hypoparathyroidism
 - Current hypocalcemia (serum calcium < 2.13 mmol/L [8.5 mg/dL])
 - Vitamin D deficiency (25-OH vitamin D level < 12 ng/mL)
 - 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, eg, osteomalacia or osteogenesis imperfecta, which may interfere with the interpretation of the findings
- Malabsorption syndrome
- Height, weight, and girth which may preclude accurate DXA measurements
- Advanced scoliosis or extensive lumbar fusion
- History of any fracture occurring after the age of 25 years
- Presence of any vertebral fractures on screening spinal X-rays
- Less than 2 lumbar vertebrae (L1-L4) evaluable for DXA
- Known sensitivity to mammalian cell-derived drug products
- Any organic or psychiatric disorder, or laboratory abnormality which, in the opinion of the investigator, would prevent the subject from completing the trial or interfere with the interpretation of the trial results
- Evidence of alcohol or substance-abuse within the last 12 months that the investigator believes would interfere with understanding or completing the trial
- Subject had any kind of disorder that compromises the ability of the subject to give written informed consent and/or to comply with trial procedures.
- Subject was enrolled in or had not yet completed at least 30 days since ending other investigational device or drug trial(s), or subject was receiving other investigational agent(s).

Reviewer Comments:

- *The inclusion and exclusion criteria appear to be adequate.*
- *It is unclear if subjects had oral bisphosphonate administration < 3 months required a minimum wash-out period before being randomized to trial drug.*

Study Medication:

After a screening period of up to 56 days, subjects were randomized to blinded treatment with either denosumab or placebo. Subjects were classified by the number of years since menopause (≤ 5 years or > 5 years) and equally allocated (1:1) to treatment groups using a stratified randomization schedule developed using random permuted blocks. Blinded denosumab 60 mg (1 mL) or placebo (1 mL) was administered subcutaneously every 6 months (day 1 and at months 6, 12, and 18).

Concomitant medications:

All subjects received at least 1,000 mg elemental calcium and at least 400 IU vitamin D daily through month 48. Subjects received ≥ 400 IU vitamin D (if screening 25[OH] vitamin D was > 20 ng/mL) or ≥ 800 IU vitamin D (if screening 25[OH] vitamin D was 12 to 20 ng/mL). Trial investigators could prescribe any

concomitant medications or treatments that were necessary, except for those that might affect bone mass or bone metabolism. Medications that were proscribed during the trial included: bisphosphonates, adrenocorticotrophic hormone, fluoride (for osteoporosis), growth hormones, strontium, cinacalcet, systemic estrogen, lithium, selective estrogen receptor modulators (eg, raloxifene), systemic glucocorticoids, tibolone, protease inhibitors, calcitonin, chronic heparin or heparin derivatives (> 7 days), anabolic steroids, aromatase inhibitors, parathyroid hormone (or a derivative), anticonvulsants (benzodiazepines are allowed), calcitriol, methotrexate, chronic systemic ketoconazole (> 1 month), antineoplastic chemotherapeutics, androgens, and gonadotropin-releasing hormone agonists.

Reviewer Comments:

- ***Since the period just after menopause is associated with rapid bone turnover and accelerated bone loss, the enrollment was stratified by time since the onset of menopause (≤ 5 years or > 5 years). Primary efficacy analyses were conducted within each stratum, then for the strata combined.***
- ***At screening, if a particular subject had a 25 (OH) vitamin D level of < 12 ng/mL, the subject was repleted with vitamin D and could return for a repeat vitamin D test. If the repeat vitamin D level was < 12 ng/mL, then the subject was ineligible; if the repeat vitamin D level was between 12 and 20 ng/mL, then the subject was eligible for the trial and was instructed to take at least 800 IU vitamin D daily.***

Efficacy Measures

Trial tests and procedures were initiated only after written informed consent was obtained. All screening procedures were completed within 56 days before randomization, with the exception of the screening hematology and chemistry measurements which were completed within 1 month before day 1. During the trial, every effort was made to keep the subjects on schedule. The screening date was defined as the date the first trial-related procedure was performed, and day 1 was defined as the day that the initial dose of investigational product was administered to the subject.

- Month 1 visit: within ± 10 days of the scheduled day
- Months 6 through 48 visits: ± 28 days of the scheduled day
- Additional pharmacokinetic samples (after the second and third doses of investigational product): ± 1 week

BMD assessments by DXA of the lumbar spine, hip (total hip, femoral neck, and trochanter), distal 1/3 radius, and total body were performed according to the schedule of assessments. The same DXA machine was used for all trial

procedures for an individual subject. If possible, the left side was to be used for the hip and distal radius scans. Lumbar spine scans included L1 through L4.

Although not a primary or secondary endpoint, the trial also captured fractures, including new vertebral, non-vertebral and clinical fractures. For the purposes of this trial, these terms are defined as follows:

- **New Vertebral Fracture:** an incident vertebral fracture in a vertebra without a prevalent fracture at baseline (ie, an increase of at least 1 grade postbaseline from a baseline grade of 0). New vertebral fractures were defined based on X-rays using the Genant Semiquantitative Scoring Method.
- **Non-vertebral Fracture (Osteoporotic Fracture):** a fracture present on an x-ray and/or documented in a radiology report at sites typically associated with osteoporotic fractures (i.e., sacrum, coccyx, ribs, sternum, clavicle, scapula, humerus, radius, ulna, carpus, acetabulum, femur neck, femur intertrochanter, femur subtrochanter, femur midshaft, femur distal, patella, fibula, tibia, metatarsals, tarsus, ilium, ischium, and pubis). Fractures at sites not typically associated with osteoporosis (i.e., skull, facial, mandible, metacarpus, finger phalanges, and toe phalanges) were not included in this category. In addition, only fractures with the following characteristics were considered to be non-vertebral fractures: fall from standing height or less; falls on stairs, steps, or curbs; falls from about a height of approximately 20 inches; minimal to moderate trauma other than a fall.
- **Clinical Fracture:** a symptomatic new vertebral fracture or a non-vertebral fracture.

Primary Efficacy Endpoint

The primary objective of this trial 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 (≤ 5 years since menopause) and late (> 5 years since menopause) postmenopausal women with osteopenia (lumbar spine BMD T-score between -1.0 and -2.5). Primary efficacy analyses were conducted within each menopause stratum, then for the strata combined.

Secondary Efficacy Endpoints

The secondary objectives were to assess the effect of denosumab on:

- a) Percent change from baseline in BMD as measured by DXA at the hip (total hip, femoral neck, and trochanter), distal radius, and total body (without head) at 24 months
- b) Percent change from baseline in trabecular, cortical, and total volumetric BMD as measured by quantitative computerized tomography (QCT) at the distal radius at 24 months.

Tertiary Efficacy Endpoints

Exploratory on-treatment objectives were to evaluate the effect of denosumab on:

- Percent change from baseline in BMD of the lumbar spine, total hip, femoral neck, and trochanter at 1, 6, and 12 months
- Percent change from baseline in BMD of the distal 1/3 radius and total body at 12 months
- Percent of BMD responders (>0% change from baseline) in lumbar spine, total hip, femoral neck, and trochanter at 1, 6, 12, and 24 months
- Levels of BMD response ($\leq 0\%$, 0 to 3%, >3%) in lumbar spine, total hip, femoral neck, and trochanter at 1, 6, 12, and 24 months
- Percent change from baseline in bone markers (serum Type 1 CTX, TRAP 5b, and P1NP), at 1, 6, 12, 18 and 24 months of treatment
- Percent change from baseline in biomarkers (OPG, RANKL, iPTH)
- Percent change from baseline in other QCT parameters as deemed appropriate at 1, 6, 12, and 24 months of treatment
- Changes from baseline in hip structural analysis (HSA) parameters based on hip DXA at 24 months of treatment
- Incidence of new vertebral fractures at or before month 24
- Incidence and time to first clinical fracture at or before month 24

Off-treatment Period – Tertiary endpoints

Exploratory endpoints assessing the off-treatment effect of denosumab

- Percent change from the baseline in BMD of the lumbar spine, total hip, femoral neck and distal radius at months 30, 36, 42 and 48
- Percent change from the month 24 value in BMD of the lumbar spine, total hip, femoral neck and distal radius at months 30, 36, 42 and 48
- Percent change in BMD of the total body from the baseline and the month 24 value at month 36 and 48
- Percent change from the baseline value in bone turnover markers (serum Type 1 CTX, TRAP 5b, PINP) at months 27, 30, 36, 42, and 48
- Change from the month 24 value in bone turnover markers (serum Type 1 CTX, TRAP 5b, and P1NP) at months 27, 30, 36, 42, and 48
- Percent change from the baseline value in biomarkers (OPG, RANKL, iPTH) at months 24, 27, 30, 36, 42, and 48
- Incidence of new vertebral fractures during the 24-month off-treatment period
- Incidence and time to first clinical fracture during the 24-month off-treatment period

All efficacy endpoints are summarized in Table 112. Efficacy endpoints other than the primary and secondary endpoints described above were considered exploratory.

Table 112. Summary of Efficacy Endpoints

	Time Points of Interest (month)									
	1	6	12	18	24	27 ^c	30 ^c	36 ^c	42 ^c	48 ^c
Percent change from baseline in BMD (by DXA)										
Lumbar spine	X	X	X	-	X ^a	-	X	X	X	X
Total hip	X	X	X	-	X ^a	-	X	X	X	X
Femoral neck	X	X	X	-	X ^a	-	X	X	X	X
Trochanter	X	X	X	-	X ^a	-	X	X	X	X
Distal 1/3 radius	-	-	X	-	X ^a	-	X	X	X	X
Total body (without head)	-	-	X	-	X ^a	-	-	X	-	X
Percent change from baseline in QCT measures at distal radius										
Trabecular volumetric BMD (g/cm ³)	X	X	X	-	X ^a	-	-	-	-	-
Cortical volumetric BMD (g/cm ³)	X	X	X	-	X ^a	-	-	-	-	-
Total volume (cm ³)	X	X	X	-	X ^a	-	-	-	-	-
BMD responder and level of response										
Lumbar spine	X	X	X	-	X	-	-	-	-	-
Total hip	X	X	X	-	X	-	-	-	-	-
Femoral neck	X	X	X	-	X	-	-	-	-	-
Trochanter	X	X	X	-	X	-	-	-	-	-
Fracture Endpoints										
New vertebral fractures	-	-	-	-	X	-	-	-	-	X
Clinical fractures (incidence)	-	-	-	-	X	-	-	X	-	X
Clinical fractures (time to event)	Assessed continually									
Change in HSA endpoints (narrow neck, intertrochanter, and shaft)										
Bone mineral density (g/cm ²)	-	-	-	-	X	-	-	-	-	-
Cross-sectional area (cm ²)	-	-	-	-	X	-	-	-	-	-
Cross-sectional moment of inertia (cm ⁴)	-	-	-	-	X	-	-	-	-	-
Outer diameter (cm)	-	-	-	-	X	-	-	-	-	-
Section modulus (cm ³)	-	-	-	-	X	-	-	-	-	-
Endosteal diameter (cm)	-	-	-	-	X	-	-	-	-	-
Average cortical thickness (cm)	-	-	-	-	X	-	-	-	-	-
Average buckling ratio	-	-	-	-	X	-	-	-	-	-
Actual, change and percent change from baseline in bone markers (CTX1, TRAP 5b, P1NP)	X	X	X	X	X	X	X	X	X	X
Actual, change and percent change from baseline in biomarkers (OPG, RANKL, iPTH)	-	-	-	-	X	X	X	X	X	X

X = assessment done at the indicated time point; -- = assessment not done at the time point
BMD = bone mineral density; CTX1 = serum type 1 C-telopeptide; DXA = dual energy x-ray absorptiometry; HSA = hip structural analysis; iPTH = intact parathyroid hormone; OPG = osteoprotegerin; P1NP = procollagen type 1 N terminal peptide; QCT = quantitative computerized tomography; RANKL = receptor activator of nuclear factor- κ B ligand; TRAP 5b = tartrate resistant acid phosphatase 5b

a Primary efficacy endpoint;
b Secondary efficacy endpoints
c Change measures at post-24-month time points will be taken with respect to baseline and with respect to month 24.
Source: Clinical Trial Report for Trial 20040132 (24-month results), Table 7-2, page 83 of 2440.

Safety Measures:

The primary safety objective was to characterize the safety and tolerability of denosumab in postmenopausal women with osteopenia based on adverse event incidences, changes in laboratory profiles, electrocardiograms (ECGs), and immunogenicity to denosumab.

Trial Methods:

Scheduled tests and procedures were to be performed within the following windows.

- Month 1 visit: within ± 10 days of the scheduled day
- Months 6 through 48 visits: ± 28 days of the scheduled day
- Pharmacokinetic samples (after the second and third doses of trial drug): ± 1 week

The schedule of assessments during the trial are summarized below in Figure 19.

Figure 19 Schedule of Assessments

Procedures	Screen-ing	Day 1 ^a	On-treatment Period							Off-treatment Period				
			Study Month											
			1	6	Post-2 nd Dose PK ^b	12	Post-3 rd Dose PK ^b	18	24 ^c	27	30	36	42	48 ^c
Medical and medication history	X	-	-	-	-	-	-	-	-	-	-	-	-	-
25(OH) vitamin D	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Physical exam	X	X ^d	-	-	-	X	-	-	X	-	-	X	-	X
Vital signs	X	X	X	X	-	X	-	X	X	X	X	X	X	X
ECG	-	X ^e	X	-	-	X	-	X	X	-	-	-	-	-
Lateral spine x-ray	X	-	-	-	-	-	-	-	X	-	-	-	-	X
DXA spine	X	-	X	X	-	X	-	-	X	-	X	X	X	X
DXA hip	-	X	X	X	-	X	-	-	X	-	X	X	X	X
DXA distal 1/3 radius	-	X	-	-	-	X	-	-	X	-	X	X	X	X
DXA total body (without head)	-	X	-	-	-	X	-	-	X	-	-	X	-	X
QCT distal radius	-	X	X	X	-	X	-	-	X	-	-	-	-	-
Serum chemistry panel (Table 7-8)	X	X	X	X	-	X	-	X	X	X	X	X	X	X
Hematology panel (Table 7-8)	X	X	-	X	-	X	-	X	X	X	X	X	X	X
Bone turnover markers ^f (Table 7-8)	-	X	X	X	X ^g	X	X ^g	X	X	X	X	X	X	X
Biomarkers (Table 7-8)	-	X ^h	-	-	-	-	-	-	X	X	X	X	X	X
Anti-denosumab antibody	-	X	X	X	-	X	-	X	X	-	-	-	-	-
Investigational product administration	-	X	-	X	-	X	-	X	-	-	-	-	-	-
Concomitant medications	-	X	X	X	-	X	-	X	X	X	X	X	X	X
Adverse event collection and clinical fracture recording	-	-	X	X	-	X	-	X	X	X	X	X	X	X
Serum denosumab level	-	X	X	X	X	X	X	X	X	X	X	X	-	-
Biomarker archive samples	-	X	X	-	-	X	-	-	X	X	X	X	X	X
Pharmacogenetic sample	-	X	-	-	-	-	-	-	-	-	-	-	-	-

- a Day 1 procedures were completed before dosing.
 - b The first additional PK visit was 3.5 to 5 months (16 to 21 weeks) after the 6-month dose. The second additional PK visit was 1.5 to 3.5 months (6 to 15 weeks) after the 12-month dose.
 - c If the subject withdrew prior to the month 24 visit, all procedures planned for the month 24 visit were conducted. If the subject withdrew after month 24, all procedures planned for the month 48 visit were conducted.
 - d Not necessary if baseline was within 1 week of screening.
 - e Three independent 12-lead ECGs were required before administration of trial drug.
 - f Samples taken in fasting subjects before dose administration. Day 1 blood samples for CTX1 and TRAP 5b were taken before dosing and 6 to 8 hours following dosing (fasting not required for second sample).
 - g Only CTX1 and P1NP at these visits
 - h Retrospective testing of OPG/RANKL/iPTH
- Source: Clinical Trial Report for Trial 20040132 (24-month results), Figure 7-7, page 69 of 2440.

The panels include the following analytes:

- **Serum chemistry:** albumin, albumin-adjusted calcium, total alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, magnesium, potassium, phosphorus, sodium, total bilirubin, total protein.
- **Hematology:** red blood cell (RBC) count, hemoglobin concentration, reticulocyte count, platelet count, white blood cell (WBC) count with differential count (neutrophils, bands/stabs, eosinophils, basophils, lymphocytes, and monocytes).
- **Bone turnover markers:** serum type 1 C-telopeptide (CTX1), tartrate-resistant acid phosphatase (TRAP) 5b, intact N-terminal propeptide of type 1 procollagen (P1NP).
- **Biomarkers:** osteoprotegerin (OPG), receptor activator of nuclear factor- κ B ligand (RANKL), intact parathyroid hormone (iPTH)

The analyte results were blinded, except that panic values were provided to the sites as needed.

Withdrawal criteria:

Every subject had the right to withdraw fully or partially from the trial at any time and for any reason without prejudice to her future medical care by the physician or the institution. *Withdrawal of full consent* meant that the subject did not wish to receive further investigational treatment and did not wish to or was unable to continue further trial participation. *Withdrawal of partial consent* meant that the subject did not wish to take investigational product any longer but was still willing to participate in all subsequent trial visits or procedures. A subject who withdrew consent to participate in the trial was removed from further treatment and/or trial observation immediately upon the date of request.

The investigator and applicant also had the right to withdraw subjects from the trial in the event of intercurrent illness, adverse events, protocol violation, or other reasons. Subjects could be removed from trial for any of the following reasons:

- withdrawal of consent
- administrative decision by the investigator or applicant
- ineligibility
- significant protocol deviation
- subject noncompliance
- adverse event (which may include disease progression)

If a subject withdrew from the trial, all efforts were made to complete and report trial-scheduled observations as thoroughly as possible up to the date of withdrawal. In addition, if a subject withdrew prior to completion of the trial, an early termination visit was to be performed when possible. If a subject withdrew prior to the month 24 visit, then all procedures normally done at the month 24 visit were to be conducted. If a subject withdrew after month 24, all procedures from the month 48 visit were to be conducted.

If a subject experienced an osteoporosis-related fracture or a significant decrease in BMD, the investigator was to evaluate the clinical data and discuss alternative treatment options with the subject. If a decision was made to remove the subject from trial medication, every effort was to be made to complete all her remaining trial visits. Enrolled subjects who were removed from the trial were not replaced.

Statistical Analyses

The Statistical Analysis Plan (SAP) (version 3.0 dated 16 March 2007) was provided by the applicant in the initial BLA submission. The SAP was amended twice during the trial; these changes were made before database lock and unblinding the data.

After the database was unblinded, systematic biases were identified in the QCT data. These were conveyed to the imaging vendor (b) (4). The imaging vendor traced the data inconsistencies to the CT instruments used across sites, then revised its analyses to improve data standardization. The imaging vendor remained blinded to subject treatment assignment throughout these assessments and revisions. A new dataset was submitted to the applicant and the QCT data were reanalyzed using the planned statistical programs.

Reviewer Comment:

The Applicant identified biases in QCT data after unblinding. The imaging vendor identified the source of the bias and revised its analyses. Although

the imaging vendor was blinded, perhaps the Applicant influenced the vendor in its revised analyses.

The trial design included 2 periods:

- On-treatment period - baseline through month 24
- Off-treatment period - months 25 through 48

In the initial BLA submission, only data for the on-treatment period was summarized.

Three analyses were planned for this trial:

- 24-month analysis (provided in the initial BLA submission)
- Two exploratory analyses of the off-treatment effect of denosumab at:
 - 36 months
 - 48 months

The Applicant calculated that a sample size of 75 subjects per menopause stratum per treatment group had 90% power to detect a 2 percentage point (SD of 3.25) difference from baseline in lumbar spine BMD between denosumab and placebo within each menopause stratum, assuming a type 1 error rate of 0.025. The calculation accounted for 5% of subjects per year being lost to follow-up.

All efficacy analyses were performed according to subjects' original randomized treatment assignment, regardless of treatment received. All efficacy endpoints were summarized and analyzed separately within each of the randomized early or late menopause and overall.

Primary Efficacy Endpoint:

The primary analysis methodology was the comparison between denosumab and placebo in the percent change from baseline in the lumbar spine BMD (by DXA) at 24 months of treatment, stratified by the number of years since menopause (≤ 5 years or > 5 years).

The primary efficacy analysis was performed on all randomized subjects who had a baseline and at least 1 postbaseline evaluation. Missing baseline BMD at any anatomical site was not imputed. The primary analysis used the last observation carried forward (LOCF) approach (missing postbaseline values were imputed using the last previous postbaseline value). The overall significance level for testing the primary endpoints was controlled at 0.05 by using a Bonferroni adjustment split equally between early ($\alpha = 0.025$ for ≤ 5 years since menopause) and late ($\alpha = 0.025$ for > 5 years since menopause) postmenopausal osteopenic women. The Hochberg procedure and hierarchical testing strategy were used to control type I error for multiple comparisons.

To assess the robustness of the ANCOVA LOCF analysis, supportive analyses were performed using the MOTH imputation (mean of the other group) of missing postbaseline values. Specifically, in subjects with missing postbaseline BMD data, identify other subjects with similar baseline characteristics (e.g., length of time since menopause, baseline BMD values) and replace the missing BMD value by the mean BMD at the same time point from subjects with the same baseline categories in the other treatment group.

Sensitivity analyses were conducted within each randomized menopause stratum and overall to evaluate the robustness of the ANCOVA LOCF analysis as follows:

- *Method of imputation:* analyses were performed using the MOTH imputation for missing lumbar spine BMD at month 24. This analysis was based on the primary efficacy subset using the ANCOVA model.
- *Alternate model:* the repeated measures model was applied to data through month 24. The least-squares mean estimate for the treatment difference at month 24 was presented with corresponding confidence interval and p-value.

Secondary Efficacy Endpoints

The principal secondary endpoints at 24 months were the comparisons between denosumab and placebo in percent change from baseline in BMD (by DXA) of the total hip, femoral neck, trochanter, distal 1/3 radius, and total body (without head) and the percent change from baseline in trabecular, cortical, and total volumetric BMD of the distal radius as measured by QCT.

Missing baseline BMD at any anatomical site was not imputed. The primary analysis used the LOCF approach, similar to that used for the primary endpoint. Type I errors for multiple comparisons were controlled for as follows:

- Statistical inferences of the treatment effect on the secondary efficacy endpoints were only made if the treatment effect on the primary efficacy endpoint was declared statistically significant between denosumab and placebo.
- Hochberg's procedure was employed for multiplicity adjustment of the secondary efficacy endpoints to maintain the overall 2-sided significance level within each time-since-menopause stratum at 0.025.

In addition, the number and percentage of subjects with at least 1 new vertebral fracture and clinical fracture over the 24-month treatment period for the menopause strata and overall were summarized by treatment group. Time to first clinical fracture was summarized using the Kaplan-Meier estimates to estimate the cumulative incidence of fractures during the 24-month treatment period. Subjects who withdrew from IP, but continued trial were followed for fracture endpoints. Subjects lost to follow-up or withdrawn from trial who had not yet experienced any event were considered censored at the trial day of last on-trial contact.

Reviewer's Comments:

- ***Only the 24-month results for this trial were provided in the initial BLA submission and were reviewed herein.***

The following additional subset analyses were conducted:

- ***Per Protocol Subset:*** included subjects in the Primary Efficacy Subset who were compliant with the protocol (received ≥ 3 doses of IP) and did not have deviations from the key entry criteria. If a subject received the incorrect IP or had an important protocol deviation, all data collected after the first occurrence of either were excluded from analyses in this subset.
- ***Observed Data Subset:*** included subjects who were randomized and had values of the endpoint at the time of interest. For endpoints that required values at baseline and at the time of interest (e.g., change and percent change), this subset included subjects who had the necessary values. Subjects in this subset were analyzed according to their original randomized treatment assignment, regardless of the actual treatment received.
- ***Full Analysis Subset:*** included all randomized subjects. Subjects in the full analysis subset were analyzed according to their original randomized treatment assignment, regardless of the actual treatment received. This analysis subset was used for the time-to-first-clinical-fracture endpoint.
- ***Safety Subset:*** included all randomized subjects who received at least 1 dose of trial drug. These subjects were analyzed according to their actual treatment received; subjects who received at least 1 dose of denosumab were analyzed in the denosumab treatment group regardless of the randomized treatment. Subjects without a value for a particular safety endpoint were excluded from the analysis of that endpoint.
- ***Pharmacokinetic Analyses Subset:*** included all randomized subjects who received at least 1 dose of denosumab and had at least 1 serum concentration level.

Subgroups

The primary efficacy endpoint was analyzed within each menopause stratum using the ANCOVA model for each of the following subgroups:

- Age (< 65 years, ≥ 65 years)
- Race (Caucasian, non-Caucasian)
- Baseline weight (kg) (< 55, 55 to < 65, 65 to < 75, 75 to < 85, and ≥ 85)
- Baseline BMI (kg/m^2) (< 22, 22 to < 24, 24 to < 26, 26 to < 30, and ≥ 30)
- Previous bisphosphonate use (Yes, No)
- Previous SERM use (Yes, No)

The analyses of these subgroups were exploratory and conducted only if there were at least 10% of subjects within each subcategory.

Planned Covariates

Efficacy endpoints were analyzed separately within each menopause stratum. The primary efficacy endpoint within each menopause stratum also was analyzed adjusting for each of the following covariates separately as well as adjusting for all of the following covariates simultaneously.

- Age
- Race (Caucasian, non-Caucasian)
- Baseline weight (kg)
- Baseline body mass index (BMI) (kg/m^2)

Statistical Models for Efficacy Endpoints

ANCOVA Model

Within each menopause stratum, the ANCOVA model included fixed effects for treatment, baseline value of the endpoint, machine type (Hologic or Lunar), and machine type-by-baseline value interaction. For overall subjects, the ANCOVA model included fixed effects for treatment, early or late menopause stratum (stratification factor), baseline value of the endpoint, machine type (Hologic or Lunar), and machine type-by-baseline value interaction. The terms of machine type (Hologic or Lunar) and machine type by baseline value interaction were excluded from the model statements above for the HSA and QCT endpoints. The least-squares mean of the treatment difference (denosumab – placebo) and the corresponding confidence interval were summarized by time points of interest for each time-since-menopause strata as well as for overall.

Repeated Measures Model

The repeated measures model was used to analyze parameters (such as BMD) derived by DXA and QCT.

Within each early or late menopause strata, the repeated measures model included treatment, visit, baseline value of the endpoint, machine type (Hologic or Lunar), treatment-by-visit interaction, and machine type by baseline value interaction as fixed effects using an unstructured variance-covariance structure.

For overall subjects, the repeated measures model included treatment, early or late menopause stratum (stratification factor), visit, baseline value of the endpoint, machine type (Hologic or Lunar), treatment-by-visit interaction, and machine type-by-baseline value interaction as fixed effects using an unstructured variance-covariance structure.

The point estimates for the least-squares means and the corresponding confidence interval were presented at the time point(s) of interest for each menopause strata as well as for overall.

Protocol Amendments

The initial protocol was submitted on 24 June 2004.

Amendment 1 dated 20 June 2005 provided for the following changes in the protocol:

- Two visits were added to obtain additional pharmacokinetic, CTX1, and P1NP samples. The purpose of the additional samples is to produce a more uniform distribution of sampling times throughout the 6-month dosing interval.
- The list of proscribed therapy of drugs known or suspected to have activity on bone metabolism was made more comprehensive.
- Change to the timing of trial procedures so that only blood draws were required before noon. Imaging procedures could be done on different days than other procedures, but had to be done within a 1-week window and prior to trial drug dose.
- The consent form was revised to reflect the use of a diary to record adverse events and concomitant medications and the 2 additional visits for pharmacokinetic sampling.
- The safety profile section was updated to include an event of hypocalcemia that occurred in a subject on another trial. The standard denosumab template consent form was updated to include this event and the number of subjects exposed.
- Trochanter was added to the list of anatomical sites of interest for BMD.
- Clarification of the endpoints and analysis methods to ensure consistency between the protocol and the planned analysis. Changes were made to the endpoints for QCT, HSA, and ECG related to what can be measured and analyzed with the technologies available and in keeping with the exploratory nature of some of these endpoints.
- The planned subgroup analysis to assess the consistency and robustness of the treatment effects was defined. Additionally, explorative analyses were included to assess the impact of various clinical risk factors for fractures on treatment effects, such as baseline bone turnover markers, substance exposure, and parental fracture history.
- Supplementation and repletion with vitamin D was clarified.
- The blinding of serum calcium, albumin-adjusted calcium, total alkaline phosphatase, and phosphorus lab values to the site was added.

Amendment 2 dated 21 August 2006 mainly extended the current trial for 2 years to describe the safety profiles during the denosumab off-treatment period as well the off-treatment effect on BMD and bone turnover markers.

Amendment 3 dated 06 February 2008 contained minor administrative changes and the following change to the statistical analysis, performed prior to database lock:

Prior to database lock for month 24, the active treatment phase, the Statistical Analysis Plan was amended to change the primary analysis model from repeated measures to ANCOVA with LOCF in order to conform to current regulatory reporting practices. The statistical section in the protocol is also being amended to separate the analyses (e.g. safety) for the on-treatment and off-treatment periods in order to more accurately document and report those events temporally related to active drug exposure.

Reviewer's Comment:

- ***The applicant noted the following in the 36 Month Trial Report:
"At the suggestion of FDA reviewers, the primary analysis method for primary and secondary efficacy endpoints was changed from a repeated measures model with no imputation of missing data to an ANCOVA model with LOCF imputation of missing data."***
- ***The statistical reviewer did not identify any statistical issues in this trial.***

Results

Subject Disposition:

There were slightly more discontinuations in the recently menopausal group, with 85% of this group completing the trial at 24 months and 88% completion rate for subjects who were more than 5 years since menopausal. There was a slightly higher rate of discontinuation of IP in recently menopausal women who were randomized to denosumab (12%) as compared to the placebo group (10%).

Table 113. Subject Disposition in the first 24 Months of Trial 20040132

	≤ 5 years since menopause			> 5 years since menopause			Overall		
	Placebo	Denos.	All	Placebo	Denos.	All	Placebo	Denos.	All
	(N=81) n (%)	(N=81) n (%)	(N=162) n (%)	(N=85) n (%)	(N=85) n (%)	(N=170) n (%)	(N=166) n (%)	(N=166) n (%)	(N=332) n (%)
Randomized	81 (100)	81 (100)	162 (100)	85 (100)	85 (100)	170 (100)	166 (100)	166 (100)	332 (100)
Completed	70 (86)	67 (83)	137 (85)	74 (87)	75 (88)	149 (88)	144 (87)	142 (86)	286 (86)
• Completed* IP	66 (81)	63 (78)	129 (80)	72 (85)	73 (86)	145 (85)	138 (83)	136 (82)	274 (83)
• Discontin. IP	4 (5)	4 (5)	8 (5)	2 (2)	2 (2)	4 (2)	6 (4)	6 (4)	12 (4)
Didn't Complete	11 (14)	14 (17)	25 (15)	11 (13)	10 (12)	21 (12)	22 (13)	24 (14)	46 (14)
• Completed* IP	3 (4)	2 (2)	5 (3)	0 (0)	1 (1)	1 (1)	3 (2)	3 (2)	6 (2)
• Discontin. IP	8 (10)	10 (12)	18 (11)	10 (12)	9 (11)	19 (11)	18 (11)	19 (11)	37 (11)
• Never got IP	0 (0)	2 (2)	2 (1)	1 (1)	0 (0)	1 (1)	1 (1)	2 (1)	3 (1)

IP = Investigational Product

* Subjects completed IP if they received all 4 planned doses.

Source: Clinical Trial Report for Trial 20040132 (24-month results), Table 8-1, page 111 of 2440.

The most common reasons for trial discontinuation were withdrawal of consent and subjects lost to follow-up. Adverse events were reported as the reason for trial discontinuation in 1% of subjects, regardless of treatment randomization.

Table 114. Reasons for Trial Discontinuation in the first 24 Months of Trial 20040132

	≤ 5 years since menopause			> 5 years since menopause			Overall		
	Placebo	Denos.	All	Placebo	Denos.	All	Placebo	Denos.	All
	(N=81) n (%)	(N=81) n (%)	(N=162) n (%)	(N=85) n (%)	(N=85) n (%)	(N=170) n (%)	(N=166) n (%)	(N=166) n (%)	(N=332) n (%)
Randomized	81	81	162	85	85	170	166	166	332
Discontinued prior to 24 mos	11 (14)	14 (17)	25 (15)	11 (13)	10 (12)	21 (12)	22 (13)	24 (14)	46 (14)
• Ineligible	0 (0)	2 (2)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	2 (1)
• Protocol deviation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
• Noncompliance	0 (0)	2 (2)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	2 (1)
• Adverse event	2 (2)	0 (0)	2 (1)	0 (0)	1 (1)	1 (1)	2 (1)	1 (1)	3 (1)
• Consent withdrawn	6 (7)	6 (7)	12 (7)	9 (11)	4 (5)	13 (8)	15 (9)	10 (6)	25 (8)
• Subject request	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
• Disease progression	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
• Req. alternative therapy	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
• Administrative decision	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
• Lost to follow-up	3 (4)	3 (4)	6 (4)	2 (2)	4 (5)	6 (4)	5 (3)	7 (4)	12 (4)
• Death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
• Pregnancy	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
• Other	0 (0)	1 (1)	1 (1)	0 (0)	1 (1)	1 (1)	0 (0)	2 (1)	2 (1)

Source: Clinical Trial Report for Trial 20040132 (24-month results), Table 8-8 pages 128-129 of 2440.

More subjects in the placebo group (11%) withdrew trial consent as compared to denosumab (5%) in women more than 5 years since menopause. More subjects in the denosumab group (5%) were lost to follow-up as compared to placebo (2%) in women more than 5 years since menopause.

Reviewer's Comments:

- **Adverse events were the reason for trial discontinuation in only 1% of subjects and did not appear to differ by treatment randomization.**

- ***The higher number of subjects lost to follow-up in the denosumab group of women more than 5 years since menopause may represent subjects who were experiencing adverse events and chose to discontinue therapy.***

The reasons for trial discontinuation in the first 12 months off-treatment were summarized in the 36-month trial report. Among the 128 subjects randomized to placebo, 8% discontinued from the trial, primarily by withdrawing consent. Among the 128 subjects randomized to denosumab, 9% discontinued from the trial with 5% withdrawing consent and 4% lost to follow-up.

Table 115. Reasons for Trial Discontinuation During the First 12 Months of Off-Treatment Phase of Trial 20040132

	Placebo	Denosumab	All
	n (%)	n (%)	n (%)
Randomized	166	166	332
Enrolled in the off-treatment phase	128	128	256
Discontinued in the first 12 months of off-treatment period	10 (8)	12 (9)	22 (9)
• Consent withdrawn	8 (6)	6 (5)	14 (5)
• Lost to follow-up	1 (<1)	5 (4)	6 (2)
• Other	1 (<1)	1 (<1)	2 (<1)
Ongoing at month 12 during off-treatment phase	118 (92)	116 (91)	234 (91)

Source: Clinical Trial Report for Trial 20040132 (36-month results), Table 11-1.2.2, page 125 of 2181.

Reviewer Comments:

Overall the rate of discontinuation from trial seems reasonable for a trial of this duration for an indication which is not symptomatic.

Overall there were no major differences between subjects randomized to denosumab or placebo, except that there were slightly more subjects in the denosumab group who were lost to follow-up.

One cannot rule out that the slightly higher number of denosumab subjects lost to follow-up may have been due to adverse events.

Protocol Violations:

The applicant considered a subject to have had an important protocol deviation if she: did not meet eligibility criteria, missed more than 2 doses of trial drug, missed assessments of the primary endpoint, received excluded medications

during the trial, received the incorrect treatment assignment, or was not withdrawn from trial after meeting trial withdrawal criteria. The important on-trial protocol deviations during the first 24 months of the trial are summarized below in Table 116.

Table 116. Important On-trial Protocol Deviations in the First 24 Months of Trial 20040132

	≤ 5 years since menopause			> 5 years since menopause			Overall		
	Plac.	Denos.	All	Plac.	Denos.	All	Plac.	Denos.	All
	(N=81) n (%)	(N=81) n (%)	(N=162) n (%)	(N=85) n (%)	(N=85) n (%)	(N=170) n (%)	(N=166) n (%)	(N=166) n (%)	(N=332) n (%)
No. w/ ≥ 1 impt inclus, /exclus, criteria or on-study protocol violation	18 (22)	8 (10)	26 (16)	11 (13)	11 (13)	22 (13)	29 (17)	19 (11)	48 (14)
Inclusion criteria violation	5 (6)	1 (1)	6 (4)	5 (6)	3 (4)	8 (5)	10 (6)	4 (2)	14 (4)
Exclusion criteria violation	3 (4)	3 (4)	6 (4)	3 (4)	1 (1)	4 (2)	6 (4)	4 (2)	10 (3)
Exclusionary medication taken on study	4 (5)	4 (5)	8 (5)	1 (1)	3 (4)	4 (2)	5 (3)	7 (4)	12 (4)
Investigational product administration	5 (6)	0 (0)	5 (3)	2 (2)	3 (4)	5 (3)	7 (4)	3 (2)	10 (3)
Missing data	1 (1)	0 (0)	1 (1)	0 (0)	1 (1)	1 (1)	1 (1)	1 (1)	2 (1)
DXA not done	1 (1)	0 (0)	1 (1)	0 (0)	1 (1)	1 (1)	1 (1)	1 (1)	2 (1)

Source: Clinical Trial Report for Trial 20040132 (24-month results), Tables 14-1.4.1, 14-1.4.2., and 14-1.4.3., pages 224-227 of 2440.

For subjects enrolled in the first 12 months of the off-treatment phase, there were no important on-trial protocol deviations during the off-treatment phase.

Reviewer comments:

- *The number of subjects with one or more important inclusion or exclusion criteria or protocol violations was equal or less in the denosumab group compared to placebo.*
- *The reported violations appear to be random and are acceptable to this reviewer.*

Demographics:

The mean (SD) age of subjects enrolled in the trial was 59.4 (7.5) years with 22% of enrolled subjects ≥ 65 years of age. The age range at enrollment was 43-83 years and the median was 58 years. The mean (SD) weight was 68.13 (12.54) kg with a mean BMI of 26.4 (4.8) kg/m². The onset of menopause was ≤ 5 years for 162 subjects (48.8%) and > 5 years for 170 subjects (51.2%). The overall percentages for each stratum within each treatment group were similar as for the overall population.

All subjects in the trial were female; the majority (83%) identified themselves as White or Caucasian. The trial enrolled very few Asians, Japanese or American Indian/Native Alaskans; these groups comprised 4%, 1% and $<1\%$ of the overall trial population.

Table 117. Demographics for Trial 20040132

	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)
Baseline Total Hip BMD T-score, mean (SD)	-1.01 (0.71)	-0.98 (0.7)
Fracture risk by FRAX tool		
10-year osteoporotic fracture risk	9.5%	10%
10-year hip fracture risk	0.8%	1.0%

Source: Clinical Study Report for Trial 20040132 (24-month results), Table 8-5, pages 120-122 of 2440

Overall, the baseline mean (SD) BMD T-score at the lumbar spine was -1.61 (0.42) (range: -0.5 to -2.6). Mean baseline BMD T-scores were similar for the treatment groups and for the time-since-menopause strata. Mean baseline BMD T-scores for the total hip, femoral neck, trochanter, and distal 1/3 radius also were similar for the treatment groups and for the time-since-menopause strata.

Table 118. Baseline Bone Mineral Density T-Scores (by DXA) for Trial 20040132 at 24 Months

T-Scores	n	Mean	SD	Min	Q1	Med	Q3	Max
Lumbar spine BMD T-score								
• Placebo (N=166)	166	-1.66	0.44	-2.5	-2	-1.7	-1.3	-0.5
• Denosumab 60 mg Q6M (N=166)	165	-1.55	0.41	-2.6	-1.8	-1.5	-1.3	-0.8
• All (N=332)	331	-1.61	0.42	-2.6	-1.9	-1.6	-1.3	-0.5
Total hip BMD T-score								
• Placebo (N=166)	165	-1.01	0.71	-3.1	-1.4	-1	-0.5	1.5
• Denosumab 60 mg Q6M (N=166)	165	-0.98	0.7	-2.8	-1.4	-1	-0.6	1
• All (N=332)	330	-0.99	0.7	-3.1	-1.4	-1	-0.5	1.5
Femoral neck BMD T-score								
• Placebo (N=166)	165	-1.46	0.69	-3.6	-1.9	-1.6	-1	0.4
• Denosumab 60 mg Q6M (N=166)	165	-1.5	0.65	-3.2	-1.9	-1.6	-1.1	1.3
• All (N=332)	330	-1.48	0.67	-3.6	-1.9	-1.6	-1.1	1.3
Trochanter BMD T-score								
• Placebo (N=166)	165	-0.87	0.68	-2.6	-1.3	-0.9	-0.5	2
• Denosumab 60 mg Q6M (N=166)	165	-0.85	0.77	-2.6	-1.4	-0.9	-0.3	1.3
• All (N=332)	330	-0.86	0.73	-2.6	-1.3	-0.9	-0.4	2
Distal 1/3 radius BMD T-score								
• Placebo (N=166)	165	-0.85	1.19	-4.9	-1.4	-0.7	-0.1	1.8
• Denosumab 60 mg Q6M (N=166)	164	-0.74	1.06	-3.4	-1.4	-0.6	0	1.6
• All (N=332)	329	-0.8	1.13	-4.9	-1.4	-0.6	-0.1	1.8

n = number of subjects with data at baseline; N = number of randomized subjects.

Source: Clinical Trial Report for Trial 20040132 (24-month results), Table 8-6, page 125 of 2440.

If a subject had a prior history of any fracture after the age of 25 years, they were excluded from the trial. There were 12% of subjects in the denosumab group and 11% of subjects in the placebo group with a fracture prior to the age of 25 years (any type). No subjects had a prior history of hip fracture and 1 subject in the denosumab group had a prior history of vertebral fracture. Based on baseline x-rays evaluated by the central imaging vendor, prevalent vertebral fractures were present in 4 subjects in the denosumab group and 6 subjects in the placebo group.

For the 128 subjects in each treatment group that were monitored in the off-treatment period, the baseline demographics were very similar to those of the

subjects enrolled in the treatment period. The mean (SD) age of subjects continuing into the off-treatment period was 59.1 (7.1) years and 20% of enrolled subjects were ≥ 65 years of age. Mean (SD) years since menopause for subjects continuing in the off-treatment period was 9.9 (8.5) years. The mean (SD) lumbar spine BMD T-score was -1.61 (0.43) with a range of -2.6 to -0.5. Overall, 11% of subjects enrolled had a history of a prior fracture (any type), with 10% in the placebo group and 12% in the denosumab group. A total of 5% of placebo and 6% of denosumab subjects had a prior non-vertebral fracture. There were no prior vertebral fractures in either group.

Reviewer comments:

- *The majority subjects were White or Caucasian, representing 83% of the overall trial population*
- *Minorities were poorly represented with Hispanics, Blacks and Asians representing 7%, 4% and 4%, respectively, of the overall trial population.*
- *According to the National Osteoporosis Foundation, low bone mass is estimated to occur in women ≥ 50 years of age in approximately 50% of non-Hispanic Caucasians, Asian and Hispanic women and 35% of non-Hispanic black women (<http://www.nof.org/osteoporosis/diseasefacts.htm>).*
- *Asian, Hispanic, and black women appear to have been underrepresented in this trial. However, this is acceptable because it is often difficult to recruit minority subjects in studies.*
- *The number of subjects with prior fractures was balanced between the two treatment groups.*
- *The subjects enrolled in the off-treatment period appear to be very similar to those enrolled in the on-treatment period.*

Concomitant Medications:

Calcium and vitamin D supplementation was required during the trial. Subjects received daily supplementation of ≥ 1 g elemental calcium and either ≥ 400 IU vitamin D (if screening 25[OH] vitamin D was > 20 ng/mL) or ≥ 800 IU vitamin D (if screening 25[OH] vitamin D was ≥ 12 to ≤ 20 ng/mL).

In addition, investigators could prescribe any concomitant medications considered necessary to provide adequate supportive care except for those that might affect bone mass or bone metabolism, including:

- Adrenocorticotrophic hormone
- Anabolic steroids
- Anticonvulsants (benzodiazepines okay)
- Antineoplastic chemotherapeutics
- Androgens
- Aromatase inhibitors
- Bisphosphonates
- Calcitonin
- Calcitriol
- Cinacalcet
- Fluoride (for osteoporosis)
- Gonadotropin-releasing hormone agonists
- Growth hormones
- Heparin or derivatives (> 7 days)
- Lithium
- Methotrexate
- Parathyroid hormone (or a derivative)
- Protease inhibitors
- Strontium
- Systemic estrogen
- Selective estrogen receptor modulators
- Systemic glucocorticoids
- systemic ketoconazole (> 1 month)
- Tibolone

Concomitant medication use was assessed at every trial visit, except for visits for pharmacokinetic sampling. Types of concomitant medications (for example, proscribed medication taken during the trial) were summarized by proportions of subjects using medications by preferred term.

Baseline use of concomitant medications:

Appropriate wash-out periods for osteoporosis medications were incorporated into the exclusion criteria for the trial. Previous use of medications (SERMs, bisphosphonate, osteoporosis medications) and substances (caffeinated beverages, alcoholic beverages, and tobacco) that might affect bone biology were similar overall for the treatment groups at baseline. Previous use of the above medications was imbalanced across the treatment groups in the ≤ 5 years-since-menopause stratum (25% denosumab; 12% placebo) and in the > 5 years-since-menopause stratum (15% denosumab; 24% placebo).

Use of Proscribed/Prohibited Meds:

Proscribed medications were administered during the trial to 7 subjects (4%) in the denosumab group and 5 subjects (3%) in the placebo group. The most frequently reported proscribed concomitant medications were (denosumab, placebo) prednisone (1%, 1%), valproate (1%, 1%), and lithium (1%, 1%); all other proscribed medications were administered to 1 subject each.

Primary Efficacy Outcomes

General Discussion of Endpoints:

The primary endpoint in Trial 20040132 is whether denosumab treatment can prevent lumbar spine bone loss in both early (≤ 5 years since menopause) and late (> 5 years since menopause) postmenopausal women with osteopenia (lumbar spine BMD T-score between -1.0 and -2.5). Lumbar spine bone loss is measured by percent change from baseline in the lumbar spine BMD [by DXA] at 24 months of treatment at L1-L4. Primary efficacy analyses were conducted within each menopause stratum, then for the strata combined.

Secondary endpoints included the percent change from baseline in BMD at 24 months as measured by DXA at the hip (total hip, femoral neck, and trochanter), distal radius, and total body (without head) and in trabecular, cortical, and total volumetric BMD at 24 months as measured by quantitative computerized tomography (QCT) at the distal radius. This trial had many exploratory/tertiary efficacy endpoints in both the on-treatment and off-treatment periods, which have been previously noted.

Efficacy Findings

Primary Endpoint:

The primary endpoint in Trial 20040132 is whether denosumab treatment can prevent lumbar spine bone loss in both early (≤ 5 years since menopause) and late (> 5 years since menopause) postmenopausal women with osteopenia (lumbar spine BMD T-score between -1.0 and -2.5). Lumbar spine bone loss is measured by percent change from baseline in the lumbar spine BMD [by DXA] at 24 months of treatment at L1-L4.

As outlined in the table below (Table 119), increases in lumbar spine BMD from baseline to Month 24 were greater for denosumab compared to placebo, for all subjects, subjects ≤ 5 years since menopause and subjects > 5 years since menopause. The applicant conducted a preplanned analysis using the ANOVA model to test for superiority of denosumab overall and each of two strata (see Table 19). The increase in lumbar spine (L1 – L4) BMD seen with denosumab was superior to that of placebo for all subjects, subjects ≤ 5 years since menopause and subjects > 5 years since menopause. The mean increase in lumbar spine (L1 – L4) BMD at 24 months with denosumab 60 mg every 6 months was shown to be statistically significantly greater than that in the placebo group (p -value < 0.0001), regardless of menopause stratum.

This reviewer created the following summary (Table 119) based on a review of analysis dataset in JMP software package using subjects in the primary efficacy subset with the last observation carried forward (LOCF).

Table 119. Percent Change from Baseline to Month 24 in Lumbar Spine BMD by DXA – Primary Efficacy Subset (LOCF)

Treatment Arm / Stratum	No. of subjects	% Change from Baseline in BMD Median (range)
Overall		
Denosumab	163	6.16 (-8.41 to 25.40)
Placebo	163	-1.10 (-11.76 to 10.97)
Postmenopausal women \leq 5 years		
Denosumab	79	6.03 (-8.41 to 13.3)
Placebo	80	-1.40 (-11.76 to 5.97)
Postmenopausal women $>$ 5 years		
Denosumab	84	6.37 (-1.91 to 25.40)
Placebo	83	-0.88 (-8.67 to 10.97)

The applicant reported similar numbers using the least squares mean the following in the 24-month trial report:

Table 120. Lumbar Spine BMD by DXA – Percent Change From Baseline to Month 24 (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
\leq 5 years since menopause						
Placebo (N = 80)	80	-1.2	(-2.3, -0.2)			
Denos. (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)			
Denos. (N = 84)	84	6.8	(5.6, 7.9)	6.7	(5.4, 8.0)	<0.0001
Overall						
Placebo (N = 163)	163	-0.6	(-1.2, 0.1)			
Denos. (N = 163)	163	6.5	(5.8, 7.2)	7	(6.2, 7.8)	<0.0001

n = Number of subjects with values at baseline and at ≥ 1 postbaseline visit at or prior to the time point of interest

N = Number of subjects with values at baseline and at least ≥ 1 postbaseline 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 Trial Report for Trial 20040132 (24-month results), Table 9-1, page 133 of 2440.

The data was also independently summarized by this reviewer, with similar results obtained for treatment effect.

Table 121. Lumbar Spine BMD by DXA – Relative Change From Baseline to Month 24 (ITT, LOCF)

	Treatment	
	Placebo	Denosumab
N, ITT	166 (%)	166 (%)
Mean Baseline BMD (n)	166	165
(g/cm ²) ± SD	0.870 ± 0.054	0.879 ± 0.047
Mean Month 12 BMD (n)	163	163
(g/cm ²) ± SD	0.866 ± 0.060	0.916 ± 0.052
Mean Month 24 BMD (n)	163	163
(g/cm ²) ± SD	0.863 ± 0.061	0.932 ± 0.054
Mean Absolute Change (g/cm ²) ± SD	-0.009 ± 0.034	0.053 ± 0.030
Mean % Change from Baseline ± SD	-1.0 ± 4.0	6.1 ± 3.6
Treatment Effect at Month 24*		7.1
*Difference in the mean % change from baseline compared to control		

Reviewer Comments:

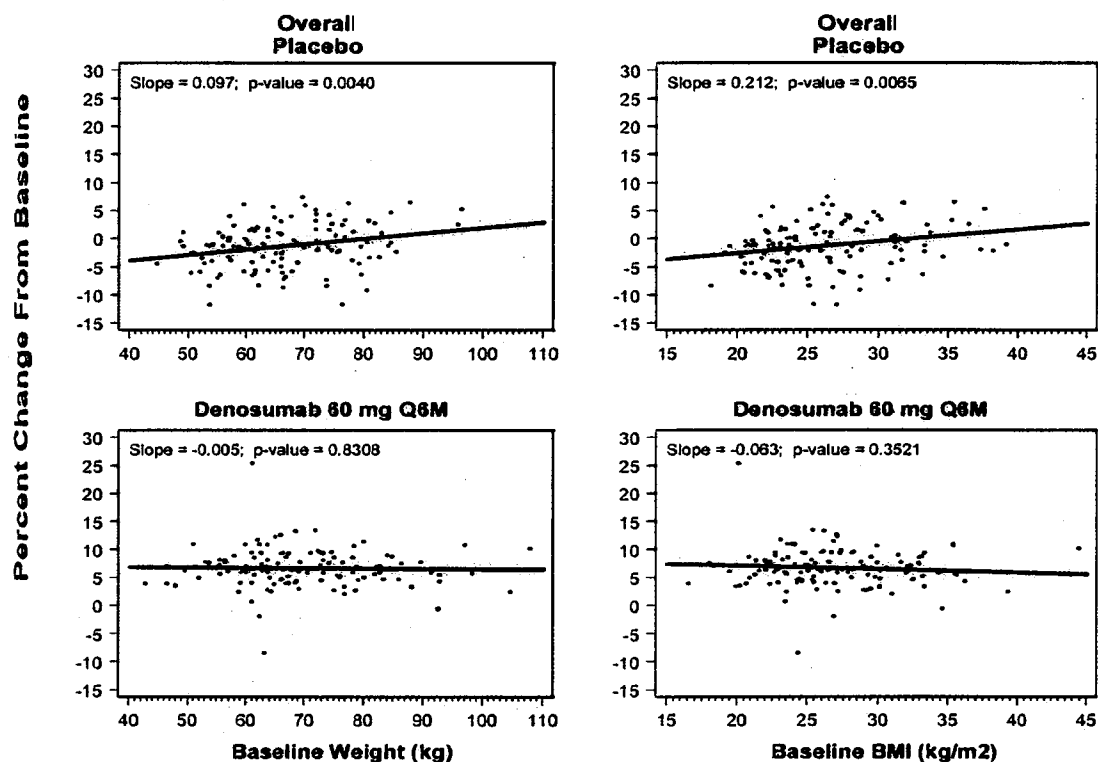
- *It is clear from the summary table that compared to baseline the denosumab group gained BMD at the lumbar spine while the placebo group lost BMD at the lumbar spine through Month 24.*
- *Two subjects in the placebo group > 10% decrease in BMD at Month 24 in the lumbar spine compared to baseline. The BMD of the lumbar spine decreased by 8.4% compared to baseline for one subject in the denosumab group who had received 3 injections of denosumab.*

Multiple subgroup analyses were performed, including race (Caucasian vs. non-Caucasian), baseline weight (< 55, 55 to < 65, 65 to < 75 and ≥ 75 kg), and baseline BMI (< 22, 22 to < 24, 24 to < 26 and 26 to < 30, and ≥ 30 kg/m²), age subgroup (< 65 and ≥ 65 years) for subjects ≤ 5 years since menopause and > 5 years since menopause and for overall subjects. In all subgroups, the difference in the percent change from baseline to Month 24 in lumbar spine (L1 – L4) BMD was consistent with the results seen in the overall group.

The applicant analyzed the primary endpoint by baseline weight and BMI to determine if the efficacy was affected by these parameters. In placebo group, a higher baseline weight and BMI was correlated with maintenance of lumbar spine BMD by DEXA. For the denosumab group, there was no linear correlation for either baseline weight or BMI. No linear correlations were noted for either weight or BMI with change in BMDs of the

total hip, trochanter, femoral neck, or distal 1/3 radius for either the denosumab or placebo group.

Figure 20. Linear Regression Analysis of Percent Change from Baseline to Month 24 in Lumbar Spine BMD (by DXA) Using Baseline Weight and BMI



Source: Clinical Trial Report for Trial 20040132 (24-month results), Figure 9-26, page 171 of 2440.

Reviewer Comments:

- This reviewer agrees with the applicant's conclusion that the denosumab group gained BMD at the lumbar spine while the placebo group lost BMD at the lumbar spine through Month 24.
- Although not presented herein, similar results were seen with women ≤ 5 years since menopause and > 5 years since menopause.
- There was one 74-year-old subject (SID 2004132-107072) in the denosumab group who reportedly had a 25.4% increase in lumbar spine BMD at Month 24, with an increase from 0.807 at baseline to 1.012 g/cm² at Month 24 (absolute change of 0.205 g/cm²). After receiving all 4 scheduled doses of denosumab, this subject had increases in BMD of 5.75% at the intertrochanter region, 7% at the ultradistal radius and 3.76% of the total body (without head). This subject

had Vitamin D 5-hydroxy levels within the normal range at baseline and did not have a fracture in the lumbar spine either at baseline or during the trial.

- No other subjects had an absolute change greater than 0.125 g/cm² or greater than 13.5% change from baseline in BMD at the lumbar spine.*
- When the applicant analyzed the primary endpoint by baseline weight and BMI, they determined that there was no linear correlation for either baseline weight or BMI for denosumab. However, a linear correlation between baseline weight and BMI was demonstrated for placebo subjects, which is reasonable given the physiologic mechanism of increased mechanical load in heavier subjects. It is noteworthy that heavier subjects on denosumab lost as much BMD as the subjects who were of normal or below normal weight.*
- The statistics reviewer did not identify any statistical issues in this submission. The Applicant adhered to statistical methods for the primary and important secondary endpoints as specified in the protocol and Statistical Analysis Plan. The trial provides supportive evidence demonstrating the efficacy of Prolia (s.c. denosumab 60 mg twice yearly) Injection for the prevention of osteoporosis in postmenopausal women based on the stated endpoints.*

Secondary Endpoints

The secondary endpoints for this trial included percent change from baseline in BMD at 24 months as measured by DXA at the hip (total hip, femoral neck, and trochanter), distal radius, and total body (without head).

Hip, Distal Radius and Total Body BMD, Relative Change:

Increases in BMD from baseline to Month 24 were greater in denosumab group for the total hip, femoral neck and trochanter, distal radius and total body compared placebo. In analyses of the least squares (LS) mean of the relative change from baseline in BMD, the difference from placebo ranged from 3.5 in the distal radius to 6.0 in the trochanter ($p < 0.001$) for all locations. The percent change from baseline in BMD for subjects randomized to denosumab was greater in women who were ≤ 5 years since menopause as compared to those subjects > 5 years since menopause. Regardless, there was a statistically significant change from baseline to Month 24 in BMD for each of the menopause strata and subjects overall.

Table 122. Hip, Distal Radius and Total Body BMD by DXA – Relative Change From Baseline to Month 24 (ITT, 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
Total Hip						
Placebo (N = 163)	163	-1.1	(-1.5, -0.8)			
Denos. (N = 163)	163	3.4	(3.0, 3.7)	4.5	(4.0, 5.0)	<0.0001
Femoral Neck						
Placebo (N = 163)	163	-0.9	(-1.4, -0.3)			
Denos. (N = 163)	163	2.8	(2.3, 3.3)	3.7	(2.9, 4.4)	<0.0001
Trochanter						
Placebo (N = 163)	163	-0.8	(-1.3, -0.3)			
Denos. (N = 163)	163	5.2	(4.7, 5.6)	6.0	(5.3, 6.6)	<0.0001
Distal 1/3 Radius						
Placebo (N = 163)	156	-2.1	(-2.6, -1.6)			
Denos. (N = 163)	156	1.4	(0.9, 1.9)	3.5	(2.8, 4.3)	<0.0001
Total Body (without head)						
Placebo (N = 163)	154	-1.4	(-1.9, -0.8)			
Denos. (N = 163)	156	2.4	(1.9, 2.9)	3.8	(3.1, 4.5)	<0.0001

n = Number of subjects with values at baseline and at ≥ 1 postbaseline visit at or prior to the time point of interest

N = Number of subjects with values at baseline and at least ≥ 1 postbaseline 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 Trial Report for Trial 20040132 (24-month results), Table 9-1, pages 138-140 of 2440.

Trabecular, cortical, and total volumetric BMD by QCT

Another set of secondary endpoints involved an experimental quantitative computerized tomography (QCT) method using clinical whole body spiral CT scanners to determine trabecular, cortical, and total volumetric BMDs of the distal radius. These results are reported below in Table 21. There was a statistically significant increase in cortical and total volumetric BMD at 24 months for both strata and overall subjects for denosumab compared with placebo. The increase in trabecular volumetric BMD with denosumab compared to placebo was significant for subjects overall, but not for individual strata.

Table 123. Trabecular, Cortical and Total Volumetric BMD at 24 months by QCT at Distal Radius – Relative Change From Baseline to Month 24 (ITT, 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 ^c
Trabecular BMD (QCT)						
Placebo (N = 131)	131	-0.7	(-6.6, 5.3)			
Denos. (N = 144)	144	8.7	(3.0, 14.4)	9.4	(1.1, 17.6)	0.03
Cortical BMD (QCT)						
Placebo (N = 153)	152	-1.4	(-1.8, -0.9)			
Denos. (N = 156)	156	0.3	(-0.1, 0.8)	1.7	(1.1, 2.3)	<0.0001
Total BMD (QCT)						
Placebo (N = 153)	153	-1.9	(-2.6, -1.1)			
Denos. (N = 156)	156	0.8	(0.0, 1.6)	2.6	(1.5, 3.8)	<0.0001

n = Number of subjects with values at baseline and at ≥ 1 postbaseline visit at or prior to the time point of interest

N = Number of subjects with values at baseline and at least ≥ 1 postbaseline visit

a Based on ANCOVA models (on BMD by DXA for each stratum) that adjust for treatment, baseline value, machine type, and baseline value-by machine type interaction; and ANCOVA models (on volumetric BMD by QCT for each stratum) that adjust for treatment and baseline value; the models (for overall assessment) also adjust for strata.

b 97.5% CI for each stratum and 95% CI for the overall assessment

c p-values are adjusted for multiple comparisons using Hochberg's procedure.

Source: Clinical Trial Report for Trial 20040132 (24-month results), Table 14-4.5.7, page329 of 2440.

Reviewer Comments:

- **For secondary endpoints, the relative change in BMD from baseline to Month 24 was greater in the denosumab group compared to placebo in the total hip, femoral neck and trochanter, distal radius and total body. The percent change from baseline in BMD for subjects randomized to denosumab was greater in women who were ≤ 5 years since menopause as compared subjects > 5 years since menopause, but the change from baseline to Month 24 in BMD was statistically significant for each of the menopause strata and subjects overall.**
- **The relative change in volumetric BMD by QCT was greatest for trabecular bone. However, the increase in trabecular volumetric BMD with denosumab compared to placebo was only significant for subjects overall. There was a lot of variability in this measurement of trabecular bone, which is probably due to the scarcity of trabecular bone at the distal radius.**

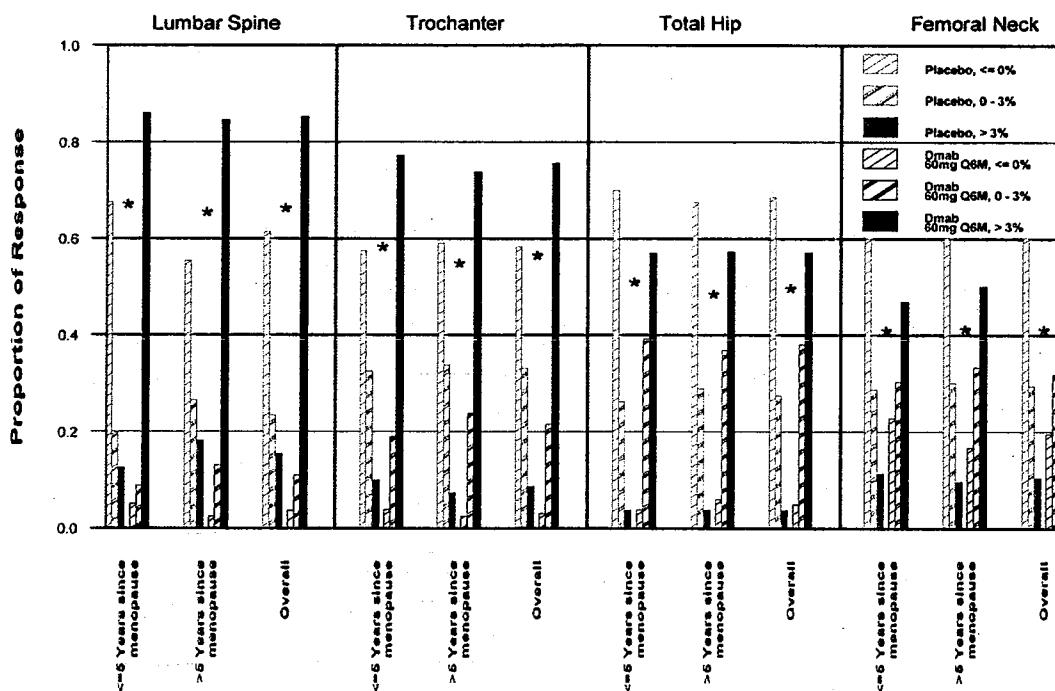
Tertiary/Exploratory Endpoints

This trial had many exploratory/tertiary efficacy endpoints in both the on-treatment and off-treatment periods, which were previously summarized.

Denosumab significantly increased BMD beginning in month 1 for total hip (early menopause stratum and overall subjects) and for trochanter (overall subjects). Denosumab significantly increased BMD starting at month 6 for the femoral neck for each strata and overall subjects. Denosumab significantly increased BMD at month 12 for the distal 1/3 radius and total body, which was the first evaluation point after initiation of therapy.

In the applicant's analysis of BMD changes, the denosumab group had more subjects with BMD changes of >3% from baseline compared to placebo; this difference was statistically significant across both menopause strata and in the overall trial population. This same pattern was observed at all time points evaluated.

Figure 21. Proportion of Subjects with BMD Changes $\leq 0\%$, 0% to 3% and > 3% from Baseline to Month 24 (LOCF)



* Indicates significance at a 2.5% nominal level for each stratum and at a 5% nominal level for overall assessment that the odds of greater % BMD is greater in denosumab 60mg Q6M than placebo based on odds ratio from proportional odds model

Source: Clinical Trial Report for Trial 20040132 (24-month results), Figure 9-22, page 161 of 2440.

An experimental QCT method using clinical whole body spiral CT scanners was used to evaluate the trabecular, cortical, and total volumetric BMDs of the distal radius. Denosumab significantly increased trabecular volumetric BMD starting at month 12 (both strata combined). Cortical volumetric BMD was statistically increased starting at

month 6 (late menopause stratum and overall subjects). Total volumetric BMD was significantly increased starting at month 6 (overall subjects). No multiplicity adjustment was made for the multiple time points.

Using DXA data, cross-sections of the hip at the narrow neck, intertrochanter, and shaft were assessed by Hip Structural Analysis (HSA). Data were reported as least-squares mean values with confidence intervals with the data summarized for overall subjects. Denosumab decreased average buckling ratio (a measure of susceptibility to axial compressive loads) and increased BMD, cross-sectional area, cross-sectional moment of inertia, section modulus (a measure of resistance to bending loads) and average cortical thickness at all 3 cross-sections. Denosumab had no effect on outer diameter at all 3 cross sections. Denosumab had no effect on endosteal diameter at the narrow neck and intertrochanter, but decreased endosteal diameter at the shaft. The results within each menopause strata were similar to overall subjects, except that no differences between treatment groups were noted in the early menopause stratum at the shaft for cross-sectional moment of inertia and section modulus.

Table 124. Hip Structural Analysis for Overall Subjects – Least Squares Mean Change from Baseline to Month 24 (ANCOVA Model, LOCF)

Parameter	Narrow Neck		Intertrochanter		Shaft	
	Mean	p-value	Mean	p-value	Mean	p-value
BMD (g/cm ²)	0.039	<0.0001	0.037	<0.0001	0.032	<0.0001
Cross-sectional area (cm ²)	0.114	<0.0001	0.176	<0.0001	0.085	<0.0001
Cross-sectional moment of inertia (cm ⁴)	0.065	<0.0001	0.407	<0.0001	0.047	0.0113
Outer diameter (cm)	0.001	0.9142	-0.01	0.4631	-0.001	0.7996
Section modulus (cm ³)	0.045	<0.0001	0.172	<0.0001	0.032	0.0052
Endosteal diameter (cm)	-0.015	0.1447	-0.066	0.2624	-0.03	0.0018
Average cortical thickness (cm)	0.008	<0.0001	0.016	<0.0001	0.015	<0.0001
Average buckling ratio	-0.592	<0.0001	-0.472	<0.0001	-0.093	0.0001

Least squares mean difference from placebo. Based on an ANCOVA model (for overall assessment) that adjusts for strata, treatment, and baseline value. Denosumab group: n = 146; placebo group: n = 143.

Some of the exploratory endpoints included changes in bone markers and biomarkers at various time points in the trial. The samples for serum bone markers and biomarkers were collected immediately prior to dosing after a 10 hour fast. Thus, these measurements represent trough values taken at the end of the dosing interval. As outlined in the table below, mean baseline serum type 1 C-telopeptide (CTX1), tartrate-resistant acid phosphatase 5b (TRAP 5b) and N-terminal propeptide type I procollagen (P1NP) values were comparable in the two treatment groups. At all time points, the decrease from baseline in serum CTx, TRAP 5b and P1NP was greater in the denosumab group than the placebo group.

Table 125. Exploratory Endpoints: Bone Markers – Relative Change From Baseline to Month 24 (ITT, LOCF)

Visit Month	CTX1 Levels		TRAP 5b		P1NP	
	Placebo	Denos.	Placebo	Denos.	Placebo	Denos.
Baseline						
Median	0.5	0.501	4.12	4.09	52.48	52.58
Month 1						
Median	0.49	0.049	4.01	2.06	54.54	34.77
Median % Δ BL*	-3.14%	-89.3%	-0.24%	-49.54%	-3.52%	-32.38%
Month 6						
Median	0.503	0.101	3.62	2.25	46.71	12.4
Median % Δ BL*	-4.27%	-77.3%	-12.4%	-45.75%	-14.13%	-73.5%
Month 12						
Median	0.468	0.121	3.47	2.14	46.75	14.6
Median % Δ BL*	-7.13%	-71.01%	-11.57%	-43.3%	-9.79%	-67.5%
Month 18						
Median	0.534	0.15	3.66	2.38	50.5	15
Median % Δ BL*	-1.20%	-69.57%	-8.64%	-40.01%	-8.26%	-70.11%
Month 24						
Median	0.51	0.183	3.53	2.44	49.2	16.3
Median % Δ BL*	-5.89%	-62.97%	-8.7%	-39.18%	-5.5%	-64.91%

BL = baseline; P1NP = N-terminal Propeptide Type I Procollagen; CTX 1 = Serum Type 1 C-Telopeptide; TRAP 5b = Tartrate-Resistant Acid Phosphatase 5b

* Median % Δ BL = mean percent change from baseline in value

The changes in the biomarkers osteoprotegerin (OPG), receptor activator nuclear kappa B ligand (RANKL), intact parathyroid hormone (iPTH) were also measured during the trial. The mean baseline values for these biomarkers were comparable in the two treatment groups. The changes in OPG, RANKL and iPTH were not consistent for either the placebo or denosumab groups at the time points used in the trial.

Table 126. Exploratory Endpoints: Biomarkers – Relative Change From Baseline to Month 24 (ITT, LOCF)

Visit Month	OPG Levels		RANKL		iPTH	
	Placebo	Denos.	Placebo	Denos.	Placebo	Denos.
Baseline						
Median	55.59	54.75	10	10	33.5	38
Month 12						
Median	62.94	55.86	-	-	41.5	70
Median % Δ BL*	-6.38%	-22.89%	-	-	-10.63%	3.64%
Month 18						
Median	55.67	56.97	-	-	64	90.5
Median % Δ BL*	-2.78%	14.96%	-	-	59.55%	19.8%
Month 24						
Median	54.63	55.33	10	10	36.5	38.5
Median % Δ BL*	-1.0%	0.923%	0%	0%	1.64%	6.27%

BL = baseline; OPG = Osteoprotegerin; RANKL = Receptor Activator Nuclear KappaB Ligand, iPTH = Intact Parathyroid Hormone

* Median % Δ BL = mean percent change from baseline in value

Fractures

Some final tertiary/exploratory endpoints in the on-treatment period were the incidence of vertebral fracture and clinical fractures at or before month 24. There was one vertebral fracture identified in a subject in the placebo group in the first 24 months of the trial. A total of 23 clinical fractures were reported in a total of 21 subjects. There were 8 subjects (4.9%) in the denosumab group and 13 subjects (8%) in placebo group who had a confirmed fracture. One subject in the placebo group had 3 fractures reported at the same time (fibula, foot and tibia fracture after severe trauma other than a fall). In addition, there were 2 fractures (one in each treatment group) that were not confirmed; these were fractures of the ankle and tarsus following falls on stairs, steps or curbs.

Table 127. Exploratory Endpoints: Clinical Fractures at or before Month 24

Coded Fracture Term	Treatment Group		Total
	Placebo	Denosumab	
Ankle fracture	1	0	1
Clavicle fracture	0	1	1
Fibula fracture	1	1	2
Foot fracture	5	4	9
Hand fracture	1	1	2
Humerus fracture	2	0	2
Patella fracture	1	1	2
Radius fracture	1	0	1
Rib fracture	1	0	1
Tibia fracture	2	0	2
TOTAL	15	8	23

The applicant summarized only those events reported by the investigators that were confirmed by the central imaging vendor. 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 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. The most frequent fractures involved the foot.

Off-treatment

There were slightly more fractures in the denosumab group in the first 12 months of the off-treatment period, with 6 denosumab subjects and 3 placebo subjects reporting events of fracture.

Table 128. Adverse Events of Fracture by Preferred Term in Descending Order of Frequency During the Off-treatment Phase

	Placebo N=128	Denosumab N=128
Fracture Term	n (%)	n (%)
No. of subjects reporting AE of fracture	3 (2.3)	6 (4.7)
Foot fracture	2 (1.6)	2 (1.6)
Fibula fracture	1 (0.8)	1 (0.8)
Lumbar vertebral fracture	0 (0.0)	1 (0.8)
Patella fracture	0 (0.0)	1 (0.8)
Radius fracture	0 (0.0)	1 (0.8)
Humerus fracture	1 (0.8)	0 (0.0)

Source: Clinical Trial Report for Trial 20040132 (36-month results), Table 11-6.4.6, page 553 of 2440.

The nonvertebral osteoporotic fracture is defined as a fracture present on a radiograph and/or documented in a radiology report (confirmed by vendor), excluding skull, facial,

mandible, metacarpus, finger phalanges, and toe phalanges and high trauma severity or pathologic fractures.

Table 129. Nonvertebral Fractures (Osteoporotic) by Preferred Term during First 12 Months Off-Treatment Period

	Placebo N=128	Denosumab N=128
Fracture Term	n (%)	n (%)
Subjects reporting AEs of osteoporotic fracture	2 (1.6)	2 (1.6)
Fibula fracture	1 (0.8)	1 (0.8)
Radius fracture	0 (0.0)	1 (0.8)
Foot fracture	2 (1.6)	0 (0.0)

Source: Clinical Trial Report for Trial 20040132 (36-month results), Table 11-6.4.6, page 553 of 2440.

Reviewer Comments:

- *For tertiary/exploratory endpoints on-treatment, the number of overall fractures and the number of subjects with confirmed fractures was greater in the placebo group. The types of fractures did not differ across treatment.*
- *More subjects in the denosumab group had BMD changes of >3% from baseline compared to placebo; this difference was statistically significant across both menopause strata and in the overall trial population. This same pattern was observed at all time points evaluated.*
- *At all time points, the decreases from baseline in serum CTx, TRAP 5b and P1NP were greater in the denosumab group than the placebo group. The changes in OPG, RANKL and iPTH were not consistent for either the placebo or denosumab groups at the time points used in the trial.*

Off-treatment period:

There were many exploratory off-treatment endpoints, which were previously summarized. As the off-treatment period was still being analyzed at the time of the initial BLA submission, data is only available through Month 36.

Within the first 12 months of the off-treatment period, any gain in BMD for subjects receiving denosumab was lost, with BMD returning to approximately baseline levels. Over the entire 36-month observation period, BMD changes from baseline were 0.1% at the lumbar spine, 0.0% at the total hip, -0.5% at the femoral neck, 1.4% at the trochanter, 0.8% at the distal 1/3 radius, and 0.0% at the total body. Subjects who were receiving placebo had a decline in BMD in the first 36 months of the trial, with a decrease at the lumbar spine of 1.7%, total hip by 1.5%, femoral neck by 1.6%, trochanter by 0.9%, distal 1/3 radius by 3.0%, and total body by 2.0%.

Some of the exploratory endpoints included changes during the off-treatment period in bone markers and biomarkers. As outlined in the table below, mean baseline CTX1,

TRAP 5b and P1NP values were comparable in the two treatment groups. At all time points, the increase from baseline to the specific time point of interest for serum CTx, and TRAP 5b was greater in the denosumab group than the placebo group. The change in P1NP off-therapy was inconsistent, with an initial decrease in both groups at Month 27, followed by an increase over time with denosumab while the placebo group decreased from baseline to Months 30 and 36.

Table 130. Exploratory Endpoints: Bone Markers – Relative Change From Baseline to Month 36 (ITT, LOCF)

	CTX1 Levels		TRAP 5b		P1NP	
	Placebo	Denos.	Placebo	Denos.	Placebo	Denos.
Visit Month	Baseline					
Median	0.5	0.501	4.12	4.09	52.48	52.58
	Month 27					
Median	0.503	0.61	4.46	4.61	49.2	49.57
Median % Δ BL*	0%	26.6%	9.9%	23.5%	-7.22%	-6.8%
	Month 30					
Median	0.520	0.833	4.28	5.7	47.49	75.83
Median % Δ BL*	2.07%	66.77%	8.18%	39.2%	-11%	42.5%
	Month 36					
Median	0.48	0.704	4.44	5.3	48.83	77.46
Median % Δ BL*	-7.3%	34.2%	3.89%	23.95%	-10.84%	47.7%

BL = baseline; P1NP = N-terminal Propeptide Type I Procollagen; CTX 1 = Serum Type 1 C-Telopeptide; TRAP 5b = Tartrate-Resistant Acid Phosphatase 5b

* Median % Δ BL = mean percent change from baseline in value

The change in bone markers during the off-treatment period was compared to levels measured at Month 24. Median levels of serum CTX1 and TRAP 5b increased to values above baseline and remained elevated throughout the first 12 months of the off-treatment period. Serum CTX1 and TRAP 5b levels were highest at month 30 and then trended downwards. The increase in levels of P1NP was similar to CTX1 and TRAP 5 for the denosumab group. For the placebo group, the levels of serum CTX1, TRAP 5b, and P1NP remained unchanged compared to baseline.

The changes in the biomarkers OPG, RANKL, and iPTH off-treatment were also measured during the trial. The mean baseline values for these biomarkers were comparable in the two treatment groups. The changes in OPG, RANKL and iPTH in the off-treatment period were not consistent for either the placebo or denosumab groups at the time points used in the trial. There was no apparent difference between the treatment groups at the time points used in the trial.

Clinical and vertebral fractures were also examined in the off-treatment period. In the first 12 months of the off-treatment period, one additional vertebral fracture was reported in the same subject in the placebo group who had an on-treatment vertebral fracture. There were no vertebral fractures identified in the denosumab group. In the first 12 months of the off-treatment period, one additional clinical fracture was reported in the denosumab group. There were 8 additional clinical fractures that were not confirmed at the time of the update (3 additional in the placebo group and 5 additional in the denosumab group).

Reviewer Comments:

- *For tertiary/exploratory endpoints off-treatment, the number of clinical and vertebral fractures did not differ significantly from the on-treatment period.*
- *In the first 12-months of the off-treatment period, subjects who were randomized to denosumab lost BMD and returned to approximately baseline levels of BMD.*
- *Levels of the bone markers CTX1 and TRAP 5b increased to values above baseline and remained elevated throughout the first 12 months off-treatment. The increase in levels of P1NP was similar to CTX1 and TRAP 5 for the denosumab group. For placebo subjects, levels of serum CTX1, TRAP 5b, and P1NP remained unchanged compared to baseline in off-treatment period.*
- *In terms of the biomarkers OPG, RANKL and iPTH, there was no apparent difference between the treatment groups at the time points used in the trial.*

Efficacy Conclusions:

The use of denosumab 60 mg Q6months was associated with a statistically significant increase in lumbar spine BMD (by DXA) from baseline to Month 24, as compared to placebo, for all subjects, subjects ≤ 5 years since menopause and subjects > 5 years since menopause (p -value < 0.0001). Using a least squares mean analysis, the difference from baseline in lumbar spine BMD for placebo was -0.6 and 6.5 for denosumab and the difference between denosumab and placebo was 7 at Month 24 for overall subjects (p -value < 0.0001). Similar statistically significant differences between denosumab and placebo were observed for subjects ≤ 5 years since menopause and subjects > 5 years since menopause.

Increases in BMD from baseline to Month 24 were greater in denosumab group for the total hip, femoral neck and trochanter, distal radius and total body compared placebo. In analyses of the least squares (LS) mean of the relative change from baseline in BMD, the difference from placebo ranged from 3.5 in the distal radius to 6.0 in the trochanter ($p < 0.001$) for all locations. The percent change from baseline in BMD for subjects randomized to denosumab was greater in women who were ≤ 5 years since menopause as compared to those subjects > 5 years since menopause. Regardless, there was a

statistically significant change from baseline to Month 24 in BMD for each of the menopause strata and subjects overall.

For subjects treated with denosumab, BMD at all anatomic sites increased during the 24-month period of active treatment. By month 24, BMD had increased from baseline at the lumbar spine by 6.4%, total hip by 3.6%, femoral neck by 2.9%, trochanter by 5.6%, distal 1/3 radius by 1.4%, and total body (without head) by 2.3%. Also, higher proportions of subjects treated with denosumab, as compared with placebo, experienced changes in BMD > 0% and > 3% at the lumbar spine, femoral neck, trochanter, and total hip at most time points assessed.

Denosumab decreased levels of the bone markers CTX1, P1NP, and TRAP 5b from baseline to periodic assessments at months 1, 6, 12, 18 and 24 ($p < 0.0001$). There were no differences between treatment groups for the biomarkers iPTH, OPG, and RANKL during the trial period. There were few clinical fractures during the period of the trial, with slightly more fractures in the placebo group, most involved the foot. There were only 2 vertebral fractures confirmed during the first 36 months of the trial; both vertebral fractures occurred in the placebo group.

Safety

Events Rates:

As shown in the table below, 95% of subjects in either treatment group experienced adverse events during the trial. There were no deaths in the first 36 months of the trial. Serious adverse event rates were higher in the denosumab group, with 11% of denosumab and 5.5% of placebo subjects experiencing serious adverse events. Trial drug withdrawals due to adverse events were almost equally distributed between the denosumab and placebo groups.

Table 131. Adverse Event Rates Through Month 24 (Safety Population)

	Placebo (N = 165)	Denosuma b (N = 164)
	n (%)	n (%)
Deaths	0	0
Serious Adverse Events	9 (5.5)	18 (11.0)
I.P. Withdrawal due to AE	6 (3.6)	5 (3.0)
All Adverse Events	156 (94.5)	156 (95.1)

Off-treatment Phase:

All 256 subjects (denosumab - 128 subjects, placebo - 128 subjects) who enrolled in the off-treatment phase were evaluated for safety at Month 36. In the first 12 months off-

treatment, 76% of denosumab and 68% of placebo subjects reported adverse events. Serious adverse events were reported by 2.3% of denosumab and 4.7% of placebo subjects.

Exposure:

The planned duration of treatment was 24 months with a total of 4 doses administered every 6 months. A total of 85% of subjects in each group received all 4 I.P. doses.

Table 132. Total Number of Trial Drug Doses Received in the Safety Population through Month 24

	Placebo N=165	Denosumab N=164
Total no. of trial drug doses	n (%)	n (%)
1	11 (7)	7 (4)
2	8 (5)	11 (7)
3	5 (3)	7 (4)
4	141 (85)	139 (85)

Trial drug was discontinued after a single dose in 7% of placebo and 4% of denosumab subjects.

Deaths:

No subjects died in the on-treatment period or during the first 12 months off-treatment.

Serious Adverse Events:

Serious adverse events (SAEs) were reported for 18 subjects (11%) in the denosumab group and 9 subjects (5.5%) in the placebo group with a total of 23 SAEs and 11 SAEs reported in the denosumab and placebo groups, respectively. There was 1 placebo subject who had 3 SAEs during the on-treatment period, which were related to episodes of depression. There was 1 denosumab subject who had 3 SAEs during the on-treatment period, which involved 1 hospitalization for urinary tract infection, pyelonephritis, and septicemia (SID 302008). There were 3 denosumab subjects who each reported 2 SAEs during the on-treatment period of the trial, including diverticulitis and pneumonia over a 5-month period in one subject (SID 102017), cellulitis and osteoarthritis in another subject (SID 103048), and finally diverticulitis and obstructive incisional hernia in a third subject (SID 105011) over a one month period.

Table 133. SAEs* by System Organ Class – 24 Months On-treatment

	Placebo N=165	Denosumab N=164
System Organ Class	n	n
Gastrointestinal disorders	0	2
Hepatobiliary disorders	1	0
Infections	1	11
Injuries	1	2
Musculoskeletal disorders	2	3
Neoplasms benign, malignant & unspec.	1	4
Nervous system disorders	1	0
Psychiatric disorders	3	0
Reproductive system disorders	1	1

* Data summarized at the event level, not subject level.

The four SAEs in the Neoplasm SOC in the denosumab group included breast cancer in situ (Trial Day 297), ovarian cancer (Trial Day 479), uterine cancer (Trial Day 681) and mycosis fungoides (Trial Day 58) in four subjects. The increased incidence of serious adverse events in the denosumab group was primarily due to a greater incidence of infection reported in subjects who received denosumab. All the serious events of infection were assessed by the investigator as unrelated to IP. These events are summarized in the section Adverse Events of Special Interest.

Off-treatment:

In the first 12 months off-treatment, 3 subjects (2.3%) in the denosumab group and 6 subjects (4.7%) in the placebo group had 10 SAEs. There were 2 SAEs in the Neoplasms SOC for both treatment groups; the placebo group included one subject with a benign ovarian tumor and another with breast cancer. In the denosumab group, one subject (SID 103021) had "metastatic atypical spindle cell carcinoid tumor" in the mediastinal lymph nodes (SD 931) and another subject (SID 116006) was diagnosed with meningioma (SD 792). One placebo subject experienced 2 SAEs (benign ovarian tumor and bowel ileus) in the first 12 months of the off-treatment period.

Table 134. SAEs* by System Organ Class – 12 Months Off-treatment

	Placebo N=165	Denosumab N=164
System Organ Class	n	n
Cardiac Disorders	1	0
Gastrointestinal disorders	1	0
Infections	1	1
Injuries	1	0
Musculoskeletal disorders	1	0
Neoplasms benign, malignant & unspec.	2	2

* Data summarized at the event level, not subject level, from Months 25 to 36.

Reviewer Comments:

- *There is an imbalance in the number of SAEs of infection between treatment groups, with SAEs of infection reported in only one placebo subject and 9 events in 8 subjects receiving denosumab during the on-treatment period.*
- *The most commonly reported serious event of infection was pneumonia (1 placebo subject, 3 denosumab subjects), followed by diverticulitis (2 denosumab subjects) and sepsis (2 denosumab subjects).*
- *The SAEs in the first 12 months off-treatment did not differ from the on-treatment SAEs.*

Adverse Events Leading to Withdrawal:

During the on-treatment period, 5 denosumab subjects (3%) and 6 placebo subjects (4%) discontinued trial drug due to adverse events. There were 2 SAEs leading to I.P. withdrawal, including mycosis fungoides and breast cancer in situ in the denosumab group. Gastrointestinal events led to treatment discontinuation in 2 subjects, including nausea (denosumab) and abdominal bloating (placebo).

Adverse Events:

Common AEs:

The most commonly reported adverse events through Month 24 were arthralgia, nasopharyngitis, back pain, headache, pain in extremity, upper respiratory tract infection, constipation, urinary tract infection and shoulder pain for the denosumab group. Similar events were reported in the placebo group, except that constipation and shoulder pain were not as common with placebo and sinusitis was more common with placebo. Events reported at a difference in incidence of $\geq 4\%$ for denosumab as compared to placebo were headache, constipation, shoulder pain, pharyngolaryngeal pain, diarrhea and rash; these events are shaded in Table 135 below.

Table 135. Most Commonly Reported*† Adverse Events Through Month 24 (Safety Population)

	Placebo N=165	Denosumab N=164
Preferred Term	n (%)	n (%)
No. of Subjects Reporting AEs	156 (94.5)	156 (95.1)
Arthralgia	42 (25.5)	41 (25.0)
Nasopharyngitis	31 (18.8)	36 (22.0)
Back pain	33 (20.0)	32 (19.5)
Headache	19 (11.5)	26 (15.9)
Pain in extremity	20 (12.1)	24 (14.6)
Upper respiratory tract infection	22 (13.3)	19 (11.6)
Constipation	8 (4.8)	18 (11.0)
Urinary tract infection	17 (10.3)	18 (11.0)

	Placebo N=165	Denosumab N=164
Preferred Term	n (%)	n (%)
Shoulder pain	10 (6.1)	17 (10.4)
Nausea	12 (7.3)	16 (9.8)
Influenza	18 (10.9)	15 (9.1)
Pharyngolaryngeal pain	5 (3.0)	15 (9.1)
Diarrhoea	7 (4.2)	14 (8.5)
Rash	5 (3.0)	14 (8.5)
Insomnia	15 (9.1)	13 (7.9)
Muscle spasms	13 (7.9)	12 (7.3)
Cough	5 (3.0)	11 (6.7)
Myalgia	12 (7.3)	11 (6.7)
Depression	6 (3.6)	10 (6.1)
Sinusitis	17 (10.3)	10 (6.1)
Abdominal pain	7 (4.2)	9 (5.5)
Dyspepsia	10 (6.1)	9 (5.5)
Gastroesophageal reflux disease	6 (3.6)	9 (5.5)
Procedural pain	5 (3.0)	9 (5.5)
Dizziness	9 (5.5)	7 (4.3)
Fatigue	12 (7.3)	7 (4.3)
Hypertension	14 (8.5)	6 (3.7)
Hypoaesthesia	9 (5.5)	5 (3.0)

* Subject incidence $\geq 5\%$ in either treatment group by Preferred Term

† Preferred Terms that are shaded represent AEs that occurred more often in denosumab group with an incidence difference $\geq 4\%$.

Source: Clinical Trial Report for Trial 20040132 (24-month results), Table 11-7, page 191 of 2440.

Off-treatment:

In the first 12 months off-treatment, 97 denosumab subjects (75.8%) and 87 placebo subjects (68.0%) reported an adverse event. The 3 most frequent adverse events were nasopharyngitis (9.4% denosumab, 7.8% placebo), back pain (7.8% denosumab, 12.5% placebo), and arthralgia (7.8% denosumab, 10.2% placebo).

Adverse events were most commonly reported in the infections (31% denosumab, 30% placebo), musculoskeletal (31% denosumab, 33% placebo), gastrointestinal (18% denosumab, 13% placebo) and the injuries SOCs (16% denosumab, 10% placebo). Constipation was reported in 3% of denosumab and 1% of placebo subjects. Contusions were reported in 4% of denosumab and 1% of placebo subjects.

Adverse Events of Special Interest:

Infections:

There were more serious infections in denosumab group, particularly involving pneumonia, diverticulitis and sepsis.

Table 136. SAEs in the Infections & Infestations SOC – 24 Months On-treatment

Treatment Group	SID	Preferred Term(s)	Trial Day	Days From Prior Dose	Duration of Event (days)	Hospital Stay (days)
Placebo	132103041	Lobar pneumonia	512	120	4	3
Denosumab	132102017	Diverticulitis	367	169	9	6
	"	Pneumonia	518	150	20	2
	132103048	Cellulitis	345	162	3	2
	132105011	Diverticulitis	209	12	3	1
	132107072	Pneumonia	361	177	8	3
	132123026	Pneumonia	176	4	6	4
	132124011	Sepsis	484	113	4	3
	132302008	Urinary tract infection	605	52	28	2
	"	Pyelonephritis	607	54	26	2
	"	Sepsis	607	54	26	2
	132307019	Appendicitis	211	29	2	2

Source: Clinical Trial Report for Trial 20040132 (24-month results), Table 11-5, page 184 of 2440.

There was no difference between treatment groups when all adverse events (includes serious and non-serious) were examined by treatment group. Similar results were obtained when the events were reviewed by high level term, with no differences between treatment groups.

Table 137. All Events in the Infections & Infestations SOC – 24 Months On-treatment

High Level Group Term	Placebo N=165 n (%)	Denosumab N=164 n (%)
Bacterial infectious disorders	5 (3.0%)	3 (1.8%)
Fungal infectious disorders	6 (3.6%)	6 (3.7%)
Infections - pathogen class unspecified	86 (52.1%)	89 (54.3%)
Rickettsial infectious disorders	1 (0.6%)	0 (0%)
Viral infectious disorders	29 (17.6%)	27 (16.4%)

Reviewer Comments:

- There is an imbalance in the number of SAEs of infection between treatment groups, with SAEs of infection reported in only one placebo subject and 9 events in 8 subjects receiving denosumab.
- The most commonly reported serious event of infection was pneumonia (1 placebo subject, 3 denosumab subjects), followed by diverticulitis (2 denosumab subjects) and sepsis (2 denosumab subjects)

- *There were 2 denosumab subjects with infectious events that persisted (≥ 20 days duration), including pneumonia on study day (SD) 518 and UTI, pyelonephritis and sepsis beginning on SD 605.*
- *One denosumab subject had two serious events of infection during the 24 months of treatment, with diverticulitis on SD 367 and pneumonia on SD 518.*

Off-treatment:

A similar proportion of subjects in each treatment group had adverse events of infection during the first 12 months off-treatment (31% and 30% for denosumab and placebo groups, respectively). The 3 most frequent adverse events of infection were (denosumab, placebo) nasopharyngitis (9.4%, 7.8%), sinusitis (2.3%, 3.1%), and bronchitis (1.6%, 3.9%). However, there were more serious events of infection in the denosumab group, with 8 denosumab subjects and 2 placebo subjects experiencing serious infection in the first 12 months off-treatment.

Table 138. Serious Adverse Events in the Infections SOC by High Level Group Term – First 12 Months Off-Treatment:

Preferred Term	Placebo N = 165	Denos. N = 164
Diverticulitis	1 (0.6%)	0 (0%)
Pneumonia	0 (0%)	1 (0.6%)

All adverse events (serious and non-serious) pertaining to infection were also reviewed. Subjects receiving denosumab did not appear to have more adverse events of infection, except that there were a few more upper respiratory tract infections in denosumab subjects in the first 12 months off-treatment.

Table 139. All Adverse Events* in the Infections SOC by High Level Group Term and High Level Term - First 12 Months Off-Treatment:

High Level Group Term	High Level Term	Placebo			Denosumab		
		Serious		Total	Serious		Total
		N	Y		N	Y	
Bacterial infectious disorders	Streptococcal infections	2	0	2	1	0	1
Fungal infectious disorders	Fungal infections NEC	1	0	1	1	0	1
	Tinea infections	0	0	0	1	0	1
Infections - pathogen unspecified	Abdominal & gastrointestinal infections	1	1	2	3	0	3
	Dental & oral soft tissue	1	0	1	1	0	1
	Ear infections	4	0	4	1	0	1
	Eye and eyelid infections	1	0	1	2	0	2
	Lower respiratory tract & lung	6	0	6	4	1	5

High Level Group Term	High Level Term	Placebo			Denosumab		
		Serious			Serious		
		N	Y	Total	N	Y	Total
	Sepsis, bacteraemia, viraemia, fungaemia	0	0	0	1	0	1
	Skin structures & soft tissue	0	0	0	1	0	1
	Upper respiratory tract infections	19	0	19	27	0	27
	Urinary tract infections	4	0	4	5	0	5
Mycobacterial infectious disorders	Atypical mycobacterial infections	0	0	0	1	0	1
Protozoal infectious disorders	Giardia infections	1	0	1	0	0	0
Viral infectious disorders	Herpes viral infections	2	0	2	5	0	5
	Influenza viral infections	2	0	2	1	0	1
	Viral infections NEC	4	0	4	6	0	6

N = non-serious; Y = serious

* Data summarized at event level, not subject level; includes serious and non-serious events, per regulatory definition.

ONJ

No cases were adjudicated as ONJ during the treatment phase of the trial or the first 12 months of the off-treatment phase.

Fracture Healing Complications:

There were no reports of nonvertebral fractures having delayed healing time or nonunion at 6 months post fracture. For 1 subject (SID 102049) in the placebo group who had a humerus fracture, fracture healing status at 6 months was reported unknown at the time of the data cutoff at Month 12 off-treatment.

Hypocalcemia

The mean, median and standard deviation for corrected calcium levels at each of the visit months were reviewed for the on-treatment period to the first 12 months off-treatment. In analyses of serum calcium concentrations, the concentrations were adjusted for albumin if the serum albumin concentration was < 40 g/L. The following formula was used for the adjustment:

$$\text{albumin-adjusted serum calcium (mmol/L)} = \text{serum calcium (mmol/L)} + [40 \text{ g/L} - \text{serum albumin (g/L)}] * 0.02$$

The applicant used the term "albumin-adjusted calcium" whenever describing summary statistics of calcium concentrations (comprising both albumin adjusted and nonadjusted values, depending on the applicability of the above formula).

Corrected calcium concentrations decreased in the denosumab group relative to the placebo group from baseline to month 1 (mean percent change): -3% in the denosumab group and 0.2% in the placebo group. At month 24, mean percent changes from baseline in corrected calcium concentrations were -1.5% in the denosumab group and -0.7% in the placebo group. No subjects had grade 3 or greater toxicities of hypocalcemia, 2 denosumab and no placebo subjects had grade 2 toxicities of hypocalcemia, and 2 denosumab subjects and no subjects in the placebo group had grade 1 toxicities of hypocalcemia.

Table 140. Corrected Calcium Levels Through Month 36

Visit Month	Lab Test Result			Lab Test Result % Δ from Baseline		
	Mean	Median	Std Dev	Mean	Median	Std Dev
Placebo						
0	2.44	2.43	0.10	-	-	-
1	2.43	2.43	0.10	0.24	0	3.69
6	2.43	2.43	0.09	0.29	0	4.24
12	2.48	2.485	0.10	2.05	1.99	4.87
18	2.42	2.40	0.09	-0.17	-1.00	4.11
24	2.41	2.40	0.10	-0.68	-1.04	4.61
27	2.36	2.35	0.10	-2.61	-3.09	4.16
30	2.37	2.35	0.10	-2.07	-2.33	4.09
36	2.41	2.40	0.10	-0.47	-1.01	4.03
Denosumab						
0	2.42	2.43	0.09	-	-	-
1	2.34	2.35	0.12	-2.88	-3.06	4.97
6	2.40	2.40	0.10	-0.61	-1.01	4.54
12	2.44	2.43	0.10	1.05	1.04	4.24
18	2.40	2.40	0.11	-0.45	0	4.93
24	2.38	2.38	0.10	-1.49	-1.08	4.51
27	2.39	2.38	0.09	-0.96	-1.01	4.17
30	2.38	2.38	0.09	-1.58	-2.00	3.76
36	2.40	2.40	0.10	-0.40	0	4.28

Adverse Events:

As stated noted in the protocol, abnormal laboratory findings without clinical significance (investigator's assessment) were not recorded as adverse events. If a change in a laboratory value was considered clinically significant and either required therapy or an adjustment in prior therapy, it was considered an adverse event. No adverse events of hypocalcemia were reported during the first 24 months of the trial. However, there were several events that were potentially indicative of hypocalcemia, which are summarized below in Table 141. The overall incidence of adverse events considered potential clinical manifestations of hypocalcemia was 5% in the denosumab group and 8% in the placebo group. No events of tetany were reported.

Table 141. All Adverse Events Potentially Indicative of Hypocalcemia by Treatment Group Through Month 24

	Placebo N=165	Denosumab N=164
	n (%)	n (%)
Hypoaesthesia	9 (5.5)	5 (3)
Hypoaesthesia facial	1 (< 1)	0
Hypoaesthesia oral	1 (< 1)	0
Paraesthesia	4 (2.4)	4 (2.4)
Paraesthesia oral	1 (< 1)	0

Reviewer Comments:

- *There was a decrease of 3% in corrected calcium concentrations in the denosumab group from baseline to month 1 and an increase of 0.2% in the placebo group.*
- *At month 24, mean percent changes from baseline in corrected calcium concentrations were -1.5% in the denosumab group and -0.7% in the placebo group.*
- *No subjects had grade 3 or greater toxicities of hypocalcemia, 2 denosumab and no placebo subjects had grade 2 toxicities of hypocalcemia, and 2 denosumab subjects and no subjects in the placebo group had grade 1 toxicities of hypocalcemia.*
- *There were fewer adverse events potentially indicative of hypocalcemia in the denosumab group as compared to placebo.*

Cardiac Events

On-treatment:

There were no serious events in the on-treatment period of the trial. There very few cardiac events during the trial, with 6 (3.6%) placebo subjects and 9 (5.5%) denosumab subjects reporting cardiac events. The majority of the denosumab cardiac events were categorized under the HLGT cardiac arrhythmias. There were very few events in the investigations SOC that related to potential cardiac events. There did not appear to be any meaningful differences between the treatment groups.

Off-treatment:

In the first 12 months off-treatment, cardiac events were reported in 3 placebo subjects and 2 denosumab subjects. Only one event of ischemic coronary artery disorder was assessed as serious; this subject had received placebo.

Reviewer Comments:

- *There were no serious cardiac events during the on-treatment period.*

- *In the on-treatment period, cardiac events occurred in 3.6% of placebo and 5.5% of denosumab subjects. The majority of the denosumab cardiac events were categorized under the HLT cardiac arrhythmias.*
- *There were no differences between treatment groups in regards to vascular events or cardiac investigations.*
- *An internal cardiology and QT consult has been requested.*

Malignancy

On-treatment

During the on-treatment period, there were 2 reproductive cancers (ovarian, uterine), 1 breast cancer, 1 skin cancer (basal cell carcinoma) and 1 T-cell lymphoma (mycoses fungoides) with denosumab. In the placebo group, there was 1 report of B-cell lymphoma, 1 malignancy at an unspecified site (squamous cell carcinoma) and 1 possible skin neoplasm ("growth right thumb"). These events are summarized in the table below.

Table 142. All Malignancies by Treatment Group Through Month 24

High Level Group Term	High Level Term	Placebo n (%) Study Day	Denosumab n (%) Study Day
Breast neoplasms malignant and unspec.	Breast and nipple neoplasms malignant	0 (0%)	1 (0.6%) SD 297
Lymphomas non-Hodgkin's B-cell	B-cell lymphomas	1 (0.6%) SD 452	0 (0%)
Lymphomas non-Hodgkin's T-cell	Mycoses fungoides	0 (0%)	1 (0.6%) SD 58
Misc. and site unspec. neoplasms malignant & unspec.	Neoplasms malignant site unspec.	1 (0.6%) SD 485	0 (0%)
Reproductive neoplasms female malignant and unspec.	Ovarian neoplasms malignant	0 (0%)	1 (0.6%) SD 479
	Uterine neoplasms malignant	0 (0%)	1 (0.6%) SD 681
Skin neoplasms malignant and unspecified	Skin neoplasms malignant and unspecified	1 (0.6%) SD 636	1 (0.6%) SD 451

Mycosis fungoides (MF) occurred in a 77-year-old female (SID 102040) on Trial Day 58. This malignancy is the most common type of cutaneous T-cell lymphoma that commonly affects older adults (median age 55 to 60 years). It is rare in the United States, with approximately 1,000 new cases of mycosis fungoides occurring per year, i.e., 0.29 cases per 100,000 population. MF often has a long natural history. The disease may present with nonspecific, slightly scaling skin lesions that wax and wane

for years. The median duration from the onset of skin symptoms to a diagnosis of MF may be 5 years or longer.¹ MF was diagnosed in this subject on Trial Day 58. A causal role of denosumab in the development of MF seems unlikely, given the long natural history of the disease and the typical delay in diagnosis.

Breast cancer and reproductive malignancies (1 report each of uterine and ovarian cancer) occurred in the denosumab group in the first 24 months of treatment. These subjects had been on trial drug for 297 days or more when the malignancy was diagnosed. These malignancies were not reported in the placebo group. The placebo group had 1 report of B-cell lymphoma and squamous cell carcinoma; there was one additional report of "skin growth right thumb" that was not described further.

Off-treatment:

In the first 12 months of the off-treatment period, there was one subject who was diagnosed with meningioma and metastatic atypical carcinoid (metastatic neoplasm) in the denosumab group. In the placebo group, there was one subject diagnosed with breast cancer and another with squamous cell carcinoma. The metastatic neoplasm in SID 103021 was described as a "metastatic atypical spindle cell carcinoid tumor" in the mediastinal lymph nodes diagnosed on SD 931. In addition, there was one denosumab subject (SID 116006) who was diagnosed with meningioma on SD 792.

Table 143. All Malignancies by Treatment Group – First 12 Months Off-Treatment

Preferred Term	Placebo N=128	Denosumab N=128
	n (%) Trial Day	n (%) Trial Day
Metastatic neoplasm	0 (0.0)	1 (0.8) SD 931
Breast cancer	1 (0.8) SD 983	0 (0.0)
Squamous cell carcinoma	1 (0.8) SD 980	0 (0.0)

Source: Clinical Trial Report for Trial 20040132 (36-month results), Table 11-6.1.2, page 532 of 2440.

Reviewer Comments:

- It is noteworthy that breast cancer and reproductive malignancies (1 report each of uterine and ovarian cancer) occurred in the denosumab group after receiving denosumab for 297 days or more. These malignancies were not reported in the placebo group.*

¹ Chapter 119: Mycosis Fungoides and the Sezary Syndrome - Richard T. Hoppe, MD, Youn H. Kim, MD, Ranjana Advani, MD In: Holland-Frei Cancer Medicine - 7th Ed. (2006).

- *The single report of mycosis fungoides on Trial Day 58 is unlikely to be related to the use of denosumab*
- *At 12 months off-treatment, one denosumab subject was diagnosed with "metastatic atypical spindle cell carcinoid tumor" in the lymph nodes.*

Laboratory

Adverse Events:

As outlined in the table below, 11 subjects had adverse events related to laboratory parameters. The majority of events occurred in the denosumab group and were related to cardiac evaluations. ECG changes are discussed in more detail below.

Table 144. Laboratory Adverse Events Through Month 24

HLGT	HLT	PT	Placebo N=165		Den. N=164	
			n	%	n	%
Cardiac and vascular investigations	ECG investigations	ECG QRS complex abnl.	0	0%	1	0.6%
	ECG investigations	ECG T wave abnormal	0	0%	1	0.6%
	Heart rate & pulse investigations	Heart rate increased	1	0.6%	0	0%
		Heart rate irregular	0	0%	3	1.8%
	Vasc. Auscultatory.	Carotid bruit	1	0.6%	0	0%
	Vascular tests NEC	Blood pressure abnormal	1	0.6%	0	0%
Lipid anal.	Cholesterol analyses	Blood cholesterol increased	1	0.6%	2	1.2%

Marked Laboratory Abnormalities:

Clinical Laboratory Abnormalities:

Liver Function tests:

Among subjects with a normal baseline ALT level, there were no subjects with an ALT >3 times the upper limits of normal (ULN) at any visit. Among subjects with a normal baseline AST level, there were no subjects with an AST > 3 times ULN at any visit. No subjects had a total bilirubin that increased from normal at baseline to > 3 times ULN. No trends in the shifts of liver function tests were noted. There were no adverse event reports of hepatic impairment, hepatic insufficiency or hepatic failure on-treatment.

Renal Function:

No subjects with a normal baseline serum creatinine (SCr) experienced a doubling in serum creatinine during the trial. No subjects with a normal blood urea nitrogen (BUN) at baseline experienced a doubling BUN during the trial. No trends in the shifts of renal function were noted. There were no reports of renal insufficiency, renal impairment or renal failure during the first 24 months of the trial.

Mean Change from Baseline:

There were no clinically significant differences between the placebo group and the denosumab groups in mean percent change in laboratory parameters from baseline to Month 24. When the two menopause strata were reviewed, the time since menopause was not associated with a meaningful difference in laboratory parameters.

Table 145. Laboratory Values: Mean % Change from Baseline to Month 24

	Placebo		Denosumab 60mg Q6months	
	<= 5 yr PM	> 5yrs PM	<= 5 yr PM	> 5yrs PM
ALT	6.45	-2.28	-2.60	7.27
AST	11.27	4.52	10.46	12.27
Albumin	-0.73	-0.05	0.21	-0.78
BUN	2.86	-3.29	3.42	0.49
Creatinine	5.90	6.92	10.12	6.53
Ca++ (Corr)	-1.05	-0.30	-1.88	-1.19
Phosphorus	0.16	1.09	-4.39	0.41
Magnesium	15.30	9.02	15.01	9.27
Sodium	-0.50	-0.24	-0.18	-0.35
Potassium	0.37	0.50	0.44	-0.45
Chloride	-0.19	-0.61	0.15	-0.54
WBC	1.56	4.20	7.14	-0.67
Hemoglobin	-1.19	-0.14	-1.10	-1.38
Platelets	4.83	3.45	1.26	7.17

Shifts:

Events were examined according to the Common Terminology Criteria for Adverse Events (CTCAE) to assess the severity of the change in laboratory parameter. Three denosumab subjects had a laboratory CTC grade of 3 for sodium, ALT and white blood cells. One placebo subject had a glucose that with a CTC grade of 3. Thus, severe changes in laboratory values were rarely reported and were seemingly unique.

Table 146. Incidence of Laboratory CTC Grade ≥ 3 - First 12 Months Off-Treatment

Laboratory Parameter	Direction from Normal	Toxicity Grade	Placebo (N = 128) n (%)	Denosumab (N = 128) n (%)
Sodium	Below	Grade 3	0 (0)	1 (<1)
ALT	Above	Grade 3	0 (0)	1 (<1)
Glucose	Above	Grade 3	1 (<1)	0 (0)
White Blood Cells	Below	Grade 3	0 (0)	1 (<1)

Source: Clinical Trial Report for Trial 20040132 (36-month results), Table 8-4, page 116 of 2181.

The majority of subjects had laboratory values for all parameters that remained in the normal range during the trial. As outlined in the table below, decreases in phosphorus

levels from normal into the low range was the most common laboratory shift, occurring in 11 (7%) of the denosumab subjects and 1 (1%) of the placebo subjects.

Table 147. Pertinent Laboratory Values: Shift* Table

	Placebo N=165	Denosumab N=164
	n (%)	n (%)
AST, NI to Hi	0	2 (1%)
Corrected Calcium, NI to Low	0	2 (1%)
Phosphorus, NI to Low	1 (1%)	11 (7%)
Potassium, NI to Hi	0	1 (1%)
Sodium, NI to Low	2 (1%)	0
WBC, NI to Low	1 (1%)	0
Platelets, NI to Low	1 (1%)	0
Hemoglobin, NI to Low	2 (1%)	0

* Shift of 2 or more grades from a normal baseline.

Vital Signs:

Vital signs (systolic and diastolic blood pressure, pulse, body temperature, body weight, and BMI) were obtained at each dosing visit. During the first year of the off-treatment period, vital signs were collected at months 27, 30, and 36.

The median pulse was 68 beats per minute at baseline for both treatment groups (ranges: 48-100 for placebo, 44-101 for denosumab). The median systolic blood pressure at baseline was 120 mm Hg (range 90-166) for the placebo group and 122 mm Hg (range 90-168) for the denosumab group. The median diastolic blood pressure at baseline was 74 mm Hg (range 46-103) for the placebo group and 74 mm Hg (range 40-100) for the placebo group. There was no clinically significant change in median blood pressure or pulse for either treatment group through the first 36 months of the trial.

Mean (SD) weight at baseline was 68.85 (13.01) kg for denosumab and 67.41 (12.0) kg for placebo. Mean (SD) BMI at baseline was 26.6 (4.8) kg/m² for denosumab and 26.2 (4.8) kg/m² for placebo. No significant changes were noted though the first 36 months of the trial for either treatment group. The mean (SD) temperature at baseline was 36.3 (0.44) for denosumab and 36.3 (0.50) for placebo. No significant changes were noted though the first 36 months of the trial for either treatment group.

Electrocardiograms:

Electrocardiograms (ECG) were performed during the trial at screening, Month 1, Month 12, Month 18 and 24, prior to dosing. Measurements of heart rate and of RR, QT, and QTc intervals were based on the ECG machine computer-based interpretation at the site. Bazett's and Fridericia's corrections of QTc intervals were performed by Amgen using the machine-determined RR and uncorrected QT intervals.

Mean (SD) QTc intervals were similar for the denosumab and placebo groups at baseline for both Bazett's and Fridericia's correction formulas (denosumab 412.5 [26.8] msec, placebo 413.7 [23.7] msec; and 405.4 [23.9] msec, 407.7 [22.9] msec, respectively). During the trial, absolute values for QTc using Bazett's correction at each measurement time point ranged from 412.8 to 418.1 msec for the denosumab group and from 410.1 to 414.4 msec for the placebo group. Using Fridericia's correction, the range of mean absolute values was 407.3 to 410.6 msec in the denosumab group and 404.9 to 408.9 msec in the placebo group. Change from baseline ranged from +0.9 to +5.9 msec and -2.9 to +1.6 msec for Bazett's correction in the denosumab and placebo groups, respectively, and from +2.2 to +5.3 msec and -2.5 to +2.2 msec for Fridericia's correction in the denosumab and placebo groups, respectively. There were no clinical sequelae associated with the interval changes.

The corrected QT intervals for electrocardiogram (ECG) data by trial visit are summarized in the tables below.

Table 148. QTcB Interval By Visit (Safety Population)

QTcB	Change from BL (msec)		Actual Value (msec)	
	> 30	> 60	> 470	> 500
Month 1	n (%)*	n (%)*	n (%)*	n (%)*
- Placebo (N=165)	12 (8)	0 (0)	1 (1)	0 (0)
- Den. 60mg Q6M (N=164)	22 (14)	3 (2)	3 (2)	1 (1)
Month 12				
- Placebo (N=165)	11 (7)	3 (2)	3 (2)	2 (1)
- Den. 60mg Q6M (N=164)	19 (12)	1 (1)	7 (4)	2 (1)
Month 18				
- Placebo (N=165)	11 (7)	2 (1)	0 (0)	0 (0)
- Den. 60mg Q6M (N=164)	16 (11)	4 (3)	1 (1)	0 (0)
Month 24				
- Placebo (N=165)	11 (8)	5 (4)	0 (0)	0 (0)
- Den. 60mg Q6M (N=164)	18 (13)	2 (1)	4 (3)	1 (1)

* Only subjects with nonmissing values were included in calculation

Source: Clinical Trial Report 20040132, Table 11-10, page 204 of 2440.

Table 149. QTcF Interval By Visit (Safety Population)

QTcF	Change from BL (msec)		Actual Value (msec)	
	> 30	> 60	> 470	> 500
Month 1	n (%)*	n (%)*	n (%)*	n (%)*
- Placebo (N=165)	0 (0)	0 (0)	0 (0)	0 (0)
- Den. 60mg Q6M (N=164)	4 (3)	0 (0)	1 (1)	1 (1)
Month 12				
- Placebo (N=165)	2 (1)	0 (0)	0 (0)	0 (0)
- Den. 60mg Q6M (N=164)	4 (3)	0 (0)	2 (1)	1 (1)
Month 18				
- Placebo (N=165)	3 (2)	0 (0)	0 (0)	0 (0)
- Den. 60mg Q6M (N=164)	2 (1)	0 (0)	4 (3)	0 (0)
Month 24				
- Placebo (N=165)	2 (1)	0 (0)	0 (0)	0 (0)
- Den. 60mg Q6M (N=164)	2 (1)	0 (0)	4 (3)	0 (0)

* Only subjects with nonmissing values were included in calculation

Source: Clinical Trial Report 20040132, Table 11-11, page 205 of 2440.

The investigator reported outcomes on electrocardiograms (ECGs) conducted in the trial are summarized below in Table 150. All abnormal, clinically significant ECGs occurred in the denosumab group; however, 2% of the denosumab group had abnormal ECGs at baseline.

Table 150. Electrocardiogram Outcomes by Visit Through Month 24 (Manual Reading)

	Normal	Abnormal, not clinically significant	Abnormal, clinically significant
Baseline	n (%)	n (%)	n (%)
Placebo (N = 165)	106 (64)	57 (35)	0 (0)
Den. 60 mg Q6M (N = 164)	97 (59)	63 (38)	4 (2)
Month 1			
Placebo (N = 165)	113 (68)	44 (27)	0 (0)
Den. 60 mg Q6M (N = 164)	114 (70)	45 (27)	3 (2)
Month 12			
Placebo (N = 165)	108 (65)	43 (26)	0 (0)
Den. 60 mg Q6M (N = 164)	108 (66)	44 (27)	6 (4)
Month 18			
Placebo (N = 165)	111 (67)	38 (23)	0 (0)
Den. 60 mg Q6M (N = 164)	105 (64)	39 (24)	2 (1)
Month 24			
Placebo (N = 165)	100 (61)	40 (24)	0 (0)
Den. 60 mg Q6M (N = 164)	100 (61)	37 (23)	3 (2)

Source: Trial Report 20040132, Table 14-8.2.15, page 761 of 2440.

Reviewer comment:

A thorough QT trial was not performed and an internal consult of the QT findings has been requested to fully evaluate these findings.

Safety Conclusions:

There were no deaths during the 24 months of treatment and the first 12 months off-treatment. Approximately 95% of subjects experienced adverse events during the trial with equal distribution between the denosumab and placebo groups. There were no deaths in the first 36 months of the trial. Serious adverse event rates were higher in the denosumab group, with 11% of denosumab and 5.5% of placebo subjects experiencing serious adverse events. Trial drug withdrawals due to adverse events were almost equally distributed between the denosumab and placebo groups.

Serious adverse events (SAEs) were reported in 11% of denosumab and 5.5% of placebo subjects. In the denosumab group, the serious adverse events were primarily due to a greater incidence of infection for denosumab, including multiple serious events of infection. There were 4 denosumab subjects who had SAEs in the Neoplasm SOC, including breast cancer in situ, ovarian cancer, uterine cancer and mycosis fungoides; 1 placebo subject developed B-cell lymphoma. In the first 12 months off-treatment, 2.3% of denosumab and 4.7% of placebo subjects experienced SAEs. There were 2 SAEs in the Neoplasms SOC for both treatment groups.

In the on-treatment period, 3% of denosumab and 4% of placebo subjects discontinued I.P. due to adverse events. The most commonly reported adverse events through Month 24 were arthralgia, nasopharyngitis, back pain, headache, pain in extremity, upper respiratory tract infection, constipation, urinary tract infection and shoulder pain for the denosumab group. Similar events were reported in the placebo group, except that constipation and shoulder pain were not as common with placebo and sinusitis was more common with placebo. Events reported at a difference in incidence of $\geq 4\%$ for denosumab as compared to placebo were headache, constipation, shoulder pain, pharyngolaryngeal pain, diarrhea and rash;

Events of special interest for denosumab are hypocalcemia, ONJ, delayed fracture healing, cardiac events, infections and malignancy. For infections, there were more serious infections in denosumab group, particularly involving pneumonia, diverticulitis and sepsis. There were 9 SAEs of infection in 8 subjects receiving denosumab, while only one placebo subject had an infection SAE. There were 2 denosumab subjects with infectious events that persisted (≥ 20 days duration), including pneumonia in one subject and UTI, pyelonephritis and sepsis in another subject. There was no difference between treatment groups when all adverse events (includes serious and non-serious) were examined by treatment group. Similar results were obtained when the events were reviewed by high level term, with no differences between treatment groups.

There were no reports of delayed fracture healing or ONJ in the 24 months on-treatment and the 12 months off-treatment. There were no adverse events of hypocalcemia in the on-treatment period. When corrected calcium levels were examined, no subjects had grade 3 or greater toxicities of hypocalcemia, 2 denosumab and no placebo subjects had grade 2 toxicities of hypocalcemia, and 2 denosumab subjects and no subjects in the placebo group had grade 1 toxicities of hypocalcemia. Overall, correct calcium concentrations decreased in the denosumab group relative to the placebo group from baseline to month 1 (mean percent change): -3.0% in the denosumab group and 0.2% in the placebo group. At month 24, mean percent changes from baseline in albumin-adjusted serum calcium concentrations were -1.5% in the denosumab group and -0.7% in the placebo group.

In regards to cardiac events, there were no serious cardiac events in the on-treatment period of the trial. Cardiac events were reported in 5.5% of denosumab and 3.6% of placebo subjects. The majority of the denosumab cardiac events were categorized under the HLGT cardiac arrhythmias. A cardiology and QT consult has been requested.

The majority of subjects had laboratory values for all parameters that remained in the normal range during the trial. Three denosumab subjects had a laboratory CTC grade of 3 for sodium, ALT and white blood cells. One placebo subject had a glucose that with a CTC grade of 3. Seven percent of denosumab subjects had shifts in phosphorus levels from normal at baseline into the low range. There were no clinically significant differences between the placebo group and the denosumab groups in mean percent change in laboratory parameters from baseline to Month 24. When the two menopause strata were reviewed, the time since menopause was not associated with a meaningful difference in laboratory parameters. There were no clinically meaningful changes in renal or liver function tests during the trial.

There were no clinically meaningful changes in vital signs for either treatment group. There were some ECG changes noted by the investigator at the site. The Applicant's analysis did not yield notable changes in QTc by either correction method. This data was reviewed by the Cardiorenal division.

Discussion and Conclusions:

The primary objective of this trial was to determine whether denosumab administered as 60mg Q6 months could prevent lumbar spine bone loss in both early and late postmenopausal women with osteopenia. This trial achieved its primary outcome - denosumab 60 mg Q6months was associated with a statistically significant increase in lumbar spine BMD from baseline to 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 difference from baseline in lumbar spine BMD for placebo was -0.6 and 6.5 for denosumab and the difference between denosumab and placebo was 7 at Month 24 for overall subjects (p-value < 0.0001).

9.4.3 Trial 20010223

The title of the trial is "A Randomized, Double-blind, Placebo-controlled, Multi-dose Phase 2 Trial to Determine the Efficacy, Safety, and Tolerability of denosumab in the Treatment of Postmenopausal Women With Low Bone Mineral Density." The trial was conducted at 29 centers in the United States.

Objectives:

Primary

The primary objective of this trial was to determine the effect of denosumab treatment compared with placebo over 12 months on bone mineral density (BMD) of the lumbar spine in postmenopausal women with low BMD.

Secondary

The secondary objectives were to:

- choose a dose regimen of denosumab for future studies, based on changes from baseline in BMD and bone turnover markers over 12 months;
- evaluate the effect of denosumab relative to placebo on BMD of the total hip, distal radius, and total body, and the safety and tolerability profile (including bone safety profile based on histology and histomorphometry) over 12 months;
- evaluate the effect of denosumab relative to placebo on efficacy (based on BMD and bone turnover marker changes) and safety over 48 months;
- assess whether denosumab treatment has a different efficacy or safety profile compared with alendronate;
- assess the off-treatment effect of denosumab based on BMD and bone turnover marker changes;
- assess the efficacy and safety of retreatment with denosumab; and
- assess the administrative feasibility of subject-reported outcomes assessments, and to determine the reliability and validity of the scales.

Exploratory

Exploratory/Tertiary objectives were to evaluate characterize the efficacy and safety of denosumab following IP withdrawal and retreatment in a subset of subjects.

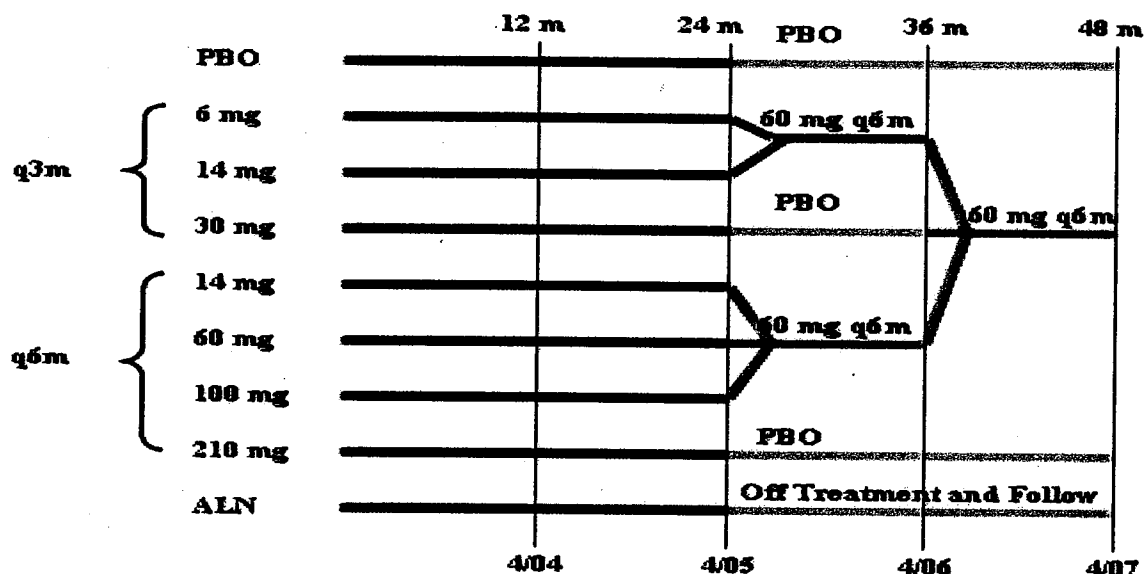
Reviewer Comments:

- ***These primary, secondary and exploratory objectives seem reasonable given the trial design.***

Trial Design:

This multicenter, randomized, double-blind, placebo-controlled, multi-center, parallel group, dose ranging Phase 2 trial enrolled postmenopausal women with low bone mineral density (BMD). The data obtained from the first 12 months of the trial were used to assess if the primary and secondary trial objectives were met. Data from additional observations during months 12 to 48 were also analyzed. Subjects were randomized (1:1) into nine cohorts with approximately 40 subjects per cohort (see Figure 18). Up until Month 24, one cohort received placebo every 3 months, seven cohorts received denosumab and one cohort received open-label alendronate 70 mg orally every week. The denosumab cohorts were given double-blind trial 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. Beginning at Month 24, the denosumab cohorts of 6 mg and 14 mg every 3 months and 14 mg, 60 mg, and 100 mg every 6 months were given denosumab 60 mg SC every 6 months. The denosumab 30 mg every 3 months cohort received placebo every 6 months at Months 24 and 30, then denosumab 60 mg at months 36 and 42. The high dose denosumab cohort (210mg every 6 months) received placebo every 6 months. The placebo cohort received placebo every 6 months; and the alendronate cohort received no treatment from months 24 to 48, but were monitored until Month 48. All subjects were followed for a total of 48 months after initial trial drug administration. All subjects were told to take daily supplements of calcium (at least 1 g of elemental calcium) and vitamin D (at least 400 IU).

Figure 22. Dosing Scheme for Trial 20010223



Source: Clinical Trial Report for Trial 20010223, page 4 of 9933.

The first subject was enrolled on 09 May 2002 and the trial was completed on 16 April 2007.

Population:

The trial population included ambulatory postmenopausal women with low bone mineral density as noted by T-score ≤ 1.8 at either the lumbar spine, femoral neck, or total hip, but not lower than -4.0 at the lumbar spine, or -3.5 at the femoral neck or total hip). These subjects were not receiving medication that affected bone metabolism and were free from any underlying condition that might have resulted in abnormal bone metabolism. See below for additional inclusion and exclusion criteria.

Inclusion Criteria

Subjects were eligible for this trial if they met all of the criteria listed below:

- Women not more than 80 years old on date of randomization
- At least 1 year postmenopausal on date of randomization
- Ambulatory
- If ≤ 60 years old or post bilateral oophorectomy based on medical history, will require serum FSH > 50 mU/mL or serum estradiol < 20 pg/mL to be eligible;
- Low bone mineral density (BMD t-score ≤ -1.8 at any one of the following sites: lumbar spine, femoral neck, or total hip; BMD t-scores must not be lower than -4.0 at the lumbar spine, or -3.5 at the femoral neck or total hip).
- Ethical - Before any trial specific procedure, including the screening DXA, the subject must give informed consent for participation in the trial

Exclusion Criteria

Medication Exclusions:

Subjects were not eligible for this trial if they met any of the criteria listed below:

- Fluoride treatment for osteoporosis within the last 2 years before the enrollment date;
- Bisphosphonate use within the last 12 months before the enrollment date
- Administration of the following medications within the last 6 months before enrollment date: Tibolone, Parathyroid hormone (or any derivative), Systemic glucocorticosteroids (> 5 mg oral, prednisone equivalent per day for more than 10 days), Inhaled corticosteroids (> 2,000 µg per day for more than 10 days), Anabolic steroids or testosterone.
- Administration of the following medications within the last 3 months before the enrollment date: Systemic hormone replacement therapy, Selective estrogen receptor modulators (SERMs), Calcitonin, Calcitriol

Medical History Exclusions:

Evidence of any of the following conditions per subject self report or medical chart review:

- a) Current hyper- or hypothyroidism (stable on thyroid replacement therapy is allowed, if the TSH is within the normal range)
- b) Current hyper- or hypoparathyroidism
- c) Albumin-adjusted serum calcium < 8.5 mg/dL
- d) Osteomalacia
- e) Rheumatoid arthritis
- f) Paget's disease
- g) Malignancy within the last 5 years prior to enrollment (except cervical carcinoma in situ or basal cell carcinoma)
- h) Renal disease (creatinine clearance \leq 35 mL/min using the following equation):
- i) Any bone disease, other than osteoporosis, which may interfere with the interpretation of the findings (e.g., osteogenesis imperfecta or osteopetrosis)
- j) Malabsorption syndrome
- k) Weight, height or girth which may preclude accurate DXA measurements
- l) Less than 2 lumbar vertebrae (L1-L4) evaluable by DXA
- m) Recent long bone fracture (within 6 months)
- n) Osteoporosis-related fracture (i.e., crush or wedge vertebral fracture or hip fracture) known or suspected to have occurred within 2 years of randomization.
- o) More than one single, grade 1 vertebral fracture.

Other Exclusion Criteria:

Additional exclusions included the following:

- Currently enrolled or has participated within the previous 30 days in other investigational device or drug trial(s). For some trials, this may be allowed after discussion and written approval from Amgen.
- Known sensitivity to mammalian-derived drug preparations (e.g., Herceptin®).

- Any organic or psychiatric disorder, serum chemistry, or hematology, which, in the opinion of the investigator, may prevent the subject from completing the trial or interfere with the interpretation of the trial results.
- Self-reported alcohol or drug abuse within the previous 12 months.
- Any disorder that compromises ability to give truly informed consent for participation in this trial.
- Prior administration of denosumab.
- Known sensitivity or contraindication to Fosamax®.
- Known sensitivity or contraindication to tetracycline derivatives (biopsy subset subjects only).

Reviewer Comments:

- *The inclusion and exclusion criteria appear to be adequate.*

Trial Medication:

After a screening period, subjects were randomized to blinded treatment with either denosumab or placebo or alendronate within 72 hours of Trial Day 1. Subjects were randomly assigned within each center to 1 of 9 treatment cohorts (placebo, 1 of 7 denosumab cohorts, or open-label alendronate).

At month 24, treatment assignments were reallocated since the dosing intervals were set at 6-month intervals and some subjects discontinued trial drug. The 210 mg cohort was now off-treatment and the 30 mg Q3month cohort became the retreatment cohort (retreatment began at Month 36). The treatment allocation for each of the 9 cohorts is depicted in Figure 23 below.

Figure 23. Trial 20010223 Treatment Schema

Randomized Cohorts	Months 0 to 12	Months 12 to 24	Months 24 to 36 ^a	Months 36 to 48 ^a
Placebo	placebo Q3M	placebo Q3M	placebo Q6M	placebo Q6M
Denosumab				
every 3 months (Q3M)				
6 mg	6 mg denosumab Q3M	6 mg denosumab Q3M	60 mg denosumab Q6M ^f	60 mg denosumab Q6M ^f
14 mg	14 mg denosumab Q3M	14 mg denosumab Q3M	60 mg denosumab Q6M ^f	60 mg denosumab Q6M ^f
30 mg	30 mg denosumab Q3M	30 mg denosumab Q3M	placebo Q6M ^g	60 mg denosumab Q6M ^h
every 6 months (Q6M) ^b				
14 mg	14 mg denosumab Q6M	14 mg denosumab Q6M	60 mg denosumab Q6M ^f	60 mg denosumab Q6M ^f
60 mg	60 mg denosumab Q6M	60 mg denosumab Q6M	60 mg denosumab Q6M ^f	60 mg denosumab Q6M ^f
100 mg	100 mg denosumab Q6M	100 mg denosumab Q6M	60 mg denosumab Q6M ^f	60 mg denosumab Q6M ^f
210 mg	210 mg denosumab Q6M	210 mg denosumab Q6M	placebo Q6M ^g	placebo Q6M ^h
Alendronate 70 mg weekly	70 mg alendronate weekly	70 mg alendronate weekly	Discontinue treatment ^c	Discontinue treatment ^c

^a Denosumab and placebo were administered every 6 months from month 24 to the end of the study.

^b To maintain the blind among all subjects receiving placebo and denosumab, cohorts receiving denosumab every 6 months also received placebo at months 3, 9, 15, and 21.

^c Evaluation visits only from month 24 to the end of the study.

^d Retreatment cohort

^e Off-treatment cohort

^f Continuous denosumab treatment cohort

Source: Clinical Trial Report for Trial 20010223, Figure 7-2, page 103 of 9933.

An equal volume and number of injections of blinded denosumab or placebo was administered subcutaneously to subjects every 3 months. All subjects were advised to take at least 1,000 mg elemental calcium and at least 400 IU vitamin D daily.

Reviewer Comments:

- ***There were approximately 40 subjects in each of the 9 cohorts.***
- ***The blind was maintained within the dosing cohorts by injecting similar volumes of trial drug every 3 months, regardless of treatment allocation. Subjects randomized to denosumab every 6 months received placebo injections every 3 months.***
- ***Only a small group of personnel at Amgen were aware of the treatment randomization when data was unblinded to determine the appropriate denosumab dosing regimen to use in Months 24-48. None of these personnel had direct interactions with trial centers during day-to-day management of the trial.***

Efficacy Measures

Primary Endpoint:

Trial tests and procedures were initiated only after written informed consent was obtained. All screening procedures were completed within 2 months prior to dosing with trial drug. The screening date was defined as the date the first trial-related procedure was performed, and day 1 was defined as the day that the initial dose of IP was administered to the subject.

The primary endpoint was the percent change from baseline to month 12 in the bone mineral density (BMD) of the lumbar spine for the placebo and denosumab treatment arms. Bone densitometry was performed by dual X-ray absorptiometry (DXA) according to schedule of assessments listed in Figure 19 and Figure 25. Only Lunar and Hologic bone densitometers were used in the trial. The same DXA machine was to be used for all scans for an individual subject. Scans were obtained of the lumbar spine, proximal femur (for calculation of the total hip, femoral neck, and trochanter BMD), distal radius (for calculation of the distal 1/3 radius BMD), and total body (the head was excluded in calculation of total body BMD). Lumbar spine scans included L1 through L4. If possible, the left side was used for the proximal femur and distal radius scans. The side used for baseline scans was used for subsequent scans during the trial.

Screening Bone Mineral Density Assessments

To determine eligibility based on BMD, DXA scans of the lumbar spine and proximal femur were analyzed by the central imaging center. These scans were performed in duplicate (the subjects were removed from the table between scans). Clearly fractured lumbar spine vertebrae (visible on the DXA scan) were excluded from the DXA analysis to determine eligibility. The entry criteria for densitometer-specific BMD values are listed below in Table 151. Both duplicate values must have satisfied the cutoff criteria for a specific anatomic site to meet the inclusion criteria (e.g., if a Hologic machine was used, both lumbar spine BMD values must have been between 0.849 g/cm² and 0.607 g/cm²).

Table 151. Densitometer-specific BMD Values

T-score	GE Lunar			Hologic		
	-4.0	-3.5	-1.8	-4.0	-3.5	-1.8
Lumbar spine	0.700		0.964	0.607		0.849
Total hip		0.580	0.766		0.515	0.719
Femoral neck		0.560	0.764		0.461	0.640

Source: Clinical Trial Report for Trial 20010223, Table 7-5, page 123 of 9933.

On-trial Bone Mineral Density Assessments

The day 1 predose distal radius and total body DXA scans may have been completed within 1 month before IP administration, but only if the subject had met all of the

eligibility criteria. All DXA scan data were submitted electronically to the central imaging center for final blinded analysis. The results from the central imaging center were used as the final dataset.

Vertebrae that were clearly fractured were excluded from the lumbar spine DXA analysis. After analysis by the central imaging center, the trial center may have been asked to repeat a scan. All trial centers had to scan a set of standard phantoms at least once on the DXA machines used for the trial. The month-12 lumbar spine and proximal femur scans were performed in duplicate.

The central imaging center analyzed all DXA scans and forwarded all results to the trial center. Trial staff did not analyze any trial-related DXA scans or share any subject-specific BMD data with the trial subject, except for the subject's screening DXA results.

Secondary endpoints:

The secondary endpoints included:

- a) percent change from baseline to month 12 in urine N-telopeptide/Creatinine (uNTX/Cr) and serum C-TX of type I collagen (CTX 1) for all treatment arms and the percent change from baseline to month 12 in BMD of the lumbar spine for the alendronate arm;
- b) percent change from baseline to months 24, 36, 42, and 48 in BMD of the lumbar spine and uNTX/Cr and serum CTX 1 for all treatment arms;
- c) percent change from baseline to months 12, 24, 36, 42, and 48 in BMD of the total hip, distal radius, and total body and bone-specific alkaline phosphatase (BAP) for all treatment arms.
- d) assess the administrative feasibility of subject-reported outcomes assessments, and to determine the reliability and validity of the scales.

Serum and Urine Laboratory Assessments

Serum and urine samples were collected according to schedule of assessments listed in Figure 19 and Figure 25. All serum and urine samples were processed and sent to the central laboratory. The central laboratory was responsible for either completing assessments or shipping samples to Amgen for assay (depending on the assessment).

Screening and day-1 bone turnover marker assessments (uNTX/Cr, serum CTX 1, and serum BAP) were completed at least 24 hours apart and before the initial administration of IP. For the subjects participating in the biopsy substudy, the screening and day-1 bone turnover marker assessments were performed before the biopsy procedure, and centers were to ensure that the day-1 sample was obtained within 1 month before IP administration. In addition, the month-12 bone turnover marker assessments should have been obtained before the biopsy procedure.

Subject Reported Outcomes Assessments

Five subject reported outcome measures were selected for evaluation during the trial:

- 1) Medical Outcomes Trial Short-form 36 (SF-36):** to assess health-related quality of life dimensions relevant to overall health status;
- 2) Quality of Life in Reflux and Dyspepsia (QOLRAD):** to measure the impact of gastrointestinal problems associated with 5 health-related quality of life (HRQOL) dimensions;
- 3) Gastroesophageal Reflux Disease Symptom Assessment Scale (GSAS):** to measure the number, frequency, severity, and distress of symptoms associated with gastrointestinal symptoms;
- 4) Treatment Satisfaction Assessment (TSA):** an experimental instrument to measure medication efficacy, convenience, side effects, and willingness to use;
- 5) EuroQol – 5 Dimensions (EQ-5D):** to measure physical, mental, and social functioning.

Exploratory

Exploratory/Tertiary objectives were to evaluate characterize the efficacy and safety of denosumab following IP withdrawal and retreatment in a subset of subjects.

Substudies:

There were two substudies to assess safety – a bone biopsy substudy and an immune cell assessment substudy.

The bone biopsy substudy examined the effects of denosumab on bone histology, histomorphometry and micro-computerized tomography (microCT) of the trabecular and cortical regions. In this substudy, 40 subjects from 8 centers were asked to undergo iliac crest biopsies during screening (within a month prior to the first dose) and before the visit at Month 12 (within 1 month prior to the Month 12 dose). If subjects did not undergo the baseline biopsy procedure, they still underwent the month-12 biopsy procedure.

All subjects scheduled for the bone biopsy followed a double tetracycline (baseline) or demeclocycline (month 12) labeling procedure before undergoing the biopsy. The labeling procedure may have been initiated more than 1 month before the scheduled day-1 or month-12 dose, as long as the timing allowed the actual biopsy to be performed within 1 month before trial drug dosing on Day 1 or Month 12.

The immune cell assessment substudy enrolled approximately 80 subjects from 5 centers. These subjects underwent enumeration of T- and B-cells by flow cytometry and WBC and lymphocyte cell counts. Blood samples used for this substudy were from baseline and 3, 6, 12, 18 and 24 months after dosing.

Safety Measures:

The primary safety objective was to characterize the safety and tolerability of denosumab in postmenopausal women with osteopenia based on adverse event incidences, changes in laboratory profiles, electrocardiograms (ECGs), changes in bone

morphometry, changes in immune cell enumeration, and immunogenicity to denosumab.

The schedule of assessments through Month 24 of the trial is summarized below in Figure 19.

Figure 24. Schedule of Assessments Through Month 24

Procedures	Study Day																	Study Months							
	Screen	1 ^a	4	1	2	3	4	5	6	6 (d3) ^b	7	8	9	10	11	12	15	18	21	24					
Medical history	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medication history	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pharmacogenetic sample	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Physical exam	X	X ^c	-	-	-	X	-	-	X	-	-	-	-	-	-	X	-	X	-	X	-	-	-	-	X
ECG	X	-	-	X	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-	-	-
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DXA (lumbar spine, hip)	X ^d	-	-	X	-	X	-	-	X	-	-	-	-	-	-	X ^e	-	X	-	-	-	-	-	-	X
DXA (radius, total body)	-	X	-	-	-	-	-	-	X	-	-	-	-	-	-	X	-	X	-	-	-	-	-	-	X
Hematology	X	X	-	X	X	X	-	-	X	-	-	-	-	-	-	X	-	X	-	X	-	-	-	-	X
Serum chemistry	X	X	X	X	X	X	-	-	X	X	X	-	X	-	-	X	X	X	X	X	X	X	X	X	X
Urine NTX, CTX	X ^f	X ^f	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum CTX 1	X ^f	X ^f	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BAP	X ^f	X ^f	-	X	-	X	-	-	X	-	-	-	X	-	-	X	X	X	X	X	X	X	X	X	X
Intact PTH	-	X	-	X	-	X	-	-	X	-	-	-	-	-	-	X	-	X	-	-	-	-	-	-	X
Denosumab antibody	-	X	-	X	X	X	-	-	X	-	-	-	X	-	-	X	X	X	X	X	X	X	X	X	X
Immune cell enumeration ^g	-	X	-	-	-	X	-	-	X	-	-	-	-	-	-	X	-	X	-	-	-	-	-	-	X
Dosing ^h	-	X	-	-	-	X	-	-	X	-	-	-	X	-	-	X	X	X	X	X	X	X	X	X	X
Concomitant meds	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Iliac crest bone biopsy ^h	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-	-	-
AE collection	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fracture Recording	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK assessments ^b	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject Reported	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
• SF-36	-	X	-	X	-	-	-	-	X	-	-	-	-	-	-	X	-	X	-	-	-	-	-	-	X
• QLQ-RAD	-	X	-	X	-	X	-	-	X	-	-	-	X	-	-	X	-	X	-	-	-	-	-	-	X
• GSAS	-	X	-	X	-	X	-	-	X	-	-	-	X	-	-	X	-	X	-	-	-	-	-	-	X
• TSA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-
• EQ-5D	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-	X

a Day 1 procedures were completed before dosing.

b Subjects were to return 3(+) days after month 6 dose administration

c Not necessary if screening procedure was completed within 1 week of Day 1.

d Duplicate scans; subjects were to get off DXA table between measurements.

e Screen and Day 1 samples must have been collected at least 24 hours apart, and prior to Day 1 dose.

f Subjects enrolled at 5 selected sites (target 80 subjects).

g Cohorts 1-7, 9 only; Cohort 8 dosed weekly (with last dose 1 week prior to Month 24).

h In subjects enrolled at 8 selected sites (target 40 subjects). Note: tetracycline/demeclocycline labeling procedure must have been completed prior to biopsy.

Source: Clinical Trial Report for Trial 20010223, Figure 7-3, page 121 of 9933.

Trial Assessments after Month 24 were conducted every 6 months. Figure 25 below shows the assessments at each trial visit.

Figure 25. Schedule of Assessments Months 24 to 48

Procedures	Study Months			
	30	36	42	48
Dosing	X	X	X	—
Physical exam	—	X	—	X
ECG	—	X	—	X
Vital signs	X	X	X	X
DXA (lumbar spine, hip)	—	X	X ^a	X
DXA (radius, total body)	—	X	X ^a	X
Hematology	X	X	X	X
Serum chemistry	X	X	X	X
Urine NTX, CTX	X	X	X	X
Serum CTX 1	X	X	X	X
BAP	X	X	X	X
Intact PTH	—	X	—	X
Denosumab antibody	X	X	X	X
Concomitant meds	X	X	X	X
AE collection	X	X	X	X
Fracture Recording	X	X	X	X
PK assessments	X	X	X	X
Subject Reported	—	—	—	—
• SF-36	X	X	X	X
• QOLRAD	X	X	X	X
• GSAS	X	X	X	X
• TSA	—	—	—	X
• EQ-5D	X	X	X	X

^a If month 42 visit occurred, but not by more than 3 months (month 45), DXA scans were to be acquired. If the month 42 visit had occurred and it had been more than 3 months (past month 45), DXA scans did not have to be acquired. Subjects were to get their regularly scheduled DXA scans at the month 48 visit.

Concomitant and Proscribed Medications:

Investigators could prescribe any concomitant medications considered necessary to provide adequate supportive care except for those that might affect bone mass or bone metabolism, including:

- bisphosphonates (except alendronate for subjects randomized to cohort 8)
- estrogens or estrogen derivatives
- systemic glucocorticosteroids (> 5 mg prednisone equivalent daily)
- fluoride (for osteoporosis treatment)
- Calcitonin
- Anabolic steroids
- thyroid replacement therapy (unless used as before trial entry)
- PTH (or a derivative)
- Calcitriol

- any other medication known or suspected to have activity on bone metabolism (except calcium and vitamin D)

Withdrawal criteria:

If a subject experienced an osteoporosis-related fracture (ie, crush vertebral, hip fracture, etc), the investigator was to withdraw IP and offer treatment with an approved agent for the treatment of osteoporosis. If the subject were removed from IP, every effort was made to complete all remaining trial visits.

A central imaging center monitored BMD over the course of the trial, and alerted investigators to any subject who lost $\geq 7\%$ bone mass at the lumbar spine or total hip within any 12-month period of the trial, or $\geq 10\%$ bone mass at the lumbar spine or total hip from baseline. Except when the bone loss was $\geq 10\%$ in a 12-month period (when the protocol mandated the subject be withdrawn from IP), it was the obligation of the investigator to consider the subject's status and to determine her future management, including alternative therapies. The decision as to whether the subject was withdrawn from IP or the trial was at the discretion of the investigator.

After month 24, alerts from the central imaging vendor described above continued to be in effect. Additional parameters for BMD loss were established and required subjects be withdrawn from IP. When a subject lost $\geq 10\%$ bone mass at the lumbar spine or total hip at the 36- or 42-month visit, the imaging vendor was to alert investigators and Amgen personnel. Subjects were required to return for a DXA scan to confirm bone loss. Subjects were encouraged to remain in the trial for additional assessments.

Every subject had the right to withdraw fully or partially from the trial at any time and for any reason without prejudice to her future medical care by the physician or the institution. The investigator and Applicant also had the right to withdraw subjects from the trial in the event of intercurrent illness, adverse events, protocol violation, or other reasons. Subjects not completing the trial were not replaced. Subjects could be removed from trial for any of the following reasons:

- withdrawal of consent
- administrative decision by the investigator or Applicant
- pregnancy
- ineligibility
- protocol deviation
- subject noncompliance
- adverse event
- disease progression

If a subject withdrew from the trial, all efforts were made to complete and report trial-scheduled observations as thoroughly as possible up to the date of withdrawal. In addition, if a subject withdrew prior to completion of the trial, an early termination visit

was to be performed when possible with all procedures from the month 48 visit conducted.

Reviewer Comments:

- *The withdrawal criteria were adequate to ensure patient safety.*

Statistical Analyses

The primary hypothesis was that denosumab administration significantly increases lumbar spine BMD and is a bone antiresorptive agent (as measured by uNTx/Cr) as compared with placebo after 12 months of treatment. Published clinical trial data in postmenopausal women with low BMD have shown a clinically relevant effect at a placebo-adjusted difference of 3% in postmenopausal women with low BMD.² The Applicant used an array of group means for the placebo group and the denosumab dose cohorts were estimated. It was assumed that the mean percent change in BMD at month 12 would be 0% for subjects who received placebo, as well as for one subtherapeutic denosumab dose cohort. It was also assumed that there would be a clinically relevant placebo-adjusted difference of 3% for at least 1 dose cohort and that the remaining placebo-adjusted mean differences would be > 0% and < 3%; 2 denosumab dose cohorts would attain a 1% placebo-adjusted difference, and the remaining 3 denosumab dose cohorts would attain a 2% placebo-adjusted difference. This array of group means resulted in an estimated variance of means of 0.984.

To account for an estimated drop-out rate of 20%, 360 subjects (40 per group) needed to be randomized to retain 32 subjects through Month 12 of the trial within each treatment arm. An equal number of subjects (40) was randomized to receive alendronate in an unblinded fashion. Data from this treatment arm are descriptive in nature. Sample sizes were calculated using the software nQuery version 4.0.

Using these sample sizes, a 1-way analysis of variance (ANOVA) of the percent change from baseline in the lumbar spine BMD at 1 year would have 90% power to detect differences in the treatment means using a significance level of 0.05, assuming a common standard deviation of 3.6%. This sample size would also have 90% power to detect a 30% difference between any denosumab treatment cohort and placebo with respect to the percent change from baseline in uNTX/Cr at 1 year, assuming a common standard deviation (SD) of 35% (trial 20010124).

As prospectively defined in the protocol, data from the first 12 months of the trial was analyzed before completion of the 48-month trial evaluation period. The primary endpoint was based on the 12-month completers in the modified intent-to-treat subset.

² Bilezikian JP. Efficacy of bisphosphonates in reducing fracture risk in postmenopausal osteoporosis. *Amer J Medicine* 2009;122:S14-S21.

The 12-month analysis is the final analysis of the trial with respect to the primary objective and several of the secondary objectives.

Assessments from months 12 to 48 of the trial were designed to collect longer-term safety data. Hypothesis testing using results from the data collected after 12 months was considered exploratory. Although the Applicant presented p-values for these assessments, they should be considered descriptive statistics because the family-wise type 1 error rate of 0.05 was planned and applied for the 12-month assessment. Any inferences for time points after month 12 were made using 0.001 as the statistical significance level.

The primary analysis of the efficacy parameters employed an analysis of covariance (ANCOVA) model with treatment as the main effect and geographic location and baseline value as covariates. The mean percent changes in BMD reported in this report are the model-adjusted (least-squares) means derived from the ANCOVA model.

Pair-wise comparisons between each denosumab dose cohort and the placebo group were performed for each efficacy parameter. Hypotheses were tested across denosumab doses within an endpoint using Hochberg's procedure at a significance level of 0.05 to account for multiple testing. Any values for post-12 months' results were considered descriptive statistics.

The following analysis subsets were used in this trial:

- **Primary Efficacy Subset:** included all subjects who were randomized and had a nonmissing baseline measurement and nonmissing value for the endpoint of interest. Subjects were analyzed according to their original treatment assignment, regardless of treatment received.
- **Secondary Efficacy Subset:** this "efficacy subset" included all subjects who were randomized and had a nonmissing baseline and at least 1 postbaseline measurement for the parameter of interest. Subjects were analyzed according to their original treatment assignment, regardless of treatment received. This subset was used for sensitivity analyses of the primary efficacy analyses.
- **Clinical Fracture Subset:** included any subject in the secondary efficacy subset who reported a clinical fracture after the first date of IP administration. This subset was also used for sensitivity analyses of the efficacy parameters.
- **Safety Subset:** included all subjects who were randomized and received at least 1 dose of IP. This subset was used for all safety analyses, in which subjects were grouped by highest actual dose of denosumab received, if other than what the subject was randomized to receive.
- **Pharmacokinetic Subset:** included all subjects treated with denosumab who had serum samples and had any reported serum denosumab concentration. The pharmacokinetic analyses for the 12-month analysis were based on a different subset, which included all subjects treated with denosumab who had a sufficient number of serum samples to estimate pharmacokinetic parameters, as

determined by the pharmacokinetic scientist, and if a parameter could not be calculated for a subject (eg, if extrapolation could not be performed), this subject was excluded from the analysis of that parameter.

- **Subject Reported Outcomes Subset:** included all subjects in the secondary efficacy subset.

Planned Covariates

The statistical significance of the following baseline characteristics was used to explore their effect on the primary and secondary efficacy endpoints: age; race/ethnicity; smoking status; years since menopause; baseline BMD of lumbar spine, total hip, femoral neck, trochanter, distal 1/3 radius, and total body; history of clinical fractures; previous osteoporosis medication use; baseline uNTX/Cr and serum CTX levels; baseline iPTH level; baseline body mass index (BMI); geographic region within the United States

Psychometric analyses were used to assess the reliability and validity of the subject-reported outcomes scales. Baseline descriptive statistics were also calculated. In addition, completion rates were calculated to assess administrative feasibility for all health-related quality of life (QOL) instruments at various time points.

Summary statistics, including mean, SD, % coefficient of variation (%CV), and median values, for C_{min} were calculated for the pharmacokinetic analyses. Summary statistics were reported by nominal time points. A value was excluded if the sample for C_{min} was obtained either after dosing or more than 7 days before dosing. Comparisons of mean serum concentrations were made using graphs and tables of data.

Amendments to the Statistical Analysis Plan

The Statistical Analysis Plan (SAP) (version 1.3 dated 16 February 2006) was provided by the Applicant in the initial BLA submission. The SAP was amended six times during the trial.

Protocol Amendments

The initial protocol was submitted on 30 March 2002. The protocol was amended 7 times during the trial. A summary of each of the amendments is provided below.

Amendment 1 dated 11 March 2002 provided for the following changes:

- Eligibility criteria were clarified to ensure appropriate osteoporosis treatment was not withheld from subjects with a very low BMD or recent osteoporosis-related fractures.
 - For the inclusion criterion: BMD T-scores must not be < -4.0 at the lumbar spine, or -3.5 at the femoral neck or total hip.
 - The following exclusion criterion was added: osteoporosis-related fracture (ie, crush or wedge vertebral fracture) within 6 months.
- Guidelines for continuation of the trial after an osteoporosis-related fracture were clarified. If a subject experienced an osteoporosis-related fracture, the investigator was

to discuss alternative therapy with the subject (including withdrawing trial medication). Procedures for subjects who withdrew from IP also were added.

Amendment 2 dated 01 August 2002 provided for the following changes:

- The last active denosumab dose was modified to occur at month 15 for 3-monthly dosing cohorts (Cohorts 1 to 4) and at month 12 for the 6-monthly dosing cohorts (Cohorts 5 to 7). An objective, "to characterize the sustainability of effect with respect to BMD changes from last denosumab dose (month 12 or 15) to month 18 and month 24," was added. Endpoints were modified to reflect the changes in dosing and follow-up schedules and to address the new objective.
- Month 18 day 3 and month 19 visits were removed and modifications were made to the timing of screening procedures.
- All subjects (rather than only those in cohorts 1 to 7) at the centers selected for the biopsy substudy were asked to undergo biopsy procedures.
- An ECG was added to the month 1 and 12 visits.
- Estrogen therapy wash-out period decreased from 6 to 3 months.
- To address ethnic differences, the eligible T-score was increased from -2.0 to -1.8.
- The number of trial centers was increased from 15 to 25.

Amendment 3 dated 12 September 2002 provided for the following:

- A denosumab 14 mg every 6 months dose arm with 40 subjects was added to characterize the dose-response relationship for denosumab more completely.
- The number of trial centers was increased from 25 to 35, the planned sample size was increased from 320 subjects to 360 subjects, and the estimated trial duration was increased from 32 to 35 months.

Amendment 4 dated 16 December 2002 provided for the following:

- To address Western IRB's guidelines issued in November 2002 for the review of placebo-controlled osteoporosis studies, the following eligibility criteria were revised. (The sample informed consent was also revised to specify the risk of fracture in subjects who may be randomized to placebo.)
 - Maximum age at randomization was revised from ≤ 85 years to ≤ 80 years.
 - The exclusion criterion regarding osteoporosis-related fracture (ie, crush or wedge vertebral fracture or hip fracture) was revised to exclude any subjects with known or suspected fractures to have occurred within 2 years of randomization.
 - The following exclusion criterion was added: subjects with more than 1 single, grade 1 vertebral fracture.
- An additional subject-reported outcomes questionnaire, the EQ-5D, was added.
- To obtain as much information as possible on bone health after 12 months of treatment, all subjects enrolled at biopsy substudy centers were requested to undergo a month-12 biopsy procedure, whether or not a baseline bone biopsy was obtained.
- Guidelines for continuation of the trial after an osteoporosis-related fracture were changed to specify that if a subject experienced an osteoporosis-related fracture, the

investigator was to withdraw IP and offer active treatment with an approved agent for the treatment of osteoporosis.

Amendment 5 dated 11 November 2003 provided for the following changes:

- The protocol was extended from 24 to 48 months to obtain long-term safety and efficacy data. The third objective of the trial was consequently changed to extend the evaluation to 48 months. The fourth objective of the trial, "to characterize the sustainability of effect with respect to BMD changes from last denosumab dose (month 12 or 15) to month 18 and month 24," was removed. Also, trial endpoints were modified to reflect the extension of the trial and changes in objectives.
- The last objective of the trial was modified from "to assess the feasibility of functional ability and subject-reported outcomes assessments" to "to assess the administrative feasibility of subject-reported outcomes assessments and to determine reliability and validity of the scales." Percent completion in subject-reported outcomes, scale reproducibility, and scale criterion validity were added as trial endpoints.
- The statistical analysis section to allow for at least 2 interim analyses before the final month-12 analysis.
- Added a bone turnover marker assessment (urine Type II CTX/creatinine) and micro-computerized tomography analyses of bone biopsy samples.

Amendment 6 dated 24 May 2004 provided for the following changes:

- The dose reallocation schema for months 24 through 48 was established.
- Two secondary objectives were added: to assess the off-treatment effect of denosumab based on BMD and bone turnover marker changes and to assess the efficacy and safety of retreatment with denosumab.

Amendment 7 dated 01 August 2006 provided for the following changes:

- The main purpose of this amendment was to incorporate the recommendations made by the external Data Monitoring Committee (DMC) regarding the monitoring of trial subject bone mineral density (BMD).
 - Any subject who had a $\geq 10\%$ decrease in BMD at either 12 or 18 months following the withdrawal of denosumab was discontinued from IP. Because of the time between the month 36 DXA scan and the time these decisions were made, Amgen requested that any subject who had a $\geq 10\%$ decrease in lumbar spine or total hip BMD at either 12 or 18 months from the month 24 visit undergo a confirmatory DXA before being discontinued from IP.
 - Note: Previous protocol-required alerts for loss in BMD were unaffected by this amendment (ie, the central imaging center monitored BMD over the course of the trial, and alerted investigators to any subject who lost $\geq 7\%$ bone mass at the lumbar spine or total hip within any 12-month period of the trial, or $\geq 10\%$ bone mass at the lumbar spine or total hip from baseline).
- The clinical experience of denosumab was updated to reflect the most current clinical data available from clinical trials, including month 36 data.
- Analysis of urine Type II CTX/creatinine was removed.

- Current adverse event reporting processes were updated.
- Interim (months 24 and 36) and planned (month 42) analyses were added to the statistical procedures.
- The process for maintaining the double-blind for this trial was updated.
- The SF-36, GSAS, and QOLRAD would not be required by protocol.

Reviewer's Comment:

- ***The amendments all appear to be reasonable and appropriate.***
- ***The amendments are generally to strengthen monitoring of the trial subjects, changes prompted by evolving knowledge of the product or to ensure appropriate osteoporosis treatment was not withheld from subjects with a very low BMD or recent osteoporosis-related fractures***

Results

Subject Disposition:

A total of 412 subjects (319 denosumab, 46 placebo, 47 alendronate) were enrolled at 29 trial centers in the United States. The number of subjects enrolled into each of the 7 denosumab dose cohorts ranged from 41 to 54 subjects, with 47 subjects enrolled cohort for the to-be-marketed dose (60 mg Q6months).

An average of 64% of all subjects completed the trial. The percentage of subjects in the denosumab cohorts completing the trial ranged from 51% (30 mg Q3months) to 85% (60 mg Q6months). Ten subjects in the denosumab group remained on trial after discontinuing IP, and 8 of those subjects completed the trial.

Overall, the most common reasons for subjects in the denosumab, placebo, and alendronate treatment groups to discontinue the trial were because of withdrawn consent (23%, 24%, and 21%, respectively) adverse events (4%, 4%, and 6%), and loss to follow-up (3%, 7%, and 4%). Adverse events were reported in the denosumab cohorts at a range of 2.13% (denosumab 60 mg Q6 months) to 12.2% (denosumab 30 mg Q3months).

Table 152. Trial 20010223: Subject Disposition

	placebo	D6q3m	D14q6m	D14q3m	D30q3m	D60q6m	D100q6 m	D210q6 m	Alen.
Yearly dose	n/a	24	28	56	120	120	200	420	n/a
Randomized	46	44	54	44	41	47	42	47	47
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Informed consent signed	46 (100)	44 (100)	54 (100)	44 (100)	41 (100)	47 (100)	42 (100)	47 (100)	47 (100)
Completed	33 (71.74)	31 (70.5)	40 (74.1)	27 (61.4)	21 (51.2)	40 (85.1)	28 (66.7)	32 (68.1)	39 (83)
Administrative decision	0 (0)	0 (0)	1 (1.9)	3 (6.8)	0 (0)	0 (0)	1 (2.4)	1 (2.1)	1 (2.1)
Adverse event	2 (4.35)	3 (6.8)	2 (3.7)	5 (11.4)	5 (12.2)	1 (2.1)	2 (4.8)	3 (6.4)	5 (10.6)
Consent withdrawn	11 (23.91)	8 (18.2)	14 (25.9)	11 (25)	13 (31.7)	6 (12.8)	13 (31)	9 (19.2)	10 (21.3)
Death	0 (0)	0 (0)	0 (0)	1 (2.3)	0 (0)	0 (0)	2 (4.8)	0 (0)	0 (0)
Lost to follow-up	3 (6.52)	5 (11.4)	1 (1.9)	1 (2.3)	1 (2.4)	1 (2.1)	1 (2.4)	2 (4.3)	2 (4.3)
Noncompliance	0 (0)	0 (0)	0 (0)	1 (2.3)	1 (2.4)	0 (0)	0 (0)	0 (0)	0 (0)
Other	0 (0)	0 (0)	1 (1.9)	1 (2.3)	1 (2.4)	0 (0)	0 (0)	0 (0)	0 (0)
Subject request	2 (4.35)	0 (0)	0 (0)	3 (6.8)	0 (0)	0 (0)	0 (0)	1 (2.1)	0 (0)
Disease progression	1 (2.17)	0 (0)	0 (0)	0 (0)	3 (7.3)	0 (0)	0 (0)	6 (12.8)	0 (0)
Protocol deviation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.1)	0 (0)
Ineligibility determined	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0%)	0 (0)	1 (2.1)

D = denosumab

Reviewer's Comment:

- Overall the rate of discontinuation from trial seems reasonable for a trial of this duration for an indication which is not symptomatic.
- Overall there were no major differences between subjects randomized to denosumab, placebo or alendronate.
- Within the 7 denosumab cohorts, subjects receiving denosumab 30mg Q3 months had the lowest percentage of completion and the highest percentage of adverse events.

Protocol Violations:

The Applicant considered a subject to have had an important protocol deviation if she: did not meet eligibility criteria, received proscribed medications during the trial, missed doses of trial drug, missed assessments of the primary endpoint, or was not withdrawn from trial after meeting certain trial withdrawal criteria. The important trial protocol deviations included 13% of denosumab, 9% of alendronate and 4% of placebo subjects

who received a proscribed medication during the trial. All other important protocol deviations were balanced across treatment groups.

Reviewer comments:

- *There were more subjects in the denosumab cohort that received proscribed medications during the course of the trial.*
- *The use of proscribed medications that may affect bone metabolism may impact the evaluation of the efficacy of denosumab.*
- *The reported violations appear to be random across all 9 dosing cohorts and are overall acceptable to this reviewer.*

Demographics:

The mean (SD) age of subjects enrolled in the trial was 62.5 (8.1) years with 38% of enrolled subjects ≥ 65 years of age. The age range at enrollment was 43-83 years and the median was 62.0 years. The ages of subjects across the cohorts were very similar, with 43.5% of placebo, 37.9% of denosumab and 40.4% of alendronate subjects aged 65 years or older.

All subjects in the trial were female; the majority (86%) identified themselves as White or Caucasian. Approximately 9.5% of subjects identified themselves as Hispanic or Latino and 2.9% identified themselves as Black or African American; across each of the dosing cohorts, there was a fair amount of variability because of the limited size of the cohorts. The trial enrolled very few Asians, Japanese or American Indian/Native Alaskans.

The mean (SD) weight was 68.23 (13.06) kg with a median weight of 66.14 kg (range 40.5 to 113.6 kg). Subjects had a mean BMI of 26.42 (5.03) kg/m² with a median BMI of 25.21 kg/m² (range 16.9 to 45.5 kg/m²). The weights were generally similar across the dosing cohorts as shown in Table 153 below.

Table 153. Baseline Subject Weight for Trial 20010223

Arm	Weight at Baseline (Kg)				
	Mean	Std Dev	Median	Min	Max
Placebo	66.63	11.15	65.91	40.5	93.2
Denosumab 6 mg q3m	67.13	12.35	66.36	41.4	96.5
Denosumab 14 mg q6m	67.93	14.40	66.55	43.6	109.5
Denosumab 14 mg q3m	68.46	11.54	67.89	49.7	100.2
Denosumab 30 mg q3m	69.91	15.13	66.82	45.91	113.6
Denosumab 60 mg q6m	70.90	14.87	69.09	45	112.7
Denosumab 100 mg q6m	67.26	12.04	64.55	50	103.6
Denosumab 210 mg q6m	66.95	12.75	64.80	43.5	100
Alendronate 70 mg qw	69.02	13.03	68.18	47.4	99.1

Overall, 83% of subjects had no prior use of an osteoporosis medication. Approximately half of subjects reported a prior history of fracture, with a range of 43% in the denosumab 14 mg Q3months and 14 mg Q6months cohort to 55% in the denosumab 210mg Q6months cohort. The majority of fractures occurred in the foot or wrist bones.

Subjects were a mean (SD) of 16.20 (9.89) years since menopause, with a median of 14.5 years (range 1.2 to 50.2 years). The placebo group had the smallest number of years since menopause with mean of 14.83 years (median of 10.8 years) at baseline.

Table 154. Baseline Number of Years Since Menopause for Trial 20010223

Arm	Number of Years Since Menopause (Yr)				
	Mean	Std Dev	Median	Min	Max
Placebo	14.83	11.05	10.8	1.8	42.6
Denosumab 6 mg q3m	17.21	8.93	17.4	1.4	40.3
Denosumab 14 mg q6m	17.41	8.20	16.9	5.5	36.6
Denosumab 14 mg q3m	14.18	7.90	12.5	2.4	34.2
Denosumab 30 mg q3m	15.89	10.38	12.9	1.1	40.6
Denosumab 60 mg q6m	16.04	10.10	13.6	2.5	50.2
Denosumab 100 mg q6m	18.62	11.79	18.5	1.2	44.9
Denosumab 210 mg q6m	16.26	10.72	14.4	1.7	44.1
Alendronate 70 mg qw	15.34	9.71	12.7	1.7	39.4

Overall, the baseline mean (SD) BMD T-score at the lumbar spine were -2.14 (0.78) and -1.44 (0.71) at the total hip. Overall, baseline BMD T-scores at each anatomic site were comparable across treatment groups and dose cohorts.

Table 155. Baseline Bone Mineral Density T-Scores (by DXA) at Lumbar Spine and Total Hip for Trial 20010223

Arm	DXA BMD T-Score (Lumbar Spine)				
	Mean	Std Dev	Median	Min	Max
Placebo	-2.2492	0.804	-2.250	-3.850	2.600
Denosumab 6 mg q3m	-1.9514	0.975	-2.000	-4.700	1.500
Denosumab 14 mg q6m	-2.2509	0.679	-2.200	-4.250	0.300
Denosumab 14 mg q3m	-2.0112	0.911	-2.100	-4.400	2.550
Denosumab 30 mg q3m	-2.1788	0.750	-2.250	-4.400	0.050
Denosumab 60 mg q6m	-2.1150	0.773	-2.100	-4.100	0.500
Denosumab 100 mg q6m	-2.0053	1.010	-1.950	-4.850	1.150
Denosumab 210 mg q6m	-2.3718	0.843	-2.450	-4.550	1.700

Arm	DXA BMD T-Score (Lumbar Spine)				
	Mean	Std Dev	Median	Min	Max
Placebo	-2.2492	0.804	-2.250	-3.850	2.600
Denosumab 6 mg q3m	-1.9514	0.975	-2.000	-4.700	1.500
Alendronate 70 mg qw	-2.0733	0.987	-2.150	-4.350	1.150
Arm	DXA BMD T-Score (Total Hip)				
	Mean	Std Dev	Median	Min	Max
Placebo	-1.6202	0.807	-1.650	-3.900	0.700
Denosumab 6 mg q3m	-1.5255	0.839	-1.500	-3.450	0.450
Denosumab 14 mg q6m	-1.6151	0.868	-1.700	-4.500	0.850
Denosumab 14 mg q3m	-1.6514	0.807	-1.750	-3.550	1.100
Denosumab 30 mg q3m	-1.5187	0.772	-1.550	-3.650	0.400
Denosumab 60 mg q6m	-1.6319	0.831	-1.700	-3.850	0.450
Denosumab 100 mg q6m	-1.6746	0.843	-1.750	-3.650	1.150
Denosumab 210 mg q6m	-1.6871	0.783	-1.650	-4.000	0.500
Alendronate 70 mg qw	-1.7079	0.85159	-1.700	-4.050	0.950

Overall, baseline raw BMD values by DXA (g/cm²) at each anatomic site were comparable across treatment groups and dosing cohorts.

Reviewer comments:

- *The majority subjects were White or Caucasian, representing 86% of the overall trial population*
- *Minorities were poorly represented with Hispanics, Blacks and Asians representing 9.5%, 2.9% and 1%, respectively, of the overall trial population. It is often difficult to recruit minority patients in studies, so the trial population is acceptable.*
- *The mean age of subjects enrolled in the trial was 62.5 years with 38% of enrolled subjects ≥ 65 years of age, which is acceptable given the indications sought by the Applicant.*
- *Baseline BMD T-score and raw BMD values were comparable across dosing cohorts.*

Concomitant Medications:

Calcium and vitamin D supplementation was recommended during the trial. Subjects were advised to take daily supplementation of ≥ 1 g elemental calcium and either ≥ 400 IU vitamin D. Concomitant medication use was assessed at every trial visit. The most common concomitant medications reported by subjects in all treatment groups were vitamins, dietary supplements, and nonsteroidal anti-inflammatory agents.

Primary Efficacy Outcomes

General Discussion of Endpoints:

The primary objective of this trial was to determine the effect of denosumab treatment compared with placebo over 12 months on bone mineral density (BMD) of the lumbar spine in postmenopausal women with low BMD.

As prospectively defined in the protocol, data from the first 12 months of the trial was analyzed before completion of the 48-month trial evaluation period. The primary endpoint was based on the 12-month completers in the modified intent-to-treat subset. The 12-month analysis is the final analysis of the trial with respect to the primary objective and several of the secondary objectives.

Efficacy Findings

Primary Endpoint:

The primary endpoint was the percent change from baseline to Month 12 in the bone mineral density (BMD) of the lumbar spine (L1 through L4) for the placebo and denosumab treatment arms as measured by DXA.

The primary analysis of the efficacy parameters employed an analysis of covariance (ANCOVA) model with treatment as the main effect and geographic location and baseline value as covariates. The mean percent changes in BMD reported in this report are the model-adjusted (least-squares) means derived from the ANCOVA model.

Pair-wise comparisons between each denosumab dose cohort and the placebo group were performed for each efficacy parameter. Hypotheses were tested across denosumab doses within an endpoint using Hochberg's procedure at a significance level of 0.05 to account for multiple testing. Any values for post-12 months' results were considered descriptive statistics.

The Applicant noted that at Month 12, denosumab increased BMD of the lumbar spine from baseline in all denosumab cohorts (range: 3.0% to 6.7%). The differences between each denosumab cohort and placebo (- 0.8% change from baseline) were statistically significant ($p < 0.001$). Sensitivity analyses supported these findings. The dose that the Applicant proposed to use in Phase III trials is shaded in Table 19 below.

Table 156. Lumbar Spine BMD by DXA – Percent Change From Baseline to Month 12 (ANCOVA Model, Primary Efficacy Subset, LOCF)

Treatment Arm / Dosing Cohort	Difference from Baseline		Difference from Placebo		
	n	Least Squares Mean (SEM) ^a	Least Squares Mean (SEM) ^a	95% C.I.	P- value ^b
Placebo (N = 46)	46	-0.67 (0.46)	--	--	--
Denos 6 mg q3m (N = 44)	40	4.14 (0.48)	4.81 (0.65)	3.53, 6.09	<0.001
Denos 14 mg q6m (N = 54)	53	2.92 (0.42)	3.59 (0.61)	2.39, 4.78	<0.001
Denos 14 mg q3m (N = 44)	43	4.51 (0.47)	5.18 (0.64)	3.92, 6.44	<0.001
Denos 30 mg q3m (N = 41)	40	5.99 (0.49)	6.66 (0.65)	5.38, 7.94	<0.001
Denos 60 mg q6m (N = 47)	46	4.29 (0.46)	4.96 (0.63)	3.73, 6.20	<0.001
Denos 100 mg q6m (N = 42)	41	5.33 (0.48)	6.00 (0.65)	4.72, 7.28	<0.001
Denos 210 mg q6m (N = 47)	46	4.85 (0.46)	5.52 (0.63)	4.29, 6.76	<0.001
Alendronate 70 mg qw (N = 47)	46	4.49 (0.45)	5.16 (0.63)	3.92, 6.40	<0.001

N = Number of subjects enrolled.

n = Number of subjects with values at baseline and 1 or more post baseline visits at or prior to month 12.

a Based on ANCOVA model adjusting for treatment, geographical location, and baseline value.

b p-values for denosumab vs. placebo are adjusted for multiple comparisons using Hochberg's procedure. Nominal p-value is reported for alendronate vs. placebo.

Source: Clinical Trial Report for Trial 20010223, Table 14-4.3.9.1, pages 529-531 of 9933.

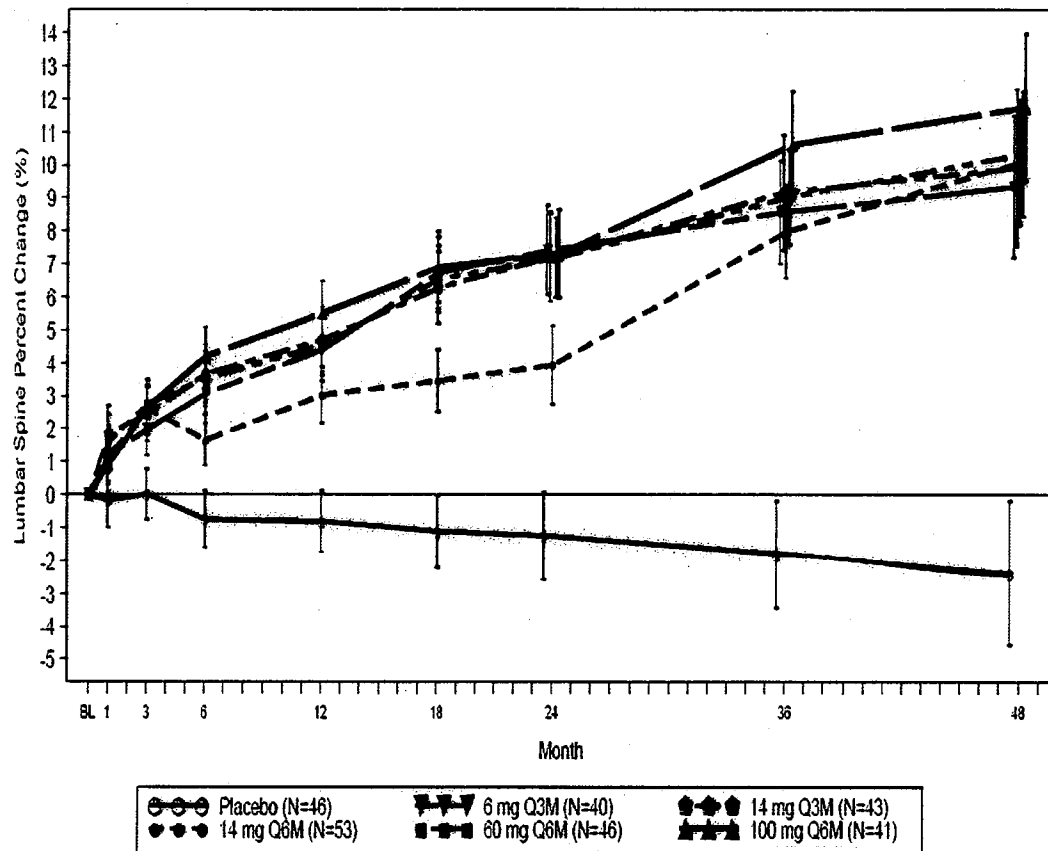
In a summary prepared by this reviewer, the percent change from baseline in lumbar spine BMD is shown below in Table 157. The denosumab cohorts all had an increase in lumbar spine BMD from baseline to Month 12 while the placebo cohort had a decrease in lumbar spine BMD. The denosumab cohort of 14 mg Q6months had the smallest increase in lumbar spine BMD. The denosumab 60 mg Q6months cohort was approximately equal to alendronate; this dose (shaded below in the table) was the dose the Applicant proposed to use in Phase III trials.

Table 157. Percent Change from Baseline in Bone Mineral Density (by DXA) at Lumbar Spine at Month 12 for Trial 20010223 – Primary Efficacy Subset

Arm	Percent Change in BMD from Baseline to Month 12				
	Mean	Std Dev	Median	Min	Max
Placebo	-0.540	2.869	-0.43	-6.27	5.78
Denosumab 6 mg q3m	4.112	2.574	3.72	-3.58	11.62
Denosumab 14 mg q6m	2.987	2.809	2.84	-2.61	12.07
Denosumab 14 mg q3m	4.506	2.986	4.13	-4.52	11.32
Denosumab 30 mg q3m	6.045	3.360	5.77	0.00	14.45
Denosumab 60 mg q6m	4.422	3.227	4.90	-6.76	9.78
Denosumab 100 mg q6m	5.315	2.927	4.92	-1.53	10.77
Denosumab 210 mg q6m	4.991	3.284	4.91	-0.95	16.26
Alendronate 70 mg qw	4.513	3.105	4.48	-2.26	13.99

The placebo group had a decrease in BMD during the course of the trial, with a 1.3% decrease noted at Month 24. As noted previously, the denosumab cohorts had similar increases in the BMD of the lumbar spine with a range of 3.9% to 8.8% at Month 24, with the least increase in BMD in the denosumab 14 mg Q6months cohort. Thus, the denosumab dosing cohorts, except for 14 mg Q6months, were roughly comparable when evaluated by percent change in lumbar spine BMD (see Figure 26 below). Bone mineral densities of the total hip, distal 1/3 radius, total body (without head), femoral neck, and trochanter increased at each assessment point and were greater for all denosumab dose cohorts than placebo through Month 24. In general, the magnitudes of mean percent increases in BMD at each anatomic site were similar between denosumab and alendronate. The Applicant chose a dose of 60 mg Q6months to use in Phase III trials based on a similar response to alendronate and the convenience of Q6month dosing.

Figure 26. Percent Change from Baseline in Lumbar Spine BMD



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.

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Covariate Analysis:

Analyses on the effect of covariates are summarized below in **Table 158**. There were statistically significant treatment-by-covariate interactions for age, baseline BMD of the total body (without head), baseline serum CTX and baseline uNTX/Cr ($p < 0.05$). However these treatment-by-covariate interactions were not consistent across all the denosumab dosing cohorts. These covariates contributed a minimal amount to the overall denosumab treatment effect and after adjustment for these interactions, the denosumab treatment effect was still statistically significant.

Table 158. Covariate Analysis of Lumbar Spine BMD Percent Change from Baseline to Month 12 (20010223 48-month Analysis)

Covariate	Interaction Model ^a	Covariate Model ^b	
	P-value for Treatment-by-Covariate Interaction	P-value for Covariate	Coefficient for Covariate
Age (year)	0.0481	0.2379	-0.0238
Race (White vs. Non-white)	0.4817	0.4451	0.3764
Smoking status (Yes vs. No)	0.5393	0.6079	0.2638
Years since menopause	0.9103	0.9359	-0.0013
Total hip BMD	0.3625	0.4399	1.4339
Femoral neck BMD	0.0866	0.6251	0.9440
Trochanter BMD	0.0887	0.5387	1.3528
Distal 1/3 radius BMD	0.0707	0.3768	-2.0179
Total body (without head) BMD	0.0080	0.9335	-0.2389
History of clinical fractures (Yes vs. No)	0.7111	0.9275	0.0289
Previous osteoporosis medication use (Yes vs. No)	0.8854	0.0765	-0.7296
Serum C-Tx (ng/mL)	0.0029	0.0005	2.1272
Urine N-Tx/Creatinine (nmol/mmol)	0.0195	0.0264	0.0124
i-PTH (pmol/L)	0.5877	0.2905	0.0778
Body mass index (kg/m ²)	0.1112	0.5800	-0.0180
Weight (kg)	0.3330	0.8251	0.0028

Page 1 of 1

^aThe interaction model for each covariate contains independent effects for treatment, geographical location, baseline lumbar spine BMD, covariate, and treatment-by-covariate interaction.

^bThe covariate model for each covariate contains independent effects for treatment, geographical location, baseline lumbar spine BMD, and covariate.

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Source: Clinical Trial Report for Trial 20010223, Table 14-4.11, page 632 of 9933.

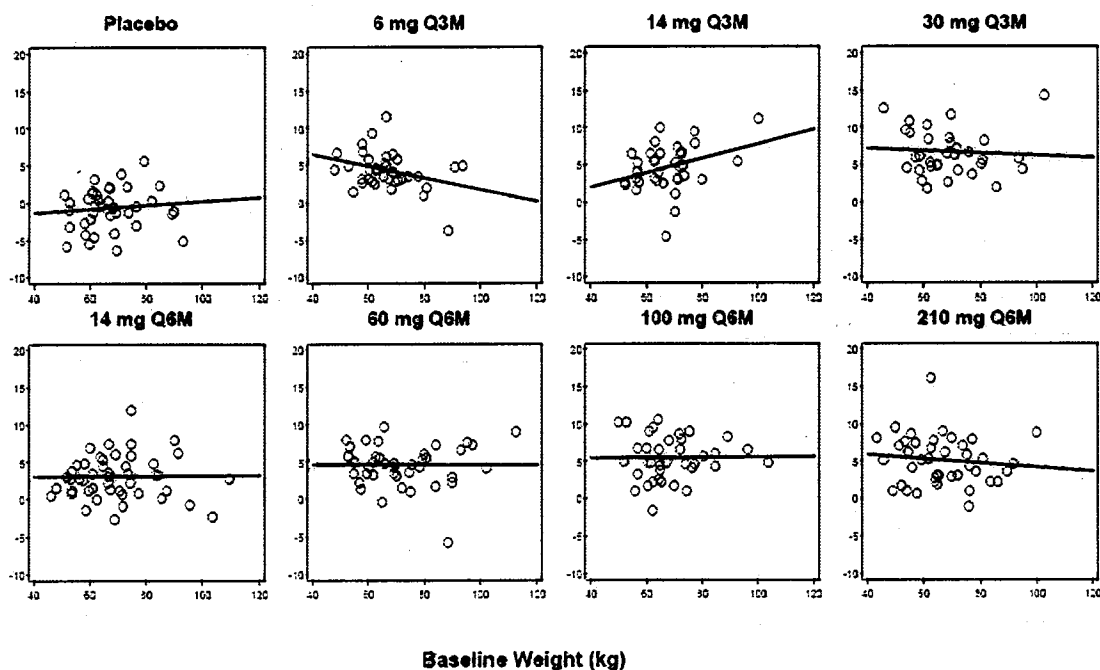
Reviewer Comments:

- **At Month 12, denosumab increased BMD of the lumbar spine from baseline in all denosumab cohorts. The differences between each denosumab cohort and placebo (- 0.8% change from baseline) were statistically significant ($p < 0.001$). This reviewer agrees with the Applicant's conclusion that this trial achieved the primary endpoint.**
- **The covariate analysis showed that there were statistically significant treatment-by-covariate interactions for age, baseline BMD of the total body (without head), baseline serum CTX and baseline uNTX/Cr ($p < 0.05$). However these treatment-by-covariate interactions contributed little to the treatment effect and were not consistent across all the denosumab dosing cohorts. After adjustment for these interactions, the denosumab treatment effect was still statistically significant.**
- **The denosumab dosing cohorts, except for 14 mg Q6months, were roughly comparable when evaluated by percent change in lumbar spine BMD in the trial.**
- **The treatment effect of denosumab on BMD was approximately equal to alendronate at all anatomic sites evaluated.**

Effect of Body Weight and Body Mass Index (BMI)

The Applicant proposed fixed dosing for all subjects, irrespective of body weight or BMI, for this trial, future studies and the to-be-marketed dose. The Applicant analyzed the effect of body weight and BMI on the treatment effects of denosumab in regards to BMD and serum CTX 1. In placebo group, a higher baseline weight and BMI was correlated with maintenance of lumbar spine BMD. For the denosumab group, there was no linear correlation for either baseline weight or BMI and lumbar spine (see Figure 27 and Figure 28). No linear correlations were noted for either weight or BMI with change in BMDs of the total hip, trochanter, femoral neck, or distal 1/3 radius for either the denosumab or placebo group. Thus, there was no significant treatment-by-weight ($p = 0.333$) or treatment-by-BMI ($p = 0.112$) interactions on the primary endpoint (mean percent change from baseline in BMD at the lumbar spine at Month 12).

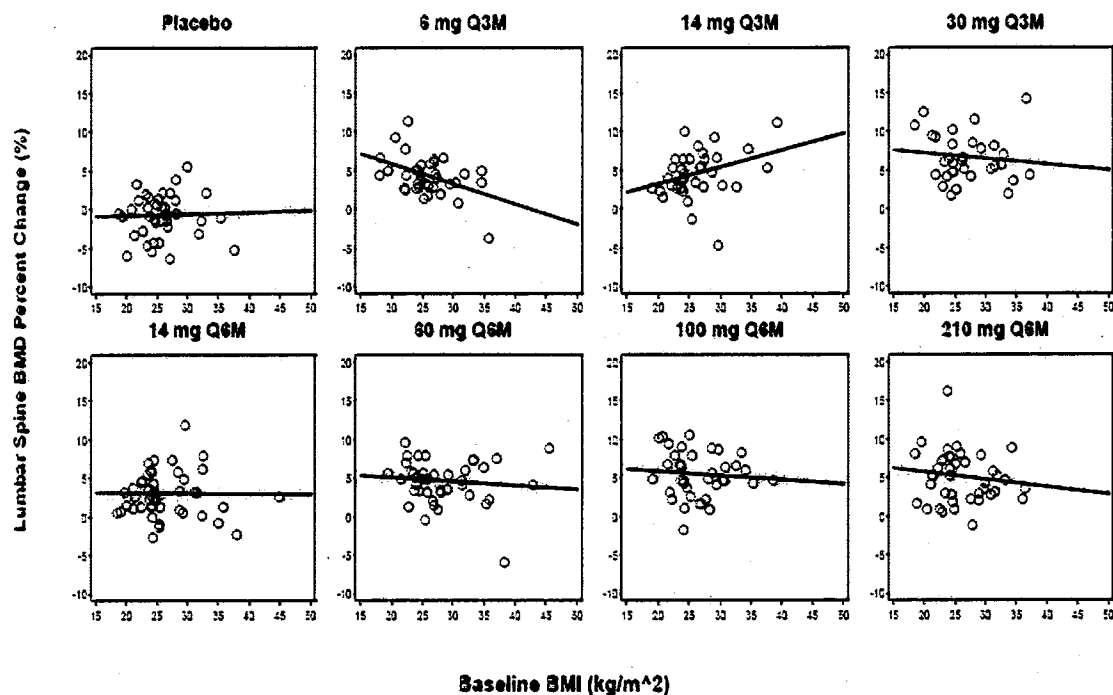
Figure 27. Lumbar Spine BMD Percent Change From Baseline to Month 12 by Baseline Body Weight With Linear Regression Line



ran: /stat/ang162/oste/20010223/analysis/final_48mon/graphs/program/g_scatter_bmd_bwt_m12.sas
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Source: Clinical Trial Report for Trial 20010223, Figure 9-2.1, page 3297 of 9933.

Figure 28. Lumbar Spine BMD Percent Change From Baseline to Month 12 by Baseline BMI With Linear Regression Line



Program: /stat/amp162/osteo/20010223/analysis/final_48mon/graphs/program/g_scatter_bmd_bfmi_m12.sas
 Output: g9-03_001_scatter_bmd_bfmi_m12_pohg_spine.qgm (Date Generated: 25SEP2007 14:54:32)
 Source Data: /stat/amp162/osteo/20010223/analysis/final_48mon/statdata/adam/adam.abmdxa, adam.asibase

Source: Clinical Trial Report for Trial 20010223, Figure 9-3.1, page 3304 of 9933.

Although changes at the lumbar spine at Month 12 were not statistically significant, there were statistically significant treatment-by-weight and treatment-by-BMI interactions for the femoral neck ($p = 0.0266$ and $p = 0.0041$, respectively). These results suggested that the effect of weight and BMI on percent increase from baseline in BMD of the femoral neck at Month 12 was different among denosumab dosing cohorts. Similar results were also seen at Month 24.

Figure 29. Significance of Treatment-by-Body Weight or Body Mass Index (BMI) Interactions on Percent Change in BMD and Bone Resorption After 12 Months of Treatment (20010223 48-month Analysis)

	Treatment-by-Weight interaction		Treatment-by-BMI interaction	
	n	p-value	n	p-value
Bone mineral density				
Lumbar spine	310	0.2635	310	0.1361
Total hip	311	0.9789	311	0.9760
Femoral neck	311	0.0266	311	0.0041
Trochanter	311	0.5053	311	0.8192
Distal 1/3 radius	301	0.9860	301	0.8838
Total body (without head)	292	0.5507	292	0.5163
Bone resorption				
CTX	303	0.7589	303	0.6840

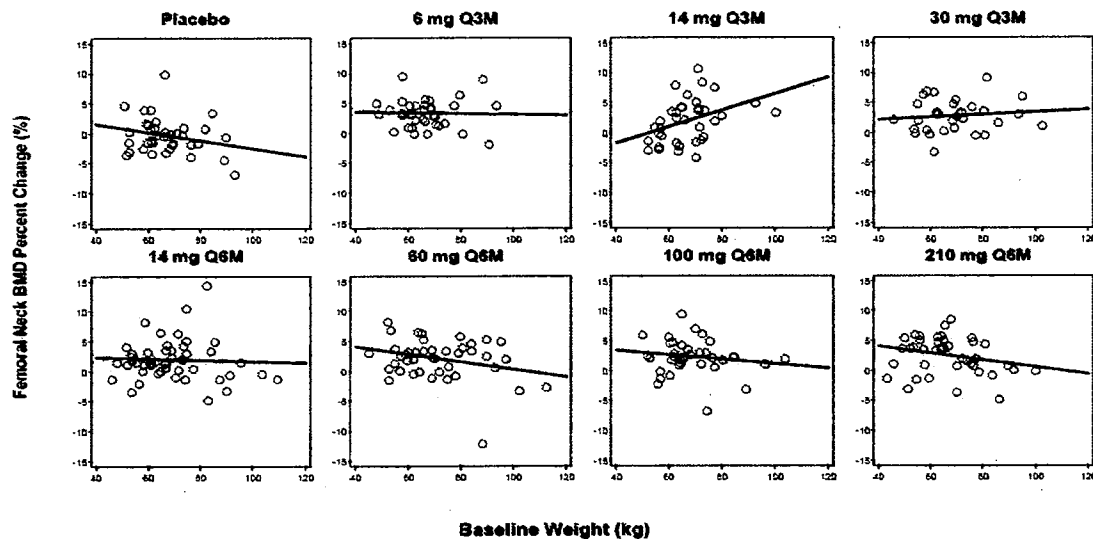
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The interaction models for each endpoint contain independent effects for treatment, geographical location, baseline BMD (or CTX), baseline weight (or BMI), and treatment-by-weight (or BMI) interaction. Subjects treated with alendronate were excluded. Nominal p-values were reported. No adjustments were made for multiple testings.
 n = number of observations used

Program: /stat/amg162/osteo/20010223/analysis/final_48mon/tables/program/t_bmdxa_btm_bwt_bmi_effect_m12.sas
 Output: t14-04_010_001_001_bmdxa_btm_bwt_bmi_effect_m12.rtf (Date Generated: 20SEP2007:11:37:06) Source Data: adam.abmdxa, adam.albbsp, adam.asibase

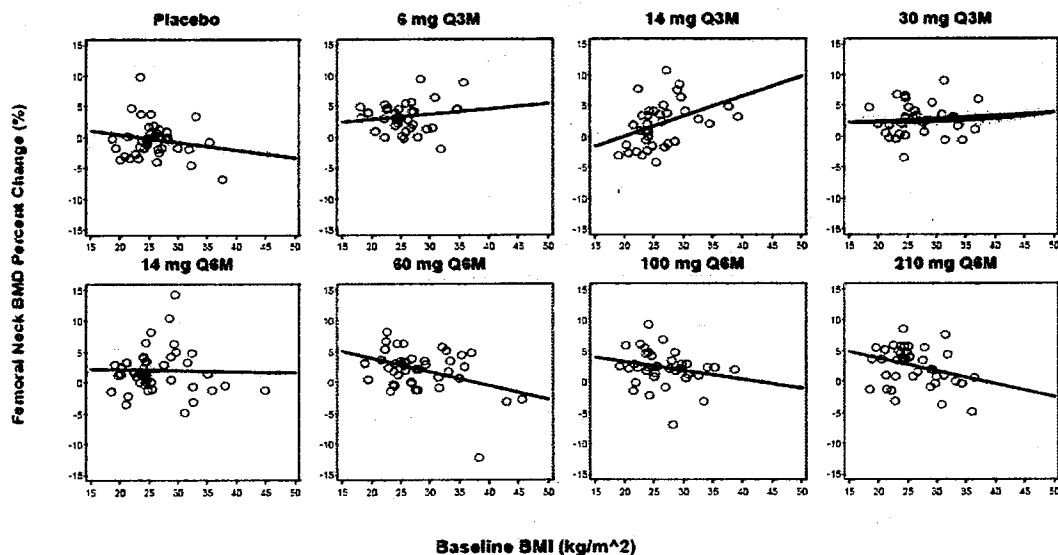
Source: Clinical Trial Report for Trial 20010223, Table 14-4.10.1.1, page 624 of 9933.

Figure 30. Femoral Neck BMD Percent Change From Baseline to Month 12 by Baseline Body Weight With Linear Regression Line



Source: Clinical Trial Report for Trial 20010223, Figure 9-2.3, page 3299 of 9933.

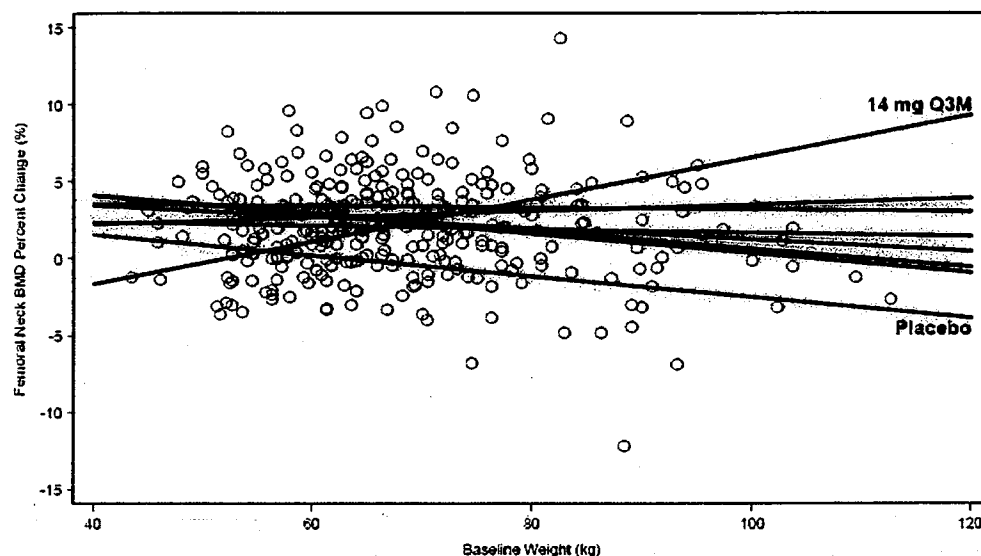
Figure 31. Femoral Neck BMD Percent Change From Baseline to Month 12 by Baseline BMI With Linear Regression Line



Source: Clinical Trial Report for Trial 20010223, Figure 9-3.2, page 3305 of 9933.

To explore this further, the Applicant plotted the percent change from baseline in BMD of the femoral neck at Month 12 against the baseline values for weight and BMI for each denosumab dose cohort. Linear regression lines for all denosumab dose cohorts for weight were superimposed on these plots. The denosumab 14 mg Q3months dosing cohort had a different response than the other dosing cohorts when examined by body weight and BMI.

Figure 32. Femoral Neck BMD Percent Change From Baseline to Month 12 by Baseline Weight With Linear Regression Line



Only subjects treated with placebo and/or denosumab are included.

Program: /stat/amp162/osteol/20010223/analysis/final_48mon/graphs/program/n_scatter_bmd_bhwt_m12_pchg_neck_14mgq3m.sas
 Output: 09-01-003-001_scatter_bmd_bhwt_m12_pchg_neck_14mgq3m.gm (Date Generated: 25OCT2007 14:18:17)
 Source Data: /stat/amp162/osteol/20010223/analysis/final_48mon/statdata/adam/adam.abmdxa.adam.asibase

Source: Clinical Trial Report for Trial 20010223, Figure 9-2.3.1, page 3300 of 9933.

A positive relationship between baseline body weight and the percent change in BMD of the femoral neck at 12 months was only true for the 14 mg every 3 months dose cohort ($p < 0.05$); there were no statistically significant relationships between baseline weights and BMD values of the femoral neck for all other denosumab dose cohorts. When an analysis of the ANCOVA model was refitted without the 14 mg every 6 months denosumab dose cohort, the treatment-by-body weight interaction was no longer statistically significant. There was no apparent relationship between BMI and percent change in BMD at month 12.

Effect of Body Weight and BMI on CTX1 Levels

The effect of body weight and BMI on CTX 1 was investigated at month 24. No statistically significant treatment-by-weight interactions occurred at month 24.

Reviewer Comments:

- ***There was not a treatment-by-weight nor a treatment-by-BMI effect on lumbar spine BMD for the denosumab dosing cohorts.***
- ***There was an apparent treatment-by-weight or treatment-by-BMI effect on femoral neck BMD for the denosumab dosing cohorts at Months 12 and 24.***
- ***Further analysis of the denosumab dosing cohorts showed that this effect was mainly due to the denosumab 14 mg Q6month cohort. When this cohort was removed from the analysis, there was no statistically significant treatment-by-weight or treatment-by-BMI effect on femoral neck BMD.***
- ***The Clinical Pharmacology Reviewer stated that the proposed dosing regimen was found to be appropriate for all patients recommended for use.***

Secondary Endpoints

The 7 secondary endpoints for this trial are listed below:

- Choose a dose regimen of denosumab for future studies, based on changes from baseline in BMD and bone turnover markers over 12 months;
- Evaluate the effect of denosumab relative to placebo on BMD of the total hip, distal radius, and total body, and the safety and tolerability profile (including bone safety profile based on histology and histomorphometry) over 12 months;
- Evaluate the effect of denosumab relative to placebo on efficacy (based on BMD and bone turnover marker changes) and safety over 48 months;
- Assess whether denosumab treatment has a different efficacy or safety profile compared with alendronate;
- Assess the off-treatment effect of denosumab based on BMD and bone turnover marker changes;
- Assess the efficacy and safety of retreatment with denosumab; and
- Assess the administrative feasibility of subject-reported outcomes assessments, and to determine the reliability and validity of the scales.

First Secondary Endpoint:

The first secondary endpoint was to choose a denosumab dose for future studies and the Applicant chose a denosumab dose regimen of 60 mg every 6 months. As mentioned previously there was a similar treatment effect with denosumab doses of 6, 14, and 30 mg denosumab administered every 3 months and 14, 60, 100, and 210 mg administered every 6 months. Dosing with denosumab 60 mg every 6 months increased BMD at all anatomic sites and suppressed bone turnover markers over the entire dosing interval with an effect that was at least as effective as 70 mg of alendronate administered once a week. Since denosumab was effective when dosed either using a 3- or a 6-month dosing interval, the 6-month dosing interval was selected for reasons of increased convenience and compliance

The changes in bone turnover markers over 12 months were also examined. The bone formation marker bone-specific alkaline phosphatase (BALP) decreased by 60% or

more from baseline to Month 12 in all denosumab dosing cohorts, except the denosumab 14 mg q6months cohort that only experienced a decrease of 36% from baseline. In the lower dose cohorts, the bone turnover markers trended towards baseline levels before the next scheduled dose. The alendronate group had a decrease of 61% from baseline to Month 12, similar to the majority of denosumab dosing cohorts. There was minimal change in the placebo group.

The bone resorption marker C-telopeptide (CTX) was measured in this trial as the percent change from baseline to Month 12 in urine N-telopeptide/Creatinine (uNTX/Cr) and serum C-TX of type I collagen (CTX 1) for all treatment arms. Bone turnover markers were suppressed up to 89% for serum CTx, 73% for uNTX/Cr at Month 12. Across the denosumab dose cohorts, the maximal suppression of bone turnover markers was similar. In the lower dose cohorts, the bone turnover markers trended towards baseline levels before the next dose.

Second Secondary Endpoint:

The Applicant also evaluated the effect of denosumab relative to placebo on BMD of the total hip, distal radius, and total body, and the safety and tolerability profile (including bone safety profile based on histology and histomorphometry) over 12 months;

The changes in total hip, distal radius and total body BMD are presented in

Table 159, Table 160, and Table 161, respectively. There was a statistically significant change from baseline in BMD at all anatomic sites to Month 12 for all denosumab dosing cohorts, except the 14 mg q6month cohort did not achieve a statistically significant change in total body BMD. The alendronate cohort achieved a statistically significant change from baseline to Month 12 in total hip, distal radius and total body BMD.

Table 159. Total Hip BMD by DXA – Percent Change From Baseline to Month 12 (ANCOVA Model, Primary Efficacy Subset, LOCF)

Treatment Arm / Dosing Cohort	Difference from Baseline		Difference from Placebo		
	n	Least Squares Mean (SEM) ^a	Least Squares Mean (SEM) ^a	95% C.I.	P-value ^b
Placebo (N = 46)	46	-0.44 (0.35)	--	--	--
Den. 6 mg q3m (N = 44)	40	2.92 (0.37)	3.35 (0.50)	2.37, 4.34	<0.001
Den. 14 mg q6m (N = 54)	53	1.77 (0.32)	2.21 (0.47)	1.29, 3.12	<0.001
Den. 14 mg q3m (N = 44)	43	2.40 (0.36)	2.84 (0.49)	1.88, 3.80	<0.001
Den. 30 mg q3m (N = 41)	40	2.96 (0.38)	3.40 (0.50)	2.42, 4.38	<0.001
Den. 60 mg q6m (N = 47)	46	3.53 (0.35)	3.97 (0.48)	3.02, 4.91	<0.001
Den. 100 mg q6m (N = 42)	41	2.25 (0.37)	2.69 (0.50)	1.72, 3.67	<0.001
Den. 210 mg q6m (N = 47)	46	2.40 (0.35)	2.84 (0.48)	1.89, 3.78	<0.001
Alen. 70 mg qw (N = 47)	46	2.02 (0.35)	2.46 (0.48)	1.51, 3.41	<0.001

N = Number of subjects enrolled.

n = Number of subjects with values at baseline and 1 or more post baseline visits at or prior to month 12.

a Based on ANCOVA model adjusting for treatment, geographical location, and baseline value.

b p-values for denosumab vs. placebo are adjusted for multiple comparisons using Hochberg's procedure. Nominal p-value is reported for alendronate vs. placebo.

Source: Clinical Trial Report for Trial 20010223, Table 14-4.3.9.1, pages 529-531 of 9933.

Table 160. Distal Radius BMD by DXA – Percent Change From Baseline to Month 12 (ANCOVA Model, Primary Efficacy Subset, LOCF)

Treatment Arm / Dosing Cohort	Difference from Baseline		Difference from Placebo		
	n	Least Squares Mean (SEM) ^a	Least Squares Mean (SEM) ^a	95% C.I.	P-value ^b
Placebo (N = 46)	42	-1.92 (0.48)	--	--	--
Den. 6 mg q3m (N = 44)	38	0.91 (0.50)	2.83 (0.68)	1.50, 4.17	<0.001
Den. 14 mg q6m (N = 54)	48	1.05 (0.44)	2.97 (0.64)	1.70, 4.23	<0.001
Den. 14 mg q3m (N = 44)	39	0.18 (0.50)	2.10 (0.68)	0.77, 3.43	0.002
Den. 30 mg q3m (N = 41)	34	0.95 (0.54)	2.87 (0.70)	1.49, 4.25	<0.001
Den. 60 mg q6m (N = 47)	45	1.24 (0.47)	3.16 (0.65)	1.88, 4.44	<0.001
Den. 100 mg q6m (N = 42)	39	0.89 (0.49)	2.81 (0.67)	1.49, 4.14	<0.001
Den. 210 mg q6m (N = 47)	39	0.98 (0.50)	2.90 (0.67)	1.57, 4.22	<0.001
Alen. 70 mg qw (N = 47)	42	-0.52 (0.48)	1.40 (0.66)	0.10, 2.71	0.035

N = Number of subjects enrolled.

n = Number of subjects with values at baseline and 1 or more post baseline visits at or prior to month 12.

a Based on ANCOVA model adjusting for treatment, geographical location, and baseline value.

b p-values for denosumab vs. placebo are adjusted for multiple comparisons using Hochberg's procedure. Nominal p-value is reported for alendronate vs. placebo.

Source: Clinical Trial Report for Trial 20010223, Table 14-4.3.9.1, pages 529-531 of 9933.

Table 161. Total Body BMD by DXA – Percent Change From Baseline to Month 12 (ANCOVA Model, Primary Efficacy Subset, LOCF)

Treatment Arm / Dosing Cohort	Difference from Baseline		Difference from Placebo		
	n	Least Squares Mean (SEM) ^a	Least Squares Mean (SEM) ^a	95% C.I.	P-value ^b
Placebo (N = 46)	40	-0.42 (0.44)	--	--	--
Den. 6 mg q3m (N = 44)	38	1.70 (0.44)	2.12 (0.61)	0.92, 3.31	0.001
Den. 14 mg q6m (N = 54)	47	0.70 (0.40)	1.12 (0.58)	-0.02, 2.25	0.054
Den. 14 mg q3m (N = 44)	40	2.01 (0.44)	2.43 (0.60)	1.25, 3.61	<0.001
Den. 30 mg q3m (N = 41)	31	2.77 (0.50)	3.19 (0.64)	1.93, 4.45	<0.001
Den. 60 mg q6m (N = 47)	44	2.37 (0.42)	2.78 (0.58)	1.63, 3.93	<0.001
Den. 100 mg q6m (N = 42)	37	1.70 (0.45)	2.12 (0.61)	0.92, 3.33	0.001
Den. 210 mg q6m (N = 47)	41	2.14 (0.43)	2.56 (0.59)	1.39, 3.73	<0.001
Alen. 70 mg qw (N = 47)	40	1.54 (0.43)	1.96 (0.60)	0.78, 3.14	0.001

N = Number of subjects enrolled.

n = Number of subjects with values at baseline and 1 or more post baseline visits at or prior to month 12.

a Based on ANCOVA model adjusting for treatment, geographical location, and baseline value.

b p-values for denosumab vs. placebo are adjusted for multiple comparisons using Hochberg's procedure. Nominal p-value is reported for alendronate vs. placebo.

Source: Clinical Trial Report for Trial 20010223, Table 14-4.3.9.1, pages 529-531 of 9933.

Bone Biopsy Results

Bone safety was evaluated by transiliac bone biopsy with histomorphometry with double tetracycline labeling and micro-computerized tomography (microCT) of the trabecular and cortical regions. Bone biopsies were obtained during screening (within a month prior to the first dose) and before the visit at Month 12 (within 1 month prior to the Month 12 dose). All subjects scheduled for the bone biopsy followed a double tetracycline (baseline) or demeclocycline (month 12) labeling procedure before undergoing the biopsy. If subjects did not undergo the baseline biopsy procedure, they still underwent the month-12 biopsy procedure.

In this substudy, 40 subjects from 8 centers were asked to undergo iliac crest biopsies during screening. Sixty-two subjects enrolled in the substudy (52 denosumab, 6 placebo, 4 alendronate). At baseline, biopsies were obtained from 39 subjects, of which 37 were evaluable (31 denosumab, 5 placebo, and 1 alendronate). At 12 months, biopsies were obtained from 51 subjects, 49 of which were evaluable (41 denosumab, 4 placebo, and 4 alendronate). The subjects who participated in the bone biopsy substudy were younger (60.2 versus 63 years) and had less prior use of osteoporosis therapy (11.3% versus 17.7%) and had a higher percentage of black subjects (9.7% versus 1.7%) than the overall trial population. For both static and dynamic bone

histomorphometric analyses, small numbers of paired bone biopsy specimens led to large variances in results. Therefore, the Applicant presented the data as unpaired biopsy evaluations.

Bone Histomorphometry Evaluation:

Data for histomorphometric findings are presented in Table 162.

Bone Formation Parameters:

Osteoid thickness can be used a marker of bone formation. The normal range for osteoid thickness is 5.5-12.0 μm . The mean osteoid thickness at Month 12 was decreased from baseline and less than placebo for both denosumab and alendronate. In addition, both the denosumab and placebo groups were below the normal range for osteoid thickness; this would be an expected finding for an anti-resorptive agent. Two alendronate subjects and 28 denosumab subjects had an osteoid thickness $< 5.5 \mu\text{m}$, including two denosumab subjects with an osteoid thickness $< 3.3 \mu\text{m}$ at Month 12. There were similar decreases in osteoid volume, osteoid surface, and mineralizing surface for both denosumab and alendronate when compared to baseline and placebo.

Remodeling Parameters:

Mineral apposition rate (MAR) is an indicator of mineralized bone accrual at remodeling sites. The normal range for MAR is 0.360-0.630 $\mu\text{m}/\text{day}$. A clear reduction in MAR during treatment could indicate impairment of mineralization and the potential of a drug to induce osteomalacia. In this trial, the mean MAR for the denosumab group at Month 12 was decreased as compared to baseline and the placebo group. The MAR for the denosumab group was within the normal range at Month 12. A decrease in MAR was not observed in the alendronate group at Month 12. Two subjects, both in the denosumab group, had a MAR $< 0.360 \mu\text{m}/\text{day}$.

Mineralization lag time (MLT) represents the mean time interval between deposition of osteoid and its mineralization, and is the most sensitive index of abnormalities in mineralization. Frequently, it is the earliest change at the onset of osteomalacia. The normal range for MLT is 24-80 days. Although increased from baseline to Month 12, the mean MLT was in the normal range for the denosumab and placebo treatment groups. However, outliers were also present. Overall, 1 subject in the alendronate group and 4 subjects in denosumab group had a MLT greater than 80 days; no subjects in the placebo group had a MLT greater than 80 days. Four subjects in the denosumab group had a MLT greater than 100 days, of which 2 had a MLT greater than 200 days after 12 months of denosumab treatment. Activation frequency is the rate at which bone remodeling units are formed and is an important indicator of bone remodeling. The mean activation frequency for the denosumab group at Month 12 was decreased as compared to baseline and the placebo group. There was a similar decrease in the alendronate group.

Structure parameters (e.g., bone volume, trabecular thickness, cortical thickness) did not change from baseline to Month 12 for subjects receiving denosumab. The resorption parameter osteoclast surface percentage was decreased from baseline to Month 12 for both denosumab and alendronate groups and were less than placebo.

Table 162. Bone Histomorphometry at Baseline and Month 12 in Unpaired Biopsies (Trial 20010223)

	Placebo Mean (SE)	Denosumab Mean (SE)	Alendronate Mean (SE)
FORMATION PARAMETERS	BL (n=5) M12 (n=4)	BL (n=31) M12 (n=41)	BL (n=1) M12 (n=4)
Osteoid Thickness (µm)			
• Baseline	5.26 (0.80)	5.82 (0.20)	4.80 (NA)
• 12 months	7.45 (0.94)	4.96 (0.20)	4.70 (0.72)
Osteoid Volume (%)			
• Baseline	1.738 (0.548)	1.579 (0.217)	2.710 (NA)
• 12 months	1.900 (0.346)	0.740 (0.159)	1.293 (0.617)
Osteoid Surface (%)			
• Baseline	18.106 (7.258)	12.944 (1.810)	19.240 (NA)
• 12 months	16.575 (5.183)	7.410 (1.341)	11.663 (3.574)
Mineralizing Surface (%)			
• Baseline	5.728 (2.191)	7.977 (1.109)	3.470 (NA)
• 12 months	10.840 (5.078)	0.520 (0.191)	0.483 (0.254)
REMODELING PARAMETERS	BL (n=5) M12 (n=4)	BL (n=30) M12 (n=13)	BL (n=1) M12 (n=2)
Mineral Apposition Rate (µm/d)			
• Baseline	0.660 (0.053)	0.577 (0.020)	0.590 (NA)
• 12 months	0.740 (0.117)	0.498 (0.030)	0.625 (0.065)
Formation Period (d)			
• Baseline	472.2 (364.5)	102.0 (13.2)	255.0 (NA)
• 12 months	113.5 (49.9)	405.7 (104.7)	387.0 (62.0)
Adjusted Apposition Rate (µm/d)			
• Baseline	0.336 (0.139)	0.380 (0.036)	0.110 (NA)
• 12 months	0.413 (0.113)	0.161 (0.037)	0.075 (0.005)
Mineralization Lag Time (days)			
• Baseline	65.04 (45.41)	19.10 (2.15)	44.80 (NA)
• 12 months	25.43 (9.93)	75.27 (21.21)	66.55 (22.25)
Bone formation rate surface (µm/µm ² /yr)			
• Baseline	14.660 (5.905)	17.300 (2.430)	7.500 (NA)
• 12 months	23.225 (7.384)	2.831 (1.051)	2.050 (0.850)
Bone formation rate volume (%/yr)			
• Baseline	0.180 (0.063)	0.235 (0.028)	0.150 (NA)
• 12 months	0.218 (0.056)	0.044 (0.020)	0.030 (0.006)
Activation Frequency (per yr)			
• Baseline	0.484 (0.184)	0.571 (0.076)	0.270 (NA)
• 12 months	0.753 (0.213)	0.095 (0.034)	0.075 (0.25)

	Placebo Mean (SE)	Denosumab Mean (SE)	Alendronate Mean (SE)
RESORPTION PARAMETERS	BL (n=5) M12 (n=4)	BL (n=30) M12 (n=13)	BL (n=1) M12 (n=2)
Osteoclast surface (%)			
• Baseline	0.326 (0.123)	0.552 (0.059)	0.100 (NA)
• 12 months	0.650 (0.336)	0.171 (0.060)	0.135 (0.029)

BL = baseline; M12 = Month 12; NA = not applicable

Source: Clinical Trial Report for Trial 20010223, Tables 11-11, 11-12, 11-13, 11-14, pages 282-285 of 9933.

Bone Histology:

The Applicant concluded the bone histology showed evidence of normal lamellar bone/mineralization and normal osteoid at baseline and Month 12. There was no evidence of pathological findings, osteomalacia, marrow dyscrasia, marrow fibrosis, woven bone, cortical trabecularization, abnormal osteoid, or other findings suggestive of deleterious effects on bone histology.

Tetracycline Labeling:

All subjects scheduled for the biopsy will follow a double tetracycline labeling procedure prior to biopsy. This step is important for bone safety assessments because tetracycline gets deposited in the newly mineralized bone and an absence of label means that there was no new bone mineralization during the tetracycline dosing period. The double tetracycline labeling procedure was initiated more than one month prior to the scheduled day 1 or month 12 dose, as long as the timing allowed the actual biopsy to be performed within the month before the day 1 or the month 12 dose.

Baseline Biopsy: Tetracycline hydrochloride (HCl) 1,000 mg/day was used for the baseline labeling procedure. For the baseline labeling procedure, oral tetracycline HCl 250 mg should be taken 4 times per day for 3 days; doses were administered on an empty stomach with plain water as follows: 1-2 hours before breakfast, 2 hours after breakfast, 2 hours after lunch and 2 hours after dinner. If a dose of tetracycline HCl was skipped/missed, it was taken as soon as possible, or with the next scheduled dose. The iliac crest bone biopsy was scheduled to occur within 10 days after the last day of tetracycline HCl administration.

Month 12 biopsy: Demeclocycline 600 mg/day was used. The same procedure for tetracycline administration was used for demeclocycline, except the dose was 150 mg 4 times per day. The Month 12 iliac crest bone biopsy was scheduled to occur within 10 days after the last day of demeclocycline administration.

As part of the laboratory analysis, presence of tetracycline and demeclocycline labels were reviewed in all biopsies obtained at baseline and at 12 months. In some subjects treated with denosumab and alendronate, single label or no label was observed, which prompted an expanded label search. Specimens underwent 4 initial sections; if

additional label were not seen, the biopsy underwent an additional 4 additional sections for a maximum of 10 sections. With this reevaluation, double-label observations at baseline remained unchanged and the proportion increased at 12 months. These additional biopsy samples with newly found labels were not included in histomorphometric analyses. There was not a specific dose-response relationship observed, but the highest number of specimens with no label (n = 4) occurred in the 210 mg denosumab cohort.

Table 163. Tetracycline Label Disposition of Unpaired Bone Biopsy Specimens

	Placebo (n)	Denosumab (n)	Alendronate (n)
Planned Samples			
Baseline			
• Double label	5	30 ^a	1
12 Months ^b			
• No label	0	14	1
• Single label	0	11	1
• Double label	4	13	2
Expanded Label Search			
Baseline			
• Double label	5	30 ^a	1
12 Months ^c			
• No label	0	9	1
• Single label	0	9	1
• Double label	4	18	2

^a Cortex of 1 biopsy in the denosumab group showed labeling.

^b Cortex of 1 biopsy in the denosumab group showed labeling.

^c Cortex of 1 biopsy in the denosumab group showed labeling.

Source: Clinical Trial Report for Trial 20010223, Table 11-15, page 286 of 9933.

Bone Biopsy MicroCT Evaluation

Bone biopsies obtained in the substudy were further evaluated by microCT analysis. There were 38 biopsies at baseline (32 denosumab, 5 placebo, and 1 alendronate) and 50 biopsies at Month 12 (42 denosumab, 4 placebo, and 4 alendronate). There were a total of 26 paired biopsies (22 denosumab, 3 placebo, and 1 alendronate). In the denosumab group, 5 of the 32 biopsies at baseline and 8 of the 42 biopsies at month 12 had only one evaluable cortex. These biopsy samples were included in the analyses where cortical parameters were not averaged.

After 12 months of treatment, trabecular and cortical BMD evaluations showed similar findings compared with baseline in both denosumab and placebo groups. Evaluation of trabecular and cortical parameters showed changes within the standard error for both denosumab and placebo groups. MicroCT data obtained in the bone biopsy substudy did not show consistent changes from baseline in trabecular and cortical bone parameters after treatment for 12 months, which may be due to the few number of

biopsies available. There were no notable findings from the bone biopsy microCT analysis.

Reviewer Comments:

- *The initial plan was to review 4 biopsy samples per subject at Month 12. When the Applicant identified few denosumab samples with single and double labeling at Month 12, they conducted a more extensive label search on the existing biopsy samples. This expanded label search involved a review of up to 10 biopsy samples per subject.*
- *Absence of label suggests suppressed bone formation. There were no biopsy samples in the placebo group with no label or single label, while there were 9 and 1 of single and double labels in the denosumab and alendronate groups, respectively at Month 12.*
- *A reduction in mineral apposition rate (MAR) during treatment could indicate impairment of bone mineralization at remodeling sites; two subjects in the denosumab group had a MAR below the normal range.*
- *Mineralization lag time (MLT) is the most sensitive index of abnormalities in mineralization. The mean MLT was within the normal range for the denosumab group, but 4 denosumab subjects had a MLT > 100 days including 2 denosumab subjects with a MLT > 200 days after 12 months of denosumab treatment.*
- *Activation frequency is an important indicator of bone remodeling. The mean activation frequency for the denosumab group at Month 12 was greatly decreased as compared to baseline and the placebo group in this substudy.*
- *There were no notable findings on histologic analyses or microCT evaluation.*

Third Secondary Endpoint:

The Applicant evaluated the efficacy of denosumab relative to placebo based on BMD and bone turnover marker changes and safety over 48 months. The Applicant noted that denosumab treatment resulted in rapid and sustained decreases in bone turnover markers serum CTx, uNTX/Cr, and BAP through month 24. At month 24, the decreases in bone turnover markers were 73% for serum CTx, 50% for uNTX/Cr, and 58% for BAP for denosumab dosing cohorts. Across the denosumab dose cohorts, the maximal suppression of bone turnover markers was similar. In the lower dose cohorts, the bone turnover markers trended towards baseline levels before the next dose.

Fourth Secondary Endpoint:

The Applicant assessed whether denosumab treatment had a different efficacy or safety profile compared with alendronate. In the first 24 months of the trial, BMD of the lumbar spine increased at all time points for subjects in the alendronate cohort. Overall, the magnitudes of the mean percent increases in BMD were similar between denosumab and alendronate. At 24 months, alendronate treatment was withdrawn. Mean percent changes in BMD were sustained above baseline at months 36 and 48, which is consistent with previously reported findings. Treatment-related adverse events

occurred in 22%, 20%, and 41% of subjects in the denosumab, placebo and alendronate treatment groups, respectively. The relatively higher incidence of adverse events in the alendronate group may be due to the open-label design for this group as alendronate has a well-known adverse event profile. Similar percentages of subjects in each treatment cohort withdrew from the trial due to adverse events (4% placebo, 4% denosumab, and 7% alendronate).

Fifth Secondary Endpoint:

The Applicant also assessed the off-treatment effect of denosumab based on BMD and bone turnover marker changes. There were two denosumab dosing cohorts that stopped denosumab during the trial (one cohort stopped for 12 months and then resumed denosumab at 60 mg Q6months for the remaining 12 months; the other cohort stopped denosumab for the remaining 48 months of the trial).

The Applicant noted that the BMD of all anatomic sites initially decreased for subjects in the off-treatment cohort in the first year after they were reallocated to placebo, approaching baseline levels at month 36. In the second year off-treatment (up to month 48), BMD remained similar to levels at month 36 in these subjects. BMD of all anatomic sites was numerically higher than placebo at all time points following denosumab subjects' reallocation to placebo at month 24.

There were transient increases of bone turnover markers above baseline levels following withdrawal of denosumab that returned to baseline at month 48. In the Applicant's ad hoc analysis, the relationships of BMD at baseline and following discontinuation of denosumab at months 36 and 48 in the off-treatment cohort showed reversibility of effects, as evidenced by an increase in bone turnover markers and consequent decrease in BMD with denosumab discontinuation. The magnitude of the reduction in BMD appeared associated with the subject's pretreatment BMD level.

The Applicant also summarized osteoporotic fractures; these fractures occurred in 7.0% of denosumab-treated subjects, 8.7% of placebo subjects, and 4.3% of alendronate subjects. Although the trial was not powered to detect differences among denosumab dose cohorts or treatment groups, there did not appear to be any differences in the distribution or incidences of osteoporotic fractures. The off-treatment cohorts did not appear to have a higher risk of osteoporotic fractures, although the trial was not powered to detect such differences. Four (8.7%) subjects in the off-treatment cohort had osteoporotic fractures and 1 (2.5%) subject in the retreatment cohort had osteoporotic fractures.

Sixth Secondary Endpoint: Retreatment Denosumab Cohort

The Applicant assessed the efficacy and safety of retreatment with denosumab (after 12 months off-treatment). Subjects in the retreatment denosumab cohort stopped receiving denosumab at month 24, then resumed receiving denosumab at month 36. In the year subjects were off-treatment, the BMD of all anatomic sites decreased,

approaching baseline levels at month 36. Upon resumption of treatment with denosumab at 42 and 48 months (6 and 12 months, respectively, after dosing resumed), the BMD increased to levels similar to those that occurred when denosumab was first administered. There were transient increases of bone turnover markers following withdrawal of denosumab during the 12-month period when subjects received placebo, similar to that noted for the off-treatment cohort. However, retreatment with denosumab decreased turnover marker activity to an extent similar to initial treatment.

Seventh Secondary Endpoint:

The Applicant assessed the administrative feasibility of several subject-reported outcomes assessments and determined the reliability and validity of these scales. The Applicant noted high completion rates of subject-reported outcomes questionnaires for all time points between baseline and month 12, ranging from 93.5% to 99.8% for the Medical Outcomes Trial Short-Form 36 (SF-36), Quality of Life in Reflux and Dyspepsia (QOLRAD), and Gastroesophageal Reflux Disease Symptom Assessment Scale (GSAS). The completion rate for the experimental Treatment Satisfaction Assessment (TSA) questionnaire ranged from 70% at month 18 to 80% at month 24. At month 48, completion rates for the SF-36, QOLRAD, GSAS, TSA, and EuroQol-5 Dimension (EQ-5D) were satisfactory, ranging from 87.6% to 97.7%. The Applicant noted good reliability and validity with these questionnaires. The Applicant concluded that it is feasible to conduct health-related quality of life (HRQOL) assessments in postmenopausal women with low BMD.

Reviewer Conclusions on Secondary Endpoints:

- ***Endpoint 1:*** to choose a dose regimen of denosumab for future studies, based on changes from baseline in BMD and bone turnover markers over 12 months. The Applicant chose a dosing regimen of denosumab 60 mg every 6 months; this dose increased BMD at all anatomic sites and suppressed bone turnover markers over the entire dosing interval with an effect that was at least as effective as 70 mg of alendronate administered once a week. The bone formation marker bone-specific alkaline phosphatase (BALP) decreased from baseline to Month 12 in all denosumab dosing cohorts, with the bone turnover markers trending towards baseline levels before the next scheduled dose in the lower dosing cohorts. The bone turnover markers serum CTx and uNTX/Cr were suppressed at Month 12. The maximal suppression was similar across the denosumab dosing cohorts, but trended towards baseline levels before the next dose in the lower dosing cohorts.
- ***Endpoint 2:*** to evaluate the effect of denosumab relative to placebo on BMD of the total hip, distal radius, and total body, and the safety and tolerability profile (including bone safety profile based on histology and histomorphometry) over 12 months. There was a statistically significant change from baseline in BMD at all anatomic sites to Month 12 for all denosumab dosing cohorts, except the 14 mg q6month dosing cohort did not achieve a statistically significant change in total body BMD.

- **Endpoint 3:** to evaluate the efficacy of denosumab relative to placebo based on BMD and bone turnover marker changes and safety over 48 months. Across the denosumab dosing cohorts, the maximal suppression of bone turnover markers was similar. In the lower dose cohorts, the bone turnover markers trended towards baseline levels before the next dose.
- **Endpoint 4:** to assess whether denosumab treatment has a different efficacy or safety profile compared with alendronate. The magnitudes of the mean percent increases in BMD were similar between denosumab and alendronate. Similar percentages of subjects in each treatment cohort withdrew from the trial due to adverse events.
- **Endpoint 5:** to assessment the off-treatment effect of denosumab based on BMD and changes in bone turnover markers. The BMD of all anatomic sites initially decreased in the first year of receiving placebo, approaching baseline levels at month 36. In the second year off-treatment, BMD was similar to levels at month 36. BMD of all anatomic sites was higher than placebo at all time points following reallocation to placebo. There were transient increases of bone turnover markers above baseline levels during the off-treatment period that returned to baseline at month 48.
- **Endpoint 6:** to assess the efficacy and safety of retreatment with denosumab. Subjects in the denosumab retreatment cohort stopped receiving denosumab at month 24, then resumed at month 36. In the off-treatment year, the BMD of all anatomic sites decreased, approaching baseline levels at month 36. With resumption of denosumab, the BMD increased to levels similar to that of initial administration. There were transient increases of bone turnover markers following withdrawal of denosumab, but retreatment decreased turnover marker activity to an extent similar to initial treatment.
- **Endpoint 7:** to evaluate subject-reported outcome questionnaires. The Applicant concluded that these subject-reported outcomes assessments were easy to administer and had good reliability and validity in this patient population.

Exploratory Endpoints

The exploratory/tertiary objectives were to evaluate characterize the efficacy and safety of denosumab following IP withdrawal and retreatment in a subset of subjects. In the year subjects were off denosumab treatment, BMD of all anatomic sites decreased, approaching baseline levels at month 36. Upon resumption of denosumab treatment at 42 and 48 months, the BMD increased to levels similar to those that occurred when denosumab was initially administered. There were transient increases of bone turnover markers following withdrawal of denosumab during the 12-month period when subjects were off denosumab treatment. However, retreatment with denosumab decreased turnover marker activity to an extent similar to initial treatment.

Efficacy Conclusions:

The use of denosumab was associated with a statistically significant increase in lumbar spine BMD (by DXA) from baseline to Month 12, as compared to placebo in all denosumab cohorts (range: 3.0% to 6.7%). The differences between each denosumab cohort and placebo (- 0.8% change from baseline) were statistically significant ($p < 0.001$). Sensitivity analyses supported these findings. The dose that the Applicant proposed to use in Phase III trials was 60 mg SC q6months.

The Applicant analyzed the effect of pre-specified covariates. There were statistically significant treatment-by-covariate interactions for age, baseline BMD of the total body, baseline serum CTX and baseline uNTX/Cr ($p < 0.05$), but there was no consistent effect across the denosumab dosing cohorts. The denosumab treatment effect was still statistically significant after adjustments for these covariates. Since the Applicant proposed fixed dosing for all subjects, the effect of body weight and BMI on the treatment effects of denosumab was analyzed in regards to BMD and serum CTX 1. There was no linear correlation for either baseline weight or BMI and lumbar spine. No linear correlations were noted for either weight or BMI with change in BMDs of the total hip, trochanter, femoral neck, or distal 1/3 radius for the denosumab group. Thus, there was no significant treatment-by-weight or treatment-by-BMI interactions on the primary endpoint.

The Applicant also conducted a bone biopsy substudy in 62 subjects (52 denosumab, 6 placebo, 4 alendronate) with tetracycline labeling to further evaluate the effects of denosumab on bone. Baseline biopsies were evaluable in 37 subjects (31 denosumab, 5 placebo, 1 alendronate). At Month 12, 49 evaluable biopsies were obtained (41 denosumab, 4 placebo, 4 alendronate). Nine subjects in the denosumab group had no label and 9 subjects had only single label at Month 12, while 18 denosumab subjects had a double label after the Applicant conducted an extensive search for label in the biopsy samples. Two subjects in the denosumab group had a mineral apposition rate below the normal range at Month 12, which could indicate impairment of bone mineralization at remodeling sites. The mean mineralization lag time was extended in 4 denosumab subjects and the activation frequency, an indicator of bone remodeling, was greatly decreased in the denosumab group as compared to baseline and placebo. There were no notable findings on histologic analyses or microCT evaluation.

Safety

This safety review will focus on the safety data obtained in the first 24 months of the trial when there were 7 dosing cohorts of denosumab at various doses and dosing intervals. The last 24 months of the trial used variable dosing regimens making it difficult to draw conclusions from the variable doses of trial drug. In the last 24 months of the trial, subjects were either randomized to denosumab 60 mg Q6 months, placebo (off-treatment cohort), or placebo for 12 months then 12 months of denosumab 60 mg Q6months (retreatment cohort). For subjects who received denosumab, the safety data

will be summarized as an annual dose in an attempt to identify any potential dose-related adverse events. It is noteworthy that the alendronate cohort received open-label alendronate, which may have affected ascertainment of adverse events in this cohort.

The safety subset used in this review includes all subjects who were randomized and received at least 1 dose of IP. This subset was used for all safety analyses, in which subjects were grouped by highest actual dose of denosumab received, if other than what the subject was randomized to receive. A total of 406 subjects (314 denosumab, 46 placebo, 46 alendronate) received at least 1 dose of IP and were included in the safety analysis set.

Events Rates:

Adverse event rates were similar across treatment groups with almost all subjects reporting adverse events during the trial. There were 4 deaths during the trial, all in the denosumab group. During the first 24 months of the trial, serious adverse events occurred in 11%, 18%, and 17% of placebo, denosumab and alendronate subjects, respectively.

Exposure:

The planned duration of treatment in the initial phase was 24 months with some cohorts receiving a dose of trial drug every 3 months and other cohorts receiving a dose of trial drug every 6 months, as previously described in Figure 18. The alendronate cohort received 70 mg orally every week in an open-label fashion for the first 24 months.

In the last 24 months, the alendronate group received placebo, while most other cohorts received denosumab 60mg Q6months. There was one cohort that discontinued denosumab treatment (off-treatment cohort) and another cohort that received placebo for 12 months then denosumab 60 mg Q6months for 12 months (retreatment cohort).

Deaths:

There were 4 deaths during this trial, which are summarized below in Table 164. It is noteworthy that deaths only occurred in the denosumab dosing cohorts. Three of the four deaths involved neoplasms, including a lung adenocarcinoma, gastric cancer NOS and a frontal lobe tumor NOS; all of these events occurred in the denosumab 100 mg Q6month cohort. In addition, there was one subject who died of pancreatic carcinoma about 1 year after discontinuation from trial. The subject was diagnosed with pancreatic cancer about 17 days after the initial dose of trial drug.

Table 164. Fatalities Reported in Trial 20010223

Subject ID	Age (yrs) [Trial Day]	Actual Treatment Received	Preferred Terms	Relevant Medical History or Current Conditions
329025	74 [15 mos]	Deno. 100mg Q6m	brain neoplasm	familial history of brain tumors. CT scan revealed a frontal lobe tumor and a biopsy was performed (results not provided). The subject was treated with radiation and chemotherapy, but died ~ 16 weeks later.
319013	77 [18 mos]	Deno. 100mg Q6m	gastric cancer	history of a lumpectomy of the left breast. Adenocarcinoma on biopsy.
302022	60 [33 mos]	Deno. 14mg Q3m	cerebrovascular accident	history of breast cancer, hypercholesterolemia, atrial fibrillation
307094	72 [33 mos]	Deno. 100mg Q6m	lung cancer	history of sinus bradycardia. Subject hospitalized with thromboses in left arm and leg ~ 29 mos after 1 st dose of trial drug. She was rehospitalized ~ 4 mos later & diagnosed with lung adenocarcinoma.
325002	60 [17 days]	Deno.	Pancreatic carcinoma	~ 17 days after 1 st dose of trial drug, subject underwent abdominal CT scan and biopsy for abdominal pain & bloating, nausea, and jaundice; biopsy confirmed pancreatic cancer. Blinded trial drug was discontinued and subject was withdrawn from trial. One year later the Investigator said subject died 2° to pancreatic cancer.

Reviewer Comments:

- *It is highly unusual that 3 deaths due to neoplasms would occur in a trial of this size and duration.*
- *It is noteworthy that all the deaths occurred in the denosumab group.*
- *It is also noteworthy that all 3 deaths due to neoplasms occurred in the denosumab 100 mg Q6months cohort.*

Serious Adverse Events:

During the first 24 months of the trial, serious adverse events occurred in 11%, 18%, and 17% of placebo, denosumab and alendronate subjects, respectively.

For the denosumab group, the most common System Organ Classes (SOC) for serious adverse events were the Neoplasms, Injury, Cardiac, Nervous System and Infections SOCs. Neoplasms were the most commonly reported SAE, but they occurred at an incidence less than the placebo group. Although cardiac SAEs were commonly reported in the denosumab group, they occurred at an incidence less than the placebo and alendronate groups. The Nervous System events primarily involved syncope.

There were 6 subjects in the denosumab group with serious infections, while no serious infections occurred in either the placebo or alendronate groups.

Table 165. Subject Incidence of Serious Adverse Events by System Organ Class Through Month 24

System Organ Class	Placebo (N = 46)		Denosumab (N = 314)		Alendronate (N=46)	
	n	%	n	%	n	%
Blood and lymphatic system disorders	0	0%	0	0%	1	2.17%
Cardiac disorders	2	4.35%	8	2.55%	2	4.35%
Gastrointestinal disorders	0	0%	2	0.64%	1	2.17%
General disorders & administ. site conditions	0	0%	2	0.64%	2	4.35%
Hepatobiliary disorders	0	0%	1	0.32%	1	2.17%
Infections and infestations	0	0%	6	1.91%	0	0%
Injury, poisoning & procedural complications	1	2.17%	9	2.87%	1	2.17%
Metabolism and nutrition disorders	1	2.17%	1	0.32%	1	2.17%
Musculoskeletal & connective tissue disorders	1	2.17%	2	0.64%	1	2.17%
Neoplasms benign, malignant and unspecified	2	4.35%	11	3.50%	1	2.17%
Nervous system disorders	0	0%	7	2.23%	0	0%
Psychiatric disorders	0	0%	1	0.32%	0	0%
Reproductive system and breast disorders	0	0%	1	0.32%	0	0%
Respiratory, thoracic & mediastinal disorders	0	0%	3	0.96%	0	0%
Vascular disorders	0	0%	1	0.32%	0	0%

Reviewer Comments:

- *Although neoplasms were a commonly reported SAE in the denosumab group, the incidence was less than the placebo group.*
- *Serious infections were more common in the denosumab dosing cohorts.*

Adverse Events Leading to Withdrawal:

Fifteen (4.8%) subjects in the denosumab, 1 (2.2%) in the placebo, and 8 (17.4%) in the alendronate treatment cohorts had adverse events that led to discontinuation of trial drug. Thirteen (4.1%) subjects in the denosumab treatment cohort, 1 (2.2%) in the placebo cohort, and 4 (8.7%) in the alendronate cohort withdrew from the trial due to adverse events.

Table 166. Subjects Withdrawing from Trial or Discontinuing Trial Drug due to Adverse Events Through Month 24

Dosing Cohort	Trial Drug Discontinuation (n)		Discontinuation from Trial (n)	
Placebo (N = 46)	1	2.2%	1	2.2%
Den. 6mg Q3m (24 mg/yr) (N=43)	3	7.0%	2	4.7%
Den. 14mg Q6m (28 mg/yr) (N=53)	2	3.8%	3	5.7%
Den. 14mg Q3m (56 mg/yr) (N=44)	4	9.1%	2	4.5%
Den. 30mg Q3m (120 mg/yr) (N=40)	3	7.5%	3	7.5%
Den. 60mg Q6m (120 mg/yr) (N=47)	1	2.1%	1	2.1%
Den. 100mg Q6m (120 mg/yr) (N=41)	0	0.0%	1	2.4%
Den. 210mg Q6m (420 mg/yr) (N=46)	2	4.3%	1	2.2%
Alendronate (N = 46)	8	17.4%	4	8.7%

Reviewer Comments:

- *The higher rate of discontinuations in the alendronate group may have been due to the fact that alendronate was administered in an open-label fashion.*
- *In the denosumab cohorts, there was no apparent dose-related effect in terms of trial drug discontinuations or discontinuation from trial.*

Common AEs:

The 3 most common adverse events in the placebo cohort were arthralgia (30%), upper respiratory tract infection (24%), and sinusitis (20%). The 3 most common adverse events in the denosumab cohorts were upper respiratory tract infection (28%), arthralgia (24%), and back pain (20%). The 3 most common adverse events in the alendronate cohort were upper respiratory tract infection (30%), dyspepsia (26%), and nausea (22%).

The denosumab group had a higher incidence of adverse events in the infections, injury, respiratory and skin SOC's.

Table 167. Subject Incidence of Any Adverse Event (Serious + Non-Serious) by System Organ Class Through Month 24

System Organ Class	Placebo (N = 46)		Denosumab (N = 314)		Alendronate (N=46)	
	n	%	n	%	n	%
Blood and lymphatic system disorders	1	2.2%	4	1.3%	4	8.7%
Cardiac disorders	6	13%	21	6.7%	6	13%
Ear and labyrinth disorders	1	2.2%	18	5.7%	5	10.9%
Endocrine disorders	0	0%	5	1.6%	0	0%
Eye disorders	3	6.5%	29	9.2%	7	15.2%
Gastrointestinal disorders	23	50%	150	47.8%	25	54.4%
General disorders & admin. site conditions	17	37%	104	33.1%	15	32.6%
Hepatobiliary disorders	1	2.2%	5	1.6%	2	4.4%
Immune system disorders	2	4.4%	25	8.0%	4	8.7%
Infections and infestations	26	56.5%	197	62.7%	27	58.7%
Injury, poisoning & procedural complications	14	30.4%	102	32.5%	11	23.9%
Investigations	3	6.5%	24	7.6%	4	8.7%
Metabolism and nutrition disorders	6	13%	33	10.5%	9	19.6%
Musculoskeletal & connective tissue disorders	27	58.7%	173	55.1%	26	56.5%
Neoplasms benign, malignant & unspecified	4	8.7%	29	9.2%	5	10.9%
Nervous system disorders	21	45.7%	81	25.8%	13	28.3%
Psychiatric disorders	6	13%	39	12.4%	5	10.9%
Renal and urinary disorders	3	6.5%	23	7.3%	3	6.5%
Reproductive system & breast disorders	2	4.4%	29	9.2%	4	8.7%
Respiratory, thoracic & mediastinal disorders	10	21.7%	71	22.6%	4	8.7%
Skin and subcutaneous tissue disorders	8	17.4%	92	29.3%	9	19.6%
Vascular disorders	3	6.5%	53	16.9%	8	17.4%

* Only SOC's with >2 events per dosing cohort are listed in the table.

Adverse events reported in 5% of more of subjects who received denosumab are summarized below in Table 135. Common adverse events that occurred at a much higher incidence in the denosumab group than the placebo or alendronate groups included urinary tract infection (10.51% of denosumab subjects), contusion (8.28%), insomnia (5.41%) and seasonal allergy (5.1%).

Table 168. Most Commonly Reported Adverse Events Through Month 24 (Safety Population)

Preferred Term	Placebo (N = 46)		Denosumab (N = 314)		Alendronate (N=46)	
	n	(%)	n	(%)	n	(%)
Upper respiratory tract infection	8	17.39	76	24.20	11	23.91
Arthralgia	13	28.26	60	19.11	5	10.87
Nasopharyngitis	7	15.22	56	17.83	6	13.04
Back pain	6	13.04	53	16.88	7	15.22
Pain in extremity	6	13.04	43	13.69	6	13.04
Hypertension	1	2.17	39	12.42	5	10.87
Nausea	2	4.35	35	11.15	10	21.74
Dyspepsia	3	6.52	33	10.51	12	26.09
Influenza like illness	5	10.87	33	10.51	6	13.04
Urinary tract infection	0	0	33	10.51	3	6.52
Headache	8	17.39	31	9.87	5	10.87
Gastroesophageal reflux disease	2	4.35	30	9.55	5	10.87
Sinusitis	8	17.39	29	9.24	5	10.87
Contusion	3	6.52	26	8.28	1	2.17
Muscle spasms	5	10.87	24	7.64	4	8.70
Diarrhoea	5	10.87	24	7.64	3	6.52
Myalgia	2	4.35	20	6.37	3	6.52
Dizziness	4	8.70	19	6.05	4	8.70
Constipation	1	2.17	18	5.73	4	8.70
Shoulder pain	6	13.04	18	5.73	3	6.52
Bronchitis	3	6.52	18	5.73	3	6.52
Rash	0	0	18	5.73	2	4.35
Depression	4	8.70	17	5.41	3	6.52
Hypercholesterolaemia	0	0	17	5.41	2	4.35
Insomnia	0	0	17	5.41	0	0
Seasonal allergy	1	2.17	16	5.10	1	2.17

* Subject incidence $\geq 5\%$ in the denosumab treatment group by Preferred Term

† Preferred Terms that are shaded represent AEs that occurred more often in denosumab group with an incidence difference $\geq 3\%$ as compared to placebo and alendronate.

Dose-Related Adverse Events:

The effect of dose on adverse events was examined for the 7 denosumab dosing cohorts in the first 24 months of the trial. There did not appear to be any obvious dose related effects when the adverse event data was reviewed by System Organ Class.

Table 169. Denosumab Dosing Cohort Subject Incidence of Any Adverse Event (Serious + Non-Serious) by System Organ Class Through Month 24

Cohort	6mg Q3m (24 mg/yr)		14mg Q6m (28 mg/yr)		14mg Q3m (56 mg/yr)		30mg Q3m (120 mg/yr)		60mg Q6m (120 mg/yr)		100mg Q6m (120 mg/yr)		210mg Q6m (420 mg/yr)	
N	43		53		44		40		47		41		46	
SOC*	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Blood	0	0.0%	1	1.9%	3	6.8%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Cardiac	2	4.7%	6	11.3%	4	9.1%	4	10.0%	2	4.3%	0	0.0%	3	6.5%
Ear	1	2.3%	5	9.4%	3	6.8%	1	2.5%	5	10.6%	1	2.4%	2	4.3%
Endocrine	0	0.0%	1	1.9%	2	4.5%	0	0.0%	1	2.1%	0	0.0%	1	2.2%
Eye	3	7.0%	7	13.2%	3	6.8%	6	15.0%	2	4.3%	5	12.2%	3	6.5%
Gastrointes.	18	41.9%	27	50.9%	21	47.7%	19	47.5%	23	48.9%	18	43.9%	24	52.2%
General	13	30.2%	17	32.1%	17	38.6%	11	27.5%	19	40.4%	11	26.8%	16	34.8%
Hepatobiliary	0	0.0%	1	1.9%	0	0.0%	2	5.0%	1	2.1%	0	0.0%	1	2.2%
Immune	5	11.6%	4	7.5%	4	9.1%	4	10.0%	5	10.6%	1	2.4%	2	4.3%
Infections	25	58.1%	30	56.6%	28	63.6%	28	70.0%	26	55.3%	31	75.6%	29	63.0%
Injury	9	20.9%	15	28.3%	12	27.3%	17	42.5%	18	38.3%	17	41.5%	14	30.4%
Investigation	3	7.0%	1	1.9%	6	13.6%	4	10.0%	2	4.3%	4	9.8%	4	8.7%
Metabolism	2	4.7%	5	9.4%	8	18.2%	4	10.0%	9	19.1%	1	2.4%	4	8.7%
Musculoskel.	20	46.5%	27	50.9%	30	68.2%	22	55.0%	21	44.7%	24	58.5%	29	63.0%
Neoplasms	5	11.6%	4	7.5%	6	13.6%	4	10.0%	5	10.6%	3	7.3%	2	4.3%
Nervous	6	14.0%	17	32.1%	14	31.8%	10	25.0%	14	29.8%	8	19.5%	12	26.1%
Psychiatric	1	2.3%	9	17.0%	8	18.2%	8	20.0%	3	6.4%	3	7.3%	7	15.2%
Renal	1	2.3%	8	15.1%	3	6.8%	1	2.5%	3	6.4%	4	9.8%	3	6.5%
Reproduct.	5	11.6%	3	5.7%	6	13.6%	4	10.0%	4	8.5%	4	9.8%	3	6.5%
Respiratory	9	20.9%	11	20.8%	7	15.9%	13	32.5%	8	17.0%	11	26.8%	12	26.1%
Skin	9	20.9%	12	22.6%	10	22.7%	15	37.5%	15	31.9%	17	41.5%	14	30.4%
Vascular	4	9.3%	11	20.8%	12	27.3%	6	15.0%	7	14.9%	7	17.1%	6	13.0%

* Only SOC's with >2 events per denosumab dosing cohort are listed in the table.

The high level group terms under the System Organ Classes were also reviewed to examine the effect of dose in the 7 denosumab dosing cohorts. There did not appear to be a dose related effect based on this review of the data.

Reviewer Comments:

- **The adverse event profile did not appear to differ greatly across the different denosumab dosing cohorts and there did not appear to be any dose-related adverse events.**

Adverse Events of Special Interest:

Infections:

The overall infection rate was balanced among the treatment groups; the overall incidences of adverse events in the Infections and Infestations system organ class were 66%, 67%, and 70% in the denosumab, placebo, and alendronate cohorts, respectively. Three percent of subjects receiving denosumab overall developed an infection and were hospitalized; none of the placebo or alendronate subjects were hospitalized due to infection. There did not seem to be a dose-related effect in the denosumab cohorts. No unusual pathogens or those typically associated with opportunistic infections were reported. Hospitalizations were characterized by

uncomplicated courses and successful treatment with standard antibiotics. No subjects died due to an infection.

Table 170. All Adverse Events in the Infections & Infestations SOC Through Month 24

AEHLGT	Serious	AEHLT	Placebo N=46		All Denos N=314		Alen N=46	
			n	%	n	%	n	%
Bacterial infections	N	Bacterial infections	0	0.0%	8	2.5%	0	0.0%
	N	Helicobacter infections	0	0.0%	5	1.6%	0	0.0%
Fungal infections	N	Candida infections	0	0.0%	3	1.0%	0	0.0%
	N	Fungal infections	3	6.5%	5	1.6%	0	0.0%
	N	Tinea infections	0	0.0%	4	1.3%	1	2.2%
Infections - pathogen class unspecified	N	Abdominal & gastrointestinal	4	8.7%	11	3.5%	2	4.3%
	Y	Abdominal & gastrointestinal	0	0.0%	2	0.6%	0	0.0%
	N	Dental & oral soft tissue	1	2.2%	20	6.4%	4	8.7%
	N	Ear infections	1	2.2%	6	1.9%	0	0.0%
	Y	Ear infections	0	0.0%	1	0.3%	0	0.0%
	N	Eye & eyelid infections	0	0.0%	5	1.6%	0	0.0%
	N	Infections NEC	0	0.0%	7	2.2%	0	0.0%
	N	Lower resp. tract & lung	4	8.7%	25	8.0%	5	10.9%
	Y	Lower resp. tract & lung	0	0.0%	3	1.0%	0	0.0%
	N	Muscle & soft tissue	0	0.0%	0	0.0%	1	2.2%
	N	Skin & soft tissue	0	0.0%	3	1.0%	1	2.2%
	N	Upper respiratory tract	25	54.3%	172	54.8%	22	47.8%
	N	Urinary tract infections	1	2.2%	36	11.5%	4	8.7%
Viral infect. disorders	N	Adenoviral infections	0	0.0%	0	0.0%	1	2.2%
	N	Herpes viral infections	3	6.5%	13	4.1%	0	0.0%
	N	Viral infections NEC	2	4.3%	26	8.3%	4	8.7%

Immune cell assessments were performed through the month 24 visit on a subset of 91 subjects enrolled at 5 selected sites. Blood samples were taken at baseline, and 3, 6, 12, 18 and 24 months after dosing. The following analyses were performed:

- Enumeration of T and B cells (CD3, CD4, CD8, and CD19) and natural killer (NK) cells (CD16/CD56) by flow cytometry
- WBC and lymphocytes counts

There was no evidence of a clinically significant effect of denosumab on the cell counts measured in this substudy.

Reviewer Comments:

- *There were more serious events of infection in the denosumab cohorts. No subjects died of an infection during the trial.*
- *There were no unusual or opportunistic infections noted during the trial.*
- *Within the denosumab cohort, the dose received did not appear to effect the incidence or type of infection.*

ONJ

No subjects reported events of osteonecrosis of the jaw during the trial.

Fracture Healing Complications:

There were no reports of fractures having delayed healing time or nonunion.

Hypocalcemia

The mean and median corrected calcium levels and mean percent change from baseline at trial visits were reviewed through Month 24 (see Table 171). Corrected calcium concentrations decreased in the denosumab group relative to the placebo and alendronate groups. The median percent changes in calcium for the denosumab cohorts decreased, ranging from 3.0% to 4.3% on day 4 and 1.1% to 3.9% at month 1. There appeared to be a dose related effect with higher denosumab dosing cohorts experiencing greater reductions in corrected calcium from baseline.

Table 171. Corrected Calcium Levels Through Month 24

Visit No.	Placebo			Den 6mg Q3m			Den 14mg Q6m		
	Corr Ca++		% Δ*	Corr Ca++		% Δ*	Corr Ca++		% Δ*
	Mean	Median	Mean	Mean	Median	Mean	Mean	Median	Mean
BL	9.79	9.75	--	9.73	9.6	--	9.81	9.8	--
Day 4	9.79	9.8	0.14	9.53	9.5	-1.95	9.45	9.4	-3.51
1M	9.84	9.8	0.45	9.50	9.5	-2.29	9.51	9.5	-2.96
2M	9.81	9.8	0.35	9.56	9.6	-1.67	9.59	9.7	-2.08
3M	9.80	9.7	0.11	9.78	9.7	0.61	9.64	9.6	-1.55
6M	9.89	9.85	0.66	9.72	9.7	-0.20	9.72	9.7	-0.64
6M3D	9.85	9.8	0.10	9.64	9.6	-1.10	9.43	9.45	-3.44
7M	9.87	9.85	0.86	9.64	9.7	-0.89	9.51	9.5	-2.79
9M	9.80	9.7	-0.20	9.75	9.8	0.22	9.67	9.6	-1.14
12M	9.82	9.8	0.05	9.77	9.7	0.34	9.76	9.8	-0.40
24M	9.79	9.8	0.04	9.78	9.75	0.76	9.84	9.75	0.20

	Den 14mg Q3m			Den 30 mg Q3m			Den 60mg Q6m		
	Corr Ca++		% Δ*	Corr Ca++		% Δ*	Corr Ca++		% Δ*
Visit No.	Mean	Median	Mean	Mean	Median	Mean	Mean	Median	Mean
BL	9.73	9.8	--	9.69	9.7	--	9.73	9.7	--
Day 4	9.36	9.35	-3.56	9.31	9.3	-4.12	9.41	9.3	-3.22
1M	9.37	9.3	-3.43	9.47	9.4	-2.41	9.49	9.4	-2.51
2M	9.51	9.4	-1.90	9.53	9.55	-1.34	9.57	9.5	-1.56
3M	9.58	9.6	-1.37	9.57	9.6	-1.14	9.55	9.5	-1.75
6M	9.63	9.6	-1.14	9.64	9.6	-0.18	9.72	9.7	-0.11
6M3D	9.60	9.6	-1.73	9.55	9.5	-1.19	9.64	9.6	-0.79
7M	9.55	9.5	-1.72	9.67	9.7	0.44	9.60	9.5	-1.28
9M	9.63	9.65	-1.18	9.49	9.5	-1.59	9.58	9.55	-1.47
12M	9.67	9.6	-1.04	9.67	9.7	0.20	9.73	9.6	0.30
24M	9.70	9.75	-1.04	9.62	9.6	-0.43	9.79	9.7	0.78
	Den 100 Q6m			Den 210mg Q6m			Alendronate		
	Corr Ca++		% Δ*	Corr Ca++		% Δ*	Corr Ca++		% Δ*
Visit No.	Mean	Median	Mean	Mean	Median	Mean	Mean	Median	Mean
BL	9.83	9.8	--	9.85	9.85	--	9.72	9.7	--
Day 4	9.52	9.4	-3.06	9.43	9.5	-4.18	9.69	9.7	-0.48
1M	9.56	9.5	-2.63	9.47	9.5	-3.68	9.54	9.6	-1.88
2M	9.59	9.6	-2.44	9.49	9.5	-3.75	9.58	9.6	-1.33
3M	9.63	9.7	-2.06	9.63	9.6	-2.20	9.62	9.7	-1.13
6M	9.66	9.7	-1.78	9.63	9.6	-2.26	9.64	9.6	-1.08
6M3D	9.69	9.6	-1.61	9.70	9.8	-1.62	9.74	9.7	0.45
7M	9.56	9.5	-2.65	9.61	9.65	-2.59	9.67	9.6	-0.39
9M	9.66	9.6	-1.72	9.63	9.55	-2.24	9.62	9.6	-0.86
12M	9.72	9.7	-1.16	9.64	9.6	-2.19	9.69	9.7	0.08
24M	9.72	9.6	-0.66	9.77	9.7	-1.48	9.69	9.7	-0.17

* Percent change from baseline (BL)

One subject had a single episode of grade 2 hypocalcemia (calcium < 8.0 – 7.0 mg/dL, or < 2.0 –1.75 mmol/L). This subject had a calcium level of 2.0 mmol/L at month 2, but at month 9 and thereafter, her calcium values were within normal limits. No adverse events or other abnormalities were noted in this subject. No subjects had Grade 3 or 4 decreases in serum calcium during the trial.

There were compensatory modest increases in median changes from baseline for iPTH of 46% to 82% during the first month following dosing. The magnitude of these increases diminished to near-baseline levels at Month 12, when they ranged from 11% below baseline to 22% above baseline for the denosumab cohorts. In the denosumab dose cohorts, phosphorus levels decreased 8.9% to 17.8% at Month 1. The median percent change in phosphorus in the first 24 months of the trial ranged from 1.3% above

baseline to 12.8% below baseline. Serum phosphorus generally returned to near baseline levels by Month 24.

Adverse Events:

Abnormal laboratory findings without clinical significance (investigator's assessment) were not recorded as adverse events. If a change in a laboratory value was considered clinically significant and either required therapy or an adjustment in prior therapy, it was considered an adverse event. No adverse events of hypocalcemia were reported during the first 24 months of the trial. However, there were several events that were potentially indicative of hypocalcemia. Eighteen subjects (5.7%) in the denosumab treatment cohorts, 3 (6.5%) in the placebo cohort, and none (0%) in the alendronate cohort had adverse events considered potential clinical manifestations of hypocalcemia (hypoesthesia and paresthesia). None of these were serious and no events resulted in trial drug discontinuation or withdrawal from the trial. None of the subjects who experienced adverse events of potential clinical manifestations of hypocalcemia had albumin-adjusted serum calcium below the normal range at scheduled visits.

Reviewer Comments:

- ***The median percent change in calcium for the denosumab cohorts were decreases ranging from 3.0% to 4.3% on day 4 and 1.1% to 3.9% at month 1.***
- ***One denosumab subject had an asymptomatic single episode of Grade 2 hypocalcemia at Month 2. No subjects had Grade 3 or 4 decreases in calcium.***
- ***There were fewer adverse events potentially indicative of hypocalcemia in the denosumab group as compared to placebo.***

Cardiac Events

There was no difference between treatment groups in the incidence of serious or non-serious cardiovascular events.

Electrocardiograms (ECG) were performed during the trial at screening, Month 1 and Month 12. Hardcopies of 12-lead electrocardiograms were sent for central reading. The resulting ECG data then were transferred electronically to Amgen. Bazett's and Fridericia's corrections of QTc intervals were performed by Amgen using the machine-determined RR and uncorrected QT intervals. There did not appear to be any clinically significant differences in QTc parameters among denosumab dose cohorts, nor any among the denosumab dose cohorts and placebo and alendronate for either method based on review of the Applicant's summary data.

Reviewer Comments:

- ***There were no clinically significant differences between treatment groups in serious or non-serious cardiovascular events during through Month 24 of the trial.***
- ***There were no fatal cardiac events during the entire trial period.***

- ***A review of the Applicant's data on QTc parameters did not identify any significant differences between treatment groups.***
- ***An internal cardiology and QT consult has been requested for the product.***

Malignancy

All malignancies and unspecified neoplasms are summarized by treatment group in Table 172. Malignancies were more often reported in the denosumab treatment groups, particularly breast cancer, gastrointestinal cancers, nervous system and respiratory tract cancers. However, the numbers of malignancies were small and it is difficult to draw conclusions from such a small trial population.

Table 172. All Malignancies or Unspecified Neoplasms by Treatment Group

High Level Group Term High Level Term	Placebo (N=46) n	All Denos (N=314) n	Alen (N=46) n
Breast neoplasms malignant and unspecified			
Breast and nipple neoplasms malignant	0	2	0
Breast neoplasms unspecified malignancy	0	1	0
Gastrointestinal neoplasms malignant and unspecified			
Colonic neoplasms malignant	1	1	0
Gastric neoplasms malignant	0	2	0
Pancreatic neoplasms malignant	0	1	0
Lymphomas non-Hodgkin's B-cell			
Diffuse large B-cell lymphomas	1	0	0
Follicle centre lymphoma, follic. Gr I, II, III	0	1	0
Lymphomas non-Hodgkin's unspecified histology			
Non-Hodgkin's lymphomas NEC	0	0	1
Miscellaneous and site unspecified neoplasms malignant and unspecified			
Neoplasms malignant site unsp. NEC	0	2	0
Nervous system neoplasms malignant and unspecified NEC			
Nervous syst. neoplasms unsp. malignan.	0	2	0
Plasma cell neoplasms			
Plasma cell neoplasms NEC	0	1	0
Reproductive neoplasms female malignant & unspecified			
Ovarian neoplasms malignant	0	1	0
Respiratory and mediastinal neoplasms malignant & unspecified			
Respiratory tract & pleural neoplasms malignancy unspecified NEC	0	2	0
Skeletal neoplasms malignant and unspecified			
Bone neoplasms unsp. malignancy	1	0	0
Skin neoplasms malignant and unsp.			
Skin melanomas	0	1	0
Skin neoplasms malignant & unsp.	0	1	2

Reviewer Comments:

- *There were 3 fatal malignancies or neoplasms in the denosumab 100 mg Q6 months cohort, including lung cancer, gastric cancer and brain neoplasm.*
- *Breast, gastrointestinal, nervous system and respiratory tract cancers were reported in denosumab subjects; it is difficult to draw any further conclusions from such a small trial population.*

Laboratory

Overall, there were no significant trends in serum chemistry or hematology parameters, other than modest, expected decreases in serum calcium, phosphorus, and total alkaline phosphatase during dosing with denosumab. When denosumab was withdrawn in the off-treatment and retreatment cohorts, some subjects experienced transient increases in alkaline phosphatase.

Marked Laboratory Abnormalities:

Marked laboratory abnormalities during the course of the trial are summarized in **Table 173**. There were several subjects who had isolated increases in magnesium levels, but these occurred at random times in the trial and only occurred once in subjects. All other marked laboratory abnormalities were possibly related to concomitant medications (e.g. diuretics) or medical conditions (e.g. diabetes mellitus, alcohol abuse)

Table 173. Marked Laboratory Abnormalities (3 or More Grade Shifts from Baseline in Toxicity) in Subjects Receiving Denosumab Through Month 48

Lab Test Name	Visit No.	Baseline	Abnormal Value	SID	Cohort	Comment
Glucose	Month 30	6.2 mmol/L	18.8 mmol/L	319017	D14mg Q6 m	Fluctuating glucose levels in trial. Documented medical history of diabetes.
Potassium	Day 288	4.6 mmol/L	2.6 mmol/L	310054	D30mg Q3m	Two low levels at unsched visits. Subject had history of weight loss & EtOH abuse.
Potassium	Month 7	4.1 mmol/L	6.1 mmol/L	324022	D30mg Q3m	Single abnormal lab. All other values wnl.
Potassium	Month 12	5.0 mmol/L	6.9 mmol/L	319012	D60mg Q6m	Add'l Grade 3 toxicity at Month 7. Took valsartan too (assoc w/ hyperkalemia).
Potassium	Month 7	4.9 mmol/L	6.3 mmol/L	325006	D60mg Q6m	Several high K+ levels during trial. No notable medical history.
Potassium	Month 9	3.6 mmol/L	2.9 mmol/L	324023	D210mg Q6m	One Grade 3 toxicity. Low BL value and other low K+ levels during trial.
Lymphocytes	Month 36	$1.8 \times 10^9/L$	$0.5 \times 10^9/L$	307085	D210mg Q6m	All other lymphocyte levels wnl during trial.
Magnesium	Day 4 Month 1	1.25 mmol/L	1.30 mmol/L	307074	D14mg Q3m	All other magnesium levels wnl during trial.

Clinical Review
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 BLAs 125,320; 125,331; S-000
 PROLIA™, denosumab

Lab Test Name	Visit No.	Baseline	Abnormal Value	SID	Cohort	Comment
Magnesium	Month 15	1.00 mmol/L	1.30 mmol/L	314004	D14mg Q3m	All other magnesium levels wnl during trial.
Magnesium	Month 15	1.15 mmol/L	1.30 mmol/L	326014	D14mg Q3m	All other magnesium levels wnl during trial.
Magnesium	Month 3	1.05 mmol/L	1.30 mmol/L	322011	D60mg Q6m	All other magnesium levels wnl during trial.
Magnesium	Month 6	1.00 mmol/L	1.30 mmol/L	324015	D60mg Q6m	All other magnesium levels wnl during trial.
Magnesium	Month 12	1.00 mmol/L	1.30 mmol/L	305080	D210mg Q6m	All other magnesium levels wnl during trial.
Magnesium	Month 15	1.00 mmol/L	1.30 mmol/L	316021	D210mg Q6m	All other magnesium levels wnl during trial.
Magnesium	Month 3	1.20 mmol/L	1.30 mmol/L	320004	D210mg Q6m	All other magnesium levels wnl during trial.
Sodium	Month 21	139 mmol/L	129 mmol/L	309030	D14mg Q3m	All other sodium levels wnl during trial.
Sodium	Month 6	136 mmol/L	128 mmol/L	307006	D30mg Q3m	Na ⁺ of 129 at Month 1. Used HCTZ / triamterene (assoc w/ electrolyte abn'l).
Sodium	Month 30	135 mmol/L	128 mmol/L	319012	D60mg Q6m	Na ⁺ of 129 mmol/L at Months 1 & 3. Used carvedilol (assoc w/ hyponatremia)
Phosphorus	Month 3	1.3 mmol/L	0.6 mmol/L	324018	D100mg Q6m	All other phosphorus levels wnl during trial.
Phosphorus	Month 21 Month 36	1.1 mmol/L	0.6 mmol/L	307085	D210mg Q6m	All other phosphorus levels wnl during trial.
Platelets	Month 24	257 x 10 ⁹ /L	11.0 x 10 ⁹ /L	316043	D210mg Q6m	Six days later, platelet level measured 298 x 10 ⁹ /L. All other platelet levels wnl.
AST (SGOT)	Day 283	30 U/L	283 U/L	310054	D30mg Q3m	AST 1 st increased at Month 3. Subject d/c trial d/t incr. LFTs from EtOH abuse.

Source: Clinical Trial Report for 20010223, Listing 16, pages 8293-8313 of 9933.

Mean Change from Baseline:

Mean percent change in laboratory parameters from baseline to Month 24 are presented below in Table 174. There were no clinically significant changes in laboratory parameters from baseline to Month 24. There were no obvious dose-related changes in laboratory parameters for the denosumab cohorts.

Table 174. Laboratory Values: Mean % Change from Baseline to Month 24

	Plac	D6Q3m (24mg/y)	D14Q6m (28mg/y)	D14Q3m (56mg/y)	D30Q3m (120mg/y)	D60Q6m (120mg/y)	D100Q6m (120mg/y)	D210Q6m (420mg/y)	Alen
N	46	43	53	44	40	47	41	46	46
ALT	12.68	7.77	-0.22	1.50	3.42	12.04	-0.79	-1.88	7.09
AST	5.14	8.37	4.37	1.26	5.73	10.27	7.00	-1.88	13.24
Albumin	-3.15	-3.06	-2.11	-3.70	-0.74	-0.91	-2.83	-2.42	-1.61
BUN	4.25	7.61	13.42	8.12	1.15	6.27	1.73	16.96	7.15
Creatinine	-0.74	6.43	8.51	1.89	4.49	5.46	1.99	2.98	5.68
Ca++ (Corr)	0.04	0.76	0.20	-1.04	-0.43	0.78	-0.66	-1.48	-0.17
Phosphorus	-1.92	2.52	0.27	-5.96	-3.24	-1.11	-2.61	-4.44	-7.07
Magnesium	2.96	1.67	2.96	3.16	8.47	0.95	4.79	2.30	3.26
Sodium	-1.54	-1.95	-1.57	-1.11	-1.39	-1.40	-1.50	-1.15	-1.57
Potassium	-1.67	-2.16	-1.48	-1.09	0.87	-0.90	-2.64	-1.35	-0.72
Chloride	-3.00	-4.03	-4.47	-2.60	-3.58	-3.59	-2.95	-2.58	-3.31
WBC	1.51	-1.09	-1.39	-4.93	-4.07	-6.12	-3.13	-1.76	-1.33
Hemoglobin	-1.34	-2.98	-3.67	-2.39	-3.87	-1.12	-1.65	-1.78	-0.46
Hematocrit	0.34	-1.42	0.42	-0.56	-0.91	1.76	0.29	0.57	2.36
Platelets	0.81	-3.65	-5.65	-5.06	2.39	-5.09	-6.42	-4.56	-4.50

Clinical Laboratory Abnormalities:

Liver Function tests:

Among subjects with a normal baseline alanine amino transferase(ALT), there was 1 subject in the placebo group and 6 subjects in the denosumab group with ALT >3 times the upper limits of normal (ULN) at any visit. In the denosumab group, 2 subjects were in the 210 mg Q6months cohort and there was 1 subject each in the 6 mg Q3months, 14 mg Q6months, 30 mg Q3months and 60 mg Q6months cohort. There were no subjects with ALT >5 times ULN at any visit. Among subjects with a normal baseline aspartate amino transferase (AST), there were 3 denosumab subjects with an AST > 3 times ULN at any visit. There was one denosumab subject with an AST > 5 times ULN; this subject was abusing alcohol and was removed from the trial. No subjects had a total bilirubin that increased from normal at baseline to > 3 times ULN. No trends in the shifts of liver function tests were noted. There were no adverse event reports of hepatic impairment or failure during the trial.

Renal Function:

Two subjects with a normal baseline serum creatinine (SCr) experienced a doubling in serum creatinine during the trial. One subject was in the placebo group and the other was in the alendronate group. One subject with a normal blood urea nitrogen (BUN) at baseline experienced a doubling BUN during the trial; this subject was receiving denosumab 14mg Q3months. No trends in the shifts of renal function were noted. There was one report of renal insufficiency during the trial in a subject in the alendronate cohort.

Vital Signs:

Vital signs were obtained at each visit. Physical exam was conducted at each dosing visit, except for the Month 9 visit in the first 24 months of the trial. There was no clinically significant change in mean values of systolic and diastolic blood pressures, pulse rate, and body temperature during the trial.

Among subjects with normal SBP (<120) at baseline, 1 denosumab subject and 2 alendronate subjects had SBP>160 at any visit; there were no subjects in the placebo group. One subject in the alendronate cohort had BP>190 at any visit.

Among subjects with normal diastolic BP (<90 mm Hg) at baseline, 1 subject in the denosumab cohort (receiving 210mg Q6m) had DBP>110 mm Hg at any visit; there were no subjects in the alendronate or placebo cohorts with a substantial increase in diastolic BP from baseline. There were ≤ 2 subjects in any denosumab dosing cohort or the alendronate cohort with a DBP<40 mm Hg at any visit and the placebo group had 3 subjects with DBP<40 mm Hg at any visit.

Among subjects with a normal pulse (60-100) at baseline, 1 alendronate subject developed a pulse>120 at any visit. There were no subjects in the placebo or denosumab cohorts with a normal pulse at baseline that developed an elevated pulse at any visit.

Weight gain was reported by 1 subject and 2 subjects in the alendronate and denosumab cohorts, respectively. Both denosumab subjects were receiving 14 mg Q3months. Weight loss was reported in 5 subjects in the denosumab treatment group, with 2 subjects receiving denosumab 210 mg Q6months and 1 each for the denosumab 6mg Q3months, 14 mg Q6months and 30 mg Q3months.

Reviewer Comments:

- *There were no significant changes in laboratory parameters, vital signs or physical findings during the trial.*
- *There did not seem to be any dose-related changes in vital signs for the denosumab cohorts.*

Safety Conclusions:

There were four deaths in the denosumab cohort and none in the alendronate and placebo groups during the trial. Three of the four denosumab deaths were due to malignancy, which is concerning. There were no deaths due to infection.

During the first 24 months of the trial, serious adverse events occurred in 11%, 18%, and 17% of placebo, denosumab and alendronate subjects, respectively. The 3 most common adverse events in the placebo cohort were arthralgia (30%), upper respiratory tract infection (24%), and sinusitis (20%). The 3 most common adverse events in the denosumab cohorts were upper respiratory tract infection (28%), arthralgia (24%), and

back pain (20%). The 3 most common adverse events in the alendronate cohort were upper respiratory tract infection (30%), dyspepsia (26%), and nausea (22%). The denosumab group had a higher incidence of adverse events in the infections, injury, respiratory and skin SOCs.

Overall the rate of discontinuation from trial seems reasonable for this trial. Within the 7 denosumab cohorts, subjects receiving denosumab 30mg Q3 months had the lowest percentage of completion and the highest percentage of adverse events.

This trial had a bone biopsy substudy with tetracycline labeling. Despite an unplanned, extended label search, there were no biopsy samples in the placebo group with no label or single label, while there were 9 and 1 of single and double labels in the denosumab and alendronate groups, respectively at Month 12. Two subjects in the denosumab group had a reduction in mineral apposition rate below the normal range. The mean mineralization lag time was within the normal range for the denosumab group, but 4 denosumab subjects had a MLT > 100 days including 2 denosumab subjects with a MLT > 200 days after 12 months of denosumab treatment. The mean activation frequency for the denosumab group at Month 12 was greatly decreased as compared to baseline and the placebo group in this substudy. There were no notable findings on histologic analyses or microCT evaluation.

Events of special interest reviewed herein included hypocalcemia, ONJ, delayed fracture healing, cardiac events, infections and malignancy. There were more serious events of infection in the denosumab cohorts. However, no subjects died of an infection during the trial and no denosumab subject developed any unusual or opportunistic infections. Within the denosumab cohort, the dose received did not appear to effect the incidence or type of infection.

There were no reports of delayed fracture healing or ONJ during the trial. The median percent change in calcium for the denosumab cohorts were decreases ranging from 3.0% to 4.3% on day 4 and 1.1% to 3.9% at month 1. No subjects had Grade 3 or 4 decreases in serum calcium during the trial. There were fewer adverse events potentially indicative of hypocalcemia in the denosumab group as compared to placebo. There were no other significant changes in laboratory parameters during the trial, including hepatic and renal function tests.

There were no clinically significant differences between treatment groups in serious or non-serious cardiovascular events during through Month 24 of the trial. There were no fatal cardiac events during the entire trial period. A review of the Applicant's data on QTc parameters did not identify any significant differences between treatment groups; an internal cardiology and QT consult has been requested to evaluate all QTc parameters in detail. There were no clinically significant changes in vital signs during the trial.

There were 3 fatal malignancies or unspecified neoplasms in the denosumab group, including lung cancer, gastric cancer and a brain neoplasm. The incidence of breast, gastrointestinal, nervous system and respiratory tract cancers was increased in denosumab subjects as compared to placebo or alendronate. However, it is difficult to draw any further conclusions about such infrequent events from such a small trial population.

Discussion and Conclusions:

The primary objective of this trial was to determine the effect of denosumab treatment compared with placebo over 12 months on bone mineral density (BMD) of the lumbar spine in postmenopausal women with low BMD. The Applicant noted that at Month 12, denosumab increased BMD of the lumbar spine from baseline in all denosumab cohorts (range: 3.0% to 6.7%). The differences between each denosumab cohort and placebo (- 0.8% change from baseline) were statistically significant ($p < 0.001$). Based on the data obtained from this trial, the Applicant chose a fixed dose of 60mg Q6months for future Phase III trials in postmenopausal women. Although this is a Phase II dose-finding trial, this reviewer is concerned about the number of fatal malignancies, the incidence of serious infections, and the bone histomorphometry results for denosumab.

9.5 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-lymphocyte 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

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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 $\alpha 4$ 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	radioimmunotherapeutic 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 (TNF α)	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
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

Product	Description	Indication	Date Appr	Safety Actions (Boxed Warnings)
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 fistulizing 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
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

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Product	Description	Indication	Date Appr	Safety Actions (Boxed Warnings)
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	
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	

9.6 Overview of Denosumab 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,	6 months

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Study Protocol number	Study Design	Treatment (dose)	Number of subjects/population	Study Duration
20050172	Phase 2, rand, DB, PC, dose response	denosumab 14, 60, or 100 mg or PLA SC, Q6M x 2 doses	-4 ≤ T-score ≤ -1 LS or TH N=226 Japanese women with PMO (-4.0 ≤ T-score ≤ -2.5 LS or -3.5 ≤ T-score ≤ -2.5 TH or FN)	12 months
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 trial 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 trial	denosumab 60 mg SC Q6M (8 doses)	N=200 PMP w/ low BMD who completed trial 20010223	48 months (ongoing)
20060237	Phase 3b, rand, open-label	denosumab 60 mg SC Q6M (2 doses) from either PFS or a vial	N=311 PMP with low BMD who completed trial 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	N=250 PMP w/ low BMD (-4.0 ≤ T-score ≤ -2.0 at LS,	24 months (ongoing)

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Study Protocol number	Study Design	Treatment (dose)	Number of subjects/population	Study Duration
20060289	Phase 3, open-label, single-arm extension	ALN followed by denosumab denosumab 60 mg SC Q6M (4 doses)	TH, or FN) 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 trial
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 inhibitor 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.

9.7 PTs with p value ≤ 0.1 for difference between denosumab and placebo group in trial 20030216

PT	placebo N= 3883	denosumab N=3879	risk ratio	p value
Eczema	25	50	2	0.0048
Flatulence	53	84	1.59	0.0082
Ear infection	22	42	1.91	0.0143
Resorption bone increased	12	1	0.08	0.0166
Concussion	15	4	0.27	0.0185
Restless legs syndrome	24	10	0.41	0.0191
Soft tissue injury	4	15	3.74	0.0191
Fall	250	205	0.81	0.0259
Vision blurred	2	11	5.48	0.0269
Macular degeneration	24	11	0.45	0.0305
Tinnitus	55	35	0.63	0.0339
Hot flush	32	17	0.53	0.0347
Lyme disease	10	2	0.2	0.0368
Diverticulum	21	37	1.76	0.0393
Essential hypertension	8	19	2.37	0.0405
Renal cyst	39	23	0.59	0.0418
Liver disorder	3	11	3.66	0.0466
Femur fracture	28	15	0.53	0.0484
Parkinson's disease	7	17	2.42	0.0494
Hypercholesterolaemia	236	280	1.19	0.0512

PT	placebo N= 3883	denosumab N=3879	risk ratio	p value
Gastric ulcer	12	24	1.99	0.0516
Thermal burn	15	6	0.4	0.0565
Hypotension	34	20	0.59	0.0572
Periarthritis	22	11	0.5	0.0581
Dyspepsia	213	177	0.83	0.0605
Tooth infection	41	26	0.63	0.0646
Herpes virus infection	10	3	0.3	0.0666
Oedema peripheral	155	189	1.22	0.0682
Fibula fracture	32	19	0.59	0.0688
Hypertriglyceridaemia	7	16	2.28	0.0688
Contusion	193	161	0.82	0.0697
Aortic stenosis	5	13	2.59	0.0705
Pleural effusion	3	10	3.29	0.0706
Dermatitis allergic	23	37	1.61	0.0744
Rhinitis	84	63	0.74	0.0763
Periorbital haematoma	8	2	0.25	0.0776
Tachycardia	24	38	1.58	0.0787
Diverticulum intestinal	20	33	1.65	0.079
Night sweats	8	2	0.25	0.079
Injury	8	2	0.25	0.0792
Vulvovaginal pruritus	11	4	0.36	0.082
Sick sinus syndrome	4	11	2.75	0.0834

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PT	placebo N= 3883	denosumab N=3879	risk ratio	p value
Joint range of motion decreased	6	14	2.32	0.0845
Nephrolithiasis	32	20	0.62	0.0931
Genital infection fungal	6	1	0.17	0.0962
Dupuytren's contracture	9	3	0.33	0.0967
Endometrial hypertrophy	6	1	0.17	0.0969
Maculopathy	3	9	3	0.0995
Thrombocythaemia	1	6	5.92	0.0997
Duodenal ulcer	12	5	0.42	0.0998
Respiratory tract infection viral	20	32	1.6	0.0999

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 125320,
125331

Applicant: Amgen

Stamp Date: 12/19/08

Drug Name: Denosumab (Prolia) **NDA/BLA Type:** BLA

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Section 2.5 Clinical Overview
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number:20030223 Study Title: A Randomized, Double-blind, Placebo-controlled, Multi-dose Phase 2 Study to Determine the Efficacy, Safety, and Tolerability of AMG 162 in the Treatment of Postmenopausal Women With Low Bone Mineral Density Sample Size: 412 Arms: denosumab SC (Q3M [6, 14, or 30 mg] or Q6M [14, 60, 100, or 210 mg] or placebo Active control: alendronate 70 mg QW PO Location in submission: 5.3.4.2	X			
EFFICACY					

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 20030216: A Study to Evaluate Denosumab in the Treatment of Postmenopausal Osteoporosis. FREEDOM (Fracture REDuction Evaluation of Denosumab in Osteoporosis every 6 Months) Indication: Treatment of osteoporosis in postmenopausal women Pivotal Study #2 20040132: A Randomized Double-Blind Study to Evaluate Denosumab in the Prevention of Postmenopausal Osteoporosis (DENosumab FortifiES BoNe Density – The DEFEND Trial) Indication: Prevention of osteoporosis in postmenopausal women	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			There is no formal QT study performed as this is not required due to the denosumab is a biologic agent. However, in the preBLA meeting, the sponsor was asked to submit EKG data, which is submitted in section 5.3.5.3.28.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

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	Content Parameter	Yes	No	NA	Comment
	efficacious?				
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Agency requested analyses of CV events, infections, hypocalcemia, fracture repair and bone biopsy data, which sponsor provided.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?				See statistical filing document
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?				See statistical filing document
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?				See statistical filing document
34.	Are all datasets to support the critical safety analyses available and complete?	X			Agency requested analyses of CV events, infections, hypocalcemia, fracture repair and bone biopsy data, which sponsor

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

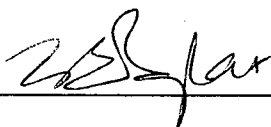
	Content Parameter	Yes	No	NA	Comment
					provided.
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				See statistical filing document
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			For study 20040132, CRFs are not submitted. However, this is an ongoing study in the extension phase. This was discussed in the pre-BLA meeting.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes__

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

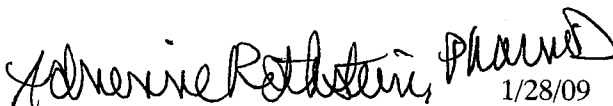
Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Vaishali Popat MD, MPH
Reviewing Medical Officer



1/28/09
Date

Adrienne Rothstein, Pharm.D.
Clinical Analyst



1/28/09
Date

Theresa Kehoe, MD
Clinical Team Leader



1/29/08
Date



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Dermatology and Dental Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993

Tel 301-796-2110
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MEMORANDUM

Date: July 20, 2009

From: Denise Cook, M.D. *DC 7/23/09*
Medical Officer, DDDP

Through: David Kettl, M.D., Clinical Team Leader and *7/23/09*
Susan Walker, M.D., Division Director, DDDP *(SW) 7/24/09*

To: Vaishali Popat, M.D., MPH, Medical Officer, DRUP
Celia Peacock, MPH, RD, DRUP

Cc: Julie G. Beitz, M.D., Office Director, ODE3
Maria Walsh, ADRA, ODE 3

Re: Consult #1168 (DDDDP#018453), received June 17, 2009 from DRUP, and assigned on June 19, 2009. The trial data revealed an increased incidence of skin and soft tissue reactions in the denosumab treated subjects (15%) compared to the placebo treated subjects (13%). DRUP has the following questions for DDDP:

1. Overall, subjects in the denosumab group were more likely to develop skin and soft tissue related adverse events. There were more bullous conditions, skin rashes, dermatitis and eczema related adverse events in the denosumab group compared to placebo. This medical officer believes that this information should be included in labeling. Do you agree? If so, please share your thoughts on what should be included in the labeling.
2. There were 4 cases of toxic skin reactions in the denosumab group, while none in placebo. Please help us evaluate these cases. Should this information be included in labeling?

3. *Would you advise any post marketing studies to evaluate these adverse events closely, especially in susceptible populations such as nursing home populations, subjects with pre-existing skin conditions, etc?*

Material Reviewed: Consultative summary, draft statistical review, sponsor narratives for all bullous, photosensitivity reactions, and toxic skin eruptions from the trials in the BLA and the CRFs for all of these adverse events of interest.

Review:

Sponsor: Amgen, Inc.
Drug: Denosumab
Proposed Indications: 'Treatment and Prevention of Postmenopausal Osteoporosis (PMO)' and 'Treatment and prevention of bone loss in patients undergoing hormone ablation (HALT) for prostate or breast cancer'.

Body of Review

Background

Denosumab is a fully humanized monoclonal antibody to receptor activator for nuclear factor- κ B ligand (RANKL). RANKL is a dominant and essential mediator of osteoclast differentiation and activation. Prevention of the RANK ligand/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass in both cortical and trabecular bone. The drug has a $t_{1/2}$ = 25 days. The trials in question with the dermatologic events were all double-blind placebo controlled trials where subjects received denosumab 60 mg SC q 6 months for either 24 or 36 months and were followed for an additional 24 months.

The consult provides potential biologic mechanisms that might be related to skin and soft tissues disorders as follows:

"Bone provides a microenvironment that is critical for the development of hematopoietic stem cells (HSCs). All cells of the mammalian immune system are derived from bone, and various immunoregulatory cytokines influence the fate of bone cells. Bone continues to play a role in adaptive immunity at stages beyond lymphocyte development. Activated T cells express the TNF superfamily member TRANCE which is a key differentiating factor for osteoclasts (OCs). Receptor activator of nuclear factor- κ B (RANK) is the signaling receptor for TRANCE.

In the adult immune system, TRANCE modulates immunity through dendritic cells (DCs). DCs are the most potent antigen presenting cells (APCs) in the human immune system and are required to initiate T-cell mediated immunity in vivo. DCs differentiate from the hematopoietic monocyte/macrophage progenitor cell lineage and are close relatives of osteoclasts (OCs). TRANCE may also be important for the survival of interstitial DCs engaged in antigen surveillance during the interim period separating immune responses. Pathogenic stimuli or self antigens are phagocytosed and presented to naïve T cells by dendritic cells (DCs). T cells provide activating signals to DCs through CD40L and in return receive optimal activating and costimulatory signals. The activated T cells are induced to express TRANCE, which provides further activating and survival signals to DCs. The DCs may negatively regulate TRANCE:RANK signaling through upregulation of the TRANCE decoy receptor, osteoprotegerin (OPG). (Denosumab is a fully human

monoclonal antibody that binds and inhibits RANKL in a manner similar to OPG.)”(See consult for references).

Review

As noted in the consult from table 1 below, there were more subjects in the denosumab group (725, 15%) with skin and soft tissue adverse events than in the placebo group (602, 13%).

Table 1 Skin and Soft Tissue Disorders by Group

Adverse Event High Level Group Term	Placebo N=4533	Denosumab N=4550
Angioedema	35	36
Cornification and dystrophic skin disorders	28	29
Cutaneous neoplasm benign	8	10
Epidermal and dermal conditions	414	520
Pigmentation disorders	6	4
Skin and subcutaneous tissue disorders NEC	40	53
Skin appendage conditions	118	118
Skin vascular abnormalities	15	18
Subjects (filtered)	602	725
Source: From consult request, page 3, ISS AAE data set including studies 20030216, 20040132, 20040135 and 20040138		

This imbalance in adverse events was primarily driven by the category of epidermal and dermal conditions. In the consult the epidermal and dermal conditions that showed an imbalance were broken down by study (table 2). This table was collapsed by this reviewer to show the incidence for the entire ITT safety database as denoted in the table 2 of this consult response.

Table 2 Epidermal and Dermal Conditions

Adverse Event High Level	Placebo N=4533	Denosumab N=4550
Bullous conditions	3 (0.07%)	11 (0.2%)
Dermatitis and eczema	95 (2.1%)	159 (3.5%)
Dermatitis ascribed to a specific agent*	1 (0.02%)	6 (0.1%)
Photosensitivity conditions	1 (0.02%)	6 (0.1%)
Pruritus NEC	112 (2.5%)	122 (2.9%)
Rashes, eruptions, and exanthems NEC	108 (2.4%)	132 (2.9%)
Exfoliative conditions	4 (0.09%)	2 (0.04%)
*May be a drug other than denosumab		
Source: Adapted from table 2 of the consult from DRUP, page 3.		

This general data suggests that denosumab causes an increased incidence of skin eruptions as compared to placebo as manifest by the percentage of subjects experiencing dermatitis and eczema in the denosumab group compared to placebo, 3.5% and 2.1%, respectively, and in the category of dermatitis ascribed to a specific agent, 0.1% vs. 0.02%, respectively. In these 2 categories, there were 4 eruptions that occurred in the denosumab group that were classified as “toxic skin eruptions” compared to none in the

placebo group that DRUP would like evaluated. Given that the incidence of bullous conditions and photosensitivity conditions, although rare, had an increased incidence in the denosumab group by almost a factor of 10, this reviewer asked for a narrative of each event and the CRF to review to determine, if possible, the characterization of these events in terms of severity and seriousness and to determine what level of certainty can be ascertained that denosumab caused these events.

It should be noted that according to the consult, there were 7/602 (1.2%) subjects in the placebo group and 10/725 (1.4%) subjects in the denosumab group with serious skin adverse events, not an appreciable difference. There were also 7 subjects in the placebo group who discontinued because of skin event (1.2%) and 12 (1.7%) who discontinued because of a skin event in the denosumab group. The reasons for discontinuations in the placebo group included dermal and epidermal conditions (1), dermatitis and eczema (1), psoriatic conditions (2), and rashes, eruptions and exanthems (3). The reasons for discontinuation in the denosumab group included bullous condition (1), dermatitis and eczema (3), papulosquamous condition (1), pruritus (5), and rashes, eruptions, and exanthems (2). Again, there is not an appreciable difference between placebo and denosumab for events that lead to discontinuation, the difference being driven by the event of pruritus rather than a specific dermatosis.

***Comment:** It is somewhat reassuring that although there is a statistically significant increase in skin related AEs (for dermatitis and eczema and rashes eruptions and exanthems, according to the draft statistical review by Dr. Yap) in the denosumab group vs. the placebo group, there was not an appreciable difference between placebo and denosumab in terms of either the number of SAEs or in the discontinuations between placebo and drug product. If one were to subtract the instances of pruritus that caused discontinuation, the two arms approach each other even more, 1.2% for placebo and 1.0% for denosumab. Thus, suggesting that most events were mild to moderate and not life-threatening.*

It should be noted that while reviewing the CRFs of these subjects, most were from foreign sites and very little, if any, information was given describing the exact characterization of the lesions of the various skin eruptions. My assessments were made from both the narratives provided by the sponsor and anything extra that could be gleaned from the CRF. Table 3 delineates the case of interest that were classified as bullous conditions, photosensitivity conditions, or toxic skin eruption that prompted this consult.

Table 3 Selected Preferred Terms in Imbalanced Epidermal and dermal Conditions

Adverse Event High Level	PT	Placebo N=3876	Denosumab N=3886
Bullous conditions	Blister	2	6*
	Dermatitis herpetiformis [@]	0	1
	Erythema multiforme [#]	1	2 [^]
	Pemphigoid	0	1
	Pemphigus	0	1
Photosensitivity conditions	Photodermatosis	0	2
	Photosensitivity allergic reaction	1	3
	Photosensitivity reaction	0	1
Dermatitis and Eczema	Toxic skin eruption	0	4
<p>* Includes 2 from the Primary HALT [@]Probable case of drug induced linear IgA dermatosis (see text) [#]Probable cases of giant urticaria (see text) [^]One of these cases is a GI case (see text) Source: Adapted from table 3 of the consult from DRUP, page 4.</p>			

Toxin skin eruptions

Only one of the toxic skin eruptions was classified as a serious and severe adverse event. Subject 6412063 was a 68 y/o female who experienced the event on study day 970, approximately 212 days (7 months) from the previous dose of denosumab. The subject had discontinued denosumab because of worsening autoimmune hepatitis. The subject was treated with oral micostatin (nystatin), 5 ml p.o. q.i.d. from (b) (4). On (b) (4), the subject was hospitalized with a generalized skin eruption and had a skin biopsy which, according to the consult, was characterized as a "toxic dermatitis". The patient was hospitalized. The nystatin was withheld and the subject was treated with steroids and paracetamol (acetaminophen in the US). The event resolved in 12 days.

Comment: The sequence of events described in this case suggest that this is a drug eruption due to oral nystatin. The timing of the event suggests nystatin as the culprit and not denosumab. The t_{1/2} of denosumab is 25 days. As such, the drug would be eliminated in 125 days or 4 months. The subject was 212 days out from her last dose of denosumab. There are some reports in the literature of generalized skin eruptions from oral nystatin treatment. One was of a patient with a flexural erythema which progressed to a febrile pustular erythroderma¹ and the other reports three cases of acute generalized exanthematous pustulosis.² I agree with the investigator that this was a dermatitis cause by a specific agent, nystatin.

Subject 6412827, an 80 year old female, reported an adverse event of mild toxic skin eruption (verbatim term: toxicoderma) on study day 627, 1/28/07, approximately 60 days from the previous dose of denosumab. The CRF does not describe the lesions of this skin eruption. The subject had an ongoing pneumonia that had been treated with Ceftriaxone,

¹ Poszepczynska-Guigné, E., et.al. Ann Dermatol Venereol. 2003 Apr; 130(4): 439-42.

² Küchler A., et.al. Br. J. Dermatol. Nov; 13(5): 808-11.

11/30/06 – 12/9/06. The subject received another dose of Ceftriaxone 1/14/07 and Acemuk 600 (mucolytic) was added 1/16/07. Ranitidine was started on 1/18/07. INH was begun on 1/28/07 and continued to 7/18/07. No action was taken to treat the eruption which resolved within 8 days. The subject remained on denosumab, receiving her last dose on study day 889 without any recurrence of the skin eruption.

Comment: This subject was on multiple drug products and the etiology of a skin eruption that apparently spontaneously resolved is unclear. However, it probably was not due to INH, as it was started the same day as the eruption. It is also unlikely that it was due to denosumab, at least as a drug eruption, for the subject tolerated subsequent doses of the medication without any skin eruption and completed the trial.

Subject 67110066, a 73 year old female, reported a moderate toxic skin eruption (verbatim term: toxicodermine) on day 520, 148 days from the previous dose. Subject had been taking HCTZ since 7/31/05 and it was stopped on 4/14/06, the same day as the start of the eruption. Eruption resolved within 7 days following treatment with hydroxyxine and prednisone. The subject received all scheduled doses of denosumab and the eruption did not recur.

Comment: It is well-known that thiazide diuretics can cause an eczematous drug eruption, particularly a photodermatitis in sun exposed areas of skin. Unfortunately, the eruption was not described in more detail. Given that the subject was on a drug known to cause a dermatitis, and the fact that it occurred beyond the elimination half-life of the drug, and the fact that the subject received subsequent doses of denosumab, this eruption was most likely due to the thiazide diuretic.

The final case of toxic skin eruption was reported by a 71 year old female who reported the event (verbatim term: toxicoderma Endog.) on study day 449, approximately 86 days from the previous dose of denosumab. There is no further description of this dermatosis except that it was mild. The subject was on a statin medication. The subject had had an earlier eczematous eruption of the hands and fingers on study day 12 which resolved within 7 days. Whether this resolved spontaneously or was treated is not noted in the CRF. The eruption cleared in 105 days with betamethasone (topical) and certirizine and another topical medication. The event did not occur with subsequent doses of denosumab.

Comment: This eruption is also not likely to have been caused by denosumab, as the subject was given subsequent doses of the drug without the eruption occurring. Although one cannot say for sure the exact nature of this eruption, the verbatim term, toxicoderma Endog., suggests that the investigator thought this eruption had an “endogenous” source rather than an “exogenous” source. The CRF does not have an item for taking a dermatologic history however, the combination of betamethasone and certirizine has often been used to treat solar urticaria.³

³ Levy et. al. JAAD. December 2008, Vol. 59:No. 6, page 915.

In conclusion, for these 4 cases of toxin skin eruption, the data does not make a convincing case for these eruptions to be secondary to denosumab.

Photosensitivity Conditions

Photosensitivity allergic reactions

Subject 6302034 was a 68 year old female who reported an adverse event of moderate photosensitivity allergic reaction (verbatim term: sun allergy) on study day 192, approximately 18 days from the previous dose of denosumab. The CRF does not indicate the location of the "sun allergy" but the patient, who has a history of rosacea, was treated with diphenhydramine and more importantly, 1% topical metronidazole, which is a treatment for rosacea. The event resolved with this treatment within 76 days. The subject remained on denosumab therapy and the event did not recur following further doses.

Comment: *Rosacea is a disease of the face in which subjects have erythema and papules of the face. The disease can be relapsing and remitting, although the erythema often times is persistent. The history here suggests that this event was an exacerbation of the subject's rosacea and not an allergic reaction to denosumab.*

Subject 6613037 was a 67 year old female who reported an adverse event of moderate photosensitivity allergic reaction (verbatim term: anaphylactic reaction to sun) on study day 475 (4/1/06), approximately 131 days from the previous dose of denosumab. The subject had begun taking lornoxicam on day 446. No action was taken and the event remained ongoing. Lornoxicam was discontinued in 11/06. The subject received her final dose of denosumab on day 884. Her event did not worsen.

Comment: *The sequence of events in this case make the cause of the subject's photoallergic dermatitis most probably due to lornoxicam, which she began taking 29 days prior to the onset of the eruption and it was not discontinued for 11 months, thus the continuation of the eruption. There is no description in the CRF of the actual event other than the verbatim term but the history would suggest that the patient did not have anaphylaxis, as no action was taken. Lornoxicam is not approved in the United States, but a related NSAID, piroxicam (Feldene) is approved. This drug is known to cause photoallergic drug eruptions. It usually manifests as an eczematous eruption of sun exposed areas. Denosumab as the culprit seems less likely, as the drug should have cleared the body by day 125 (5 half-lives).*

Subject 6662023 reported a mild event of photosensitivity allergic reaction (verbatim term: exantma due to photo allergy) on study day 229 (6/21/05), approximately 51 days from the previous dose of denosumab. According to the narrative, the subject had a history of photosensitivity allergic reaction (solar allergy). The subject was on a nitrate and tramadol, the latter started on day 150. No action was taken and the event resolved within 9 days. The subject received her last dose of denosumab on day 179 and discontinued the study as a result of a fatal malignant lung neoplasm on (b) (6)

Comment: *In this subject, it is not possible to rule out denosumab as a cause of the photosensitive allergic reaction. Photosensitive allergic skin reactions are not listed to be adverse events of isosorbide mononitrate or tramadol.*

Photodermatoses

Subject 6749028 reported an adverse event of mild photodermatosis. The verbatim term was severe actinic damage to the left leg(benign) on day 659, 126 days from the previous dose of denosumab. In reviewing the CRF, this subject was at first thought to have a squamous cell carcinoma (SCC) and then it was changed to the verbatim wording described above. The event resolved after 54 days following unspecified action and alteration of the protocol drug. It did not occur with further doses of the drug. The subject had a history of basal cell carcinoma of the skin.

Comment: *It seems that the “photodermatosis” referred to in this scenario is not an acute event but a result of long-term sun exposure independent of drug treatment. In a subject with a previous history of BCC, actinic damage of the skin would be expected. There is no evidence from the general categories of epidermal and dermal conditions as listed in table 2 of the consult to suggest that denosumab causes or increases the risk of actinic damage, papulosquamous conditions, or skin neoplasms.*

Subject 6304050, a 70 year old female, reported an adverse event of mild photodermatosis (verbatim term: sun damage; skin lesions) on study day 113. The subject was treated with tretinoin and the photodermatosis resolved in 638 days. The subject remained on denosumab therapy and the event did not recur or worsen following further doses.

Comment: *Again, from the treatment for the “photodermatosis”, the subject appears to have been treated for actinic damage to the skin from long term sun exposure rather than exposure to denosumab.*

Photosensitivity reaction

Subject 6661443 is a case of a subject who complained of photosensitivity of the eyes (verbatim term) and moderate irritation of the eyes on study day 125 in 2005. The subject had had cataract surgery of both eyes in 1999. He was also being treated for glaucoma with a topical and oral agent. The event was ongoing at the end of the study but the subject completed all scheduled doses of denosumab without the event worsening.

Comment: *This is a case of photophobia and eye irritation that should not be included as a dermatologic adverse event.*

In conclusion, for the photosensitivity conditions, all but one of the events has a reasonable alternative etiology for the adverse event other than denosumab and the subjects did well despite continuing the drug product. In only one subject is there a lack of another agent as the cause of the photosensitivity. This makes photosensitivity

conditions in the denosumab group no more common than in the placebo group (0.02%) where one subject had a photosensitive allergic reaction (verbatim term: solar allergy).

Bullous Conditions

Pemphigus

Subject 6430133 was a 77 year old female, who was hospitalized on (b) (6) with a diagnosis of severe pemphigus in the oral mucosa on study day 918, approximately 187 days from the previous dose of denosumab. The sponsor narrative states that the subject had a biopsy (not found in the CRF) that was inconclusive. At the time of admission, the subject was on cimetidine, which she had been taking for gastritis since 3/3/07. This was discontinued in the day of admission. The subject was treated with prednisone and the event was resolving when she was discharged on (b) (6). The subject discontinued denosumab. The subject did not test positive for antibodies to denosumab. On day 932, the event was down-graded to mild pemphigus, which remained ongoing at the end of the study. According to the sponsor's narrative, the subject did not continue with injections of denosumab because of ongoing treatment with prednisone.

Comment: *In developed countries, up to 10% of cases of pemphigus can be drug-induced and may be confined to the oral mucosa. Approximately 80% are due to a drug that contains a thiol group. In these cases of pemphigus, the disease may or may not resolve with withdrawal of the offending agent.⁴ This subject was on such a drug, cimetidine, which it seems, caused some concern for the physician taking care of the subject, as it was discontinued the same day of admission. In addition, this event occurred more than 125 days since her last dose of denosumab, thus making it unlikely to be due to the drug product. The information in this case supports a drug-induced pemphigus due to cimetidine.*

Dermatitis herpetiformis

Subject 6834120 was a 71 year old female who reported an adverse event of moderate dermatitis herpetiformis (verbatim term: Duhring disease) on approximately study day 286, in January '06, approximately 90 days from the last dose of denosumab. No further description is given in the CRF and no note of a biopsy being done is documented. Concomitant medication in this subject included perindopril and captopril, ongoing since 2005 and amlodipine and atorvastatin ongoing since 2006. The event remained ongoing at the end of the study following treatment with disulfone and other unspecified action. The subject continued in the trial, completing all scheduled doses of denosumab without worsening of the event.

Comment: *This is another case of the subject taking concomitant medication that could have caused the adverse event. First, I was unable to find any cases of drug-induced dermatitis herpetiformis (DH). A very closely related disease, linear IgA dermatosis can be drug-induced and I suspect this is what the patient had. Captopril is a drug that can cause linear IgA dermatosis. There is not enough information to actually determine the*

⁴ Bologna, Jean. et.al. Dermatology, 2003. page 346

culprit, as the subject was continued on both drugs and “suppressive” therapy. The onset of DH at the age of 71 would be very unusual.

Pemphigoid

Subject 6744111 was a 78 year old with a diagnosis of pemphigoid since 2003 who reported an adverse event of worsening of pemphogoid on study day 321, approximately 107 days from the previous dose of denosumab. The subject was on betamethasone, doxycycline and nicotinamide for her pemphigoid. The event remained ongoing following treatment with dapsone. However, the subject remained on denosumab, completed all subsequent scheduled doses without further worsening of the event.

Comment: This is also not a clear case that denosumab caused worsening of the subject’s disease. This could have been due to the natural course of the disease. One would expect, however, that if denosumab caused worsening of the disease, that the subject’s disease would have gotten progressively worse with subsequent doses, and this did not happen.

Blister

There were 6 cases of blister on the denosumab arm that will be discussed together. They included subjects 6672044, 6684041, 6725021, 6743068, all from the PMO trials and 138325015 and 138129012 from the HALT trial. Subject 6743068 will be discussed separately. For the remaining 5 subjects, all had isolated blisters that occurred either as a solitary one or two lesion or in the case of one subject, as a cluster on the buttock. This latter subject most likely had pressure bullae, secondary to hospitalization for multiple traumas after a fall from a tree. All of these events either resolved spontaneously or with treatment such as Neosporin or occlusive dressings. All subjects had subsequent doses of denosumab without reoccurrence of a blister event.

In the case of subject 6743068, this 81 year old female reported mild blisters on approximately study day 936, approximately 24 days from the previous dose of denosumab. She also complained of red itchy legs on the same day. The investigator considered these 2 separate events. The site of the blisters is not documented. Other dermatologic conditions of the subject included a history of oral lichen planus. The subject had had 2 episodes of rash throughout the trial, but each resolved without discontinuing denosumab. In the case of the blisters and pruritus, they were ongoing at the end of the trial following treatment with aqueous cream. As the subject had received her last dose of denosumab, worsening or reoccurrence of the event could not be assessed.

Comment: None of the cases of ‘blister’ appear to be serious events that could be of an autoimmune nature. Furthermore, most of the cases do not appear to be secondary to denosumab as the blisters resolved spontaneously or with treatment while continuing the drug product.. Only in the last case described, one cannot be certain that the subject’s blisters are not due to denosumab. There were 2 cases of ‘blister’ in the placebo arm. Thus, it does not appear that denosumab increases one’s risk to develop ‘blisters’.

Erythema Multiforme (EM)

Subject 6436320, a 78 year old female, reported an adverse event of moderate Erythema multiforme (verbatim term: multiform erythema). This occurred on study day 724, approximately 155 days from the previous dose of denosumab. The subject's medications included captopril and nifedipine since 1998 and acyclovir, which was begun on day 543 for herpes zoster and discontinued on day 603. The event resolved within 15 days following treatment with prednisone. The subject remained on denosumab and did not have a recurrence of the event with subsequent doses.

***Comment:** It is not clear from this narrative, the exact diagnosis of this subject. The CRF does not offer any description of the lesions. As this was also a foreign case, the verbatim terminology could also be interpreted to me that the subject had erythema that was of different shapes. There are many cases where giant urticaria has been misdiagnosed as EM.⁵ What further militates against this diagnosis of EM minor is that there is no evidence for instances where this is due to drugs. In cases of EM 50% of subjects have herpes simplex I or II and other infections including orf and histoplasmosis.⁶ Most cases of EM minor resolve either spontaneously or with treatment of the underlying disease. Finally, for EM major (Stevens-Johnson syndrome) which is a very serious condition, there is no mention of accompanying constitutional symptoms, subjects most often require hospitalization, and the course to resolution is usually 4-6 weeks. Thus, it is not likely that this was a case of erythema multiforme. This is not to say that the subject did not have some type of eruption, probably urticarial, that may or may not have been due to a drug. Denosumab seems unlikely, however, given that the eruption was not consistent with the pk profile of denosumab and subsequent doses of denosumab did not produce the event. In cases of EM major, subsequent doses of the offending drug produces more serious disease.*

The final case that was labeled EM in the narrative is that of a 78 year old female who reported the adverse event on study day 231, approximately 59 days from the previous dose of denosumab. The subject began taking fero-folgamma to treat iron deficiency anemia on day 224. On reviewing the CRF, the verbatim term used to describe the event was "gastritis erythemo exudativa". The subject was reported to have experienced an adverse event of mild erosive duodenitis and mild gastritis. The event was ongoing at the end of the study with unspecified treatment. She completed all scheduled doses of denosumab and her event did not worsen.

***Comment:** It is not clear from the CRF that the subject had a cutaneous event. The verbatim term appears to be referring to a GI problem. Given the description of EM in the previous comment, there is no evidence of erythema multiforme in this case.*

In conclusion, in the bullous conditions, there are only 3 cases in which denosumab as a possible culprit cannot be fully discounted, that of the blisters and itchy red legs, partly due to the fact that the subject could not be rechallenged; the case of worsening pemphigoid, less likely, though, because the patient continued on the drug; and the EM

⁵ Weston, JA, Weston, WL. The Overdiagnosis of Erythema Multiforme. Pediatrics, 1992; 89-802.

⁶ Bologna, Jean, et.al. Dermatology, 2003, pages 313-314.

(probable giant urticaria), in which the eruption occurred outside of the pk profile of the drug and subsequent doses did not elicit the adverse event.

In 2 cases, that of pemphigus and DH (probably linear IgA dermatosis), the etiology was most probably due to another drug known to cause the drug induced variant of each disease. However, although unlikely, completely ruling out denosumab is not possible as further follow-up of the subjects would be required.

Summary

For the 4 cases of toxin skin eruption, the data does not make a convincing case for these eruptions to be secondary to denosumab. These cases were lumped in the overall category of “dermatitis and eczema”. Deleting these cases does not change the overall increased risk for these types of eruptions that do occur on denosumab. However, it is reassuring that none of these are classified as serious adverse events.

For the photosensitivity conditions, all but one of the events has a reasonable alternative etiology for the adverse event other than denosumab and the subjects did well despite continuing the drug product. In only one subject is there a lack of another agent as the cause of the photosensitivity. This makes photosensitivity conditions in the denosumab group no more common than in the placebo group (0.02%) where one subject had a photosensitive allergic reaction (verbatim term: solar allergy).

In the bullous conditions, there are only 3 cases in which denosumab as a possible culprit cannot be fully discounted, that of the blisters and itchy red legs, partly due to the fact that the subject could not be rechallenged; the case of worsening pemphigoid, less likely, though, because the patient continued on the drug; and the EM (probable giant urticaria), in which the eruption occurred outside of the pk profile of the drug and subsequent doses did not elicit the adverse event. In 2 cases, that of pemphigus and DH (probably linear IgA dermatosis), the etiology was most probably due to another drug known to cause the drug induced variant of each disease. However, although unlikely, completely ruling out denosumab is not possible as further follow-up of the subjects would be required. Thus, accounting for these 5 cases and discounting the other 6, the difference in bullous conditions between denosumab and placebo is 0.1% vs. 0.07%.

Finally, it is reassuring that the number of SAEs and discontinuations for cutaneous events between denosumab and placebo were comparable. It is also reassuring that 13 out of the 17 dermatologic cases were rechallenged and either the event did not require or there was no increase in morbidity.

Questions

1. Overall, subjects in the denosumab group were more likely to develop skin and soft tissue related adverse events. There were more bullous conditions, skin rashes, dermatitis and eczema related adverse events in the denosumab group compared to placebo. This medical officer believes that this information should be included in labeling. Do you agree? If so, please share your thoughts on what should be included in the labeling.

Division Response

It is agreed that for those general categories where a statistical significance was found for skin conditions, they should be listed with the general table of adverse events. This would include the category, “dermatitis and eczema” and “rashes, eruptions, and exanthems”, as corroborated by the statistical review. After reviewing all the cases of photosensitivity and bullous conditions, it appears that clear cut cases that implement denosumab are tenuous, at best. However, since there is no way to know for certain, one could mention in the adverse event section that bullous eruptions, including one case of oral pemphigus, one case of worsening of pemphigoid, one event of DH, and one event of EM did occur in the trial. You may want to add that the relationship to denosumab is unclear as some subjects were on concomitant medications and that most subjects with cutaneous events were able to remain on drug with appropriate treatment and that some events spontaneously resolved.

2. There were 4 cases of toxic skin reactions in the denosumab group, while none in placebo. Please help us evaluate these cases. Should this information be included in labeling?

Division Response

See the body of the review for this consult. As stated in the summary, these cases do not, from the data given, support a role for denosumab in the adverse events.

3. Would you advise any post marketing studies to evaluate these adverse events closely, especially in susceptible populations such as nursing home populations, subjects with pre-existing skin conditions, etc?

Division Response

The level of the data that we have thus far does not merit any post marketing studies, at this point. It may also be difficult to have a postmarketing study that would give any useful information, as these are rare events and would require a very large safety database. You may want to consider consulting the division of OSE, to get their opinion on this issue. Hopefully, by addressing what we do know in the label, this will raise the level of awareness of the physician and allow for non-formal postmarketing surveillance.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring MD 20993

Tel 301-796-2110
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Memorandum

DATE: June 23, 2009

FROM: Fred Hyman, D.D.S. M.P.H, Dental Officer, DDDP

THROUGH: John Kelsey, D.D.S., M.B.A., Dental Team Leader, DDDP

THROUGH: Susan Walker, M.D., Division Director, DDDP

cc: Kelisha Turner, Project Manager, DDDP

TO: Celia Peacock, Regulatory Project Manager, DRUP

RE: BLA125320 for Denosumab, Evaluation of Osteonecrosis of the Jaw
Adverse Events
DDDP Consult #1158

Date Requested: June 30, 2009

MATERIAL REVIEWED: DRUP's summary of the BLA, the list of MedDRA Preferred Terms identified by the sponsor, electronic BLA submission.

Review:

Sponsor: Amgen

Drug: Denosumab

Indications: Treatment and prevention of postmenopausal osteoporosis

Purpose of Consult

On December 19, 2008, Amgen submitted BLA 125,320 for review of denosumab, a new monoclonal antibody that has been developed for the treatment and prevention of postmenopausal osteoporosis. Due to the prior association of the serious adverse event osteonecrosis of the jaw (ONJ) with the related bisphosphonate class of drugs to treat osteoporosis, Amgen conducted a rigorous process of examining for ONJ during their clinical trials. The Division of Reproductive and Urologic Products (DRUP), to which this BLA was assigned, is reviewing this submission, and has requested that DDDP provide comments about the manner in which Amgen elicited and evaluated the specific adverse event, ONJ.

Please note that it is not the intent of this consult to provide recommendations for regulatory action of this drug. DDDP is providing comments that reflect the expertise of a clinical reviewer who is familiar with the effect of drugs on oral/dental health. However, since the indication of this drug is to treat osteoporosis, any risk/benefit or other regulatory decisions regarding potential dental adverse events will need to be in accordance with the policies of DRUP. The following specific question was posed in DRUP's consult to DDDP:

“In your assessment, was sponsor's adjudication process adequate (to identify potential cases of ONJ)? Please suggest an appropriate next step if you believe the adjudication process was inadequate to assess the risk of ONJ.”

Summary

There is reason to suspect that denosumab has the potential to be associated with ONJ. As a result, the sponsor correctly included a plan to specifically evaluate subjects during the clinical trials for ONJ signs and symptoms. They accomplished this through formation of an adjudication committee, setting up a priori MedDRA terms which would trigger cases of potential ONJ to be reviewed by the committee. It is the opinion of this reviewer that the list of MedDRA terms chosen by the committee is fairly complete; however, DDDP has identified additional MedDRA search terms that may uncover additional potential cases of ONJ. Therefore, it may be prudent for DRUP to ask the sponsor to add these terms to their search and evaluate any additional subjects that may appear. In addition, the sponsor states that the adjudication committee reviewed all 21 of the cases that their MedDRA search revealed and of those these found none that were positive for meeting the criteria of ONJ. The sponsor should be requested to provide a narrative with any supporting data explaining which of the ONJ criteria ruled out each of the suspected cases.

Review***Impetus for Consult and Scope of Consult Responses***

The proposed biologic that is under review as BLA 125,320 in DRUP is a fully humanized monoclonal antibody to receptor activator for nuclear factor- κ B ligand (RANKL). RANKL is a dominant and essential mediator of osteoclast differentiation and activation. Prevention of the RANK ligand/RANK interaction inhibits osteoclast

formation, function and survival, thereby decreasing bone resorption and increasing bone mass in both cortical and trabecular bone. This is a very similar mechanism to the approved bisphosphonate class of drugs to prevent osteoporosis, which have become increasingly associated with a condition called osteonecrosis of the jaw (ONJ). It is believed that ONJ may be occurring through the same mechanism by which the bisphosphonates help prevent osteoporosis, i.e., by blocking osteoclastic activity.

When osteoclastic activity is blocked, areas of the jaw that may require remodeling, particularly after dental procedures such as extraction or periodontal surgery, may not heal properly. Since some cases of ONJ have been reported without a history of dental surgery, it is also believed that chronic trauma resulting from biting, chewing, or other routine forces being applied to the jaw may result in ONJ as well. Postmarketing surveillance of bisphosphonates has uncovered numerous cases of ONJ, the frequency of which appears to be between 0.1 and 0.01%, but is still under investigation. However, the concern is serious enough that class labeling for ONJ now appears on all bisphosphonate drugs. Therefore, during the development of denosumab, Amgen set up a specific system for its assessment of ONJ association. As a part of that process, Amgen created an adjudication committee, which reviewed every case of potential ONJ; prior to initiation of the trial, this group created a formal definition and formal criteria for ONJ diagnosis. They also identified a complete list of preferred terms from the MedDRA system that have the potential to be signs or symptoms of ONJ.

The remainder of this consult will focus upon the terms that the committee chose for eliciting ONJ outcomes – their appropriateness, completeness and whether it would be beneficial to add other terms to the list that were overlooked by the committee. The DRUP medical reviewer chose some additional potential cases that this consult will evaluate. Finally, in this consult, comments will be made about how to best verify the results of the adjudication committee.

1. Definition of ONJ and MEDDRA terms chosen by the Committee

The sponsor used the following definition of ONJ:

- Area of exposed alveolar or palatal bone where gingival or alveolar mucosa is normally found associated with non-healing bone 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.

Reviewer's Comment: This definition is accurate and consistent with the current literature.

The sponsor identified ONJ-related adverse events to be used for eliciting true cases of ONJ from a pre-defined list of MedDRA preferred terms. These are listed below in Table 1. In addition, each investigator had the authority to refer any clinical trial

adverse event to the adjudication committee, even if it did not match one of the pre-selected terms, as possible ONJ. Of the seven clinical trials completed for this BLA, enrolling a total of 10,930 subjects, 21 cases were identified as possible ONJ and sent to the adjudication committee. Of these 21 potential ONJ cases, the adjudication committee identified none as meeting the specified definition of ONJ. In an attempt to determine if the sponsor used a complete list of MedDRA Preferred Terms (PT's) to capture all potential ONJ cases, their terms are listed below in Table 1, and comments will be made about additional terms that may also have the ability to uncover potential ONJ cases.

Table 1: MedDRA Preferred Terms Identified by Sponsor

- | | |
|--------------------------|---------------------------|
| • Abscess jaw | • Abscess oral |
| • Alveolar osteitis | • Bone debridement |
| • Bone erosion | • Bone fistula |
| • Bone infarction | • Dental fistula |
| • Dental necrosis | • Gingival abscess |
| • Gingival erosion | • Gingival ulceration |
| • Jaw lesion excision | • Jaw operation |
| • Loose tooth | • Maxillofacial operation |
| • Necrosis | • Oral cavity fistula |
| • Oral surgery | • Oroantral fistula |
| • Osteitis | • Osteomyelitis |
| • Osteomyelitis acute | • Osteomyelitis chronic |
| • Osteomyelitis drainage | • Osteonecrosis |
| • Pain in jaw | • Periodontal destruction |
| • Periodontal infection | • Periodontal Operation |
| • Primary sequestrum | • Secondary sequestrum |
| • Sequestrectomy | • Tertiary sequestrum |

Although the above list is fairly complete, DDDP conducted a complete search of MedDRA PT's to uncover other potential terms that may be associated with signs or symptoms of ONJ; the list below contains these additional terms.

MedDRA terms not appearing on sponsor's list:

- | | |
|-------------------------------|---------------------------|
| Biopsy bone abnormal | Jaw fracture |
| Bone abscess | Musculoskeletal pain |
| Bone disorder | Imaging abnormal |
| Bone lesion | Oral infection |
| Bone Pain | Osteomyelitis bacterial |
| Bone scan abnormal | Osteomyelitis fungal |
| Bone swelling | Osteomyelitis viral |
| Buccal mucosal roughening | Osteoradionecrosis |
| Dental alveolar abnormality | Palatal dysplasia |
| Exostosis | Resorption bone increased |
| Face and mouth x-ray abnormal | Septic necrosis |
| Failure of implant | Tooth abscess |
| Impaired healing | Tooth infection |
| Implant expulsion | Ulcer |

Implant site reaction
Jaw disorder

X-ray abnormal

The balance in choosing MedDRA terms for searches hinges upon selecting terms that are likely to pick up relevant events, without also identifying large amounts of irrelevant cases – this decision may often need to be based upon the importance of uncovering the event, and is analogous to the trade-off between sensitivity and specificity. The terms that Amgen chose for their search are reasonable, and most likely a more detailed search will not uncover new ONJ cases. However, that decision is a choice for DRUP to make; if they wish to do so, they may contact the sponsor and ask them to check their database for additional subjects that may be identified with these search terms. It is possible that additional potential cases may result, which can then go back to adjudication for further investigation.

2. *Additional Cases Identified by DRUP Reviewer*

After reviewing the verbatim and dictionary-coded terms for all AE case report forms, the DRUP Medical Officer compiled a list of 21 subjects whom she believed may have been inadvertently omitted from potential ONJ diagnosis by not meeting the pre-selected MedDRA terms. On April 29, DRUP queried the sponsor to send further information about these subjects. DDDP has reviewed the information sent by the sponsor, which includes narratives of the AE, follow-up documentation from the treating dentist, and photographs. None of the events in this list meet the requirements for ONJ diagnosis. This list is below, along with an additional column at the far right, in which the DDDP reviewer has noted the reason that each event is not supportive of an ONJ diagnosis.

Table 2: Additional cases identified by DRUP using verbatim terms and preferred terms

Study	Site	USUBJID	Verbatim term	Dictionary coded term	DDDP Comments
20030216	304	20030216-304023	bone deterioration below bad tooth	Bone disorder	Bone graft successfully placed after routine extraction of non-restorable tooth with local infection
20030216	632	20030216-632004	Tooth implantation in jaw	Dental prosthesis user	Dental implant placed with resultant normal healing
20030216	719	20030216-719015	dental implant	Dental prosthesis user	Routine dental implant
20030216	633	20030216-633273	local infection after removal of tooth	Post procedural infection	Localized infection immediately after extraction
20030216	412	20030216-412461	left maxilla dental abscess	Tooth abscess	Infected tooth, resulting from decay
20030216	731	20030216-731044	dental abscess lower jaw	Tooth abscess	Local periodontal infection
20030216	661	20030216-	Teeth implantations	Dental implantation	Routine dental implant

Study	Site	USUBJID	Verbatim term	Dictionary coded term	DDDP Comments
		661158			
20030216	632	20030216-632286	Tooth implantation	Dental prosthesis user	Routine dental implant for missing tooth
20030216	723	20030216-723055	Tooth implantation	Dental prosthesis user	Routine dental implant
20030216	632	20030216-632141	infection in mouth after removal of teeth	Post procedural infection	Local infection immediately following tooth extraction
20030216	743	20030216-743119	dental abscess right lower jaw	Tooth abscess	Routine extraction with complete healing
20040132	309	20040132-309007	dental implant surgery	Dental implantation	Routine dental extraction followed by implant placement (See next row – two separate reports for same subject; one for extraction and one for implant placement)
20040132	309	20040132-309007	dental surgery	Dental operation	Routine dental extraction, following by implant placement
20040132	307	20040132-307022	bone implant-receding gums-outpatient	Bone graft	Periodontal surgery with bone grafting and complete healing
20040138	188	20040138-188004	dental surgery	Dental operation	Dental implant successfully placed
20040138	214	20040138-214005	dental implant	Dental prosthesis user	Dental implant successfully placed
20040138	639	20040138-639003	infection after molar traction jaw	Postoperative wound infection	Verbatim term should be “extraction”, not “traction.” The post-extraction infection healed, and there was no exposed bone.
20050141	125	20050141-125040	jaw lesion	Bone lesion	Implant placed in edentulous patient for denture retention. Post-placement infection, which resolved completely with no exposed bone.
20050233	29	20010223-029028	dental abscess r upper jaw	Tooth abscess	Endodontically caused infection; resolved after extraction of tooth.
20050234	502	20050234-502003	big trouble chewing (problems chewing with missing teeth)	Mastication disorder	Two individual implants placed without incident.
20060286	1	20060286-001024	post-operative infection in jaw	Post procedural infection	Transient infection during healing of multiple facial fractures - left mandibular ramus and left maxillary sinus. Infection resolved.

3. Cases that reached the Adjudication Committee for Review

The sponsor identified 21 potential ONJ cases, using their pre-specified procedures. The adjudication committee reviewed all 21 of the cases that their MedDRA search revealed and of those these found none that were positive for meeting the criteria of ONJ. The sponsor has submitted a listing of those cases, but not a rationale for eliminating them from an ONJ diagnosis. It is advised that DRUP request a concise narrative with any supporting data explaining which of the ONJ criteria ruled out each of the suspected cases.

Conclusions:

The medical officer in DRUP may wish to request that the sponsor use the additional MedDRA terms to search their database on all subjects to see if any new potential cases appear. In addition, the process by which the adjudication committee ruled out all 21 of the potential cases of ONJ should be clearly provided, including specifically which of the preset criteria for a diagnosis on ONJ were not met.





Aliza Thompson, M.D.
Division of Cardio-Renal Products, HFD-110

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Tel (301) 796-1957

Memorandum

DATE: June 12, 2009

FROM: Aliza Thompson, M.D. 
Division of Cardio-Renal Products, HFD-110

THROUGH: Norman Stockbridge, M.D., Ph.D., Director
Division of Cardio-Renal Drug Products, HFD-110 

TO: Celia Peacock, Regulatory Project Manager, Division of Reproductive and Urologic Products
Vaishali Popat, Medical Officer, Division of Reproductive and Urologic Products

SUBJECT: BLA 125,320

NAME OF DRUG: Denosumab (AMG 162)

FORMULATION: solution for subcutaneous injection

RELATED APPLICATIONS: BLA 125,331, 125,332 and 125,333

APPROVED INDICATIONS: N/A

SPONSOR: Amgen

DOCUMENTS AVAILABLE FOR REVIEW: BLA 125320 (EDR)

DATE CONSULT ASSIGNED: 4.01.2009

DESIRED COMPLETION DATE: 6.15.2009

DATE CONSULT COMPLETED: 6.12.2009

INTRODUCTION

The Division of Reproductive and Urologic Products is reviewing denosumab for the treatment and prevention of osteoporosis in post-menopausal women. Denosumab is also being reviewed by the Division of Biologic Oncology Products for the treatment and prevention of bone loss associated with hormone ablation therapy in patients with prostate cancer and the treatment and prevention of bone loss associated with hormone ablation therapy in patients with breast cancer. The Division of Reproductive and Urologic Products has posed the following questions pertaining to the cardiac safety of denosumab:

1. Do you concur with Amgen's conclusion that cardiovascular adverse events were generally balanced between the denosumab and placebo?

2. Postmenopausal women with osteoporosis are expected to be older women with many cardiovascular risk factors, who may be on this drug (if approved), for several years. Based on the available data, please comment on whether there is evidence to suggest a cardiovascular safety signal. A separate QT consult is being evaluated by IRQT.
3. If the available data are not sufficient to adequately address the cardiovascular safety, what appropriate additional testing should be performed? If further testing is recommended, please comment on whether this testing should be conducted pre or post approval.

BACKGROUND

Denosumab (AMG 162) is a fully humanized monoclonal antibody to receptor activator for nuclear factor- κ B ligand (RANKL), an important mediator of osteoclast differentiation and activation. By preventing the RANKL/RANK interaction, denosumab is thought to inhibit osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass in both cortical and trabecular bone.

During denosumab's development program, the Division of Metabolism and Endocrinology Products expressed concern for the potential for denosumab to cause atherosclerosis.¹ This concern was based on the theoretical concern that inactivation of RANKL by denosumab could result in elevated levels of osteoprotegerin (OPG) via an unopposed feedback mechanism, as well as reports in the published literature regarding a possible association between OPG levels and arterial wall calcification, cardiovascular disease and mortality (Van Campenhout et al, 2009). To aid in the assessment of cardiovascular risk, the sponsor established a committee to adjudicate possible cardiovascular events in 2 phase 3 trials, one in men (Protocol 20040138) and one in postmenopausal women (Protocol 20030216). In protocol 20030216 an analysis of changes in abdominal aortic calcification (as assessed using lateral lumbar spine radiographs) was also conducted in a subset of study subjects.²

PRECLINICAL FINDINGS

Denosumab is not pharmacologically active in mice or rats and as a result, cardiovascular safety assessments were conducted in monkeys. Preclinical evaluations included a 12-month toxicology study in cynomolgus monkey in which doses of 0, 1, 10, and 50 mg/kg were administered subcutaneously at monthly intervals (corresponding human equivalent dose of ~ 0, 20, 200 and 1000 mg). With respect to cardiovascular safety, the following was found in this study:

- Inflammatory cell foci in the heart were seen in denosumab and placebo treated animals.
- One animal in the high dose group that died during the course of the study exhibited low-grade acute focal pericarditis and minimal multifocal myocarditis. Given the small number of animals treated, the presence of similar cardiac histopathologic changes in a control animal (pericarditis and degeneration/necrosis), and the minor grade and focal (not diffuse) nature of the observed case of myocarditis and pericarditis in the treated animal, the clinical significance of this finding is unclear.

In the 12 month study and in a single dose (30 mg/kg) safety study, no substantive effect on QTc or other conduction parameters was noted. Given its size (150 kD), denosumab's potential to prolong the QT interval was not tested using an in vitro system.

¹ Teleconference 9.29.04 and comments to sponsor finalized on 3.16.06.

² A protocol amendment to Study 20030216 dated December 12, 2005 implemented these measures and defined the criteria to be used to identify patients to be included in the analysis of changes in abdominal aortic calcification.

The FDA pharm-tox review has not yet been finalized. In conversations with the reviewer, she noted that the small number of animals included in the aforementioned 12-month study limits the conclusions that can be drawn regarding denosumab's cardiovascular safety.

GENERAL OVERVIEW OF TRIALS

Protocols 20030216 and 20040138 were international, multicenter, randomized, double-blind, placebo-controlled studies; an overview of their primary objectives, key entry criteria, study duration and sample size is provided in Table 1 below. With respect to entry criteria pertaining to cardiovascular risk, study 20040138 excluded patients with uncontrolled hypertension, unstable angina, heart failure (not otherwise defined) or myocardial infarction within 6 months prior to randomization. Entry criteria for these studies did not otherwise include or exclude subjects based on cardiovascular risk factors.

Table 1. Overview of trials	
Protocol 20030216	
Primary objective	to determine whether denosumab could reduce the number of postmenopausal osteoporotic women with new vertebral fractures as compared with control (placebo plus vitamin D and calcium)
Main eligibility criteria	postmenopausal women with osteoporosis (BMD T-score < -2.5 at either the lumbar spine or the total hip, or at both locations, but ≥ -4.0 at both locations), ambulatory, in general good health, not receiving medications that affect bone metabolism, and free from any underlying conditions, other than osteoporosis, that may result in abnormal bone metabolism eligible and consenting subjects needed a modified RUTH Score ≥ 4 to participate in the sub-study on aortic calcification
Sample size	3902 were randomized to denosumab and 3906 to placebo
Study duration	subjects were treated for 30 months with an additional 6 months of follow up
Protocol 20040138	
Primary objective	to determine the treatment effect of denosumab compared with placebo on lumbar spine bone mineral density at month 24 in men with nonmetastatic prostate cancer undergoing androgen deprivation therapy
Main eligibility criteria	men ≥ 70 years of age with histologically confirmed prostate cancer, or men < 70 years of age with histologically confirmed prostate cancer and a history of osteoporotic fracture or BMD T-score at the lumbar spine, total hip, or femoral neck < -1.0 . Study subjects also had to be status post bilateral orchiectomy or initiated on androgen deprivation therapy (ADT) with gonadotropin releasing hormone agonists and expected to continue on with ADT for at least 12 months
Sample size	734 were randomized to denosumab and 734 to placebo
Study duration	36 months of treatment

As previously noted, these studies contained a prospectively defined plan for the collection and analyses of information pertaining to cardiovascular risk. This plan included a blinded external committee for the adjudication of cardiovascular events (both studies) and the assessment of changes in abdominal aortic calcification on lateral lumbar spine radiographs in a subset of study participants in Protocol 20030216. Key attributes of the cardiovascular adjudication process are shown in Table 2; an overview of the process for assessing changes in abdominal aortic

calcification is shown in Table 3. Protocol 20030216 also contained a bone marker substudy in which osteoprotegerin levels were measured.

Table 2. Key attributes of the adjudication process for potential cardiovascular events	
Committee members	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 (see sponsor's Manual of Operations)
Task of committee	<p>Categorize serious adverse events into one of the following categories, based on the definition of these events in the Manual of Operation</p> <ul style="list-style-type: none"> • acute coronary syndrome/revascularization • congestive heart failure • stroke/transient ischemic attacks • cardiac arrhythmias • and other vascular disorders/revascularization <p>Categorize deaths as cardiovascular or non-cardiovascular; cardiovascular deaths included sudden death, HF death, fatal stroke/other vascular death/arrhythmia</p>
Information given to the committee	SAE report, general event data collection form which contained category-specific site investigator narratives, source documents and an oncologist review form if completed†
Planned analysis	Time to event analyses were planned for each adjudicated cardiovascular endpoint. The Cox proportional hazards model was to include as covariates treatment and age strata (not otherwise defined).

[Source: Denosumab Event Adjudication Manual of Operations dated November 15, 2007]

†This form was to be completed by the oncologist reviewer upon the request of the cardiology reviewers for subjects enrolled in study 20040138 and was to indicate whether or not the oncologist felt the death was cancer-related

Reviewer's comment: The list of MedDRA preferred terms was likely comprehensive enough to capture serious adverse events of interest for adjudication. With respect to CV events contained in the adverse event database, the sponsor's mapping of investigator's terms to MedDRA terms seemed to be, as a whole, appropriate.

Table 3. Assessment of changes in abdominal aortic calcification in Protocol 20030216	
Population in which assessments made	Subjects deemed at higher risk of cardiovascular events based on a modified RUTH score ≥ 4 (see appendix)
Evaluation Team	Trained readers in a central reading facility who were blinded to treatment assignment
Process for evaluation	<p>Grading of lesions was prespecified using a previously described method*:</p> <p>0: no aortic calcific deposits, 1: small, scattered calcific deposits filling less than 1/3 of the longitudinal wall of the aorta, 2: 1/3 or more, but less than 2/3 of the longitudinal wall of the aorta calcified, 3: 2/3 or more of the longitudinal wall of the aorta calcified.</p> <p>To derive the total aortic calcification severity score, the scores (0 to 3) of the 8 individual anterior and posterior aortic segments from L1 to L4 were summed.</p>
Planned analysis	"absolute change in total aortic calcification (AC) severity score between baseline and month 36. Additional analyses will be conducted to evaluate absolute change from baseline in AC severity score at 12 and 24 months."

[Source: Protocol 20030216 dated October 25, 2006]

* Tanko et al, 2005; Wilson et al, 2001; Kauppila et al, 1997.

Reviewer's comment: According to the referenced paper by Wilson et al, 2001, in comparison with subjects without abdominal aortic calcific deposits (as defined by this technique), subjects with abdominal aortic calcific deposits have a greater risk of CV events (defined as transient ischemic attack, stroke, stroke death, congestive heart failure, angina pectoris, unstable angina pectoris, myocardial infarction, and coronary disease death) over ~20 years of follow up. For subjects with a baseline score between 5 and 22 (the highest tertile analyzed), the RR for CV events was 1.7 (95% CI, 1.4 to 2.1). None of the referenced papers speak to the risk associated with changes in aortic calcification score over time.

RESULTS:

Demographics and disposition of study subjects in studies 20030216 and 20040138

Baseline cardiovascular risk factors (see tables below), rates of discontinuation and reasons for discontinuation were similar in the 2 treatment arms in studies 20030216 and 20040138. In the subset of study subjects in which changes in aortic calcifications scores were assessed (study 20030216), baseline cardiovascular risk factors, rates of study discontinuation and reasons for study discontinuation were also similar in the 2 treatment arms.

Table 4. Sponsor's table of baseline cardiovascular risk factors in study 20030216

	Placebo (N = 3906) n (%)	Denosumab 60 mg Q5M (N = 3902) n (%)	All (N = 7808) n (%)
Cardiovascular risk level^a			
Low	2757 (70.6)	2676 (68.6)	5433 (69.6)
High	1149 (29.4)	1226 (31.4)	2375 (30.4)
Risk factor for cardiovascular events			
Myocardial infarction	106 (2.7)	132 (3.4)	238 (3.0)
Percutaneous coronary intervention	30 (0.8)	42 (1.1)	72 (0.9)
Coronary artery bypass graft surgery	28 (0.7)	44 (1.1)	72 (0.9)
Diabetes mellitus ^b	293 (7.5)	303 (7.8)	596 (7.6)
Age ≥ 70 years	2878 (73.7)	2872 (73.6)	5750 (73.6)
Age 65 to 69 years	820 (21.0)	824 (21.1)	1644 (21.1)
Former / current smoker	1105 (28.3)	1120 (28.7)	2225 (28.5)
Hypertension	1957 (50.1)	1980 (50.7)	3937 (50.4)
High cholesterol	1137 (29.1)	1155 (29.6)	2292 (29.4)

[Source: Table 14-2.6.1, Clinical Study Report 20030216, page 449; cardiovascular risk score based on modified Ruth criteria; b: excludes gestational diabetes mellitis]

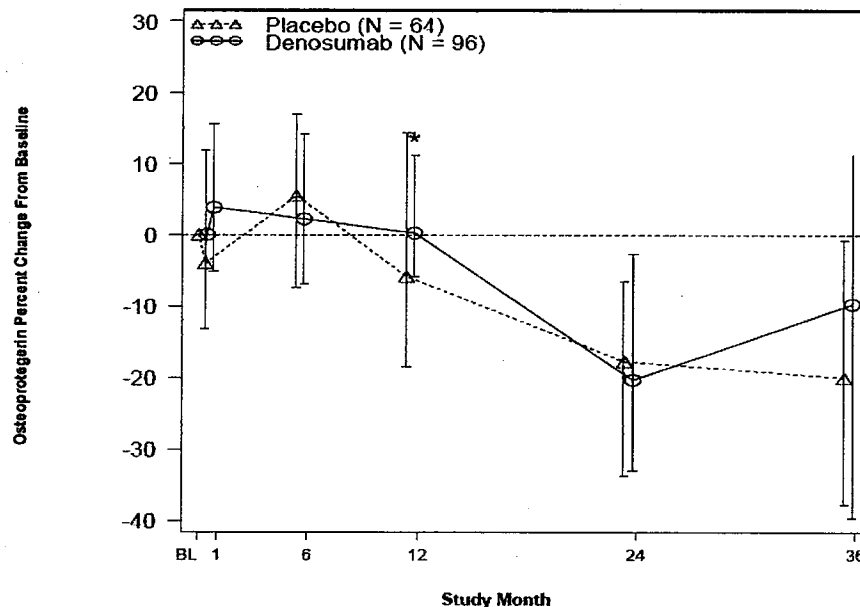
Table 5. Sponsor's table of baseline cardiovascular risk factors in study 20040138

	Placebo (N = 734) n (%)	Denosumab 60 mg Q6M (N = 734) n (%)	All (N = 1468) n (%)
Cardiovascular risk level ^a			
Low	325 (44.3)	327 (44.6)	652 (44.4)
High	409 (55.7)	407 (55.4)	816 (55.6)
Risk factor for cardiovascular events			
Myocardial infarction	74 (10.1)	80 (10.9)	154 (10.5)
Percutaneous coronary intervention	30 (4.1)	26 (3.5)	56 (3.8)
Coronary artery bypass graft surgery	48 (6.5)	62 (8.4)	110 (7.5)
Diabetes mellitus ^b	132 (18.0)	137 (18.7)	269 (18.3)
Age ≥ 70 years	611 (83.2)	610 (83.1)	1221 (83.2)
Age 65 to 69 years	68 (9.3)	75 (10.2)	143 (9.7)
Former / current smoker	418 (56.9)	446 (60.8)	864 (58.9)
Hypertension	448 (61.0)	428 (58.3)	876 (59.7)
High cholesterol ^c	259 (35.3)	272 (37.1)	531 (36.2)

[Source: Sponsor's table, Clinical Study Report 20040138, page 287; cardiovascular risk score based on modified Ruth criteria; b: includes type 1 and type 2 diabetes]

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 substudy of protocol 20030216 (N=64 placebo and N=96 denosumab). As shown in the sponsor's figure below, there was no clear increase in osteoprotegerin levels in denosumab compared to placebo-treated subjects.



N = Number of randomized subjects enrolled in the bone marker substudy
 * statistically significant (p-value ≤ 0.05); ** statistically significant (p-value ≤ 0.025);
 *** statistically significant (p-value ≤ 0.01)

Figure 1. Percent change from baseline and median and inter-quartile ranges by treatment arm and study visit for osteoprotegerin

[Source: Figure 14-9.1.5, Clinical Study Report 20030216, page 2665]

Reviewer's comment: In interpreting these findings, consideration should be given to the sensitivity of the assay used, what would be considered a minimally important difference in osteoprotegerin levels, as well as the power of the study to detect such a difference. Consideration should also be given as to whether or not changes in osteoprotegerin levels are in fact a good marker of risk, given the animal studies which suggest that osteoprotegerin may be protective against vascular calcification and the current uncertainty as to whether elevated levels in humans play a causative role in adverse cardiovascular outcomes or simply represent a compensatory response to disease (Collin-Osdoby, 2004; Montecucco et al, 2007; Van Campenhout et al, 2009).

Findings pertaining to the cardiovascular adjudication of events

In the safety subset of subjects in studies 20030216 and 20040138 (defined as subjects receiving at least one dose of investigational product), 808 events occurring in denosumab and 729 events occurring in placebo-treated subjects were submitted for adjudication. As shown in the table below, the proportion of events adjudicated as being CV-related was similar in the 2 treatment arms. Analysis of data from all enrolled subjects, regardless of whether or not they received the investigational product, produced comparable findings.

Table 6. Number of events reviewed and number of events adjudicated as CV-related in the safety subset		
	Placebo	Denosumab
Study 20030216		
Number of events reviewed by the Adjudication Committee	526	572
Number of events (%) adjudicated as CV-related	233 (44.3%)	247 (43.2%)
Study 20040138		
Number of events reviewed by the Adjudication Committee	203	236
Number of events (%) adjudicated as CV-related	105 (51.7%)	118 (50.0%)

[Source: This reviewer's analysis. Assigns subjects by treatment received (one subject with an adjudicated event was assigned to placebo but received denosumab at a follow-up visit)]

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 in both studies (see tables below).

Table 7. Incidence and hazard ratio for any adjudicated CV SAE, CV death, acute coronary syndrome, stroke/transient ischemic attack, congestive heart failure and other vascular disorders in study 20030216

	Crude Incidence at 36 Months n (%)	KM Estimate of Incidence at 36 Months (%)	Hazard Ratio ^a	
			Estimate	(95% CI)
Any adjudicated positive CV SAE				
Placebo (N = 3876)	178 (4.6)	(5.0)		
Denosumab 60 mg Q6M (N = 3886)	186 (4.8)	(5.0)	1.02	(0.83, 1.25)
CV death				
Placebo (N = 3876)	31 (0.8)	(0.9)		
Denosumab 60 mg Q6M (N = 3886)	23 (0.6)	(0.6)	0.72	(0.42, 1.24)
Acute coronary syndrome				
Placebo (N = 3876)	39 (1.0)	(1.1)		
Denosumab 60 mg Q6M (N = 3886)	47 (1.2)	(1.3)	1.17	(0.77, 1.79)
Stroke / transient ischemic attack				
Placebo (N = 3876)	54 (1.4)	(1.5)		
Denosumab 60 mg Q6M (N = 3886)	56 (1.4)	(1.5)	1.02	(0.70, 1.48)
Congestive heart failure				
Placebo (N = 3876)	22 (0.6)	(0.6)		
Denosumab 60 mg Q6M (N = 3886)	27 (0.7)	(0.7)	1.19	(0.68, 2.09)
Other vascular event				
Placebo (N = 3876)	30 (0.8)	(0.8)		
Denosumab 60 mg Q6M (N = 3886)	31 (0.8)	(0.8)	1.00	(0.60, 1.65)
Arrhythmia				
Placebo (N = 3876)	45 (1.2)	(1.2)		
Denosumab 60 mg Q6M (N = 3886)	52 (1.3)	(1.4)	1.13	(0.76, 1.69)

[Source: Table 14-6.6.2, Clinical Study Report 20030216, page 903. The crude incidence of these events was confirmed by this reviewer]

Table 8. Incidence and hazard ratio for any adjudicated CV SAE, CV death, acute coronary syndrome, stroke/transient ischemic attack, congestive heart failure and other vascular disorders in study 20040138

	Crude Incidence at 36 Months n (%)	KM Estimate of Incidence at 36 Months (%)	Hazard Ratio ^a	
			Estimate	(95% CI)
Any adjudicated positive CV SAE				
Placebo (N = 725)	80 (11.0)	(12.8)		
Denosumab 60 mg Q6M (N = 731)	80 (10.9)	(12.4)	0.97	(0.71, 1.32)
CV death				
Placebo (N = 725)	21 (2.9)	(3.3)		
Denosumab 60 mg Q6M (N = 731)	19 (2.6)	(3.0)	0.88	(0.48, 1.65)
Acute coronary syndrome				
Placebo (N = 725)	27 (3.7)	(4.4)		
Denosumab 60 mg Q6M (N = 731)	18 (2.5)	(2.7)	0.64	(0.35, 1.16)
Stroke / transient ischemic attack				
Placebo (N = 725)	17 (2.3)	(2.7)		
Denosumab 60 mg Q6M (N = 731)	21 (2.9)	(3.4)	1.21	(0.64, 2.29)
Congestive heart failure				
Placebo (N = 725)	11 (1.5)	(1.7)		
Denosumab 60 mg Q6M (N = 731)	8 (1.1)	(1.3)	0.70	(0.28, 1.74)
Other vascular event				
Placebo (N = 725)	12 (1.7)	(2.0)		
Denosumab 60 mg Q6M (N = 731)	18 (2.5)	(2.8)	1.44	(0.69, 2.99)
Arrhythmia				
Placebo (N = 725)	15 (2.1)	(2.4)		
Denosumab 60 mg Q6M (N = 731)	19 (2.6)	(3.0)	1.23	(0.62, 2.41)

[Source: Table 11-6, Clinical Study Report 20040138, page 196. The crude incidence of these events was confirmed by this reviewer.]

The point estimate for the hazard ratio for CV death was <1.0 in both studies, with a 95% upper bound to the hazard ratio of 1.2 in study 20030216 and 1.7 in study 20040138. The point estimate for the hazard ratio for any adjudicated positive cardiovascular SAE was ~1.0 in both studies with a 95% upper bound of the hazard ratio of ~1.3.

The incidence of adjudicated CV SAEs in a subset of study subjects at higher risk of CV events (based on a modified RUTH Score ≥ 4) is shown in the table below. The incidence of adjudicated acute coronary syndrome, stroke/transient ischemic attack, congestive heart failure and other vascular disorders appears to be similar in the 2 treatment arms. Of note, the slightly greater number of adjudicated strokes/transient ischemic attacks in the subset of “high risk” denosumab-treated subjects in protocol 20030216, is counterbalanced by a greater number of adjudicated strokes/transient ischemic attacks in placebo-treated subjects in the “low risk” subset in this study, suggesting that this observed imbalance represents a chance finding.

Table 9. Incidence of adjudicated CV SAEs in a subset of study subjects at high risk of CV events				
Type of SAE	Protocol 20040138		Protocol 20030216	
	Placebo N=405	Denosumab N=404	Placebo N=1142	Denosumab N=1221
Acute Coronary Syndrome	14 (3.5%)	15 (3.7%)	21 (1.8%)	25 (2.0%)
Stroke/Transient Ischemic Attack	14 (3.5%)	14 (3.5%)	16 (1.4%)	31 (2.5%)
Congestive Heart Failure	10 (2.5%)	6 (1.5%)	12 (1.1%)	16 (1.3%)
Other Vascular Event	6 (1.5%)	10 (2.5%)	17 (1.5%)	17 (1.4%)
Arrhythmia	12 (3.0%)	15 (3.7%)	23 (2.0%)	21 (1.7%)

[Source: This reviewer's analysis. "High risk" defined as a modified RUTH Score ≥ 4]

Kaplan-Meier curves of time to first adjudicated CV event, shown below, do not suggest worsening CV outcomes over time in denosumab treated subjects in study 20040138 or study 20030216.

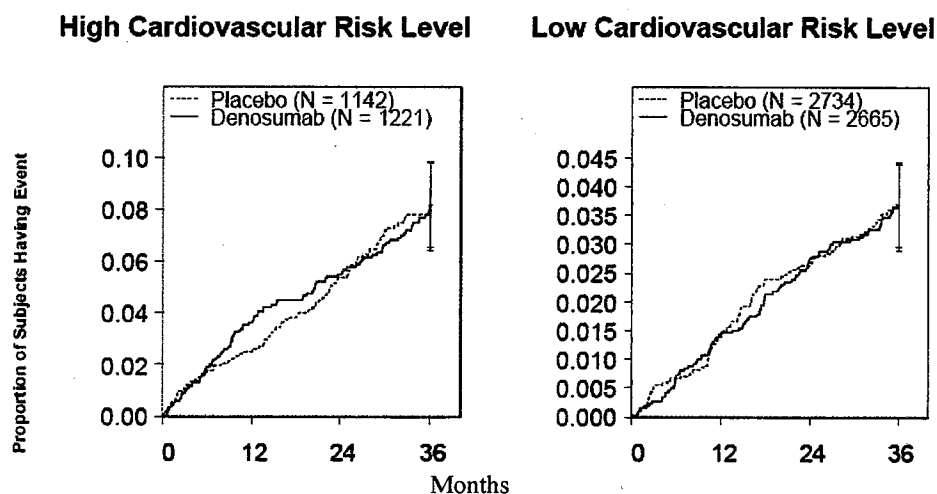


Figure 2. Kaplan-Meier Curves for time to first adjudicated positive cardiovascular serious adverse event in subjects with high and low cardiovascular risk (based on modified RUTH criteria) in study 20030216.

[Source: Figure 14-4.1.11, Clinical Study Report 20030216, page 2539]

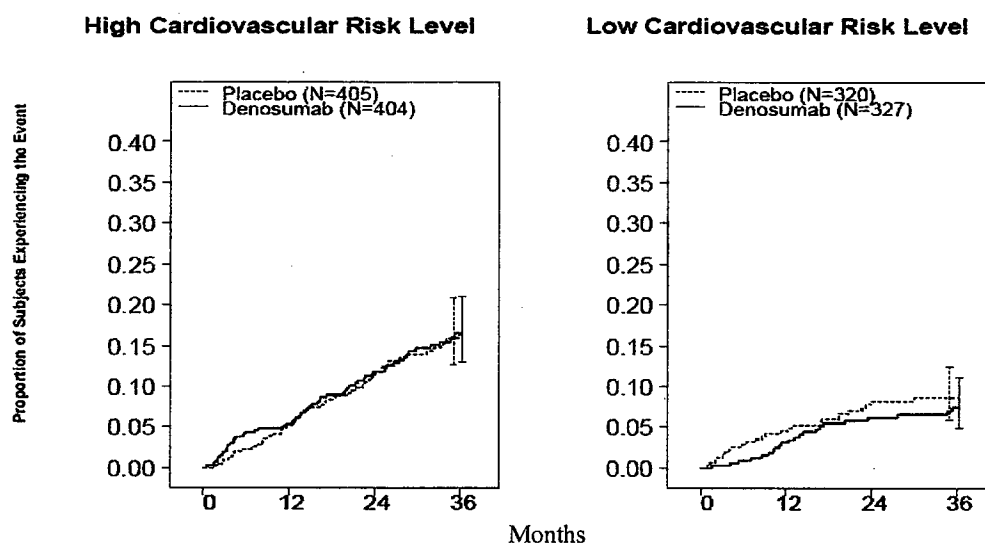


Figure 3. Kaplan-Meier Curves for time to first adjudicated positive cardiovascular serious adverse event in subjects with high and low cardiovascular risk (based on modified RUTH criteria) in study 20040138.

[Source: Figure 14-4.12, Clinical Study Report 20040138, page 1537]

Compared to the other categories of adjudicated events, the “arrhythmia” and “other vascular” events adjudication categories were perhaps broader categories of events. As part of the adjudication process, “other vascular” disorders were sub-classified as peripheral vascular disease events (defined as a vascular event occurring in an artery in the periphery [causing signs or symptoms in an extremity]), aortic disease, deep venous thrombosis and pulmonary embolism. As shown in the table below, the incidence of any individual type of “other vascular” event was low. Given the multiple comparisons being conducted, it is likely that any slight imbalance between treatment arms represents a chance finding. In analyses of data from the 2 studies, the incidence of different subtypes of arrhythmias including adjudicated atrial fibrillation or flutter, heart block, ventricular arrhythmias and other supraventricular arrhythmias was similar in the two treatment arms (results not shown).

Table 10. Incidence of adjudicated “other vascular” events				
	Protocol 20040138		Protocol 20030216	
Event	Placebo N=725	Denosumab N=731	Placebo N=3876	Denosumab N=3886
Peripheral vascular disease	1 (0.1%)	4 (0.5%)	5 (0.1%)	12 (0.3%)
Pulmonary embolism	1 (0.1%)	7 (1.0%)	11 (0.3%)	9 (0.2%)
Deep vein thrombosis	4 (0.6%)	4 (0.5%)	7 (0.2%)	8 (0.2%)
Aortic disease event	5 (0.7%)	4 (0.5%)	5 (0.1%)	0

[Source: This reviewer’s analysis. Note, some subjects had more than one type of “other vascular” event.]

Findings pertaining to abdominal aortic calcification

Approximately 23% of subjects had baseline aortic calcification scores of 0. The distribution of baseline scores was similar in the two treatment arm and, as shown in the figure below, most patients had lower baseline aortic calcification scores.

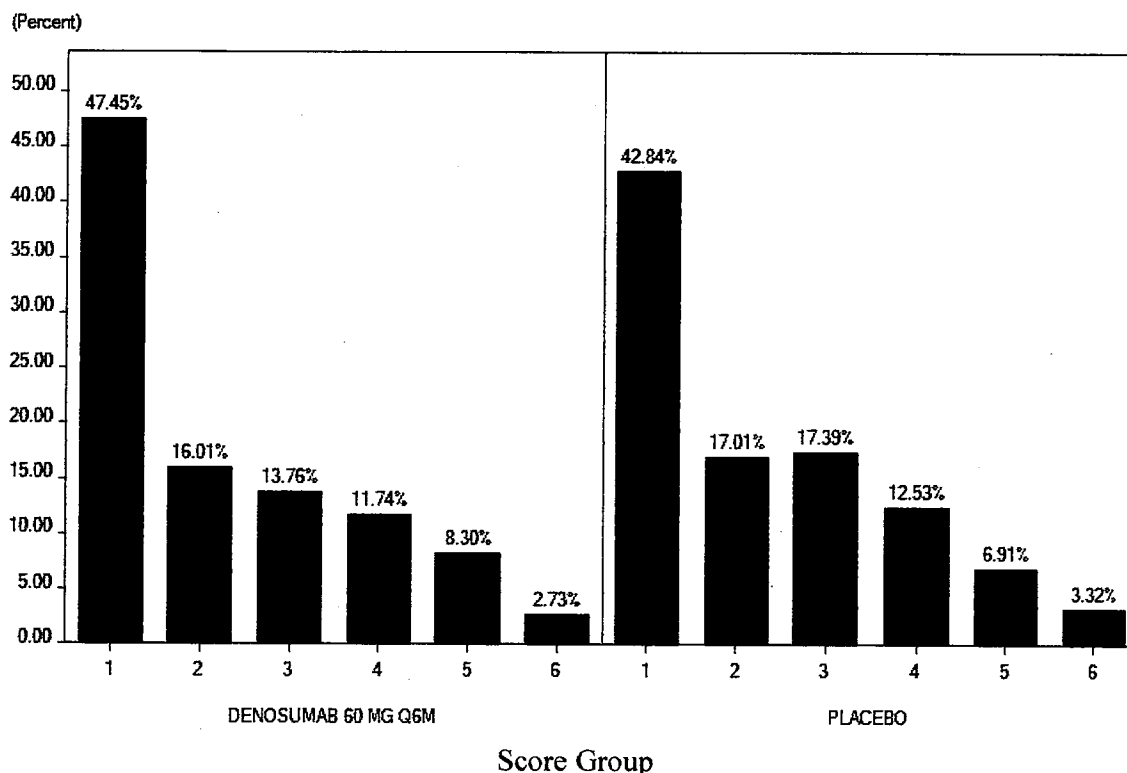


Figure 4. Distribution of baseline aortic calcification scores by treatment arm

Score groups: 1= score 0-4; 2=score 5-8; 3=score 9-12; 4=score 13-16; 5=score 17-20; 6=score 21-24.

[Source: This reviewer's analysis. The analysis was based on the safety subset (defined as subjects receiving at least one dose of investigational product).]

Mean changes in aortic calcification scores were similar in the 2 treatment arms (see Table 11). At the 36 month time point, mean changes in score were small in both treatment arms. Even in the tertile with the highest baseline level of aortic calcification (score of 10-24), mean changes in score from baseline to 36 months were less than 0.4.

Table 11. Change from baseline in aortic calcification score in subset of subjects in study 20030216 deemed to be at higher risk

	n	Mean	SD	Min	Q1	Median	Q3	Max
Month 12								
Placebo (N = 1142)	684	0.1	0.6	0	0.0	0.0	0.0	12
Denosumab 60 mg Q6M (N = 1221)	713	0.1	0.4	0	0.0	0.0	0.0	5
Month 24								
Placebo (N = 1142)	583	0.2	0.7	0	0.0	0.0	0.0	12
Denosumab 60 mg Q6M (N = 1221)	648	0.2	0.8	0	0.0	0.0	0.0	12
Month 36								
Placebo (N = 1142)	501	0.4	1.0	0	0.0	0.0	0.0	12
Denosumab 60 mg Q6M (N = 1221)	544	0.4	1.1	0	0.0	0.0	0.0	12

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N = Number of randomized subjects who received ≥ 1 dose of investigational product and belonged to the cardiovascular high risk subset

n = Number of subjects with observed data at all 8 abdominal aortic segments at baseline and at the time point of interest

[Source: Table 37, Summary of Clinical Safety, page 154]

Reviewer's comment: No difference was seen between treatment arms in aortic calcification scores. This could be because denosumab has no effect on aortic calcification. It is also possible that differences between the treatment groups were obscured by the limited sensitivity of the assay used to assess for changes in calcification (radiology readings of lateral lumbar spine radiographs), the relatively short period of follow-up and the large amount of missing data at any given time point.

Other events of interest

Reported serious adverse events of hypertension and hypertensive crisis were uncommon and were not seen at a higher incidence in denosumab compared to placebo-treated subjects in either study (see table below). According to the sponsor's analysis, mean changes from baseline in systolic and diastolic blood pressure were similar in the 2 treatment arms over time.³

Table 12. Reported serious adverse events of hypertension and hypertensive crisis by treatment arm in studies 20030216 and 20040138		
	Placebo	Denosumab
Study 20030216	N=3876	N=3886
Hypertension	22 (<1.0%)	20 (<1.0%)
Hypertensive Crisis	7 (<1.0%)	3 (<1.0%)
Study 20040138	N=725	N=731
Hypertension	5 (<1.0%)	4 (<1.0%)
Hypertensive Crisis	1 (<1.0%)	0

[Source: This reviewer's analysis]

According to the sponsor's analyses for studies 20030216 and 20040138, the incidence of adverse events including diabetes mellitus/diabetes mellitus uncontrolled/inadequate control, hyperglycemia, hypercholesterolemia, and hyperlipidemia were also similar in the 2 treatment arms.⁴ No serious adverse events of myocarditis or pericarditis were reported for either study (reviewer's analysis). According to the QT-IRT review, the sponsor's ECG evaluations appear adequate and there are no large effects on the QT interval due to denosumab.

³ Source=Clinical Study Report 20030216 (tables 14-8.1.5 and 14-8.1.6, pages 1787-1790) and 20040138 (tables 14-8.1.2 and 14-8.2.2, pages 1464, 1465, 1468, and 1469).

⁴ Source=Clinical Study Report 20030216 (table 14-6.13, pages 1301-1305) and 20040138 (tables 14-6.2.1, pages 594 and 595).

RESPONSES TO CONSULT QUESTIONS

1. Do you concur with Amgen's conclusion that cardiovascular adverse events were generally balanced between the denosumab and placebo?

Response: Yes. Analyses of adjudicated cardiovascular events in studies 20040138 and 20030216 suggest a similar incidence of adverse cardiovascular events in the two treatments arms. Importantly, both the approach to identifying these events for adjudication and the process by which these events were adjudicated seem reasonable.

2. Postmenopausal women with osteoporosis are expected to be older women with many cardiovascular risk factors, who may be on this drug (if approved), for several years. Based on the available data, please comment on whether there is evidence to suggest a cardiovascular safety signal. A separate QT consult is being evaluated by IRQT.

Response: Based on the available data, no clear cardiovascular safety signal is seen. As noted above, analyses of adjudicated cardiovascular events did not suggest harm in the populations studied. The point estimate for the hazard ratio for any adjudicated positive cardiovascular serious adverse event was ~1.0 in both studies with a 95% upper bound of the hazard ratio of ~1.3. No difference was seen between treatment arms in aortic calcification scores as assessed by lateral lumbar spine radiographs. Denosumab-induced elevations in osteoprotegerin levels, the hypothesized mechanism by which denosumab might increase cardiovascular risk, were not observed. Consistent with these clinical findings, the preclinical data also did not provide clear evidence of increased cardiovascular risk, at least according to the mechanism that provoked initial concern.

It should be acknowledged that there are limitations to assessing cardiovascular risk based on changes in osteoprotegerin levels and aortic calcification scores. In interpreting the findings pertaining to denosumab's effects on osteoprotegerin levels, consideration should be given to the sensitivity of the assay used, what would be considered a minimally important difference in osteoprotegerin levels, as well as the power of the study to detect such a difference. Consideration should also be given as to whether or not changes in osteoprotegerin levels are in fact a good marker of risk, given the animal studies which suggest that osteoprotegerin may be protective against vascular calcification and the current uncertainty as to whether elevated levels in humans play a causative role in adverse cardiovascular outcomes or simply represent a compensatory response to disease. Similarly, in interpreting the effects of denosumab on aortic calcification, it is important to keep in mind that differences between the treatment groups may have been obscured by the limited sensitivity of the assay used to assess for changes in calcification (radiology readings of lateral lumbar spine radiographs), the relatively short period of follow-up and the large amount of missing data at any given time point. That being said, the safety data, as a whole, hang together and in their totality do not suggest a cardiovascular safety signal.

3. If the available data are not sufficient to adequately address the cardiovascular safety, what appropriate additional testing should be performed? If further testing is recommended, please comment on whether this testing should be conducted pre or post approval.

Response: No clear cardiovascular signal is seen in the populations studied. Based on the available data, no additional cardiovascular safety studies are recommended prior to approval (or post) for use of denosumab in patient populations similar to those studied.

References

1. Collin-Osdoby P. Regulation of Vascular Calcification by Osteoclast Regulatory Factors RANKL and Osteoprotegerin. *Circulation Research*. 2004; 95: 1046-1057.
2. Kauppila LI, Polak JF, Cupples LA, et al. New indices to classify location, severity and progression of calcific lesions in the abdominal aorta: a 25-year follow-up study. *Atherosclerosis*. 1997;132:245-250.
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4. Tanko LB, Qin G, Alexandersen P, et al. Effective doses of ibandronate do not influence the 3-year progression of aortic calcification in elderly osteoporotic women. *Osteoporosis International*. 2005;16:184-190.
5. Van Campenhout A, Golledge J. Osteoprotegerin, vascular calcification and atherosclerosis. *Atherosclerosis*. 2009; 204: 321-329.
6. Wilson PW, Kauppila LI, O'Donnell CJ, et al. Abdominal aortic calcific deposits are an important predictor of vascular morbidity and mortality. *Circulation*. 2001;103:1529- 1534.

Appendix

Modified RUTH Criteria for Defining High-risk Population for Cardiovascular Events	
Cardiovascular Risk Factor	Points
Prior myocardial infarction, percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) surgery	4
Diabetes mellitus	3
Age ≥ 70 years	2
Age 65 to 69 years	1
Former/current smoker ^a	1
Hypertension ^a	1
High cholesterol ^a	1

[Source: Summary of Clinical Safety; A score ≥ 4 was used to define a population at high risk.]

^a An extra point is added if all 3 criteria [former/current smoker, hypertension, and high cholesterol] are met [i.e., total of 4 points].

Report of Medical Officer Consultation

Requesting Division: Division of Reproductive and Urologic Products (DRUP)

Contact: Celia Peacock, MPH, RD
Regulatory Project Manager
DRUP
Phone: (301) 796-4154

Date Received by DAIOP: March 31, 2009

Date Given to MO: March 31, 2009

Date of MO's Review: June 8, 2009, revised 6/10/09 *RLW*

Sponsoring Firm: Amgen

Device/Drug Components: Denosumab (BLAs 125320, -331, -332, -333) is a fully human monoclonal antibody that is a receptor activator of nuclear factor kappa B (RANK) ligand (RANKL) that inhibits human RANKL (huRANKL).

Trade name: unknown

Indications: Treatment and prevention of postmenopausal osteoporosis (PMO) and the treatment and prevention of bone loss in patients undergoing hormone ablation (HALT) for prostate or breast cancer.

Re: Assessment of possible increased risk of infections among patients who received denosumab versus comparators in the premarketing clinical studies.

I. Background

The Sponsor, Amgen, notes that denosumab is a fully human monoclonal antibody that is a receptor activator of nuclear factor kappa B (RANK) ligand (RANKL) that inhibits human RANKL (huRANKL) with a mechanism of action similar to the endogenous RANKL inhibitor, osteoprotegerin (OPG). It is being developed by Amgen for the treatment and prevention of postmenopausal osteoporosis (PMO) and the treatment and prevention of bone loss in patients undergoing hormone ablation (HALT) for prostate or breast cancer. Amgen has submitted the following four pending BLAs.

BLA 125,320: Treatment of osteoporosis in postmenopausal women

BLA 125,331: Prevention of osteoporosis in postmenopausal women

BLA 125,332: Treatment and prevention of bone loss associated with hormone ablation therapy with breast cancer

BLA 125,333: Treatment and prevention of bone loss associated with hormone ablation therapy in patients with prostate cancer

RANKL is expressed on activated T and B cells and in the lymph nodes. There are reports in the literature about the effect of RANKL inhibition on the immune system. It is biologically plausible that denosumab, as a RANKL inhibitor, could increase the incidence of infections.

Based on preliminary review of the Phase 3 clinical data for the postmenopausal osteoporosis indications, DRUP is concerned about the greater number of infections in denosumab subjects as compared to comparator subjects. Specifically, there were a greater number of serious infections (cellulitis, pneumonia, urinary tract infection, appendicitis, and diverticulitis) in subjects receiving active treatment in Study 20010223 (Phase 2 dose ranging study) and Study 20040132. In addition, three subjects in two Phase 1 studies were hospitalized for pneumonia ranging from 74 to 242 days post denosumab.

Therefore, DRUP requests that DAIOP review specific Phase 3 clinical data for an opinion on the possible infection risk associated with denosumab use. DRUP has also posed the following questions to DAIOP.

II. DRUP's Questions and DAIOP's Responses [in bold print]

1. Do you concur with Amgen's conclusion that infections were generally balanced between the denosumab and placebo?

DAIOP response: Based upon review of the materials provided, it appears that patients on denosumab may have had infections somewhat more frequently, had more severe cellulitis, and possibly more serious abdominal and lower respiratory tract infections. However, no specific signal for infections due to a specific opportunistic pathogen was identified, e.g., *Mycobacterium tuberculosis* or *Pneumocystis jiroveci* (previously *carinii*) pneumonia.

From a theoretical perspective, an adult with a fully functioning immune system may not be at increased risk of infection because of redundancies in immune signaling; however, individuals with underlying defects in the immune system (e.g., elderly patients with waning immunologic function, those on concomitant immunosuppressive medications, patients with uncontrolled diabetes or AIDS, etc.) who also take denosumab may be at increased risk for infection.

Because denosumab has the potential to interact with multiple layers and processes within the immune system, DAIOP recommends that, if denosumab is approved, Amgen should continue collecting information on all infection-related adverse events for the indefinite future during the postmarketing period. This may take the form of a postmarketing requirement. In addition, DAIOP recommends that the product label include language that denosumab may cause serious infections that are not limited to specific pathogens. (Please see DAIOP's response to Question 6

for additional details related to possible labeling regarding risk of infection.)
Finally, DRUP may consider consulting an immunologist to provide further clarity on the potential mechanisms of immunosuppression that may result from denosumab's inhibition of RANKL.

2. Please comment on the significance of the infection signal overall and specifically for skin infections, pneumonia, and diverticulitis and other noteworthy infections.

DAIOP response: Please see the response to Question 1.

(b) (4)

DAIOP response: No. Please see the response to Question 1 for additional details.

4. Please comment on any other significant findings like opportunistic infections, time to event onset, effect of dose, and other risk factors for infectious events.

DAIOP response: Please see the response to Question 1. DRUP may consider performing specific time-to-event (e.g., Kaplan-Meier and Cox proportional hazard modeling) and dose-to-event analyses to assess if specific safety signals become apparent. Of note, all of the tables containing infection-related adverse events were based on trials that used the denosumab 60 mg q 6 month regimen.

Given that denosumab may affect multiple layers of the immune system, a specific time-to-event signal may not yet be evident. In addition, patients' underlying immune function may also play a role in time- and dose-to-event, i.e., those with more immune dysfunction at baseline may manifest an infection sooner and at a lower dose than those with a healthier baseline immune status.

5. Please comment on whether you have concerns about the use of this product in patients with diabetes or venous stasis ulcers due to their increased risk of developing cellulitis. Do you have recommendations for labeling or postmarketing studies for this patient population?

DAIOP response: It is possible that patients already predisposed to cellulitis, such as, diabetic patients and/or those with venous stasis ulcers may be at increased risk for cellulitis. Clinical trials that specifically include such patients may provide useful information regarding infection risk in such subgroups.

6. Please provide any other suggestions on how to further evaluate the infection signal, mitigate this risk, or any additional labeling recommendations for this potential signal.

DAIOP response: Given the potential of denosumab to affect multiple layers of the immune system and given longstanding infection-related concerns with multiple biologic products, DAIOP recommends that if denosumab is approved, that Amgen

commit to continue collecting information on all infection-related adverse events. In addition, DAIOP recommends that the label include information related to the potential risk of infections beyond cellulitis (as discussed in this review), sometimes serious, in the WARNINGS AND PRECAUTIONS section of the label. DRUP may consider referring to language found in the first two paragraphs of the HUMIRA label (under section 5.1 "serious infections"). Potentially relevant concepts from the HUMIRA label follow.¹

- Patients on concomitant immunosuppressive therapy may be at increased risk of infection due to the mechanism of action of denosumab.
- Infections, sometimes serious, have been noted in multiple organ systems, that is, not solely cellulitis.
- If a patient develops a serious infection while on therapy, denosumab should probably be discontinued.
- Physicians should exercise caution when considering the use of denosumab in patients with a history of recurrent infection or underlying conditions which may predispose them to infections.

III. Materials Reviewed

1. Multiple tables and descriptions of infection-related adverse events created by the Sponsor and DRUP reviewers that were derived from data obtained from the five Phase 3 studies used to support the BLAs currently under review.
2. Case report forms and narratives for patients who experienced endocarditis during study therapy and follow-up.
3. Multiple literature references as noted in Section VI of this review.

IV. Review of Infection Data

Phase 1 Studies

Three subjects were hospitalized for pneumonia in two Phase I studies. In Study 20030148, subject 148001091 developed pneumonia on Study Day 242 after receiving a single dose of denosumab at 3.0 mg/kg. In Study 20050146, a 33 year-old male subject (SID 146001122) developed pneumonia requiring hospitalization for 13 days about 2.5 months after receiving a single dose of 60 mg of denosumab and a 24 year-old male subject (SID 146001208) developed pneumonia requiring hospitalization for 4 days on Study Day 74 after receiving a single 60 mg dose of denosumab. For both of these healthy volunteers, the investigator and sponsor were unable to confirm the hospitalizations or obtain medical records from the hospitals where the subjects reported receiving treatment.

M.O. comment: It is concerning that three healthy volunteers developed pneumonia after receiving single doses of denosumab in Phase 1 studies. It is also of concern that the Sponsor was unable to obtain additional information related to their adverse events, such as, medical records of hospitalizations and the names of the pathogens causing the pneumonias.

Main Phase 3 PMO Trials

The main trials relevant to the osteoporosis indications are Study 20030216, Study 20040132 and Study 20050141.

Study 20030216

DRUP noted the following in the consult request.

Study 20030216 was an international, multicenter, randomized, double-blind placebo-controlled study to evaluate denosumab 60 mg Q6 months in the treatment of postmenopausal osteoporosis. This 3-year study enrolled 7868 subjects (60 subjects from one site were excluded due to GCP violations).

In Study 20030216, it is noteworthy there were slightly more serious bacterial, streptococcal, abdominal tract and urinary tract infections; there were seven subjects on denosumab who developed a serious erysipelas infection with none reported in the placebo group. In addition, there were several events of concern, including one subject with aspergillosis (SID6652020), two subjects with gangrene (SID 6717022 and 6803113), one subject with endocarditis (SID 6762526), one subject with endocarditis bacterial (SID 6430063), and one subject with a liver abscess (SID 6718019).

In addition, it was identified that some patients appeared to have multiple serious events of infection during the conduct of Study 20030216. As such, we have provided a summary of subjects who experienced at least one serious event of infection in Study 20030216 for your review (see Appendix 2). Of note, there were several subjects in the denosumab group that developed multiple infections, including bronchiectasis, lower respiratory tract infection pneumonia and diverticulitis.

Table 1. Study 20030216 – Serious Adverse Events in the Infections SOC by High Level Term (provided by DRUP, highlighting added by current M.O.):

High Level Group Term High Level Term		Denos. 60 mg Q6m N = 3886 n (%)	Placebo N = 3876 n (%)
Bacterial infectious disorders		25 (0.64%)	15 (0.38%)
	Bacterial infections NEC	12 (0.31%)	4 (0.10%)
	Borrelial infections	1 (0.03%)	2 (0.05%)
	Clostridia infections	1 (0.03%)	2 (0.05%)
	Escherichia infections	1 (0.03%)	2 (0.05%)
	Helicobacter infections	2 (0.05%)	0 (0.00%)
	Pseudomonal infections	1 (0.03%)	0 (0.00%)
	Salmonella infections	0 (0.00%)	2 (0.05%)
	Staphylococcal infections	1 (0.03%)	2 (0.05%)
	Streptococcal infections	7 (0.18%)	1 (0.03%)
Fungal infectious disorders		2 (0.05%)	1 (0.03%)
	Aspergillus infections	1 (0.03%)	0 (0.00%)
	Fungal infections NEC	1 (0.03%)	1 (0.03%)
Infections - pathogen unspecified		132 (3.37%)	116 (2.96%)
	Abdominal and gastrointestinal infections	28 (0.72%)	22 (0.56%)
	Bone and joint infections	0 (0.00%)	1 (0.03%)
	Cardiac infections	1 (0.03%)	0 (0.00%)
	Central nervous system & spinal infections	0 (0.00%)	1 (0.03%)
	Ear infections	5 (0.13%)	0 (0.00%)
	Female reproductive tract infections	3 (0.08%)	1 (0.03%)

High Level Group Term High Level Term	Denos. 60 mg Q6m N = 3886 n (%)	Placebo N = 3876 n (%)
Hepatobiliary and spleen infections	2 (0.05%)	2 (0.05%)
Infections NEC	7 (0.18%)	5 (0.13%)
Lower respiratory tract and lung infections	56 (1.43%)	59 (1.51%)
Sepsis, bacteraemia, viraemia and fungaemia NEC	5 (0.13%)	7 (0.18%)
Skin structures and soft tissue infections	3 (0.08%)	2 (0.05%)
Upper respiratory tract infections	5 (0.13%)	4 (0.10%)
Urinary tract infections	28 (0.72%)	18 (0.46%)
Vascular infections	2 (0.05%)	0 (0.00%)
Mycobacterial infectious disorders	2 (0.05%)	3 (0.08%)
Tuberculous infections	2 (0.05%)	3 (0.08%)
Rickettsial infectious disorders	0 (0.00%)	1 (0.03%)
Typhus infections	0 (0.00%)	1 (0.03%)
Viral infectious disorders	6 (0.15%)	5 (0.13%)
Herpes viral infections	2 (0.05%)	2 (0.05%)
Influenza viral infections	0 (0.00%)	1 (0.03%)
Rotaviral infections	1 (0.03%)	0 (0.00%)
Viral infections NEC	3 (0.08%)	2 (0.05%)

*Totals for each HLGT may not add up due to mapping within the MedDRA hierarchy (only events mapped to a primary HLGT are shown in the total for the HLGT).

M.O. comment: In Table 1, infection-related SAEs by HLGT and HLT for Study 20030216, the following is notable:

1. Among the HLGT "Bacterial Infectious Disorders":
 - a. there were three times as many "Bacterial infections NEC [Not Elsewhere Classified]" in the denosumab group as compared to placebo
 - b. "Streptococcal infections", which tend to occur through a epithelial or mucosal surface, occurred six times more frequently among denosumab subjects
 - c. taken together, "Bacterial infections NEC" plus "Streptococcal infections" occurred nearly four times as frequently among denosumab subjects vs. placebo subjects
2. Among the HLGT "Infections - pathogen unspecified", the following infections that tend to occur through an epithelial or mucosal surface occurred more frequently among denosumab subjects: "Abdominal and gastrointestinal infections", "Ear infections", "Female reproductive tract infections", and "Urinary tract infections"

Table 2. Study 20030216 – All Adverse Events* in the Infections SOC by High Level Group Term (provided by DRUP):

High Level Group Term	Denos. 60 mg Q6m N = 3886 n (%)	Placebo N = 3876 n (%)
Bacterial infectious disorders	114 (2.91%)	114 (2.91%)
Chlamydial infectious disorders	1 (0.03%)	3 (0.08%)

High Level Group Term	Denos. 60 mg Q6m N = 3886 n (%)	Placebo N = 3876 n (%)
Ectoparasitic disorders	5 (0.13%)	3 (0.08%)
Fungal infectious disorders	97 (2.48%)	91 (2.32%)
Helminthic disorders	5 (0.13%)	3 (0.08%)
Infections - pathogen unspecified	1761 (44.97%)	1815 (46.31%)
Mycobacterial infectious disorders	2 (0.05%)	7 (0.18%)
Protozoal infectious disorders	3 (0.08%)	2 (0.05%)
Rickettsial infectious disorders	1 (0.03%)	1 (0.03%)
Viral infectious disorders	569 (14.53%)	558 (14.24%)

* Includes serious and non-serious by regulatory definition.

M.O. comment: When viewing all infection-related AEs (not just SAEs by HLGT), the incidence of infections appears to be fairly balanced between denosumab and placebo subjects.

Table 3. Study 20030216 – All Adverse Events* in the Infections SOC by High Level Term (provided by DRUP, highlighting added by current M.O.):

High Level Group Term High Level Term	Denos. 60 mg Q6m N = 3886 n (%)	Placebo N = 3876 n (%)
Bacterial infectious disorders		
Bacterial infections NEC	50 (1.28%)	34 (0.87%)
Bordetella infections	1 (0.03%)	0 (0.00%)
Borrelial infections	12 (0.31%)	24 (0.61%)
Campylobacter infections	2 (0.05%)	1 (0.03%)
Clostridia infections	2 (0.05%)	4 (0.10%)
Escherichia infections	2 (0.05%)	2 (0.05%)
Haemophilus infections	0 (0.00%)	1 (0.03%)
Helicobacter infections	15 (0.38%)	21 (0.54%)
Pseudomonas infections	1 (0.03%)	0 (0.00%)
Salmonella infections	3 (0.08%)	3 (0.08%)
Staphylococcal infections	2 (0.05%)	4 (0.10%)
Streptococcal infections	29 (0.74%)	22 (0.56%)
Treponema infections	1 (0.03%)	0 (0.00%)
Chlamydial infectious disorders		
Chlamydial infections	1 (0.03%)	3 (0.08%)
Ectoparasitic disorders		
Ectoparasitic infestations	5 (0.13%)	3 (0.08%)
Fungal infectious disorders		
Aspergillus infections	1 (0.03%)	0 (0.00%)
Candida infections	22 (0.56%)	15 (0.38%)
Fungal infections NEC	55 (1.40%)	63 (1.61%)
Tinea infections	20 (0.51%)	15 (0.38%)
Helminthic disorders		
Cestode infections	1 (0.03%)	0 (0.00%)
Helminthic infections NEC	2 (0.05%)	2 (0.05%)

High Level Group Term High Level Term	Denos. 60 mg Q6m N = 3886 n (%)	Placebo N = 3876 n (%)
Nematode infections	2 (0.05%)	1 (0.03%)
Infections - pathogen unspecified		
Abdominal and gastrointestinal infections	134 (3.42%)	137 (3.50%)
Bone and joint infections	10 (0.26%)	3 (0.08%)
Breast infections	2 (0.05%)	4 (0.10%)
Cardiac infections	2 (0.05%)	0 (0.00%)
Central nervous system and spinal infections	0 (0.00%)	1 (0.03%)
Dental and oral soft tissue infections	62 (1.58%)	68 (1.74%)
Ear infections	89 (2.27%)	63 (1.61%)
Eye and eyelid infections	17 (0.43%)	18 (0.46%)
Female reproductive tract infections	27 (0.69%)	27 (0.69%)
Hepatobiliary and spleen infections	2 (0.05%)	2 (0.05%)
Infections NEC	107 (2.73%)	116 (2.96%)
Lower respiratory tract and lung infections	512 (13.07%)	537 (13.70%)
Muscle and soft tissue infections	2 (0.05%)	0 (0.00%)
Sepsis, bacteraemia, viraemia and fungaemia NEC	8 (0.20%)	8 (0.20%)
Skin structures and soft tissue infections	37 (0.94%)	33 (0.84%)
Upper respiratory tract infections	941 (24.03%)	995 (25.39%)
Urinary tract infections	464 (11.85%)	474 (12.09%)
Vascular infections	4 (0.10%)	2 (0.05%)
Mycobacterial infectious disorders		
Tuberculous infections	2 (0.05%)	7 (0.18%)
Protozoal infectious disorders		
Amoebic infections	1 (0.03%)	1 (0.03%)
Giardia infections	2 (0.05%)	0 (0.00%)
Trichomonas infections	0 (0.00%)	1 (0.03%)
Rickettsial infectious disorders		
Bartonella infections	1 (0.03%)	0 (0.00%)
Typhus infections	0 (0.00%)	1 (0.03%)
Viral infectious disorders		
Epstein-Barr viral infections	0 (0.00%)	1 (0.03%)
Flaviviral infections	5 (0.13%)	3 (0.08%)
Hepatitis viral infections	2 (0.05%)	2 (0.05%)
Herpes viral infections	102 (2.60%)	102 (2.60%)
Influenza viral infections	338 (8.63%)	347 (8.85%)
Rotaviral infections	1 (0.03%)	0 (0.00%)
Rubella viral infections	0 (0.00%)	1 (0.03%)
Viral infections NEC	147 (3.75%)	128 (3.27%)

* Includes serious and non-serious by regulatory definition.

M.O. comment: When viewing all infection-related AEs (not just SAEs by HLGT and HLT), the following epithelial/mucosal infections occurred more frequently among denosumab subjects: "Bacterial infections NEC", "Streptococcal infections",

"Candida infections", "Tinea infections", and "Ear infections". It is also interesting to note that there were two "Giardia infections" in the denosumab group and none in the placebo group.

"Tuberculous infections" occurred less frequently among denosumab subjects.

Table 3 A. Study 20030216 – All Subjects with ≥ 1 Serious Events in the Infections SOC Listed by Treatment Group (provided by DRUP, highlighting added by current M.O.):

Unique Subject Identifier	Dictionary-Derived Term	Start Date of Adverse Event	Total No.* per subject
Subjects Randomized to Placebo			
20030216-102001	Pneumonia	18FEB2005	1
20030216-102006	Kidney infection	07SEP2006	1
20030216-110010	Bronchiectasis	17DEC2004	3
	Bronchiectasis	27JAN2005	3
	Bronchiectasis	27JUN2006	3
	Pneumonia bacterial	27JUN2006	1
20030216-117025	Pneumonia	03MAY2006	1
20030216-119005	Pneumonia	16APR2005	1
20030216-119044	Pneumonia	16MAR2006	1
	Sepsis	08NOV2005	1
	Sinusitis	08NOV2005	1
	Urosepsis	08NOV2005	1
20030216-121026	Pneumonia	01JAN2005	1
20030216-124004	Pneumonia	08OCT2006	1
20030216-131001	Appendicitis	20NOV2007	1
20030216-136005	Urinary tract infection	29JUN2006	1
20030216-304003	Lobar pneumonia	28MAY2006	1
20030216-304060	Lobar pneumonia	30OCT2005	1
	Pneumonia	22JAN2007	1
20030216-412300	Tuberculosis	21JUN2005	1
20030216-412495	Gastroenteritis	04MAY2005	1
20030216-413088	Urinary tract infection	04OCT2006	1
20030216-413096	Appendicitis	17DEC2005	1
20030216-413239	Pneumonia	29NOV2007	1
20030216-430002	Sepsis	08FEB2006	1
20030216-430130	Pneumonia	23JAN2007	1
20030216-430171	Urinary tract infection	04MAY2007	1
20030216-431022	Urinary tract infection	10NOV2005	1
20030216-432053	Bronchopneumonia	22JUN2007	1
20030216-432075	Pneumonia bacterial	27APR2007	1
20030216-432144	Subcutaneous abscess	28MAY2007	1
20030216-436150	Bronchopneumonia	03OCT2007	1
20030216-436313	Pneumonia	01SEP2006	1
	Septic shock	14NOV2007	1
20030216-450112	Pneumonia	06DEC2005	1
20030216-451008	Respiratory tract infection	06JAN2006	1
20030216-501022	<u>Diverticulitis</u>	<u>06OCT2006</u>	<u>1</u>
20030216-612025	Clostridium difficile colitis	18DEC2007	1
20030216-612053	Gastrointestinal infection	01JUL2007	1
20030216-613057	<u>Diverticulitis</u>	<u>15APR2006</u>	<u>1</u>

Unique Subject Identifier	Dictionary-Derived Term	Start Date of Adverse Event	Total No.* per subject
20030216-614018	Bronchopneumonia	01SEP2007	1
20030216-621034	Bronchitis	25OCT2007	1
20030216-622012	Urosepsis	12MAR2008	1
20030216-622015	Bronchitis	16JAN2007	1
20030216-631055	Pneumonia	09MAR2007	1
20030216-631072	Appendicitis	24AUG2007	1
20030216-631195	Pneumonia	06APR2006	1
20030216-631258	Pneumonia		1
20030216-631502	Pneumonia	15MAR2007	1
20030216-631557	Lung abscess	03JAN2007	1
	Pneumonia pneumococcal	10DEC2006	1
20030216-631816	Pneumonia	06MAR2008	1
20030216-632018	<u>Diverticulitis</u>	<u>17FEB2006</u>	<u>1</u>
20030216-632042	Pneumonia	27MAR2007	1
20030216-632048	Pneumonia	25DEC2004	1
20030216-632089	Pneumonia	14OCT2005	1
20030216-632076	Bronchitis	22MAR2006	1
	Pneumonia	05OCT2005	1
20030216-632161	Pneumonia	03MAR2007	1
20030216-632162	Cystitis	22JAN2007	1
20030216-632205	Abscess intestinal	30DEC2006	1
	<u>Diverticulitis</u>	<u>30DEC2006</u>	<u>1</u>
20030216-632235	Cystitis	20SEP2006	1
20030216-632280	Sepsis	07MAR2007	1
20030216-633044	Infected cyst	21SEP2007	1
20030216-633104	Bronchitis	07SEP2007	1
20030216-633294	Gastroenteritis	29NOV2006	1
20030216-633321	<u>Diverticulitis</u>	<u>22JAN2007</u>	<u>1</u>
20030216-633329	Cholecystitis infective	11JUL2006	1
20030216-633357	Pneumonia	30MAY2006	1
20030216-633358	Post procedural infection	23NOV2005	1
20030216-633359	Localised infection	11SEP2006	1
20030216-633388	Pneumonia	04JAN2008	1
20030216-741016	Lower respiratory tract infection	20OCT2006	1
	Pneumonia	14DEC2006	1
20030216-641071	Pyelonephritis acute	09MAR2007	1
20030216-642023	Appendiceal abscess	06JUL2006	1
20030216-651039	Paronychia	14OCT2005	1
20030216-652011	Bacterial pyelonephritis	13JUN2006	1
20030216-661042	Appendicitis	08OCT2005	1
20030216-661057	Bronchiectasis	18MAY2006	1
20030216-661058	Salmonellosis	15OCT2005	1
20030216-661208	Meningitis	28FEB2007	1
20030216-662019	Appendicitis	01JAN2006	1
	Peritoneal abscess	01JAN2006	1
20030216-686175	Pneumonia	15JAN2006	1
20030216-691030	Pneumonia	25FEB2007	1
20030216-691039	Post procedural pneumonia	15JAN2007	1
20030216-691047	Bacteraemia	20JUN2007	1
	Gastroenteritis	17JUN2007	1

Unique Subject Identifier	Dictionary-Derived Term	Start Date of Adverse Event	Total No.* per subject
	Vaginal infection	20JUN2007	1
20030216-695043	<u>Diverticulitis</u>	<u>10DEC2007</u>	<u>1</u>
20030216-743031	Peridiverticular abscess		1
20030216-743063	Cellulitis	04FEB2008	1
20030216-743119	Escherichia infection	19OCT2006	1
	Renal abscess	19OCT2006	1
20030216-746071	Sepsis	02JUL2007	1
20030216-746112	Lower respiratory tract infection	25OCT2005	1
20030216-747021	Gastroenteritis	02MAY2007	1
20030216-747027	Gastroenteritis	19MAR2006	1
20030216-747048	Arthritis viral	18FEB2006	1
	Lower respiratory tract infection	04APR2006	1
20030216-723044	Pneumonia	31JAN2008	1
20030216-725028	Pyelonephritis	01APR2006	1
20030216-729079	Appendicitis	18DEC2005	1
20030216-747091	Gastroenteritis	09FEB2006	1
20030216-748025	Infective exacerbation of chronic obstructive airways disease	09JUN2006	1
20030216-748032	Urinary tract infection	26FEB2008	1
20030216-749096	Staphylococcal infection	16FEB2006	1
20030216-754002	Bronchitis	25NOV2005	1
20030216-755104	Salmonellosis	08OCT2006	1
20030216-755197	Herpes zoster	30OCT2007	1
20030216-759048	Pyelonephritis	29DEC2007	1
20030216-759075	Pneumonia	22APR2008	1
20030216-761225	Pneumonia	01FEB2006	1
	Urinary tract infection	01FEB2006	1
20030216-762036	Encephalitis viral	23OCT2006	1
20030216-762122	Appendicitis	20NOV2004	1
20030216-762144	Pneumonia	26FEB2007	1
20030216-762153	Lyme disease	18OCT2007	1
20030216-763031	Intervertebral discitis	07AUG2007	1
20030216-782056	Bronchopneumonia	02JUN2005	1
20030216-788027	Chronic sinusitis	23AUG2006	1
20030216-790019	Urinary tract infection	02NOV2006	1
20030216-791090	Cholecystitis infective	23OCT2006	1
20030216-792041	Bronchitis	12JUL2005	1
20030216-793138	Pneumonia		1
	Pyothorax		1
20030216-795008	Bronchopneumonia	29JAN2008	1
20030216-795033	Pneumonia	15DEC2005	1
20030216-802014	Chronic sinusitis	16MAR2006	1
	Obstructive chronic bronchitis with acute exacerbation	18NOV2004	1
20030216-803107	Rhinitis	06JAN2005	1
20030216-803163	Pyelonephritis chronic		1
20030216-811005	Typhus	19JUL2007	1
20030216-821049	Pneumonia		2
	Pneumonia	20MAR2006	2
20030216-822018	Escherichia infection		1
	Urinary tract infection		1

Unique Subject Identifier	Dictionary-Derived Term	Start Date of Adverse Event	Total No.* per subject
20030216-823006	Bronchitis	07FEB2005	1
20030216-823205	Pulmonary tuberculosis	.	1
20030216-830151	Respiratory tract infection fungal	17JAN2007	1
20030216-831332	Pulmonary tuberculosis	01FEB2006	1
20030216-831350	Bronchopneumonia	02MAY2006	1
20030216-834038	Herpes zoster	20JAN2007	1
20030216-834203	Pneumonia	.	1
20030216-835035	Gastroenteritis	12JUN2005	1
20030216-839115	Pneumonia	12JUN2007	1
20030216-839139	Urinary tract infection	10JUL2005	1
20030216-840003	Pneumonia	24MAY2006	1
	Acrodermatitis chronica atrophicans		
20030216-842048	atrophicans	04JAN2007	1
20030216-843025	Influenza	05JUN2007	1
	Infective exacerbation of chronic obstructive airways disease		
20030216-851008	obstructive airways disease	12APR2006	1
20030216-853025	Staphylococcal sepsis	.	1
20030216-853116	Urinary tract infection	15DEC2006	1
20030216-855097	Clostridium difficile colitis	.	1
20030216-867067	Bronchopneumonia	31MAR2008	1
Subjects Randomized to Denosumab 60 mg Q6M			
20030216-103015	Cellulitis	19APR2007	1
20030216-103069	Urosepsis	07JAN2007	1
20030216-110002	Gastroenteritis	13MAY2007	1
20030216-110015	Urinary tract infection	06JUN2006	1
20030216-119034	Labyrinthitis	21MAY2005	1
20030216-129027	Pneumonia	06MAR2005	1
20030216-132008	Cellulitis	05MAR2008	1
20030216-136012	Urinary tract infection	16JAN2007	1
20030216-304041	Bronchiectasis	20DEC2007	1
20030216-410037	Bronchiectasis	18SEP2007	1
	Pneumonia	08JUL2005	1
20030216-410062	Pneumonia	27JUN2005	1
20030216-412009	Cellulitis	26NOV2007	1
	Erysipelas	10MAR2005	1
	Infected skin ulcer	10JUN2007	1
20030216-412179	Gastroenteritis	22AUG2006	1
20030216-412449	Erysipelas	21FEB2006	1
20030216-412827	Pneumonia	30OCT2006	1
20030216-413041	Gastroenteritis	20JAN2007	1
	Urinary tract infection	20JAN2007	1
20030216-413164	Appendicitis	20DEC2006	1
20030216-430009	Respiratory tract infection	26JAN2007	1
	Urinary tract infection	23JAN2007	1
20030216-430063	Endocarditis bacterial	02DEC2006	1
	Urinary tract infection	08NOV2006	1
20030216-431083	<u>Diverticulitis</u>	<u>31OCT2005</u>	<u>1</u>
	Pneumonia	31OCT2005	1
	Urinary tract infection	.	1
20030216-431177	Erysipelas	02DEC2007	1
20030216-432173	Labyrinthitis	15NOV2006	1

Unique Subject Identifier	Dictionary-Derived Term	Start Date of Adverse Event	Total No.* per subject
20030216-432195	Pneumonia	12APR2006	1
20030216-432330	Pyelonephritis	01JAN2007	1
20030216-433013	Labyrinthitis	20MAR2006	1
20030216-435005	Pneumonia	06JUN2005	1
20030216-436001	Urinary tract infection	15OCT2005	1
20030216-436050	Pneumonia bacterial	09FEB2008	1
20030216-436076	Labyrinthitis	08DEC2007	1
20030216-612014	Pneumonia	02AUG2006	1
20030216-612028	Bronchitis		1
20030216-612034	Skin bacterial infection		1
20030216-613069	Pyelonephritis	18JAN2006	1
	Urinary tract infection	09JAN2007	1
20030216-625001	Lymphangitis	23APR2006	1
20030216-631008	Gastroenteritis	09MAR2006	1
20030216-631014	Helicobacter infection	02MAR2007	1
20030216-631106	Pneumonia	20SEP2005	1
20030216-631270	Pneumonia	04MAR2007	1
20030216-631297	Phlebitis infective	01FEB2006	1
20030216-631345	Pneumonia	21FEB2005	1
20030216-631377	Gastroenteritis Escherichia coli	31DEC2006	1
20030216-631418	Cystitis	12JAN2006	1
20030216-631488	Sepsis	23DEC2007	1
20030216-631528	Gastroenteritis	12SEP2005	1
20030216-631677	Pneumonia	10DEC2007	1
20030216-632062	Respiratory tract infection	02MAR2007	1
20030216-632064	Sinusitis	23MAR2005	1
20030216-632099	Cystitis	16SEP2006	1
20030216-632154	Post procedural infection	14OCT2005	1
20030216-632169	Gastroenteritis	19MAY2006	1
20030216-632220	Appendicitis	12SEP2005	1
20030216-632299	Gastroenteritis	18NOV2005	1
20030216-633056	Pneumonia	01OCT2005	2
	Pneumonia	04MAY2005	2
20030216-633062	Erysipelas	29MAY2007	1
20030216-633084	Pneumonia	01AUG2005	1
20030216-633101	Pleural infection	12DEC2005	1
	Sepsis	12DEC2005	1
20030216-633150	Pneumonia	01FEB2006	1
20030216-633192	<u>Diverticulitis</u>	<u>23MAY2007</u>	<u>1</u>
20030216-633276	Abdominal abscess	02JUL2006	1
20030216-633344	Bronchitis	05DEC2005	1
20030216-633351	Pneumonia	29OCT2006	1
20030216-633355	Diverticulitis	18SEP2005	2
	Diverticulitis	19MAR2007	2
20030216-633361	Cystitis	14JUL2005	1
20030216-634016	Appendicitis	22APR2006	1
20030216-652020	Aspergillosis		1
20030216-655017	Lung infection	22SEP2005	1
20030216-663078	Anal abscess		1
20030216-672008	Bronchopneumonia	27JUN2007	1

Unique Subject Identifier	Dictionary-Derived Term	Start Date of Adverse Event	Total No.* per subject
20030216-685029	Wound infection	.	1
20030216-686034	Pneumonia	03AUG2007	1
	Respiratory tract infection	28JUN2007	1
20030216-691071	Pneumonia bacterial	25OCT2006	1
20030216-692062	Pneumonia viral	24DEC2007	1
20030216-692104	Pneumonia	24JUN2007	1
20030216-695023	Urinary tract infection	15AUG2007	1
20030216-711029	Pyelonephritis	15JUN2005	1
20030216-712008	Pyelonephritis	11FEB2007	1
20030216-717022	Gangrene	27JUN2006	1
20030216-718019	Liver abscess	10SEP2007	1
20030216-719006	Pneumonia	01MAY2006	1
20030216-721021	Gastroenteritis	31OCT2006	1
20030216-731017	<u>Diverticulitis</u>	<u>30DEC2004</u>	1
20030216-731020	Appendicitis	15SEP2005	1
20030216-731043	<u>Diverticulitis</u>	<u>20JAN2006</u>	1
20030216-731075	Pneumonia	28SEP2006	1
20030216-732008	Gastroenteritis viral	18OCT2006	1
	Lung infection	09MAR2006	1
20030216-742086	Lower respiratory tract infection	26APR2006	1
20030216-743050	Lower respiratory tract infection	.	1
20030216-743085	Lower respiratory tract infection	04APR2006	1
20030216-743088	Pneumonia	27AUG2005	1
	Sepsis	.	1
20030216-746016	Pharyngitis	06JUL2006	1
20030216-746025	Pneumonia	.	1
20030216-746085	Urinary tract infection	15NOV2005	1
20030216-747071	Skin bacterial infection	05MAR2007	1
20030216-747081	Helicobacter infection	.	1
20030216-747110	Appendicitis	02SEP2005	1
20030216-748053	Cellulitis	28SEP2005	1
20030216-749078	Clostridium difficile colitis	01JAN2006	1
	Lower respiratory tract infection	07DEC2005	1
20030216-754037	Urinary tract infection	24OCT2006	1
20030216-755055	Septic shock	16OCT2007	1
20030216-755059	Erysipelas	06MAY2007	1
20030216-755101	Cystitis	30MAR2006	1
20030216-755257	Gastric infection	18MAY2007	1
	Urinary tract infection	13APR2007	1
20030216-755320	<u>Diverticulitis</u>	<u>12MAY2006</u>	1
	Urinary tract infection	03DEC2005	1
20030216-759064	Pyometra	12JAN2006	1
20030216-761058	Cystitis	07JAN2007	1
20030216-761116	Pyelonephritis acute	10FEB2006	1
20030216-761137	Urinary tract infection	12MAY2007	1
20030216-761161	Urinary tract infection	10JUN2007	1
20030216-761176	Pneumonia	18JUL2006	1
	Pyelonephritis	02AUG2006	1
20030216-761231	Bronchitis	08FEB2008	1
20030216-761241	Gastroenteritis rotavirus	03JUL2006	1

Unique Subject Identifier	Dictionary-Derived Term	Start Date of Adverse Event	Total No.* per subject
20030216-762032	Cellulitis		1
20030216-762081	Appendicitis	11SEP2006	1
20030216-762358	Pneumonia	02NOV2007	1
20030216-762526	Endocarditis	11AUG2005	1
20030216-765025	Bronchopneumonia	30MAR2006	1
20030216-782007	Otitis media	13JUN2006	1
20030216-783060	Pneumonia	22JUL2005	1
20030216-783061	Pneumonia	20JAN2008	1
20030216-785021	Bronchopneumonia	10MAY2007	1
20030216-785023	Abdominal abscess	16APR2005	1
	Post procedural infection	16APR2005	1
	Tubo-ovarian abscess		1
20030216-791214	Appendicitis	27FEB2006	1
20030216-794025	Pyelonephritis chronic	14AUG2006	1
20030216-801052	Herpes zoster	11JUN2007	1
20030216-801067	Post procedural infection	18MAY2007	1
20030216-801099	Sinusitis	26MAR2005	1
20030216-803036	Pneumonia	04JAN2005	1
20030216-803113	Gangrene	19JUN2007	1
20030216-822005	Sinusitis	05DEC2007	1
20030216-823124	Cervicitis	30MAY2007	1
20030216-823355	Bronchopneumonia	16NOV2006	1
20030216-824095	Erysipelas	04NOV2005	1
20030216-824142	Pneumonia	08JAN2008	1
20030216-828179	Bronchiectasis	17OCT2006	1
20030216-828187	Biliary tract infection fungal		1
	Pulmonary tuberculosis	13JUL2005	1
20030216-828194	Chronic sinusitis	07JUN2005	1
20030216-830014	Bronchitis	22FEB2007	1
20030216-830018	Viral infection	13APR2005	1
20030216-830086	Pneumonia	20FEB2007	1
20030216-830248	Erysipelas	06SEP2005	1
20030216-831154	Cholecystitis infective	26MAY2005	1
20030216-831204	Pneumonia	30OCT2006	1
20030216-831228	Gastroenteritis	16OCT2005	1
20030216-831274	Pneumonia	16OCT2005	1
20030216-831286	Urinary tract infection	12NOV2006	1
20030216-834002	Pneumonia	08MAY2007	1
20030216-837003	Tuberculosis		1
20030216-837022	Herpes zoster ophthalmic	08JUL2006	1
20030216-838089	Bronchopneumonia	15OCT2006	1
20030216-839010	Borrelia infection	25JUL2006	1
20030216-844006	Cystitis	22JUL2005	1
20030216-844030	Bronchopneumonia	03SEP2005	1
20030216-851045	<u>Diverticulitis</u>	<u>03NOV2007</u>	<u>1</u>
	Pneumonia		1
20030216-853031	Staphylococcal infection	04SEP2005	1
20030216-853038	Pneumonia	27DEC2007	1
20030216-853081	Pneumonia	05MAY2007	1
20030216-853097	Cellulitis	19APR2007	1

Unique Subject Identifier	Dictionary-Derived Term	Start Date of Adverse Event	Total No.* per subject
20030216-853114	<u>Diverticulitis</u>	<u>09JAN2008</u>	1
20030216-854015	Bronchiectasis	02NOV2005	4
	Bronchiectasis	10MAR2005	4
	Bronchiectasis	11JAN2006	4
	Bronchiectasis	17DEC2004	4
	Lower respiratory tract infection	10OCT2006	5
	Lower respiratory tract infection	18JUN2007	5
	Lower respiratory tract infection	19JUL2006	5
	Lower respiratory tract infection	20DEC2005	5
	Lower respiratory tract infection	30SEP2005	5
	Lung infection pseudomonal	07FEB2007	1
	Pseudomonas infection	15OCT2007	1
20030216-854076	Lower respiratory tract infection	03JUL2006	1
20030216-867099	Gastroenteritis bacterial	13OCT2006	1

* Total No. = the total number of times a specific dictionary derived term is reported per subject

M.O. comment: Regarding subjects with multiple infection-related SAEs in Study 20030216, in the denosumab group, one subject had 4 episodes of bronchiectasis, 5 episodes of "lower respiratory tract infection", and two pseudomonal infections. Another denosumab subject experienced diverticulitis twice. Among placebo subjects, one had bronchiectasis twice and another experienced pneumonia twice.

Eight denosumab subjects and 6 placebo subjects experienced diverticulitis. One of the denosumab subjects had two episodes of diverticulitis.

Study 20040132

DRUP noted the following in the consult request.

Study 20040132 was a randomized double-blind study to evaluate denosumab 60 mg every 6 months in the prevention of postmenopausal osteoporosis and enrolled 332 women (denosumab – 166, placebo – 166); subjects received therapy for 24 months and were monitored for an additional 24 months.

In Study 20040132, it is noteworthy that there were more serious abdominal and lower respiratory tract infections. There were 3 denosumab subjects with events in the HLT sepsis, bacteraemia, viraemia and fungaemia and none in the placebo group.

Table 4. Study 20040132 (36 month data) – Serious Adverse Events in the Infections SOC by High Level Group Term (provided by DRUP, highlighting added by current M.O.):

High Level Group Term	Denos. 60 mg Q6m N = 164	Placebo N = 165
Bacterial infectious disorders	1 (0.61%)	0 (0.00%)
Infections - pathogen unspecified	7 (4.27%)	2 (1.21%)

M.O. comment: There were three and one-half times as many "Infections - pathogen unspecified" SAEs in the denosumab group as in the placebo group.

Table 5. Study 20040132 (36 month data) – Serious Adverse Events in the Infections SOC by High Level Term (provided by DRUP, highlighting added by current M.O.):

High Level Group Term High Level Term	Denos. 60 mg Q6m N = 164	Placebo N =165
Bacterial infectious disorders		
Bacterial infections NEC	1 (0.61%)	0 (0.00%)
Infections - pathogen unspecified		
Abdominal and gastrointestinal infections	3 (1.83%)	1 (0.61%)
Lower respiratory tract and lung infections	3 (1.83%)	1 (0.61%)
Sepsis, bacteraemia, viraemia & fungaemia NEC	2 (1.22%)	0 (0.00%)
Urinary tract infections	1 (0.61)	0 (0.00%)

M.O. comment: Denosumab subjects with SAEs in the HLT of "Infections - pathogen unspecified" had more "Abdominal and gastrointestinal infections", "Lower respiratory tract and lung infections" and "Sepsis, bacteraemia, viraemia & fungaemia NEC".

Of note, based on Table 5, two denosumab and no placebo subjects experienced "Sepsis, bacteraemia, viraemia & fungaemia NEC" as an SAE.

Table 6. Study 20040132 (36 month data) – All Adverse Events* in the Infections SOC by High Level Group Term (provided by DRUP):

High Level Group Term	Denos. 60 mg Q6m N = 164	Placebo N =165
Bacterial infectious disorders	4 (2.44%)	6 (3.64%)
Fungal infectious disorders	7 (4.27%)	7 (4.24%)
Infections – pathogen unspecified	93 (56.71%)	94 (56.97%)
Mycobacterial infectious disorders	1 (0.61%)	0 (0.00%)
Protozoal infectious disorders	0 (0.00%)	1 (0.61%)
Rickettsial infectious disorders	0 (0.00%)	1 (0.61%)
Viral infectious disorders	32 (19.51%)	36 (21.82%)

* Includes serious and non-serious events, per regulatory definition.

M.O. comment: When viewing all infection-related AEs (not just SAEs by HLGT), the incidence of infections appears to be fairly balanced between denosumab and placebo subjects.

Study 20050141

DRUP noted the following in the consult request.

Study 20050141 was a randomized, double-blind, active control (alendronate), double-dummy, parallel group study of the comparative efficacy, safety, tolerability of study medication in postmenopausal women with low BMD. Women received denosumab 60 mg SC Q6M (2 doses) + placebo OR alendronate 70 mg PO qweek + placebo.

In Study 20050141 comparing denosumab to alendronate, the number of serious unspecified pathogen infections was higher for denosumab than alendronate. For all adverse events (includes serious & non-serious), there were more urinary tract infections, upper respiratory tract, and dental infections in the denosumab group compared to alendronate. There were 2 denosumab subjects with events in the HLT sepsis, bacteraemia, viraemia and fungaemia and none in the alendronate group.

Table 8. Study 20050141 – Serious Events in the Infections SOC by HLGT (provided by DRUP, highlighting added by current M.O.):

High Level Group Term	Denosumab 60 mg Q6m N = 593 n (%)	Alendronate 70 mg Qweek N = 586 n (%)
Bacterial infectious disorders	1 (0.17%)	0 (0.00%)
Infections - pathogen unspecified	9 (1.52%)	6 (1.02%)

M.O. comment: There were slightly more “Infections - pathogen unspecified” SAEs among denosumab vs. alendronate subjects.

Table 9. Study 20050141 – Serious Events in the Infections SOC by HLGT & HLT (provided by DRUP, highlighting added by current M.O.):

High Level Group Term High Level Term	Denosumab 60 mg Q6m N = 593 n (%)	Alendronate 70 mg Qweek N = 586 n (%)
Bacterial infectious disorders		
Clostridia infections	1 (0.17%)	0 (0.00%)
Infections – pathogen unspecified		
Abdominal & gastrointestinal infections	3 (0.51%)	0 (0.00%)
Ear infections	1 (0.17%)	0 (0.00%)
Infections NEC	1 (0.17%)	2 (0.34%)
Lower respiratory tract & lung infections	1 (0.17%)	3 (0.51%)
Sepsis, bacteraemia, viraemia & fungaemia NEC	2 (0.34%)	0 (0.00%)
Upper respiratory tract infections	0 (0.00%)	1 (0.17%)
Urinary tract infections	1 (0.17%)	0 (0.00%)

M.O. comment: Regarding the “Infections - pathogen unspecified” SAEs, three denosumab and no alendronate subjects experienced “Abdominal & gastrointestinal infections” and two denosumab and no alendronate subjects experienced “Sepsis, bacteraemia, viraemia & fungaemia NEC”.

Table 10. Study 20050141 – All Adverse Events* in the Infections SOC by HLGT (provided by DRUP, highlighting added by current M.O.):

High Level Group Term	Denosumab 60 mg Q6m N = 593 n (%)	Alendronate 70 mg Qweek N = 586 n (%)
Bacterial infectious disorders	8 (1.35%)	6 (1.02%)
Ectoparasitic disorders	1 (0.17%)	0 (0.00%)
Fungal infectious disorders	6 (1.01%)	11 (1.88%)
Infections - pathogen unspecified	177 (29.85%)	156 (26.62%)
Viral infectious disorders	56 (9.44%)	60 (10.24%)

* Includes serious and non-serious events, per regulatory definition.

M.O. comment: When viewing all infection-related AEs (no just SAEs) by HLGT, slightly more denosumab subjects experienced "Infections - pathogen unspecified".

Table 11. Study 20050141 – All Adverse Events* in the Infections SOC by HLGT & HLT (provided by DRUP, highlighting added by current M.O.):

High Level Group Term High Level Term		Denosumab 60 mg Q6m N = 593 n (%)	Alendronate 70 mg Qweek N = 586 n (%)
Bacterial infectious disorders			
	Bacterial infections NEC	1 (0.17%)	2 (0.34%)
	Clostridia infections	2 (0.34%)	0 (0.00%)
	Helicobacter infections	2 (0.34%)	3 (0.51%)
	Streptococcal infections	3 (0.51%)	1 (0.17%)
Ectoparasitic disorders			
	Ectoparasitic infestations	1 (0.17%)	0 (0.00%)
Fungal infectious disorders			
	Candida infections	1 (0.17%)	1 (0.17%)
	Fungal infections NEC	5 (0.84%)	10 (1.71%)
	Tinea infections	0 (0.00%)	1 (0.17%)
Infections - pathogen unspecified			
	Abdominal and gastrointestinal infections	12 (2.02%)	12 (2.05%)
	Bone and joint infections	1 (0.17%)	0 (0.00%)
	Breast infections	1 (0.17%)	0 (0.00%)
	Dental and oral soft tissue infections	10 (1.69%)	6 (1.02%)
	Ear infections	9 (1.52%)	7 (1.19%)
	Eye and eyelid infections	3 (0.51%)	2 (0.34%)
	Female reproductive tract infections	1 (0.17%)	1 (0.17%)
	Infections NEC	7 (1.18%)	9 (1.54%)
	Lower respiratory tract and lung infections	29 (4.89%)	34 (5.80%)
	Sepsis, bacteraemia, viraemia and fungaemia NEC	2 (0.34%)	0 (0.00%)
	Skin structures and soft tissue infections	3 (0.51%)	1 (0.17%)
	Upper respiratory tract infections	103 (17.37%)	90 (15.36%)
	Urinary tract infections	32 (5.40%)	24 (4.10%)
Viral infectious disorders			
	Herpes viral infections	5 (0.84%)	7 (1.19%)
	Influenza viral infections	41 (6.91%)	42 (7.17%)
	Viral infections NEC	11 (1.85%)	15 (2.56%)

* Includes serious and non-serious events, per regulatory definition.

M.O. comment: Slightly more denosumab subjects experienced "Streptococcal infections" AEs. Regarding "Infections - pathogen unspecified" AEs, more denosumab subjects experienced "Dental and oral soft tissue infections", "Ear

infections”, “Sepsis, bacteraemia, viraemia and fungaemia NEC”, “Skin structures and soft tissue infections”, “Upper respiratory tract infections”, and “Urinary tract infections”. Most of these infection-related AEs were likely associated with invasion through an epidermal or mucosal surface.

Main Phase 3 HALT Studies

The pivotal studies for the HALT indications are Study 20040135 and Study 20040138.

Study 20040135

DRUP noted the following in the consult request.

Study 20040135 was a randomized, double-blind, placebo-controlled study to evaluate denosumab 60 mg SC Q6 months 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. Approximately 64% of subjects in the study had prior chemotherapy and 66% had received radiotherapy; subjects were equally distributed between the two treatment groups.

In Study 20040135, there did not appear to be a difference in serious infections between treatment groups. Overall infections (includes serious and non-serious) were more commonly reported in subjects on denosumab than placebo, particularly herpes viral infections and upper respiratory tract infections.

Table 12. Study 20040135 – Serious Adverse Events in the Infections SOC by HLGT (provided by DRUP):

High Level Group Term	Denosumab 60 mg SQ Q6M N = 127 n (%)	Placebo N = 125 n (%)
Bacterial infectious disorders	1 (0.78%)	0 (0.00%)
Infections - pathogen class unspecified	2 (1.55%)	1 (0.79%)

M.O. comment: Based on Table 12, the infection-related SAEs by HLGT were balanced between the two groups.

Table 13. Study 20040135 – All Adverse Events* in the Infections SOC by HLGT (provided by DRUP):

High Level Group Term	Denosumab 60 mg SQ Q6M N = 127 n (%)	Placebo N = 125 n (%)
Bacterial infectious disorders	5 (3.88%)	3 (2.38%)
Fungal infectious disorders	6 (4.65%)	3 (2.38%)
Infections - pathogen class unspecified	40 (31.01%)	30 (23.81%)
Viral infectious disorders	13 (10.08%)	8 (6.35%)

* Includes serious and non-serious events, per regulatory definition.

M.O. comment: Based on Table 13, all infection-related AEs by HLGT occurred more frequently in the denosumab group vs. placebo.

Table 14. Study 20040135 – All Adverse Events* in the Infections SOC by HLGT & HLT (provided by DRUP, highlighting added by current M.O.):

High Level Group Term High Level Term	Denosumab 60 mg SQ Q6M N = 127 n (%)	Placebo N = 125 n (%)
Bacterial infectious disorders		
Bacterial infections NEC	3 (2.33%)	2 (1.59%)
Bordetella infections	1 (0.78%)	0 (0.00%)
Helicobacter infections	1 (0.78%)	0 (0.00%)
Staphylococcal infections	0 (0.00%)	1 (0.79%)
Fungal infectious disorders		
Candida infections	2 (1.55%)	2 (1.59%)
Fungal infections NEC	1 (0.78%)	1 (0.79%)
Tinea infections	3 (2.33%)	0 (0.00%)
Infections - pathogen class unspecified		
Abdominal and gastrointestinal infections	1 (0.78%)	3 (2.38%)
Dental and oral soft tissue infections	2 (1.55%)	1 (0.79%)
Ear infections	2 (1.55%)	0 (0.00%)
Eye and eyelid infections	3 (2.33%)	0 (0.00%)
Female reproductive tract infections	0 (0.00%)	2 (1.59%)
Infections NEC	3 (2.33%)	4 (3.17%)
Lower respiratory tract and lung infections	7 (5.43%)	8 (6.35%)
Skin structures and soft tissue infections	1 (0.78%)	2 (1.59%)
Upper respiratory tract infections	21 (16.28%)	14 (11.11%)
Urinary tract infections	7 (5.43%)	5 (3.97%)
Viral infectious disorders		
Herpes viral infections	7 (5.43%)	2 (1.59%)
Influenza viral infections	4 (3.10%)	5 (3.97%)
Viral infections NEC	2 (1.55%)	2 (1.59%)

* Includes serious and non-serious events, per regulatory definition.

M.O. comment: Based on Table 14, denosumab subjects experienced more “Tinea infections”, “Ear infections”, “Eye and eyelid infections”, “Upper respiratory tract infections”, “Urinary tract infections”, and “Herpes viral infections”. Most of the infection-related AEs were likely associated with pathogen invasion through an epidermal or mucosal surface.

Study 20040138

DRUP noted the following in the consult request.

Study 20040138 was a randomized, double-blind, placebo-controlled study to evaluate denosumab 60 mg SC Q6 months 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. Greater than 99.6% of subjects in this study had no prior chemotherapy and greater than 25% of subjects had received radiotherapy; subjects were equally distributed between the two treatment groups.

In Study 20040138, it is noteworthy that subjects had slightly more serious infections of an unspecified pathogen, including abdominal and lower respiratory tract infections. Overall infections (including serious and non-serious) were more commonly reported in subjects on denosumab than placebo, particularly bacterial, fungal and unspecified infections. These were primarily due to abdominal, dental, respiratory and urinary tract infections.

Table 15. Study 20040138 – Serious Adverse Events in the Infections SOC by HLGT
(provided by DRUP, highlighting added by current M.O.):

High Level Group Term	Denosumab 60 mg SC Q6M N = 734 n (%)	Placebo N = 734 n (%)
Bacterial infectious disorders	12 (1.64%)	7 (0.95%)
Fungal infectious disorders	1 (0.14%)	0 (0.00%)
Infections - pathogen unspecified	34 (4.65%)	27 (3.67%)
Viral infectious disorders	1 (0.14%)	2 (0.27%)

M.O. comment: Based on Table 15, more denosumab subjects had the following infection-related SAEs by HLGT: “Bacterial infectious disorders” and “Infections - pathogen unspecified”.

Table 16. Study 20040138 – Serious Adverse Events in the Infections SOC by HLGT & HLT (provided by DRUP, highlighting added by current M.O.):

High Level Group Term High Level Term	Denosumab 60 mg SC Q6M N = 734 n (%)	Placebo N = 734 n (%)
Bacterial infectious disorders		
Bacterial infections NEC	4 (0.55%)	6 (0.82%)
Clostridia infections	2 (0.27%)	0 (0.00%)
Pseudomonal infections	1 (0.14%)	0 (0.00%)
Salmonella infections	1 (0.14%)	0 (0.00%)
Staphylococcal infections	3 (0.41%)	0 (0.00%)
Streptococcal infections	2 (0.27%)	1 (0.14%)
Fungal infectious disorders		
Aspergillus infections	1 (0.14%)	0 (0.00%)
Infections - pathogen unspecified		
Abdominal and gastrointestinal infections	7 (0.96%)	4 (0.54%)
Bone and joint infections	2 (0.27%)	0 (0.00%)
Ear infections	0 (0.00%)	1 (0.14%)
Infections NEC	3 (0.41%)	1 (0.14%)
Lower respiratory tract and lung infections	17 (2.33%)	13 (1.77%)
Male reproductive tract infections	1 (0.14%)	0 (0.00%)
Sepsis, bacteraemia, viraemia and fungaemia NEC	3 (0.41%)	9 (1.22%)
Skin structures and soft tissue infections	2 (0.27%)	0 (0.00%)
Urinary tract infections	2 (0.27%)	3 (0.41%)
Viral infectious disorders		
Influenza viral infections	0 (0.00%)	1 (0.14%)
Viral infections NEC	1 (0.14%)	1 (0.14%)

M.O. comment: Based on Table 16, nine denosumab subjects vs. one placebo subject experienced the following pathogen-specific bacterial infection-related SAEs: “Clostridia infections”, “Pseudomonal infections”, “Salmonella infections”, “Staphylococcal infections”, and “Streptococcal infections”. Regarding fungal infection SAEs, one denosumab subject and no placebo subjects experienced an “Aspergillus infection”. In addition, more denosumab subjects experienced the following infection-related (pathogen-unspecified) SAEs “Abdominal and gastrointestinal infections”, “Bone and joint infections”, “Infections NEC”, “Lower respiratory tract and lung infections”, and “Skin structures and soft tissue infections”.

Table 17. Study 20040138 – All Adverse Events* in the Infections SOC by HLG
(provided by DRUP, highlighting added by current M.O.):

High Level Group Term	Denosumab 60 mg SC Q6M N = 734 n (%)	Placebo N = 734 n (%)
Bacterial infectious disorders	22 (3.01%)	18 (2.45%)
Chlamydial infectious disorders	0 (0.00%)	1 (0.14%)
Ectoparasitic disorders	0 (0.00%)	1 (0.14%)
Fungal infectious disorders	19 (2.60%)	10 (1.36%)
Infections - pathogen unspecified	217 (29.69%)	193 (26.22%)
Mycobacterial infectious disorders	0 (0.00%)	1 (0.14%)
Rickettsial infectious disorders	1 (0.14%)	0 (0.00%)
Viral infectious disorders	43 (5.88%)	42 (5.71%)

* Includes serious and non-serious events, per regulatory definition.

M.O. comment: Based on Table 17, more denosumab subjects experienced the following AEs by HLG: “Bacterial infectious disorders”, “Fungal infectious disorders”, and “Infections - pathogen unspecified.”

Table 18. Study 20040138 – All Adverse Events* in the Infections SOC by HLG
(provided by DRUP, highlighting added by current M.O.):

High Level Group Term High Level Term	Denosumab 60 mg SC Q6M N = 734 n (%)	Placebo N = 734 n (%)
Bacterial infectious disorders		
Bacterial infections NEC	11 (1.50%)	12 (1.63%)
Borrelial infections	1 (0.14%)	0 (0.00%)
Brucella infections	1 (0.14%)	0 (0.00%)
Clostridia infections	3 (0.41%)	0 (0.00%)
Escherichia infections	1 (0.14%)	0 (0.00%)
Helicobacter infections	0 (0.00%)	1 (0.14%)
Pseudomonal infections	1 (0.14%)	0 (0.00%)
Salmonella infections	1 (0.14%)	0 (0.00%)
Staphylococcal infections	4 (0.55%)	1 (0.14%)
Streptococcal infections	3 (0.41%)	4 (0.54%)
Chlamydial infectious disorders		

High Level Group Term High Level Term	Denosumab 60 mg SC Q6M N = 734 n (%)	Placebo N = 734 n (%)
Chlamydial infections	0 (0.00%)	1 (0.14%)
Ectoparasitic disorders		
Ectoparasitic infestations	0 (0.00%)	1 (0.14%)
Fungal infectious disorders		
Aspergillus infections	1 (0.14%)	0 (0.00%)
Candida infections	3 (0.41%)	3 (0.41%)
Fungal infections NEC	9 (1.23%)	5 (0.68%)
Tinea infections	6 (0.82%)	2 (0.27%)
Infections - pathogen unspecified		
Abdominal and gastrointestinal infections	17 (2.33%)	7 (0.95%)
Bone and joint infections	2 (0.27%)	1 (0.14%)
Dental and oral soft tissue infections	11 (1.50%)	6 (0.82%)
Ear infections	4 (0.55%)	6 (0.82%)
Eye and eyelid infections	2 (0.27%)	1 (0.14%)
Infections NEC	15 (2.05%)	16 (2.17%)
Lower respiratory tract and lung infections	65 (8.89%)	56 (7.61%)
Male reproductive tract infections	5 (0.68%)	1 (0.14%)
Muscle and soft tissue infections	0 (0.00%)	2 (0.27%)
Sepsis, bacteraemia, viraemia and fungaemia NEC	4 (0.55%)	9 (1.22%)
Skin structures and soft tissue infections	5 (0.68%)	3 (0.41%)
Upper respiratory tract infections	97 (13.27%)	88 (11.96%)
Urinary tract infections	46 (6.29%)	39 (5.30%)
Vascular infections	1 (0.14%)	0 (0.00%)
Mycobacterial infectious disorders		
Tuberculous infections	0 (0.00%)	1 (0.14%)
Rickettsial infectious disorders		
Rickettsial infectious disorders NEC	1 (0.14%)	0 (0.00%)
Viral infectious disorders		
Herpes viral infections	13 (1.78%)	10 (1.36%)
Influenza viral infections	23 (3.15%)	20 (2.72%)
Viral infections NEC	8 (1.09%)	13 (1.77%)

* Includes serious and non-serious events, per regulatory definition.

M.O. comment: Based on Table 18, more denosumab subjects experienced the following AEs associated with bacterial infections: "Borrelial infections", "Brucella infections", "Clostridia infections", "Escherichia infections", "Pseudomonal infections", "Salmonella infections", and "Staphylococcal infections". Regarding fungal infections, more denosumab subjects experienced: "Aspergillus infections", "Fungal infections NEC", and "Tinea infections". Regarding infections with an unspecified pathogen, more denosumab subjects experienced: "Abdominal and gastrointestinal infections", "Dental and oral soft tissue infections", "Lower

respiratory tract and lung infections”, “Male reproductive tract infections”, “Upper respiratory tract infections”, and “Urinary tract infections”. Regarding viral infections, more denosumab subjects experienced: “Herpes viral infections” and “Influenza viral infections”.

Review of Four Endocarditis Cases

PID 20030216-762526: The subject was a 75 year old female from Estonia enrolled in Study 20030216 (denosumab 60 mg Q6 months in the treatment of postmenopausal osteoporosis) who experienced the serious AE of endocarditis on (b) (5). The subject had a history of hypertension, ischemic heart disease, arrhythmia, chronic pyelonephritis, 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, CRP=81 mg/dL and transesophageal echocardiography confirmed the diagnosis of “septic endocarditis”. The patient received cefuroxime and gentamicin with resolution of the endocarditis on (b) (5). The investigator reported that, “...there was no reasonable possibility that the event may have been caused by blinded study drug [denosumab].”

M.O. comment: *It is concerning that the Sponsor was not able to identify the causative pathogen.*

PID 20030216-430063: The subject was an 82 year old female from Brazil enrolled in Study 20030216 (denosumab 60 mg Q6 months in the treatment of postmenopausal osteoporosis) who experienced the serious AE of endocarditis on 4/27/05. 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 Sponsor’s narrative, “...the subject was diagnosed with urinary tract infection and treatment included an initiation of antibiotics [cefalexin for 5 days].” On (b) (6) the subject sustained a fall and was hospitalized, however, the Sponsor 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. The Sponsor reported that an autopsy was not performed. The investigator reported that the primary causes of death were “...multiple organ and system dysfunction, acute respiratory failure, probably acute bacterial endocarditis, urinary tract infection, and systemic arterial hypertension and stated there was no reasonable possibility the events may have been caused by blinded study drug.”

M.O. comment: *The Sponsor was unable to provide the identity of the causative pathogen.*

PID 20030216-631230: The subject was a 75 year old female from Denmark enrolled in Study 20030216 (denosumab 60 mg Q6 months in the treatment of postmenopausal osteoporosis) 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 (b) (6). The investigator reported that an echocardiogram was performed; however the Sponsor did not have the results. Amgen also reported that, "A check-up in December 2007 indicated "no changes". The event did not resolve and was ongoing."

M.O. comment: *It is highly concerning that the Sponsor was unable to provide additional information, such as, the identity of the causative pathogen and the outcome of the endocarditis adverse event.*

PID 20050233-307082: The subject was an 82 year old woman from the USA enrolled in Study 20050233 (denosumab for postmenopausal women with low bone mineral density) who experienced several serious adverse events: Staphylococcal (MSSA) bacteremia, congestive heart failure, endocarditis, and subsequent mitral valve incompetence. The subject had a history of hyperlipidemia, overactive bladder, hypertension, and heartburn. Prior to the diagnosis of endocarditis, the subject had two hospitalizations: (1) MSSA bacteremia with C5-C6 discitis and discharged on IV ceftriaxone, and (2) 6 days after the first discharge, the subject was readmitted with CHF exacerbation and emboli to the brain. The patient was reportedly discharged on continued IV ceftriaxone. Eight days after the second discharge, the subject was readmitted with severe mitral valve insufficiency and was finally diagnosed with mitral valve endocarditis. During this final hospitalization, the subject had a mitral valve replacement and also reportedly had resolution of the septic emboli on MRI of the brain. Cultures of blood and the mitral valve were reported as negative for growth. On 9/9/07, the event was reported as resolved. On 12/12/07, the subject withdrew consent to receive further study therapy due to her recent adverse events.

M.O. comment: *The subject likely had MSSA endocarditis. It is concerning that the MSSA bacteremia appeared to progress to endocarditis with septic emboli to the brain while on apparently adequate IV antibacterial therapy.*

M.O. comment: *It is concerning that all 4 subjects who experienced endocarditis were treated with denosumab. It is also notable that the Sponsor was unable to provide explicit information on the causative pathogens for any of the cases, and in most cases Amgen had no medical records for the patients' hospitalizations related to the endocarditis episodes.*

V. Discussion

The consulting M.O. reviewed the literature on the TNF-related activation-induced cytokine (TRANCE)—receptor activator of nuclear factor- κ B (RANK)—osteoprotegerin (OPG) signaling axis to better understand the potential infectious disease and immunologic implications of denosumab's inhibition of receptor activator of nuclear factor- κ B ligand (RANKL). The following paragraphs will provide additional background information and describe the following immunologic functions that appear to be influenced by the TRANCE-RANK-OPG signaling axis:

- secondary lymphoid organ development (TRANCE- and RANK-deficiency in mice leads to a lack of peripheral lymph nodes and abnormalities in B cell follicle formation and marginal zone integrity in the spleen)
- dendritic cell (a.k.a., antigen presenting cells) survival and normal functioning
- establishment of T memory formation and then to wind down remaining T-cell:dendritic cell (DC) interactions
- anti-tumor immunity enhancement
- survival of interstitial DCs engaged in antigen surveillance during the interim period separating immune responses
- immunologic tolerance to food antigens and prevention of the onset of autoimmune disease (e.g., prevent cytotoxic T lymphocyte (CTL)-mediated islet cell destruction in diabetes)
- regulation of B cell maturation, proliferation, and the development of efficient antibody responses

Finally, the M.O. will describe possible infectious disease implications.

Bone provides a microenvironment that is critical for the development of hematopoietic stem cells (HSCs). All cells of the mammalian immune system are derived from bone, and various immunoregulatory cytokines influence the fate of bone cells.² Bone continues to play a role in adaptive immunity at stages beyond lymphocyte development. Activated T cells express the TNF superfamily member TRANCE which is a key differentiating factor for osteoclasts (OCs). Receptor activator of nuclear factor- κ B (RANK) is the signaling receptor for TRANCE.³

Pathogenic stimuli or self antigens are phagocytosed and presented to naïve T cells by dendritic cells (DCs). T cells provide activating signals to DCs through CD40L and in return receive optimal activating and costimulatory signals. The activated T cells are induced to express TRANCE, which provides further activating and survival signals to DCs. The DCs may negatively regulate TRANCE:RANK signaling through upregulation of the TRANCE decoy receptor, osteoprotegerin (OPG).² (Denosumab is a fully human monoclonal antibody that binds and inhibits RANKL in a manner similar to OPG.) Inflammatory cytokines (IL-1, TNF- α) produced during successful T cell immune responses, as well as calciotropic factors (PGE2 or VitD3), induce TRANCE expression by osteoblasts (OBs), which cooperate with effector T cells to induce osteoclast (OC) differentiation by providing TRANCE to OC precursors. TRANCE signaling in mature OCs induces bone-resorbing function. OBs block TRANCE binding through secretion of OPG, whereas INF- γ and IL-4 produced by effector T cells inhibit RANK signaling. Without proper regulation, excessive bone resorption leads to osteoporosis, arthritic joint erosion, and periodontal tooth loss.²

RANK expression at the RNA level is detected in most cell types or tissues examined (e.g., skeletal muscle, thymus, liver, colon, small intestine, and adrenal gland).⁴ RANK signal transduction is mediated by adapter proteins called TNF receptor-associated factors (TRAFs). Of the six TRAFs, RANK interacts with 1, 2, 3, 5, and 6.⁵

The significance of the TRANCE-RANK-OPG signaling axis in regulating the developing immune system continues to emerge. Studies of TRANCE- and RANK-deficient mice demonstrate the importance of these signals for secondary lymphoid organ development, as these animals display a lack of peripheral lymph nodes and abnormalities in B cell follicle formation and marginal zone integrity in the spleen.⁶

In the adult immune system, TRANCE modulates immunity through dendritic cells (DCs). DCs are the most potent antigen presenting cells (APCs) in the human immune system and are required to initiate T-cell mediated immunity *in vivo*. DCs differentiate from the hematopoietic monocyte/macrophage progenitor cell lineage and are close relatives of osteoclasts (OCs). TRANCE signaling has also been implicated in the regulation of DC survival. Blockade of TRANCE signaling *in vivo* results in a slightly reduced CD4⁺ T cell response to lymphocytic choriomeningitis virus (LCMV) infection, although the response is severely inhibited in the absence of CD40 signaling.⁷ TRANCE-RANK and CD40L-CD40 function may overlap. TRANCE-RANK signaling may be more important during the waning phases of an immune response to ensure that T cell memory formation is established and then to wind down remaining T cell-DC interactions, possibly through OPG interference with TRANCE signaling. In addition, enforced autocrine TRANCE-RANK signaling but not CD40L-CD40 signaling on DCs may enhance antitumor immunity.⁸

TRANCE may also be important for the survival of interstitial DCs engaged in antigen surveillance during the interim period separating immune responses. Human CD34⁺ immature DCs express both TRANCE and RANK and can therefore provide an autocrine survival signal. Peripheral maturation of these DCs leads to down-regulation of TRANCE, suggesting a requirement for an independent source of TRANCE to validate DC activation. TRANCE signaling may also be involved in the generation and maintenance of T lymphocyte tolerance. TRANCE signaling has been directly implicated in the induction of oral tolerance to food antigens in mice.⁹ Others have demonstrated that TRANCE-mediated signaling is required to prevent the onset of autoimmune disease in a TNF- α -inducible mouse model of diabetes and that blockade of TRANCE-RANK interactions were associated with decrease in CD4⁺CD25⁺ regulatory lymphocytes, which is necessary to prevent cytotoxic T lymphocyte (CTL)-mediated islet cell destruction.¹⁰

Additionally, the TRANCE-RANK-OPG axis appears to regulate B cell maturation, proliferation, and the development of efficient antibody responses. In OPG-deficient mice there is an expansion of pro-B cells in the bone marrow, whereas the opposite has been observed in TRANCE- or RANK-deficient mice.^{11, 12} Walsh et al. noted that future studies are required to elucidate the molecular mechanisms of how TRANCE might regulate the fate of pro-B cells and what the immunological consequences of this regulation might be.²

In summary, denosumab has the potential to interact and affect multiple layers and processes within the immune system: secondary lymphoid development; B cell maturation, proliferation, and function in the development of efficient antibody

responses; dendritic cell function and survival; T cell function and interaction with dendritic cells; anti-tumor immunity; antigen surveillance; immunologic tolerance to food antigens; and prevention of the onset of autoimmune disease. Due to this, no one specific pathogen can be targeted for surveillance, as it is possible that denosumab use could predispose patients to any variety of pathogens; i.e., not just those opportunistic infections typically associated with TNF inhibition, namely, tuberculosis and progressive multifocal leukoencephalopathy.

From a theoretical perspective, an adult with a fully functioning immune system may not be at increased risk of infection because of redundancies in immune signaling; however, individuals with underlying defects in the immune system (e.g., elderly patients with waning immunologic function, those on concomitant immunosuppressive medications, patients with uncontrolled diabetes or AIDS, etc.) who also take denosumab may be at increased risk for infection.

VI. Conclusions and Recommendations

Because denosumab has the potential to interact with multiple layers and processes within the immune system, the consulting M.O. recommends that, if denosumab is approved, Amgen should continue collecting information on all infection-related adverse events for the indefinite future during the postmarketing period. This may take the form of a postmarketing requirement. In addition, the consulting M.O. recommends that the product label include language that denosumab may cause serious infections that are not limited to specific pathogens. Additionally, the M.O. recommends that DRUP consider consulting an immunologist to provide further clarity on the potential mechanisms of immunosuppression that may result from denosumab's inhibition of RANKL. Please refer to Section II of this consult review for specific responses to DRUP questions.


VII. References

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Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: May 20, 2009

From: Suchitra Balakrishnan, M.D., Ph.D.
Christine Garnett, Pharm.D.

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Celia Peacock
Regulatory Project Manager
Division of Reproduction and Urology Products

Subject: QT-IRT Consult to BLA 125320

This memo responds to your consult to us dated March 6, 2009 regarding the ECG Summary Report for denosumab under BLA 125320, sponsored by Amgen, Inc. The QT-IRT received and reviewed the following materials:

- Your Consult
- ECG Summary report submitted by the Sponsor.
- Summary of Clinical Safety (e CTD 2.7.4)
- Investigators Brochure dated February 12, 2009

Summary of Sponsor's Clinical Results

- Denosumab administration was associated with mild transient decreases in serum calcium as an indirect effect of the pharmacologic effect of RANKL inhibition on bone turnover suppression (i.e., osteoclast inhibition).
 - No relationship was observed between change from baseline in QTc and change from baseline in serum calcium concentration.
- There is no discernible relationship between denosumab pharmacokinetic exposure and changes in serum calcium.
- There is no relationship between denosumab serum concentration and change in QTcF.

- Denosumab does not appear to have either a direct or indirect (i.e., hypocalcemia) effect on QTc interval duration.

Proposed Labeling:

The Sponsor has not included any information related to ECG effects of administering denosumab in the proposed label.

QT-IRT Comments to DRUP:

The sponsor's ECG evaluations appear adequate and there are no large effects on the QT interval due to denosumab.

- Outliers (patients with absolute post-dose QTcF over 500 ms or over 60 ms change from baseline have been noted in several studies although underlying ECG abnormalities were noted in several of the studies except Study 20050172 and Study 20040114. It is important to note that subjects were not excluded because of baseline QTc prolongation. Importantly, there is no imbalance in the reports of sudden death between the denosumab and comparator groups.

Background

Denosumab (AMG 162) is a fully human monoclonal antibody to receptor activator of nuclear factor kappa B (RANK) with a molecular weight of approximately 144 kDaltons. The RANK ligand (RANKL) system has been identified as a mediator of osteoclast formation, function, and survival.

The sponsor is developing denosumab as a potential treatment for postmenopausal osteoporosis (PMO), bone loss due to hormone-ablation therapy (HALT) in subjects with cancer, (b) (4)

The QT-IRT has been consulted to review the sponsor's ECG summary report to evaluate the effect of denosumab on the QT interval duration.

Non-Clinical Experience

"In preclinical studies, no effect of denosumab on QTc interval was observed. A cardiovascular safety study also demonstrated no electrocardiogram or hemodynamic (heart rate, systemic blood pressure) effects in monkeys (Study 101606) (Table 3). Although the QTc interval was not directly measured, manual assessment of ECGs did not show any alterations that would be consistent with prolongation of the QTc.

Additionally, no adverse effects were noted on respiration. In the 12-month toxicity study (Study 102090) heart rate and evaluation of the wave intervals (P, PR, QRS, ST, QT, and QTc) and amplitudes (P, Q, R, S, and T) were calculated and interpreted by 2 consultant veterinary cardiologists. No adverse effects of denosumab were noted during the conduct of the study or following 1-year of treatment (Table 3).

Table 3. Denosumab Monkey Cardiovascular Safety Pharmacology Study and 12-month Monkey Toxicology Study

Study	Cardiovascular Safety Pharmacology – Monkey (Study 101606)	12-month Monkey (Study 102090)
Doses	0, 0.3, 3, 30 (mg/kg) single SC dose	0, 1, 10, 50 mg/kg-SC monthly
ECG Time points	Every 15 minutes from 60 minutes; Pre-dose to 3 hr post-dose; every 3 hrs from 3-24 hr post-dose; every 6 hrs through 168 hr post-dose	Pre-treatment, weeks 13, 25, 53 and 66
QTc Results	N/A ^{*a}	No treatment related differences
C _{max} or AUC	C _{max} = 291.000 ng/mL	Cumulative AUC (6 doses) = 1608 mg*hr/mL
Ionized Calcium (mmol/L)	NA	No treatment related differences for total calcium
NOAEL	30 mg/kg	50 mg/kg
Safety Margin	42 ^b	OP-150 ^b ; Oncology-15 ^c

^{*a} QT/QTc intervals not measured on this study; no ECG abnormalities attributed to AMG 162 treatment were noted during the study

Margins calculated relative to preliminary, interim estimates for 2nd 60 mg Q6M dose in ongoing phase 2 study 20010223^b and predicted exposure for the proposed dose regimen (120 mg Q4W) for phase 3 oncology studies^c

In summary, the preclinical non-human primate studies indicate no effect of denosumab on the QTc interval.”

Clinical Pharmacology

The clinical pharmacology summary of denosumab is presented as an Appendix.

Previous Clinical Experience

“As of 23 December 2008, approximately 21,000 subjects have enrolled in clinical studies and have received at least 1 dose of investigational product (i.e., denosumab [approximately 13,500 subjects], matching placebo, or active control). Cumulative doses up to 1080 mg over 6 months have been evaluated in the advanced cancer setting without evidence of dose-limiting toxicity. Repeated fixed SC doses of up to 210 mg every 6 months (Q6M) have been studied for up to 24 months in postmenopausal women with low bone mineral density (BMD). Additionally, SC doses of up to 180 mg every 4 or 12 weeks (Q4W or Q12W) have been studied for up to 25 weeks in subjects with cancer-related bone metastases, and SC doses of 60 and 180 mg Q6M have been studied for up to 12 months in subjects with rheumatoid arthritis.

“In total, deaths were infrequent in all studies included in this marketing application, and fatal adverse events were typically not reported by the study site investigators to be causally associated with investigational product. Death rates overall were consistent with the expected rates of subjects with advanced age and the underlying disease processes (osteoporosis, cancer) of the populations examined, and no pattern was apparent in the

types of fatal adverse events suggestive of a causative role for denosumab or any comparator.

“By MedDRA preferred term, adverse events in the cardiac disorders system organ class that were reported in $\geq 1\%$ of subjects in either treatment group were (denosumab, placebo) angina pectoris (2.5%, 2.3%), atrial fibrillation (2.0%, 1.9%), palpitations (1.5% in both treatment groups), cardiac failure (1.3%, 0.9%), arrhythmia (1.0% in both treatment groups), and tachycardia (1.0%, 0.6%) (IAS Table SP2-6.2.1). Most cardiac events were considered mild or moderate and unrelated to investigational product (IAS Table SP2-6.2.6, IAS Table SP2-6.2.11). Serious adverse events of the cardiac disorders system organ class were reported for 4.8% of subjects in the denosumab group and 3.9% of subjects in the placebo group; no individual event accounted for cardiac serious adverse events in $\geq 1\%$ of subjects in either treatment group (IAS Table SP2-6.4.1). Fatal cardiac disorder adverse events occurred in 18 subjects (0.4%) in the denosumab group and 23 subjects (0.6%) in the placebo group (IAS Table SP2-6.3.1). Cardiac disorder events led to discontinuation of investigational product in $\leq 0.3\%$ of subjects in both treatment groups (IAS Table SP2-6.6.1).”

Reviewer's Comments: Based on review of the Summary of Safety, adverse events related to QT prolongation, i.e. sudden death and significant ventricular arrhythmias, were balanced between the denosumab and comparator groups. However, DRUP has been concerned about increased incidence of cardiac AEs (not arrhythmias alone) in the denosumab group and a separate cardio-renal consult is being done by Dr. Aliza Thompson.

ECG Summary Report

ECG Procedures

The clinical development program included an intensive assessment of the effects of denosumab on electrocardiograms, with particular emphasis on the QTc interval. ECGs were obtained at baseline, around C_{max} and at several time points during the follow-up period in most clinical studies; with the exception of the bioequivalence studies in which ECGs were obtained at screening, day -1, predose and end of study.

In all studies, ECG assessments were based on automated readings using machines provided by the investigative sites. Paper copies of ECGs were collected and manually read (semi-automated) in a blinded fashion for Studies 20010223 and 20040132. The remaining studies did not have ECGs centrally read.

Phase 1 Electrocardiogram Evaluations

Electrocardiogram results for the phase 1 studies suggest no difference in QTc interval between the denosumab and placebo/alendronate groups. With the exception of the bioequivalence studies (20050227, 20050146, 20060446, 20060286), the alendronate to denosumab transition study (20050241) and the renal impairment study (20040245) all studies were randomized, blinded to treatment within each dose cohort, placebo controlled studies. Populations studied included healthy postmenopausal females and elderly (i.e., > 50 years of age) males, postmenopausal women with low BMD and oncology patients (breast cancer and multiple myeloma). Doses ranged from 0.01 to 3 mg/kg. Subjects received a single dose of denosumab or placebo and depending on the dose they received subjects were followed for up to 37 weeks.

Electrocardiograms were obtained at screening, predose, around C_{max} and at several time points during the follow-up period.

Reviewer's Comments: In study 20030180 (women with PMO), one subject in the lowest denosumab dose group of 0.03 mg/kg had a QTcF > 500 ms during the study.

One subject in the bioequivalence studies (study 20060286) had a QTcF change from baseline > 60 ms. For this subject, screening and day -1 QTcF values were 396 ms and 401 ms, respectively. At the end of study the QTcF was 463 ms. Non-specific T-wave changes were noted on the baseline and end of study electrocardiograms, which could confound interpretation of the QT interval.

In study 20050241, one subject who was transitioned from alendronate to denosumab 60 mg SC had a QTcF > 500 ms (i.e., 512 ms) on study day 3 which was also a > 60 ms change from baseline. Screening and day -1 QTcF values were 436 ms and 426 ms, respectively. On study days 1 and 2 QTcF values were 429 ms and 432 ms, respectively, and on days 4, 15 and 107 (end of study) were 444 ms, 467 ms, and 465 ms, respectively. Upon further review of the ECGs by an Amgen Cardiologist the subject was noted to have biphasic T waves and U waves at screening and baseline with the presence of U waves throughout the study.

In Study 20040245 (subjects with varying degrees of renal impairment), no subject with normal renal function had a maximum post-dose QTcF interval > 450 ms. The ESRD group had a greater proportion of subjects with maximum post-dose QTcF > 450 ms than the other renal groups. All 6 of the subjects with a QTcF interval > 480 ms had, per comments on the tracings, underlying cardiac abnormalities (e.g., ST-T abnormalities, abnormal repolarization, atrial fibrillation) that could confound the interpretation of the QT interval.

Phase 2 Electrocardiogram Evaluations

Study 20010223

This was a phase 2 randomized, placebo-controlled, multi-center, parallel-group, dose ranging study in postmenopausal women with low BMD evaluating the effect of denosumab treatment compared with placebo on BMD over 12 months.

The maximum change from baseline in QTc for denosumab treated subjects and subjects who received placebo and alendronate was determined for all cohorts at months 12 (Table 35). There were no significant differences in the changes from baseline in QTcF across the denosumab and placebo treatment groups. The mean maximum change from baseline for QTcF ranged from 5.7 ms to 17.5 ms across all denosumab cohorts vs. 5.6 ms for the placebo and 14 ms for alendronate treated subjects.

Table 35. Summary of Maximum Change From Baseline in Electrocardiogram
(Study 20010223)

Parameter	Denosumab Q3M				Denosumab Q6M				Alendronat e	All (N = 406)
	Placebo (N = 46)	6 mg (N = 43)	14 mg (N = 44)	30 mg (N = 40)	14 mg (N = 53)	60 mg (N = 47)	100 mg (N = 41)	210 mg (N = 46)	(N = 46)	
Baseline QTcF Interval in msec										
N	46	41	43	38	52	47	40	46	44	397
Mean	398.6	400.5	402.9	401.8	401.2	398.3	398.4	399.1	400	400.1
SD	22.2	21	20.7	21	21	21.4	18.9	24.1	27.1	21.9
Median	394.5	399	402	403	403.5	402	392.5	399	395	399
Min, Max	353, 442	351, 451	352, 451	365, 455	354, 453	355, 450	362, 455	346, 471	348, 459	346, 471
Post-Baseline Maximum QTcF Interval in msec										
N	46	43	44	40	53	47	41	46	46	406
Mean	409.1	412.5	413.5	412.2	410.5	410.2	419.3	413.2	415.8	412.8
SD	19.1	22.3	21.3	21.5	18.6	18.3	17.3	21.6	23.7	20.5
Median	407.5	415	411	410	410	410	420	413.5	414.5	412
Min, Max	372, 446	357, 473	377, 460	371, 455	375, 467	377, 450	387, 477	346, 471	371, 465	346, 477

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Bazett-Corrected QT Interval (QTcB) (millisecond) = $QT/(RR/1000)^{1/2}$
 Fridericia-Corrected QT Interval (QTcF) (millisecond) = $QT/(RR/1000)^{1/3}$
 Baseline is the last value recorded before first dose.

Program: /stat/amg162/meta/bla_2008bone/analysis/ecgeval/tables/program/t_ecg_summ_223.sas
 Output: t8-03_001_003_ecg_summ_223_m12.rtf (Date Generated: 24NOV2008: 9:34:06) Source Data: a010223.aeg

Table 35. Summary of Maximum Change From Baseline in Electrocardiogram
(Study 20010223)

Parameter	Denosumab Q3M				Denosumab Q6M				Alendronat e	All (N = 406)
	Placebo (N = 46)	6 mg (N = 43)	14 mg (N = 44)	30 mg (N = 40)	14 mg (N = 53)	60 mg (N = 47)	100 mg (N = 41)	210 mg (N = 46)	(N = 46)	
Post-Baseline Maximum Change QTcF Interval in msec										
N	43	36	41	36	50	46	39	43	44	378
Mean	3.3	11.9	8.8	6.8	6.5	8	19.7	11.1	13.2	9.8
SD	25.9	21.7	17.3	16.2	15.4	20.3	19.1	20.1	19.9	20
Median	5	5.5	7	12	6	7.5	21	13	13	9.5
Min, Max	-79, 52	-31, 83	-41, 43	-38, 32	-37, 47	-29, 77	-17, 57	-30, 50	-47, 52	-79, 83
Baseline QTcB Interval in msec										
N	46	41	43	38	52	47	40	46	44	397
Mean	404.6	407.2	408.3	407.6	406.6	407.1	404.4	403.5	406.3	406.2
SD	26.3	23.2	22.6	25.3	23.8	22.2	19.2	25.7	28.4	24
Median	403	405	411	405.5	409	406	401.5	401	401.5	404
Min, Max	357, 475	354, 457	348, 457	349, 468	367, 460	360, 447	370, 438	338, 470	356, 469	338, 475

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Bazett-Corrected QT Interval (QTcB) (millisecond) = $QT/(RR/1000)^{1/2}$
 Fridericia-Corrected QT Interval (QTcF) (millisecond) = $QT/(RR/1000)^{1/3}$
 Baseline is the last value recorded before first dose.

Program: /stat/amg162/meta/bla_2008bone/analysis/ecgeval/tables/program/t_ecg_summ_223.sas
 Output: t8-03_001_003_ecg_summ_223_m12.rtf (Date Generated: 24NOV2008: 9:34:06) Source Data: a010223.aeg

Study 20040144

In Study 20040144, patients with rheumatoid arthritis receiving denosumab 60 mg and 180 mg q 6 months or placebo were evaluated over 18 months. The post baseline mean maximum change in QTcF was 6.2 ms, 8.4 ms and 6.4 ms for the placebo, denosumab 60 mg and 180 mg dose groups, respectively. One subject in each of the 2 denosumab dose groups had a QTcF value > 500 ms while no subject in the placebo group had a QTcF value >500 ms. One subject in the placebo group and 2 subjects in the denosumab 60 mg dose group had a QTcF change from baseline >60 ms. One subject randomized to denosumab 180 mg Q6M group had a Day 1 QTc of 456 ms. The subject was subsequently found to have an intraventricular conduction delay at the 6 month visit and was diagnosed with an intermittent left bundle branch block (LBBB) on the basis of an exercise stress test. There was no evidence of arrhythmia or ischemia. In the presence of a LBBB the QTc is not evaluable. The other subject was randomized to denosumab 60 mg Q6M and upon manual over read of the ECG tracings by an Amgen physician (cardiologist) there was no prolongation of the QTc interval noted.

Study 20050172

Study 20050172 was a dose response study of 12 months duration performed in Japanese post menopausal women with osteoporosis. Subjects were randomized to receive placebo, or denosumab at doses of 14, 60 or 100 mg on day 1 and month 6.

Table 39. Summary of Baseline, Maximum, and Maximum Change Electrocardiogram (Study 20050172, All Treated Subjects)

Parameter	Placebo (N = 54)	Denosumab			Total (N = 158)
		14 mg Q6M (N = 53)	60 mg Q6M (N = 54)	100 mg Q6M (N = 51)	
Post-Baseline Maximum Change QTcF Interval in msec					
N	54	52	54	50	156
Mean	9.8	11.1	10.9	8.2	10.1
SD	12.2	16.3	14.9	12.1	14.5
Median	8.0	7.5	9.2	6.6	7.7
Min, Max	-10, 48	-23, 88	-14, 85	-19, 40	-23, 88
Baseline QTcB Interval in msec					
N	54	53	54	51	158
Mean	413.1	419.9	425.6	420.6	422.1
SD	22.3	18.9	20.8	19.9	19.9
Median	413.4	418.5	431.2	417.5	422.6
Min, Max	356, 476	372, 454	381, 509	385, 484	372, 509

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Bazett-Corrected QT Interval (QTcB) (millisecond) = $QT/(RR/1000)^{1/2}$

Fridericia-Corrected QT Interval (QTcF) (millisecond) = $QT/(RR/1000)^{1/3}$

Baseline is the last value recorded before first dose.

Program: /stat/amq162/meta/bfa 2008bone/analysis/ecqeval/tables/program/t ecq_minmax.sas

Output: t8-02_004_ecg_minmax_172.rtf (Date Generated: 10NOV2008:11:31:26) Source Data: a050172.aeg

One subject in each of the denosumab 14-mg and 60-mg dose groups had a >60-ms change from baseline in QTcF. No subject in the denosumab 100-mg dose group or placebo group had a QTcF change from baseline >60 ms. One subject in the 14-mg and two in the 60-mg denosumab groups had a QTcF >500 ms during the study while no subjects in the denosumab 100-mg dose group or the placebo group had a QTcF >500 ms.

Study 20040113

In the phase 2 oncology study in patients with breast cancer results were similar between denosumab and bisphosphonate treated subjects. The mean maximum change in QTcF ranged from 8.5 ms to 25 ms from the denosumab groups and was 23 ms for the bisphosphonate group. Only one subject (denosumab 30 mg Q4W group) had a QTcF >500 ms (Table 43). Three subjects in the bisphosphonate group and 17 in the denosumab treatment groups had a change from baseline that was >60 ms (Table 44) with the incidence being similar in the 2 groups. The incidence in the individual treatment groups was similar and there did not appear to be a relationship to dose.

**Table 43. Maximum Post-Dose QTcF/QTcB by Category
(Study 20040113, All Treated Subjects)**

	Bisphosphonate IV Q4W (N = 43)	Denosumab					Total (N = 211)
		30 mg Q4W (N = 42)	120 mg Q4W (N = 41)	180 mg Q4W (N = 43)	60 mg Q12W (N = 42)	180 mg Q12W (N = 43)	
QTcF (msec) Category							
≤ 450	32 (74.4)	37 (88.1)	36 (87.8)	38 (88.4)	37 (88.1)	36 (83.7)	184 (87.2)
>450 - 480	6 (14.0)	1 (2.4)	2 (4.9)	1 (2.3)	0 (0.0)	4 (9.3)	8 (3.8)
>480 - 500	0 (0.0)	1 (2.4)	1 (2.4)	0 (0.0)	1 (2.4)	1 (2.3)	4 (1.9)
>500	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
QTcB (msec) Category							
≤ 450	22 (51.2)	29 (69.0)	32 (78.0)	30 (69.8)	28 (66.7)	30 (69.8)	149 (70.6)
>450 - 480	12 (27.9)	7 (16.7)	4 (9.8)	8 (18.6)	9 (21.4)	8 (18.6)	36 (17.1)
>480 - 500	3 (7.0)	2 (4.8)	2 (4.9)	1 (2.3)	0 (0.0)	1 (2.3)	6 (2.8)
>500	1 (2.3)	2 (4.8)	1 (2.4)	0 (0.0)	1 (2.4)	2 (4.7)	6 (2.8)

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Bazett-Corrected QT Interval (QTcB) (millisecond) = $QT/(RR/1000)^{1/2}$
Fridericia-Corrected QT Interval (QTcF) (millisecond) = $QT/(RR/1000)^{1/3}$

Program: /stat/amq162/meta/bia_2008bone/analysis/ecgeval/tables/program/t_ecg_max.sas
Output: 18-01_001_001_ecg_max_val_113.rtf (Date Generated: 10NOV2008:11:26:37) Source Data: a040113.aeg

**Table 44. Maximum Change From Baseline QTcF/QTcB by Category
(Study 20040113, All Treated Subjects)**

	Bisphosphonate IV Q4W (N = 43)	Denosumab					Total (N = 211)
		30 mg Q4W (N = 42)	120 mg Q4W (N = 41)	180 mg Q4W (N = 43)	60 mg Q12W (N = 42)	180 mg Q12W (N = 43)	
QTcF (msec) Category							
≤ 30	21 (48.8)	26 (61.9)	25 (61.0)	30 (69.8)	30 (71.4)	32 (74.4)	143 (67.8)
>30 - 60	12 (27.9)	8 (19.0)	6 (14.6)	4 (9.3)	4 (9.5)	6 (14.0)	28 (13.3)
>60	3 (7.0)	4 (9.5)	7 (17.1)	3 (7.0)	2 (4.8)	1 (2.3)	17 (8.1)
QTcB (msec) Category							
≤ 30	21 (48.8)	24 (57.1)	26 (63.4)	30 (69.8)	31 (73.8)	30 (69.8)	141 (66.8)
>30 - 60	9 (20.9)	9 (21.4)	3 (7.3)	4 (9.3)	2 (4.8)	7 (16.3)	25 (11.8)
>60	6 (14.0)	5 (11.9)	9 (22.0)	3 (7.0)	3 (7.1)	2 (4.7)	22 (10.4)

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Bazett-Corrected QT Interval (QTcB) (millisecond) = $QT/(RR/1000)^{1/2}$
Fridericia-Corrected QT Interval (QTcF) (millisecond) = $QT/(RR/1000)^{1/3}$
Baseline is the last value recorded before first dose.

Program: /stat/amq162/meta/bia_2008bone/analysis/ecgeval/tables/program/t_ecg_max.sas
Output: 18-01_001_002_ecg_max_chg_113.rtf (Date Generated: 10NOV2008:11:26:37) Source Data: a040113.aeg

Study 20040114

In the phase 2 oncology study in patients with multiple myeloma and solid tumors results were similar between denosumab and bisphosphonate treated subjects with the mean maximum change being 12.8 ms, 5 ms and -0.8 ms, respectively (Table 45). One subject in the denosumab

180 mg q 4W group had a QTcF > 500 ms (Table 46). One subject in the bisphosphonate group and 2 in the denosumab 180-mg q 4W group had increases of > 60 ms (Table 47).

Table 45. Summary of Baseline, Maximum, and Maximum Change Electrocardiogram (Study 20040114, All Treated Subjects)

Parameter	Bisphosphonate	Denosumab		
	IV Q4W (N = 35)	180 mg Q4W (N = 38)	180 mg Q12W (N = 35)	Total (N = 73)
Post-Baseline Maximum Change QTcF Interval in msec				
N	28	30	23	53
Mean	12.8	5.0	-0.8	2.5
SD	63.0	37.7	28.6	33.9
Median	1.7	4.4	0.1	3.3
Min, Max	-40, 313	-87, 93	-61, 40	-87, 93
Baseline QTcB Interval in msec				
N	34	38	31	69
Mean	427.8	437.7	437.4	437.5
SD	55.8	59.0	37.7	50.2
Median	441.6	427.8	439.2	433.8
Min, Max	183, 505	310, 693	325, 539	310, 693

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Bazett-Corrected QT Interval (QTcB) (millisecond) = $QT/(RR/1000)^{1/2}$

Fridericia-Corrected QT Interval (QTcF) (millisecond) = $QT/(RR/1000)^{1/3}$

Baseline is the last value recorded before first dose.

Program: /stat/amg162/meta/bia_2008bone/analysis/ecgeval/tables/program/t_eog_minmax.sas
Output: t8-02_002_ecq_minmax_114.rtf (Date Generated: 10NOV2008:11:31:26) Source Data:
a040114.aeg

Table 46. Maximum Post-Dose QTcF/QTcB by Category During Treatment Phase (Study 20040114, All Treated Subjects)

	Bisphosphonate IV Q4W (N = 35)	Denosumab		
		180 mg Q4W (N = 38)	180 mg Q12W (N = 35)	Total (N = 73)
QTcF (msec) Category				
≤ 450	24 (68.6)	22 (57.9)	21 (60.0)	43 (58.9)
>450 - 480	4 (11.4)	4 (10.5)	3 (8.6)	7 (9.6)
>480 - 500	1 (2.9)	3 (7.9)	0 (0.0)	3 (4.1)
>500	0 (0.0)	1 (2.6)	0 (0.0)	1 (1.4)
QTcB (msec) Category				
≤ 450	22 (62.9)	18 (47.4)	15 (42.9)	33 (45.2)
>450 - 480	4 (11.4)	7 (18.4)	9 (25.7)	16 (21.9)
>480 - 500	2 (5.7)	1 (2.6)	0 (0.0)	1 (1.4)
>500	1 (2.9)	4 (10.5)	0 (0.0)	4 (5.5)

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Bazett-Corrected QT Interval (QTcB) (millisecond) = $QT/(RR/1000)^{1/2}$
 Fridericia-Corrected QT Interval (QTcF) (millisecond) = $QT/(RR/1000)^{1/3}$

Program: /stat/amg162/meta/bia_2008bone/analysis/ecgeval/tables/program/t_ecg_max.sas
 Output: t8-01_002_001_ecg_max_val_114.rtf (Date Generated: 10NOV2008:11:26:37) Source Data:
 a040114.aeg

Table 47. Maximum Change From Baseline QTcF/QTcB by Category During Treatment Phase (Study 20040114, All Treated Subjects)

	Bisphosphonate IV Q4W (N = 35)	Denosumab		
		180 mg Q4W (N = 38)	180 mg Q12W (N = 35)	Total (N = 73)
QTcF (msec) Category				
≤ 30	23 (65.7)	24 (63.2)	19 (54.3)	43 (58.9)
>30 - 60	4 (11.4)	4 (10.5)	4 (11.4)	8 (11.0)
>60	1 (2.9)	2 (5.3)	0 (0.0)	2 (2.7)
QTcB (msec) Category				
≤ 30	23 (65.7)	24 (63.2)	21 (60.0)	45 (61.6)
>30 - 60	3 (8.6)	2 (5.3)	2 (5.7)	4 (5.5)
>60	2 (5.7)	4 (10.5)	0 (0.0)	4 (5.5)

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Bazett-Corrected QT Interval (QTcB) (millisecond) = $QT/(RR/1000)^{1/2}$
 Fridericia-Corrected QT Interval (QTcF) (millisecond) = $QT/(RR/1000)^{1/3}$
 Baseline is the last value recorded before first dose.

Program: /stat/amg162/meta/bia_2008bone/analysis/ecgeval/tables/program/t_ecg_max.sas
 Output: t8-01_002_002_ecg_max_chg_114.rtf (Date Generated: 10NOV2008:11:26:37) Source Data:
 a040114.aeg

Phase 3 Electrocardiogram Evaluation

Study 20040132

In Study 20040132, a phase 3 study evaluating the effect of denosumab in preventing bone loss, there was no notable difference in QTcF interval between denosumab and placebo treated subjects over the 2 year treatment period.

Table 50. Summary of Baseline, Maximum, and Maximum Change Overread Electrocardiogram (Study 20040132, All Treated Subjects)

Parameter	Placebo (N = 165)	Denosumab 60 mg Q6M (N = 164)
Post-Baseline Maximum Change QTcF Interval in msec		
N	158	162
Mean	9.5	10.3
SD	13.9	13.1
Median	10.0	10.0
Min, Max	-39, 47	-38, 56
Baseline QTcB Interval in msec		
N	161	163
Mean	418.3	421.1
SD	20.7	23.2
Median	418.0	419.0
Min, Max	360, 481	364, 504

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Bazett-Corrected QT Interval (QTcB) (millisecond) = $QT/(RR/1000)^{1/2}$

Fridericia-Corrected QT Interval (QTcF) (millisecond) = $QT/(RR/1000)^{1/3}$

Baseline is the mean of the last non-missing values recorded before first dose.

Program: /stat/amg162/meta/bia_2008bone/analysis/ecgeval/tables/program/t_ecg_minmax.sas

Output: t8-02_008_ecg_minmax_132.rtf (Date Generated: 10NOV2008:11:31:26) Source Data: a040132.aeg

Table 51. QTc Interval (Fridericia's Correction) Categories by Visit (Safety Subset) (20040132 24-Month Softlock Analysis)

QTc Interval (Fridericia Correction)	Change from Baseline (msecs)		Actual Value (msecs)	
	> 30 n/n1 (%)	> 60 n/n1 (%)	> 470 n/n2 (%)	> 500 n/n2 (%)
Month 1				
Placebo (N = 165)	0/153 (0)	0/153 (0)	0/154 (0)	0/154 (0)
Denosumab 60 mg Q6M (N = 164)	4/159 (3)	0/159 (0)	1/159 (1)	1/159 (1)
Month 12				
Placebo (N = 165)	2/143 (1)	0/143 (0)	0/144 (0)	0/144 (0)
Denosumab 60 mg Q6M (N = 164)	4/153 (3)	0/153 (0)	2/154 (1)	1/154 (1)
Month 18				
Placebo (N = 165)	3/142 (2)	0/142 (0)	0/143 (0)	0/143 (0)
Denosumab 60 mg Q6M (N = 164)	2/142 (1)	0/142 (0)	4/143 (3)	0/143 (0)
Month 24				
Placebo (N = 165)	2/134 (1)	0/134 (0)	0/135 (0)	0/135 (0)
Denosumab 60 mg Q6M (N = 164)	2/135 (1)	0/135 (0)	4/136 (3)	0/136 (0)

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n = Number of subjects with incidence

n1 = Number of subjects who had nonmissing data at baseline and the timepoint of interest

n2 = Number of subjects who had nonmissing data at the timepoint of interest

Program: /stat/amq162/osteoc/20040132/analysis/mon24/adhoc/program/t eq overread qtocat.sas

Output: t14-08_002_514_eq_overread_qtocat_qtcf.rtf (Date Generated: 14OCT2008:18:12:31) Source

Data: adam.aeg

There were 11 denosumab treated subjects who had a QTcF >470 ms, one of which had a QTcF >500 ms. All 11 subjects had ECG abnormalities including left bundle branch block, altered T waves (e.g., flat, inverted), ECGs with mixed voltage, atrial fibrillation, and a ventricular pacemaker, confounding interpretation of the QT interval. One placebo treated subject had QTcF >470 ms and no placebo subjects had a QTcF >500 ms. There was one denosumab treated subject who had a QTcF value >500 ms at month 1 and month 12. The baseline QTcF value in this subject was 484 ms. Post-dose QTcF values at month 1, 12, 18 and 24 were 504 ms, 517 ms, 494 ms and 480 ms, respectively. This subject was noted to have a LBBB dating back to 1969 which persisted throughout the study.

One placebo treated subject and 6 denosumab treated subjects had a QTcF value between 470 and 480 ms during the study. Two of the denosumab treated subjects had baseline QTcF > 470; in both subjects the baseline values were higher than the post-dose QTcF values.

Thank you for requesting our input into the development of this product under IND. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

APPENDIX

Clinical Pharmacology Summary

Therapeutic dose	60 mg q 6 monthly	
Maximum tolerated dose	MTD not identified. The single and multiple-dose regimens listed in "Maximum dose tested" were well-tolerated	
Principal adverse events	No dose limiting adverse events have been identified. PMO most common adverse events: back pain (34.1% denosumab, 34.0% placebo), arthralgia (20.4% each group), hypertension (15.3% denosumab, 16.1% placebo), nasopharyngitis (14.8% denosumab, 15.6% placebo), extremity pain (11.8% denosumab, 11.2% placebo), and osteoarthritis (10.9% denosumab, 11.1% placebo). HALT most common adverse events: arthralgia (14.3% denosumab, 13.0% placebo), back pain (11.5% denosumab, 10.5% placebo), and constipation (10.2% in both treatment groups).	
Maximum dose tested	Single Dose	3 mg/kg intravenously (20010124)
	Multiple Dose	210 mg q 6 monthly for 24 months (PMO) (20010223) 180 mg q 4 weeks for 6 months (Oncology) (20040113 and 20040114)
Exposures Achieved at Maximum Tested Dose	Single Dose	3 mg/kg IV: mean (SD) C_0 = 110000 (26600) ng/mL; mean (SD) AUC_{0-inf} = 2760 (738) mcg*day/mL (Study 20010124)
	Multiple Dose	210 mg q 6 monthly: mean (SD) C_{max} = 30000 (12700) ng/mL; mean (SD) AUC_{0-4} = 2140 (988) mcg*day/mL (2 nd dose, Study 20010223) 180 mg q 4 weeks: mean (SD) C_{max} = 45300 (15300) ng/mL; mean (SD) AUC_{0-4} = 1090 (356) mcg*day/mL (dose 5, Study 20040113)
Range of linear PK	For fixed doses of 60 to 210 mg denosumab, exposure to denosumab increased approximately dose proportionally.	
Accumulation at steady state	No accumulation was observed upon multiple-dosing of 60 mg SC once every 6 months (Study 20010223, mean accumulation ratio = 0.910).	
Metabolites	None (monoclonal antibody)	
Absorption	Absolute/Relative Bioavailability	Based on population pharmacokinetic analysis, denosumab bioavailability after SC administration is 61%
	Tmax	Following a single SC dose of 60 mg, maximum serum denosumab concentrations (C_{max}) occurred in a median time of 10 days (range 2 to 28 days) Median (range) for metabolites – no metabolites; monoclonal antibody.

Distribution	Vd/F or Vd	Based on population pharmacokinetic analysis (2-compartment model): volume of central compartment = 2460 mL; volume of peripheral compartment = 1300 mL Based on non-compartmental analysis (1 mg/kg IV): mean (SD) V_{ss} = 54.1 (5.67) mL/kg
	% bound	not applicable
Elimination	Route	2 proposed mechanisms: (1) a saturable mechanism likely related to binding to RANKL ("target-mediated drug disposition") and (2) a nonsaturable mechanism likely via nonspecific catabolism by cells of the reticuloendothelial system
	Terminal t _{1/2}	Following a 60 mg SC dose, serum denosumab levels declined after C_{max} with a half-life of 26 days (range 6 to 52 days) for a period of 3 months (range 1.5 to 4.5 months) (Study 20010223). Due to non-linear PK, the half-life for the terminal portion of the concentration-time profile is shorter due to more rapid elimination (eg. mean = 8 days, 1 mg/kg SC, study 20010124) Mean (%CV) for metabolites– no metabolites; monoclonal antibody.
	CL/F or CL	Based on population PK analysis, CL = 3.03 mL/hr (nonsaturable mechanism); V_m = 3.14 mcg/hr, K_m = 216 ng/mL (saturable mechanism)
Intrinsic Factors	Age	Based on population PK analysis, the pharmacokinetics of denosumab were not affected by age in postmenopausal women or in prostate or breast cancer patients undergoing hormone ablation whose age ranged from 28 to 87 years.
	Sex	Denosumab pharmacokinetics are not markedly different between men and women. Median denosumab AUC and C_{max} values were <7% and <1% different, respectively, and overlap was observed in both AUC and C_{max} interquartile ranges between healthy adult men and women following SC administration of 60 mg.
	Race	Although data are limited in non-white subjects, there did not appear to be a notable difference in exposure in white compared to non-white subjects. Differences in mean AUC and C_{max} values were <26% and 4%, respectively, between white and non-white subjects and intersubject variability was similar (60 mg SC dose). In addition, denosumab exposure did not differ notably and intersubject variability was similar between Japanese and non-Japanese subjects.

	Hepatic & Renal Impairment	<p>In a study of 55 patients with varying degrees of renal function (Study 20040245), including patients on dialysis, the degree of renal impairment had no effect on the pharmacokinetics of denosumab.</p> <p>The PK profile of denosumab in subjects with hepatic impairment was not evaluated.</p>
Extrinsic Factors	Drug interactions	<p>No formal drug-drug interaction studies have been conducted with denosumab.</p> <p>The pharmacokinetics and pharmacodynamics of denosumab were similar in postmenopausal women with osteoporosis transitioning from alendronate therapy compared to those who had not received prior alendronate therapy and in patients receiving hormone ablation for prostate or breast cancer.</p>
	Food Effects	<p>Not evaluated; however, food effects are not expected, since denosumab is administered by subcutaneous injection.</p>
Expected High Clinical Exposure Scenario	<p>Drug-drug interactions between denosumab and concomitantly administered small molecule drugs are not expected.</p> <p>However, exposures approximately 4- to 5-fold those associated with the proposed therapeutic dose of 60 mg q 6-monthly (Study 20010223, 2nd 60 mg dose: mean C_{max} = 6940 ng/mL, mean AUC = 448 mcg*day/mL) were well-tolerated following dosing of 210 mg q 6-monthly (Study 20010223, see above "Exposures Achieved at Maximum Tested Dose")</p>	

MEDICAL REVIEW OF A PRIORITY REVIEW REQUEST

BLA: 125,320

DRUG: Prolia (denosumab, human IgG2 monoclonal antibody against RANKL)

INDICATION: Treatment and prevention of osteoporosis in postmenopausal women and treatment and prevention of bone loss in patients undergoing hormone ablation for prostate or breast cancer.

COMPANY: Amgen

DATE OF SUBMISSION: December 19, 2008

DATE OF REVIEW: January 5, 2009

Amgen has submitted this BLA for the use of Prolia (denosumab, a human IgG2 monoclonal antibody against receptor activator of nuclear factor kappa B (RANK) ligand) for the treatment and prevention of osteoporosis in postmenopausal women and treatment and prevention of bone loss in patients undergoing hormone ablation for prostate or breast cancer.

The sponsor considers that all criteria are met for priority review and is requesting priority review for all indications.

Specifically, the sponsor states that there is an unmet medical need for safe and effective treatment for each of the indications sought and that data from denosumab clinical trials clearly demonstrate that this new agent has the potential to provide:

- *A significant improvement compared to marketed products for postmenopausal osteoporosis, as demonstrated by the potential for increased patient compliance due to its mode of administration and evidence of increased efficacy for fracture risk reduction in patients at high risk for subsequent fracture, whose risk for fracture is not satisfactorily addressed with current therapies.*

Reviewer's Comment: Treatment of osteoporosis in postmenopausal women is the primary indication sought by the sponsor. For the approval of all osteoporosis therapies except estrogens, fracture efficacy must be demonstrated prior to the approval of any secondary indication which relies on bone mineral density (BMD) as the primary endpoint. The Sponsor states that denosumab provides a significant improvement compared to marketed products for postmenopausal osteoporosis as demonstrated by the potential for increased patient compliance due to its mode of

- *A safe and effective therapy with the potential for good patient compliance due to its mode of administration, which increases bone mineral density and decreases the risk of fracture in women with breast cancer and men with prostate cancer with bone loss due to hormone ablation treatment, where no satisfactory or approved alternative therapy exists.*

Reviewer's Comment: This reviewer firmly believes that the proposed indication "treatment and prevention of bone loss in patients undergoing hormone ablation for breast cancer" can be subsumed under the current indication "treatment and prevention of osteoporosis in postmenopausal women". The result of aromatase inhibition is estrogen levels that are similar or potentially less than postmenopausal levels. Although not specifically indicated for bone loss due to aromatase inhibitor therapy, bisphosphonates are currently advocated for women with breast cancer undergoing aromatase inhibitor therapy and have risk factors for fracture¹. Risk factors identified include a BMD T-score less than -1.5, age greater than 65 years, low BMI, family history of hip fracture, personal history of fragility fracture, oral corticosteroid use > 6 months and smoking. These risk factors are the same as those for postmenopausal women.

The pivotal study for this indication (treatment and prevention of bone loss in patients undergoing hormone ablation for breast cancer) is study 135. In study 135, the mean age of enrolled subjects was 59.5 years, with 30% of enrolled subjects greater than age 65 years. The mean BMD T-score at baseline was -1.1. This population is similar to the populations evaluated for the current postmenopausal osteoporosis indications. After exclusion of estrogen and estrogen agonist/antagonist products, there are twelve products currently approved for the prevention and treatment of postmenopausal osteoporosis. As previously discussed, the effectiveness achieved with denosumab for the treatment of postmenopausal osteoporosis is not significantly better than that achieved with other available therapies. In addition, the introduction of an every 6 months subcutaneous injection dosing regimen that must be administered by the healthcare provider does not offer a significant improvement for increased patient compliance.

This reviewer firmly believes that the proposed indication "treatment and prevention of bone loss in patients undergoing hormone ablation for prostate cancer" can be subsumed under the current indication "treatment to increase bone mass in men with osteoporosis". The goal of androgen deprivation therapy is to achieve serum testosterone levels that are below castrate levels (< 50 ng/dL). Trials for the current therapies for male osteoporosis included hypogonadal men. As with the denosumab trial, the primary endpoint in these studies was percent change in lumbar spine BMD at 24 months. As noted in the table below, the effectiveness achieved with denosumab is not significantly better than that achieved with other available therapies.

¹ Hadj P, et.al. Practical guidance for the management of aromatase-inhibitor associated bone loss. 2008. Annals of Oncology 19: 1407-1416.

Percent Change in Lumbar Spine BMD in Men at Month 24*					
	placebo		drug		treatment difference
Drug	n	% change	n	% change	%
Denosumab	716	-1.0%	714	5.6%	6.7
Zoledronic**		6.2%**		6.1%	
Alendronate					5.3
Risedronate	93		191		4.5
Forteo***	147	0.5	151	5.9	
<ul style="list-style-type: none"> • Data from the denosumab study 138 synopsis and from the product labels for approved osteoporosis therapies • ** active control, not placebo • *** median 10 month treatment duration 					

Summary and Recommendation: This reviewer believes that Amgen's marketing application for the use of denosumab for the treatment and prevention of osteoporosis in postmenopausal women and treatment and prevention of bone loss in patients undergoing hormone ablation for prostate or breast cancer does not meet the criteria for priority review.

Treatment of osteoporosis in postmenopausal women is the primary indication sought by the sponsor. For the approval of all osteoporosis therapies except estrogens, fracture efficacy must be demonstrated prior to the approval of any secondary indication which relies on bone mineral density (BMD) as the primary endpoint. The secondary indications sought by the sponsor all use BMD as the primary endpoint. Therefore, fracture efficacy must be demonstrated in the postmenopausal osteoporosis treatment trial prior to approval of these secondary indications. The fracture reduction effectiveness achieved with denosumab is not significantly better than that achieved with other available osteoporosis therapies. In addition, there are currently eight therapies available for the treatment of osteoporosis with dosing regimens that range from once daily oral products to a once yearly intravenous product. The introduction of an every 6 months subcutaneous injection dosing regimen which must be administered by a healthcare professional does not offer a significant improvement for increased patient compliance.