CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125320

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

MEMORANDUM

BLA/Serial Number:	BLA 125320
Drug Name:	PROLIA (denosumab)
Indication(s):	
Applicant:	Amgen
Date Review Completed:	April 29, 2010
To:	Theresa Kehoe, MD, Team Leader, DRUP
Statistical Reviewer:	Mat Soukup, PhD, Division of Biometrics VII
Concurring Reviewers:	Mark Levenson, PhD, Acting Deputy Director, Division of Biometrics VII
Medical Division:	Division Of Reproductive And Urologic Products
Clinical Team:	Carolyn A. McCloskey, MD, MPH, DEPI Cynthia J. Kornegay, PhD, Team Leader, DEPI
Subject:	Statistical Review of Protocol 20090522

1. INTRODUCTION AND BACKGROUND

The sponsor, Amgen, submitted BLA 125320 for denosumab seeking the indication for treatment of postmenopausal osteoporosis (PMO). The agency received the original application on December 19, 2008. The Division of Reproductive and Urologic Products (DRUP) sent a complete response (CR) letter dated October 16, 2009 to Amgen citing deficiencies in the proposed post-marketing observational studies. The following is the deficiency cited in the CR letter.

"We have reviewed your proposed postmarketing observational study [Protocol 20090522 (Phase B): 'Denosumab Global Safety Assessment Among Women With Postmenopausal Osteoporosis (PMO) Using Multiple Observational Databases']. Because of the design and methodological challenges noted in your proposal, there is concern that the proposed study will not successfully capture the necessary safety information regarding denosumab use.

Therefore, additional assessment of methodology and background adverse event rates as specified under Protocol 20090521 (Phase A) is needed before agreement can be reached on the design of Protocol 20090522 (Phase B)."

To address the clinical deficiency, DRUP requested the following information.

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

On January 25, 2010, Amgen resubmitted BLA 15320 which included a revised observational study plan, Protocol 20090522 (hereafter referred to as Protocol 522) as part of the response to the CR letter. The current review summarizes Protocol 522 with a focus on the sample size and power calculations.

The sponsor should be required to submit a detailed statistical analysis plan prior to study initiation. Language for this requirement and other comments that may be conveyed to the sponsor are provided in Section 3 of this review.

2. PROTOCOL 20090522

Protocol 522 is titled, "Denosumab Global Safety Assessment Among Women With Postmenopausal Osteoporosis (PMO) Using Multiple Observational Databases". Descriptions of the protocol, provided herein, are based upon the version of the protocol with a date of April 14, 2010.

Several adverse events of special interest (AESI) have been selected to be assessed in the post-marketing environment. The AESI's selected to be assessed are the following:

- 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

This study will be conducted using 4 large data systems in several countries including U.S. Medicare, United HealthCare, California Kaiser Permanente, and the Nordic national health registries.

2.1 Study Objectives

The stated objectives of the proposed study are:

1. Determine incidence rates of AESI's (as provided above) in women with PMO exposed to denosumab, women with PMO exposed to other osteoporosis medications, and women with PMO not exposed to any osteoporosis medications.
2. Describe characteristics, clinical features, and AESI risk factors in women with PMO exposed to denosumab, women with PMO exposed to other osteoporosis medications, and women with PMO not exposed to any osteoporosis medication.
3. Compare the incidence of the AESI in women with PMO exposed to denosumab, women with PMO exposed to other osteoporosis medications, and women with PMO not exposed to any osteoporosis medication.
4. Describe incidence rates of AESI in postmenopausal women.
5. Describe denosumab utilization patterns in patients who received denosumab therapy for treatment of PMO.
6. Describe denosumab utilization patterns in patients who receive denosumab therapy for unapproved indications (indication, dosage, frequency).

***Reviewer Comment**: While the protocol lists several study objectives, the following review primarily addresses the comparison of incidence rates and the power of the study to detect differences in the incidence rates of AESI's in women exposed to denosumab (Objective 3).*

2.2 Study Plan

This is a prospective study with annual assessment and reporting of descriptive findings. The primary data sources will be the following:

- U.S. Medicare, including Parts A, B, and D
- Kaiser Permanente Medical Care Program, including data from both the Northern and Southern California Kaiser Permanente organizations
- United HealthCare
- Nordic national health registry databases, including data from Denmark, Finland, Sweden, and Norway

Data will be collected for postmenopausal women overall, women with PMO, and patients who receive denosumab for unapproved indications. Among women with PMO, exposure cohorts will be established based on exposure to denosumab, other osteoporosis medications, or no osteoporosis medication. AESI will be identified using validated algorithms based on inpatient and outpatient diagnosis and procedure codes, and, for some AESI, medication codes or laboratory data. Selected AESI (e.g., ONJ) will be confirmed by medical chart review. A report will be produced annually. The duration of the study is 10 years. Analyses will include patients with at least 1 year of longitudinal data. Patients will be followed for up to 10 years.

2.2.1 Study Populations

Three study populations will be identified:

1. *Postmenopausal women*: Postmenopausal status will be determined based on age and defined as women ≥ 55 years old at study start. For the Medicare database, only women ≥ 65 years old will be included in the analysis, given that generally all individuals in the US ≥ 65 years old are eligible for Medicare coverage and data on postmenopausal women less than 65 years old will be available for only a small number of women meeting other specialized eligibility criteria. Data for postmenopausal women overall (≥ 65 years old) in Medicare will be obtained from the Medicare 100% database.
2. *Women with PMO*: Among postmenopausal women as defined above, the presence of PMO will be determined utilizing a pre-defined algorithm based upon diagnostic codes indicating osteoporosis, diagnostic codes indicating osteoporotic fracture, and/or relevant PMO treatment codes.
3. *Patients who receive denosumab for unapproved indications*: These patients will be defined as those who receive denosumab but did not receive denosumab for an approved indication as indicated by the approved product information.

2.2.2 Exposure Cohorts

Exposure will be defined on the basis of exposure to denosumab, exposure to other osteoporosis medications, or lack of exposure to any osteoporosis medication.

Exposure cohorts will be defined as follows:

- *Denosumab exposure* is defined as receiving at least 1 dose of denosumab.

- *Exposure to other (non-denosumab) osteoporosis medications* is defined as having received another osteoporosis medication.
- *Lack of exposure to any osteoporosis medication* is defined as not having received any dose of any osteoporosis medication.

Changes in therapy over time will be taken into account. For example, if a patient switches to denosumab from another osteoporosis medication during the course of follow-up, she will switch to the denosumab exposure cohort from the other osteoporosis medication cohort.

***Reviewer Comment**: The specifics of the cohort definitions for subjects who change therapy should be specified in the statistical analysis plan. Sensitivity analyses of these definitions should be explored in the study analysis.*

2.3 Sources of Confounding

Due to the nature of the study, it is reasonable to expect several sources of potential confounding in the analysis. Variables identified by the sponsor that will be evaluated as potential confounders in analyses comparing AESI incidence across exposure cohorts include, but are not necessarily limited to, the following: age, geographic location (e.g., country, state), fracture history, concurrent medication, history of treatment with osteoporosis medication, comorbidities (e.g., infections, diabetes, and disease or conditions that may increase risk of AESI), and year of PMO diagnosis.

***Reviewer Comment**: As it is difficult to ascertain all potential sources of confounding and their effects on estimating the AESI's, the study may be planned to submit a revised statistical analysis plan after several years of data collection. However, it is should noted that a detailed statistical analysis plan should be submitted prior to study initiation for Agency review and comment.*

2.4 Study Size and Estimation of Study Power

The study size is based upon the assumed number of women ≥ 65 years of age who will be included in all four data bases. To obtain an estimate of the number of person years of exposure to denosumab several assumptions must be made. The assumptions are as follows;

1. Percent of women who are diagnosed with PMO
2. Percent of women who are diagnosed with PMO and take medication to treat PMO
3. Percent of women who are diagnosed with PMO and treat PMO with denosumab

To provide estimates of assumptions 1 and 2 above, the sponsor uses several literature references as well as a sensitivity analysis to justify the values of the estimates. The assumed response rate of the percent of women who are diagnosed with PMO ranges from 30% to 40%. Of women with PMO, the sponsor assumes 50% are

treated with some medication (assumption #2). Further, the sponsor assumes that 2.5% of women treated for PMO will be treated with denosumab in the first year and 5% will be treated in years 2 through 10.

The overall number of women ≥ 65 years of age in the four data bases is expected to be 23,657,000 (20,600,000 from US Medicare, 2,400,000 from the Nordic National Registries, 450,000 from Kaiser Permanente, and 207,000 from United Healthcare). Based upon the sponsor's assumptions the estimated number of patient-years for exposure to denosumab is provided in Table 1 for all data bases as well U.S. Medicare alone.

Table 1: Estimated Number of Patient-Years for All Data Bases and U.S. Medicare

	Percent of Women Medicated	
	30%	40%
All Data Bases		
Year 2	266,141	354,855
Year 5	798,423	1,064,565
Year 10	1,685,561	2,247,415
U.S. Medicare		
Year 2	231,750	309,000
Year 5	695,250	927,000
Year 10	1,467,750	1,957,000

To assess the power of the study to detect a relative risk at 10 years post denosumab entry several additional assumptions are required.

a) The group ratio between comparator and denosumab-exposed person years with up to 10 years of follow-up
b) Incidence rate of the AESI
c) The relative risk between comparator and denosumab

The sponsor has assumed a group ratio of 10:1 and 5:1 between comparator and denosumab-exposed patient years with up to 10 years of follow-up. Additionally, the assumed incidence rates of the AESI's are based upon literature review as well as upon analyses conducted by the sponsor.

To calculate power, the sponsor conducted a simulation study using Fisher's exact test with a two-sided alpha level of 0.05. The simulation is run 5000 times and the number of times that Fisher's exact test results in a p-value < 0.05 is calculated. Power is the percent of these tests being below the nominal alpha=0.05 level. This review also conducted simulations to assess the sponosor's simulation for a variety of parameter inputs. Details of the simulation are provided in the Appendix Section A.1 of this review.

To estimate the power 12 values for the incidence rate in unexposed patients are used. These rates are 0.1, 0.3, 0.4, 0.5, 0.6, 0.8, 1, 1.5, 2, 2.5, 3, and 4 per 100,000

patient years. Then for six assumed values of the relative risk (1.5, 2, 2.5, 3, 3.5, and 4) the power is calculated from the simulation.

To determine the approximate power of the study for a given AESI, the sponsor has provided estimates of the incidence rate for each AESI based upon literature references or from their analysis. These assumed incidence rates are provided in Table 2 below. Note that the incidence rate is above 4 for all AESI's other than ONJ and Serious Dermatologic Adverse Events which occur in 1/100,000 and 0.9/100,000 patient years, respectively.

Table 2: Estimated Incidence Rates for AESI

AESI	Incidence Rate (per 100,000 patient-years)
ONJ	1
Fracture Healing Complications	95.5
Hypocalcemia Leading to Hospitalization	9
Serious Infection	1249
Serious Dermatologic Adverse Event	0.9
Pancreatitis	130
Serious Hypersensitivity	8.4
New Primary Malignancy	1668

Source: Protocol 20090522, Table 8-2.

Figure 1 below depicts the power of the study for all parameters for all four databases assessed in the study. Panels in the figure correspond to the assumptions of the number of patient years (influenced by the assumed percentage of women with PMO who are treated with medication) and the ratio of unexposed to exposed patient years. Lines in the figure correspond to different values of relative risk. The actual estimated power when the incidence rate is 1/100,000 patient years is displayed as text for relative risks of 1.5 and 2.

The least conservative calculation assumes 40% of women with PMO are treated with some medication and the ratio of exposed subjects to unexposed subjects is 10:1 (this power calculation is included in the bottom left panel of Figure 1). Under such a scenario, the study will have nearly 100% power to detect AESI's occurring in more than 4/100,000 patient years if the relative risk is 1.5 or higher. However, for ONJ and Serious Dermatologic Adverse Events, the study will have approximately 55% power to detect a relative risk of 1.5 and more than 90% power to detect a relative risk of 2 or higher.

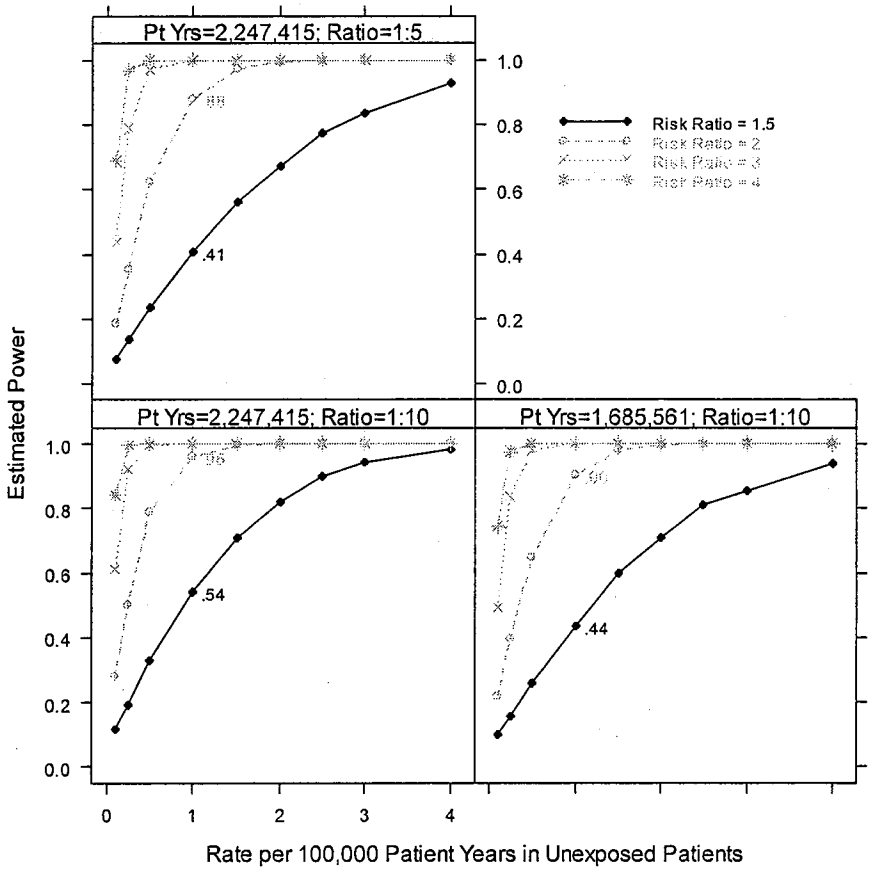
If 30% of women with PMO are treated with some medication the estimates number of patient-years of exposed subjects decreases to 1,685,561. Assuming a ratio of exposed subjects to unexposed subjects is 10:1, the bottom right panel of Figure 1 depicts power estimates for these assumptions. Note that there is not a dramatic loss of power from that depicted in the lower left panel. Under the current scenario, the study will have more than 95% power to detect AESI's occurring in more than

4/100,000 patient years if the relative risk is 1.5 or higher. For ONJ and Serious Dermatologic Adverse Events, the study will have approximately 45% power to detect a relative risk of 1.5 and more than 90% power to detect a relative risk of 2 or higher.

The most conservative analysis utilizing assumptions provided by the sponsor results in 1,685,561 patients years of exposure to denosumab and a ratio of unexposed to exposed of 5:1. Results from this analysis are presented in the top left panel of Figure 1. Overall, this conservative analysis does not greatly affect the power of the study to detect all AESI's other than ONJ and Serious Dermatologic Adverse Events. There is a reduction in power to detect ONJ and Serious Dermatologic Adverse Events using conservative estimates, but the study would still have greater than 85% power to detect a relative risk of 2 or higher.

***Reviewer Comment**: Based upon the assumptions provided by the sponsor and the simulation study using Fisher's Exact test, the planned study appears to be sufficiently powered (power calculations were verified by the reviewer). However, it should be noted that several assumptions are made in the power calculations which may not be precise based upon the information to date. The sponsor might consider conducting an analysis of the data base after several years to address the accuracy of their estimates and the potential for the study to be underpowered to detect AESI's.*

Figure 1. Power Calculations (All Databases - Year 10)



2.4 Statistical Analysis

The sponsor states, "This study is descriptive in nature. No hypotheses will be tested." However, the sponsor does provide some details of the planned analyses which are to describe characteristic of AESI incidence rates among exposure cohorts. The analyses will be conducted separately for each data system. Combined estimates of incidences of AESI's associated with denosumab exposure may be obtained using meta-analytic methods, as appropriate. The protocol goes on to describe some general considerations for the statistical analyses.

***Reviewer Comment**: The sponsor should submit to the Agency for comment a detailed statistical analysis plan prior to study initiation and include plans for how to make revisions to the SAP based upon information that arises once denosumab has market exposure. The plan should provided details on all statistical analyses outlined in the study protocol, including the meta-analysis across the data bases and the*

various methods discussed for adjustment for confounding when comparing across exposure groups.

3 COMMENTS THAT MAY BE CONVEYED TO THE SPONSOR

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

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

APPENDIX

A.1 Simulation Details

As provided in the main text of the review, a simulation study was conducted to assess the power of the study. The following sections provide details of the simulation.

A.1.1 Notation

Define the following variables

- N_{PY} = number of denosumab exposed patient-years (the values of N_{PY} used in the simulation are provided in Table 1 of the review)
- R_{CTL} = ratio of exposed to unexposed patient-years (R_{CTL}= 10 and 5 as described in Section 2.4).
- R_j = incidence rate (j = 0.1, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, and 4 per 100,000 patient years)
- rr_k = relative risk (k = 1.5, 2.0, 3.0, 4.0)

A.1.2 Iteration *i*

For a single iteration of the simulation, a random sample is conducted for each *j,k* pair described in Section A.1.1 for the incidence rate and relative risk. The random samples are from binomial distributions for both the exposed and unexposed populations with the following parameters.

- Unexposed distribution ~ Binomial(N = $N_{PY}*R_{CTL}$, p = R_j)
- Denosumab exposed distribution ~ Binomial(N = N_{PY}, p = R_j*rr_k)

The two simulated counts for the unexposed and exposed populations are compared using Fisher's exact test. If the two-sided p-value from Fisher's exact test is less than 0.05, then the value for iteration *i*, S_i, is 1.

A.1.3 Resampling

The resampling of iteration *i* is conducted 5000 times for each *j,k* pair. Thus, the power for each *j,k* pair can be calculated as the following:

$$Power(j,k) = \sum_{i=1}^{5000} I_{(S_i=1)} / 5000$$

A.1.4 Simulation Presentation

With 9 values for R_j and 4 values for rr_k, the simulation yields 36 estimates of power for all *j,k* pairs. These are provided in tabular form in Section A.2 for all four data bases as well as for U.S. Medicare data base alone at years 2, 5, and 10. A visual summary of the power estimates for the overall study at year 10 is provided in Section 2.4. In addition, graphical depictions of the combined data bases for years 2 and 5 are provided in Section A.2.

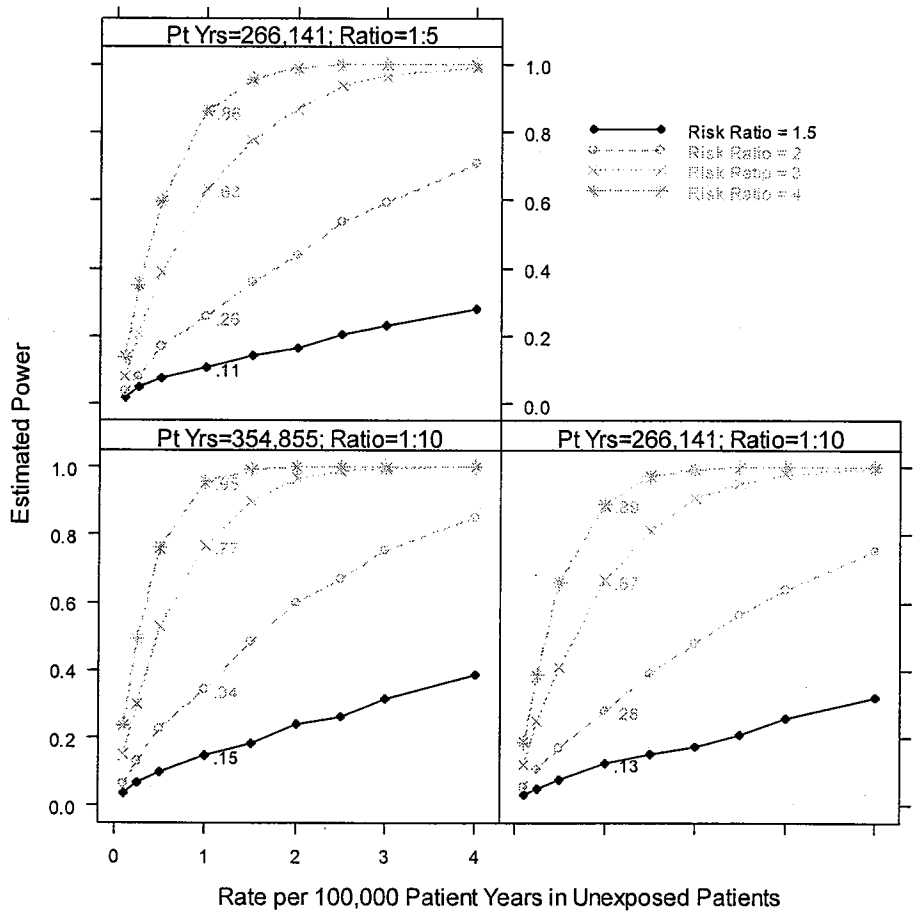
A.2 Simulation Results; Graphical and Tabular Presentations

The following sections provide power estimates from the simulation study for both the U.S. Medicare data base as well as all four data bases combined at years 2, 5, and 10.

A.2.1 Year 2 Power Estimates

Figure A.2.1-1 Provides a graphical depiction of the power estimates at year 2 for all data bases. Tabular summaries are provided in Tables A.2.1.1-1, A.2.1.1-2, and A.2.1.1-3 below.

Figure A.2.1-1. Power Calculations (All Databases - Year 2)



A.2.1.1 All Databases Tabular Summary (2 Year)

Table A.2.1.1-1: Estimated power when N_{PY} = 354,855 and R_{CTL} = 10

	Relative Risk			
Incidence Rate*	1.5	2.0	3.0	4.0
0.1	0.0384	0.0660	0.1506	0.2368
0.25	0.0702	0.1312	0.2996	0.4926
0.5	0.1010	0.2266	0.5286	0.7602
1.0	0.1478	0.3430	0.7650	0.9538
1.5	0.1818	0.4838	0.9004	0.9918
2.0	0.2396	0.5984	0.9662	0.9994
2.5	0.2646	0.6710	0.9856	0.9994
3.0	0.3156	0.7534	0.9960	1
4.0	0.3858	0.8512	0.9992	1

* Note that incidence rates are per 100,000 patient years

Table A.2.1.1-2: Estimated power when N_{PY} = 266,141 and R_{CTL} = 10

	Relative Risk			
Incidence Rate*	1.5	2.0	3.0	4.0
0.1	0.0346	0.0536	0.1202	0.1864
0.25	0.0512	0.1092	0.2504	0.3842
0.5	0.0790	0.1698	0.4074	0.6582
1.0	0.1252	0.2814	0.6664	0.8882
1.5	0.1524	0.3886	0.8118	0.9718
2.0	0.1742	0.4812	0.9074	0.9918
2.5	0.2098	0.5622	0.9518	0.9984
3.0	0.2600	0.6378	0.9798	0.9996
4.0	0.3180	0.7540	0.9950	1

* Note that incidence rates are per 100,000 patient years

Table A.2.1.1-3: Estimated power when N_{PY} = 266,141 and R_{CTL} = 5

	Relative Risk			
Incidence Rate*	1.5	2.0	3.0	4.0
0.1	0.0172	0.0368	0.0794	0.1370
0.25	0.0498	0.0820	0.2074	0.3514
0.5	0.0750	0.1680	0.3866	0.5974
1.0	0.1070	0.2588	0.6334	0.8632
1.5	0.1406	0.3570	0.7780	0.9558
2.0	0.1644	0.4368	0.8690	0.9878
2.5	0.2024	0.5342	0.9366	0.9966
3.0	0.2282	0.5932	0.9658	0.9988
4.0	0.2786	0.7076	0.9910	1

* Note that incidence rates are per 100,000 patient years

A.2.1.2 U.S. Medicare Database Tabular Summary (2 Year)

Table A.2.1.2-1: Estimated power when N_{PY} = 309,000 and R_{CTL} = 10

	Relative Risk			
Incidence Rate*	1.5	2.0	3.0	4.0
0.1	0.0348	0.0638	0.1424	0.2316
0.25	0.0594	0.1158	0.2760	0.4350
0.5	0.0894	0.1902	0.4734	0.7102
1.0	0.1364	0.3158	0.7144	0.9166
1.5	0.1740	0.4360	0.8732	0.9860
2.0	0.2096	0.5380	0.9352	0.9964
2.5	0.2348	0.6172	0.9710	0.9996
3.0	0.2698	0.6924	0.9902	0.9998
4.0	0.3562	0.8124	0.9988	1

* Note that incidence rates are per 100,000 patient years

Table A.2.1.2-2: Estimated power when N_{PY} = 231,750 and R_{CTL} = 10

	Relative Risk			
Incidence Rate*	1.5	2.0	3.0	4.0
0.1	0.0314	0.0558	0.1066	0.1688
0.25	0.0516	0.0978	0.2168	0.3520
0.5	0.0688	0.1620	0.3756	0.6060
1.0	0.1162	0.2712	0.6208	0.8548
1.5	0.1400	0.3422	0.7688	0.9492
2.0	0.1684	0.4360	0.8640	0.9848
2.5	0.1970	0.5126	0.9240	0.9950
3.0	0.2196	0.5682	0.9610	0.9982
4.0	0.2920	0.6938	0.9872	0.9996

* Note that incidence rates are per 100,000 patient years

Table A.2.1.2-3: Estimated power when N_{PY} = 231,750 and R_{CTL} = 5

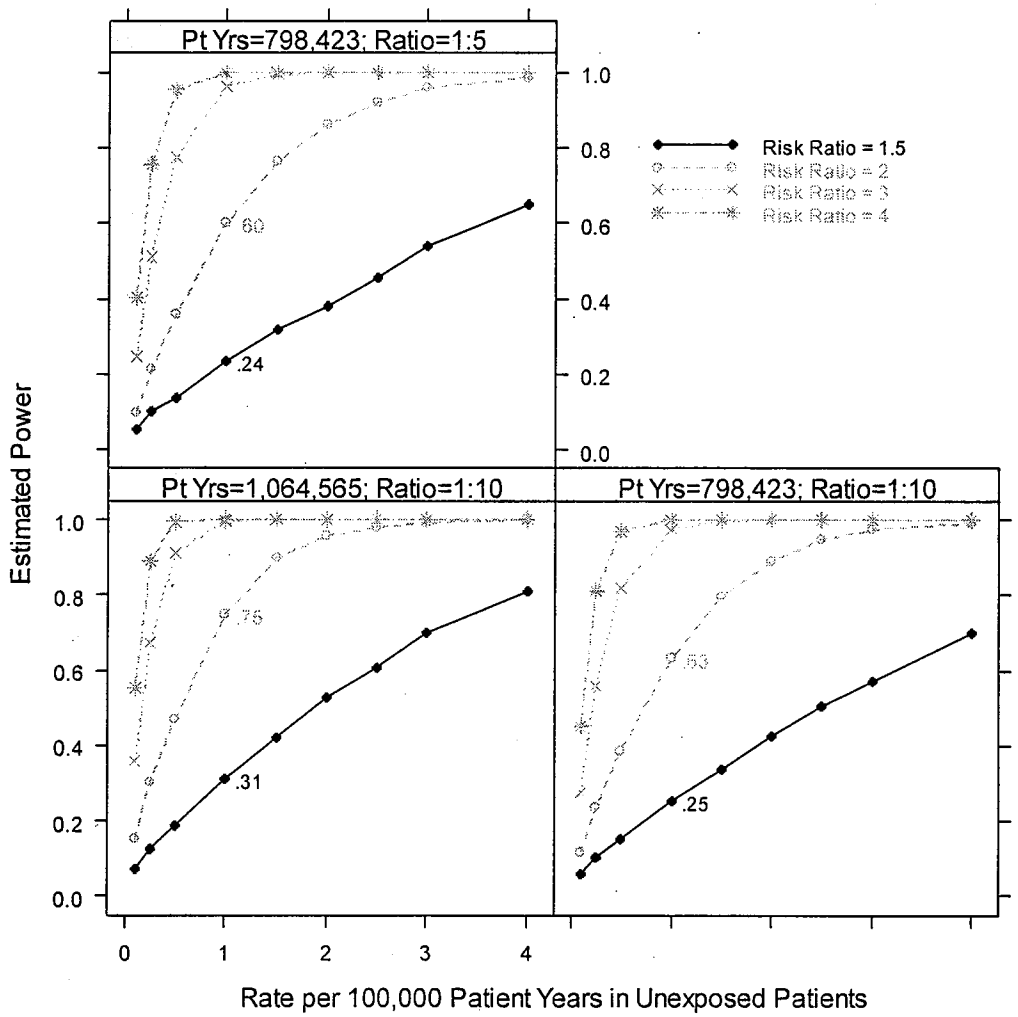
	Relative Risk			
Incidence Rate*	1.5	2.0	3.0	4.0
0.1	0.0190	0.0306	0.0706	0.1112
0.25	0.0376	0.0760	0.1756	0.2920
0.5	0.0692	0.1450	0.3524	0.5438
1.0	0.1044	0.2382	0.5584	0.8114
1.5	0.1146	0.3150	0.7186	0.9266
2.0	0.1458	0.3966	0.8176	0.9704
2.5	0.1768	0.4646	0.8996	0.9918
3.0	0.2054	0.5350	0.9498	0.9978
4.0	0.2552	0.6568	0.9802	0.9994

* Note that incidence rates are per 100,000 patient years

A.2.2 Year 5 Power Estimates

Figure A.2.2-1 Provides a graphical depiction of the power estimates at year 5 for all data bases. Tabular summaries are provided in Tables A.2.2.1-1, A.2.2.1-2, and A.2.2.1-3 below.

Figure A.2.2-1. Power Calculations (All Databases - Year 5)



A.2.2.1 All Databases Tabular Summary (5 Year)

Table A.2.2.1-1: Estimated power when N_{PY} = 1,064,565 and R_{CTL} = 10

	Relative Risk			
Incidence Rate*	1.5	2.0	3.0	4.0
0.1	0.0724	0.1532	0.3590	0.5530
0.25	0.1266	0.3034	0.6746	0.8890
0.5	0.1888	0.4710	0.9122	0.9936
1.0	0.3128	0.7474	0.9956	1
1.5	0.4232	0.8974	1	1
2.0	0.5284	0.9564	1	1
2.5	0.6082	0.9798	1	1
3.0	0.7000	0.9920	1	1
4.0	0.8100	0.9994	1	1

* Note that incidence rates are per 100,000 patient years

Table A.2.2.1-2: Estimated power when N_{PY} = 798,423 and R_{CTL} = 10

	Relative Risk			
Incidence Rate*	1.5	2.0	3.0	4.0
0.1	0.0610	0.1176	0.2754	0.4514
0.25	0.1058	0.2376	0.5586	0.8112
0.5	0.1534	0.3842	0.8194	0.9700
1.0	0.2542	0.6318	0.9744	0.9988
1.5	0.3368	0.7958	0.9974	1
2.0	0.4258	0.8910	1	1
2.5	0.5038	0.9470	1	1
3.0	0.5710	0.9720	1	1
4.0	0.6982	0.9928	1	1

* Note that incidence rates are per 100,000 patient years

Table A.2.2.1-3: Estimated power when N_{PY} = 798,423 and R_{CTL} = 5

	Relative Risk			
Incidence Rate*	1.5	2.0	3.0	4.0
0.1	0.0540	0.0982	0.2474	0.4034
0.25	0.1020	0.2120	0.5100	0.7564
0.5	0.1390	0.3578	0.7764	0.9536
1.0	0.2356	0.6010	0.9634	0.999
1.5	0.3194	0.7636	0.9954	1
2.0	0.3794	0.8612	1	1
2.5	0.4576	0.9212	1	1
3.0	0.5398	0.9578	1	1
4.0	0.6516	0.9876	1	1

* Note that incidence rates are per 100,000 patient years

A.2.2.2 U.S. Medicare Database Tabular Summary (5 Year)

Table A.2.2.2-1: Estimated power when N_{PY} = 927,000 and R_{CTL} = 10

	Relative Risk			
Incidence Rate*	1.5	2.0	3.0	4.0
0.1	0.0606	0.1294	0.3066	0.5150
0.25	0.1198	0.2616	0.6294	0.8500
0.5	0.1764	0.4364	0.8682	0.9868
1.0	0.2834	0.6946	0.9872	1
1.5	0.3756	0.8472	0.9996	1
2.0	0.4742	0.9312	1	1
2.5	0.5554	0.9656	1	1
3.0	0.6316	0.9872	1	1
4.0	0.7504	0.9980	1	1

* Note that incidence rates are per 100,000 patient years

Table A.2.2.2-2: Estimated power when N_{PY} = 695,250 and R_{CTL} = 10

	Relative Risk			
Incidence Rate*	1.5	2.0	3.0	4.0
0.1	0.0540	0.1058	0.2552	0.3990
0.25	0.0958	0.2202	0.5096	0.7460
0.5	0.1370	0.3382	0.7620	0.9458
1.0	0.2212	0.5818	0.9578	0.9982
1.5	0.3094	0.7444	0.9968	1
2.0	0.3934	0.8478	0.9996	1
2.5	0.4574	0.9090	1	1
3.0	0.5254	0.9496	1	1
4.0	0.6402	0.9870	1	1

* Note that incidence rates are per 100,000 patient years

Table A.2.2.2-3: Estimated power when N_{PY} = 695,250 and R_{CTL} = 5

	Relative Risk			
Incidence Rate*	1.5	2.0	3.0	4.0
0.1	0.0476	0.0888	0.2068	0.3616
0.25	0.0936	0.1864	0.4554	0.7048
0.5	0.1378	0.3232	0.7284	0.9264
1.0	0.2010	0.5412	0.9400	0.9972
1.5	0.2888	0.6998	0.9898	1
2.0	0.3558	0.8102	0.9982	1
2.5	0.4120	0.8882	1	1
3.0	0.4810	0.9360	1	1
4.0	0.5994	0.9762	1	1

* Note that incidence rates are per 100,000 patient years

A.2.3 Year 10 Power Estimates

A.2.3.1 All Databases Tabular Summary (10 Year)

Table A.2.3.1-1: Estimated power when N_{PY} = 2,247,415 and R_{CTL} = 10

	Relative Risk			
Incidence Rate*	1.5	2.0	3.0	4.0
0.1	0.1158	0.2804	0.6124	0.8424
0.25	0.1934	0.5004	0.9208	0.9944
0.5	0.3300	0.7872	0.9962	1
1.0	0.5410	0.9622	1	1
1.5	0.7108	0.9952	1	1
2.0	0.8174	0.9996	1	1
2.5	0.9004	1	1	1
3.0	0.9448	1	1	1
4.0	0.9824	1	1	1

* Note that incidence rates are per 100,000 patient years

Table A.2.3.1-2: Estimated power when N_{PY} = 1,685,561 and R_{CTL} = 10

	Relative Risk			
Incidence Rate*	1.5	2.0	3.0	4.0
0.1	0.1010	0.2190	0.4910	0.7434
0.25	0.1586	0.3972	0.8374	0.9756
0.5	0.2590	0.6486	0.9796	0.9996
1.0	0.4362	0.9042	1	1
1.5	0.5964	0.9776	1	1
2.0	0.7072	0.9946	1	1
2.5	0.8114	0.9992	1	1
3.0	0.8566	0.9996	1	1
4.0	0.9394	1	1	1

* Note that incidence rates are per 100,000 patient years

Table A.2.3.1-3: Estimated power when N_{PY} = 1,685,561 and R_{CTL} = 5

	Relative Risk			
Incidence Rate*	1.5	2.0	3.0	4.0
0.1	0.0776	0.1858	0.4382	0.6880
0.25	0.1396	0.3536	0.7894	0.9680
0.5	0.2354	0.6220	0.9728	0.9998
1.0	0.4090	0.8780	0.9996	1
1.5	0.5618	0.9704	1	1
2.0	0.6724	0.9932	1	1
2.5	0.7722	0.9984	1	1
3.0	0.8336	0.9998	1	1
4.0	0.9274	1	1	1

* Note that incidence rates are per 100,000 patient years

A.2.3.2 U.S. Medicare Database Tabular Summary (10 Year)

Table A.2.3.2-1: Estimated power when N_{PY} = 1,957,000 and R_{CTL} = 10

	Relative Risk			
Incidence Rate*	1.5	2.0	3.0	4.0
0.1	0.1100	0.2440	0.5528	0.7976
0.25	0.1820	0.4570	0.8836	0.9898
0.5	0.2930	0.7162	0.9928	1
1.0	0.5160	0.9386	1	1
1.5	0.6598	0.9884	1	1
2.0	0.7808	0.9992	1	1
2.5	0.8584	0.9988	1	1
3.0	0.9156	1	1	1
4.0	0.9672	1	1	1

* Note that incidence rates are per 100,000 patient years

Table A.2.3.2-2: Estimated power when N_{PY} = 1,467,750 and R_{CTL} = 10

	Relative Risk			
Incidence Rate*	1.5	2.0	3.0	4.0
0.1	0.0792	0.1818	0.4474	0.6878
0.25	0.1452	0.3596	0.7884	0.9502
0.5	0.2298	0.5950	0.9632	0.9986
1.0	0.3942	0.8664	0.9996	1
1.5	0.5418	0.9638	1	1
2.0	0.6628	0.9872	1	1
2.5	0.7482	0.9978	1	1
3.0	0.8212	0.9992	1	1
4.0	0.9126	1	1	1

* Note that incidence rates are per 100,000 patient years

Table A.2.3.2-3: Estimated power when N_{PY} = 1,467,750 and R_{CTL} = 5

	Relative Risk			
Incidence Rate*	1.5	2.0	3.0	4.0
0.1	0.0794	0.1722	0.4102	0.6408
0.25	0.1348	0.3348	0.7474	0.9422
0.5	0.2200	0.5624	0.9522	0.9992
1.0	0.3792	0.8436	0.9988	1
1.5	0.5020	0.9442	1	1
2.0	0.6116	0.9878	1	1
2.5	0.7156	0.9946	1	1
3.0	0.7906	0.9992	1	1
4.0	0.8840	1	1	1

* Note that incidence rates are per 100,000 patient years

Mat Soukup, Ph.D.
Acting Team Leader, Biometrics 7

Concur: Mark Levenson, Ph.D.
Acting Deputy Director, Biometrics 7

Cc:
BLA 125320
DRUP/Kehoe
DRUP/McCloskey
DRUP/Kornegay
DRUP/Crisostomo
OBIO/Patrician
DB7/Chakravarty
DB7/Levenson
DB7/Soukup

Memorandum of Statistical Review

BLA/Sequence Number:	125320 / 0047
Drug Name:	Prolia (denosumab)
Indication(s):	Treatment of osteoporosis in postmenopausal women
Applicant:	Amgen, Inc.
Date(s):	*Letter Date*: January 25, 2010 *PDUFA Date*: July 23, 2010
Review Priority:	1 Standard
Biometrics Division:	Division of Biometrics 3
Statistical Reviewer:	Sonia Castillo, Ph.D.
Biometrics Team Leader:	Mahboob Sobhan, Ph.D.
Medical Division:	Division of Reproductive and Urologic Products
Clinical Team:	Stephen Voss, M.D., Clinical Reviewer Theresa Kehoe, M.D., Team Leader
Project Manager:	Nenita Crisostomos

The Applicant submits this complete response to the Action Letter dated October 16, 2009 issued to the denosumab biologic license application (BLA) for the treatment of osteoporosis in postmenopausal women. The submission contains information about the following information requested in the Action Letter:

- safety postmarketing observational study protocol,
- Risk Evaluation and Mitigation Strategies (REMS) requirements plan
- proposed product labeling
- safety postmarketing requirement for a long-term observational study protocol
- postmarketing requirement for long-term safety surveillance program
- safety postmarketing requirement for a long-term pregnancy exposure study protocol
- safety update

No new efficacy data was submitted. The submission is located under sequence number 0047 in the CBER EDR at: \\cbsap58\m\eCTD_Submissions\STN125320.

The Clinical Studies section is the portion of the label that requires statistical input. Since this submission deals with safety issues and because the Clinical Studies section was reviewed during the initial application submission, there are no further comments for the Applicant and the submitted label is acceptable from a statistical perspective.

Sonia Castillo 3-15-2010

Sonia Castillo, Ph. D.
Primary Statistical Reviewer

Mahboob Sobhan 3-15-2010

Mahboob Sobhan, Ph.D.
Statistical Team Leader

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

MEMORANDUM

Date: September 14, 2009

Date In: August 27, 2009

To: Theresa Kehoe, MD
Team Leader
Division of Reproductive and Urologic Products

From: Paul H. Schuette, PhD
Mathematical Statistician
Quantitative Safety and Pharmacoepidemiology Division
Office of Biostatistics

Through: George Rochester, MA, PhD, RAC
Division Director
Quantitative Safety and Pharmacoepidemiology Division
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Yu-te Wu, PhD
Secondary Reviewer
Mathematical Statistician
Quantitative Safety and Pharmacoepidemiology Division
Office of Biostatistics

Drug: PROLIA (denosumab)

BLA: 125320/125331

Subject: Quantitative Safety Analysis of Infections in trial 20040132

Summary

This review considers the distribution of adverse events of infections and infestations among subjects treated with denosumab or placebo in trial 20040132 from the submission for BLA 125320/125331. This review considers all infectious adverse events, including both serious and non-serious events, as well as considering only serious infectious adverse events. Based on this review, we may observe the following points:

- In aggregate, infections appear to be similarly distributed in both denosumab and placebo arms.
- During the treatment phase of the trial, serious infections were imbalanced and occur more frequently in the denosumab arm.
- Both treatment arms each had a single subject experience one serious adverse event of infection in the extension phase, months 25 to 48, of the trial.
- The under-ascertainment of adverse events during the extension phase of the trial, months 25 to 48, is a potential concern.

Objective

The objective of the consult request was to evaluate trial 20040132 from BLA 125320/125331 (denosumab) for a change in overall infections, and serious infections using data from 24 months (treatment) and two extension periods, 36 months and 48 months.

Background

At the August 13, 2009 Advisory Committee for denosumab, serious infections were identified as adverse events of interest. A consult request has been received from the Division of Reproductive and Urologic Products (DRUP), the medical division for this indication, to determine if infection rates return to baseline after discontinuation of treatment.

Methods

Infections and infestations were determined by considering the variable AEBODSYS in the sponsor's adverse event analysis data set AAE for 24 month, 36 month and 48 month data and selecting those with "Infections and infestations." Using the variable AEDECOD, these events reviewed to confirm that all events were actually infections. Hence, infection and infestation events will be referred to as infection events. Serious adverse events were determined by the AESER flag in the sponsor's sponsor's adverse event analysis data sets. The safety population was considered for all analyses. χ^2 and Fisher's exact statistic were used to compute exploratory p values as measures of imbalance.

Aggregated Infections

Table 1 below indicates that infection events reported by month 24 were balanced between the denosumab and the placebo treatment groups, with $\chi^2 = 0.0247$, and $p \approx 0.88$. It may be noted that most subjects experienced at least one infectious event by month 24 of the trial.

Table 2 and Table 3 below indicate infectious events continue to balanced between the trial arms at months 36 and 48, with more subjects experiencing an infectious event over time. For Table 2, we have $\chi^2 = 0.2523$, and $p \approx 0.62$. For Table 3, we have $\chi^2 = 0.0015$, and $p \approx 0.97$. In aggregate, infections appear to be balanced between denosumab and placebo arms.

Table 1: Subjects Experiencing an Infection by Month 24

	Denosumab (%)	Placebo (%)
Infection AE	99 (60.4)	101 (61.2)
No Infection AE	65 (39.6)	64 (38.8)
Total	164 (100)	165 (100)

Table 2: Subjects Experiencing an Infection by Month 36

	Denosumab(%)	Placebo(%)
Infection AE	104 (63.4)	109 (66.1)
No Infection AE	60 (36.6)	56 (33.9)
Total	164 (100)	165 (100)

Table 3: Subjects Experiencing an Infection by Month 48

	Denosumab (%)	Placebo (%)
Infection AE	110 (67.1)	111 (67.27)
No Infection AE	54 (32.9)	54 (32.7)
Total	164 (100)	165 (100)

Distribution of Infectious Events over Time

Figure 1 shows a count of infectious events versus the start date of the event and includes both on-treatment and extension phases of the trial. In general, both the denosumab and placebo arms appear to have similar distributions.

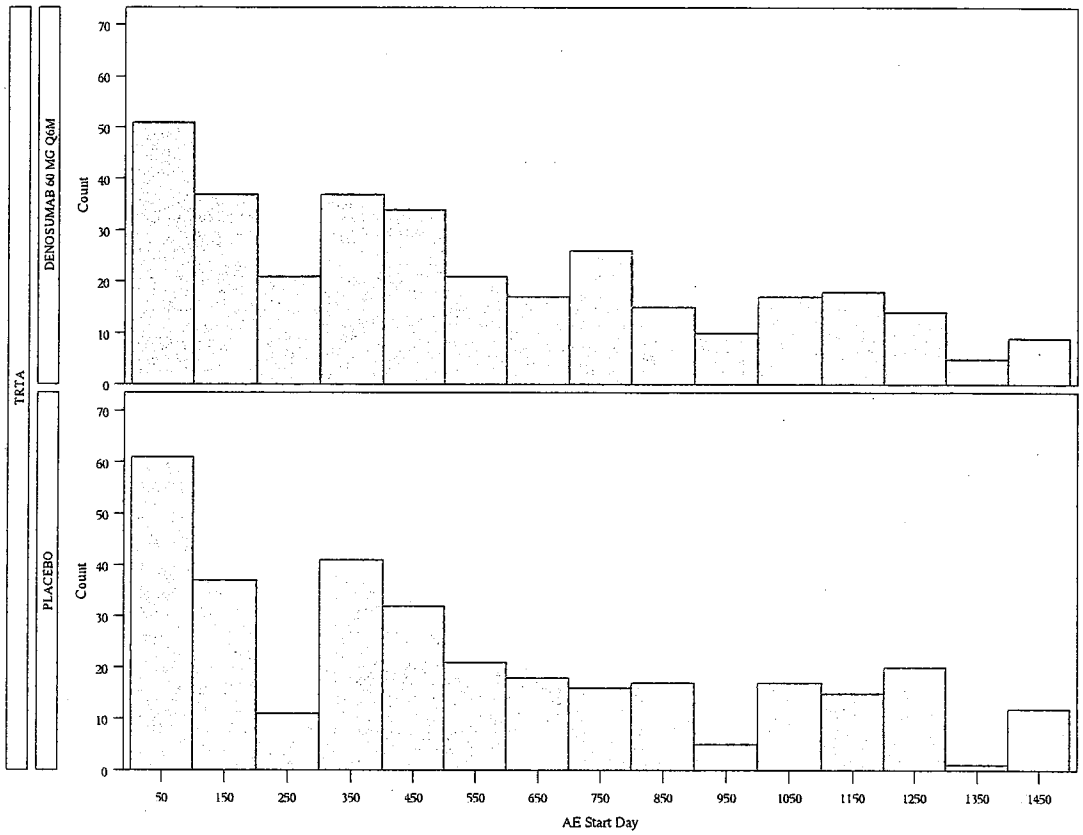

Figure 1: Start Dates of Infectious Events

Figure 2 shows a count of infectious events versus the days since the last dose of drug, including both on-treatment and extension phases of the trial. Both the denosumab and placebo distributions exhibit a pronounced right skew.

Table 4 suggests that the distribution over time of aggregated infectious adverse events is similar in both trial arms. One may note that there is a pronounced decline in the number of infectious adverse events reported in the extension phase of the trial, months 25 to 48.

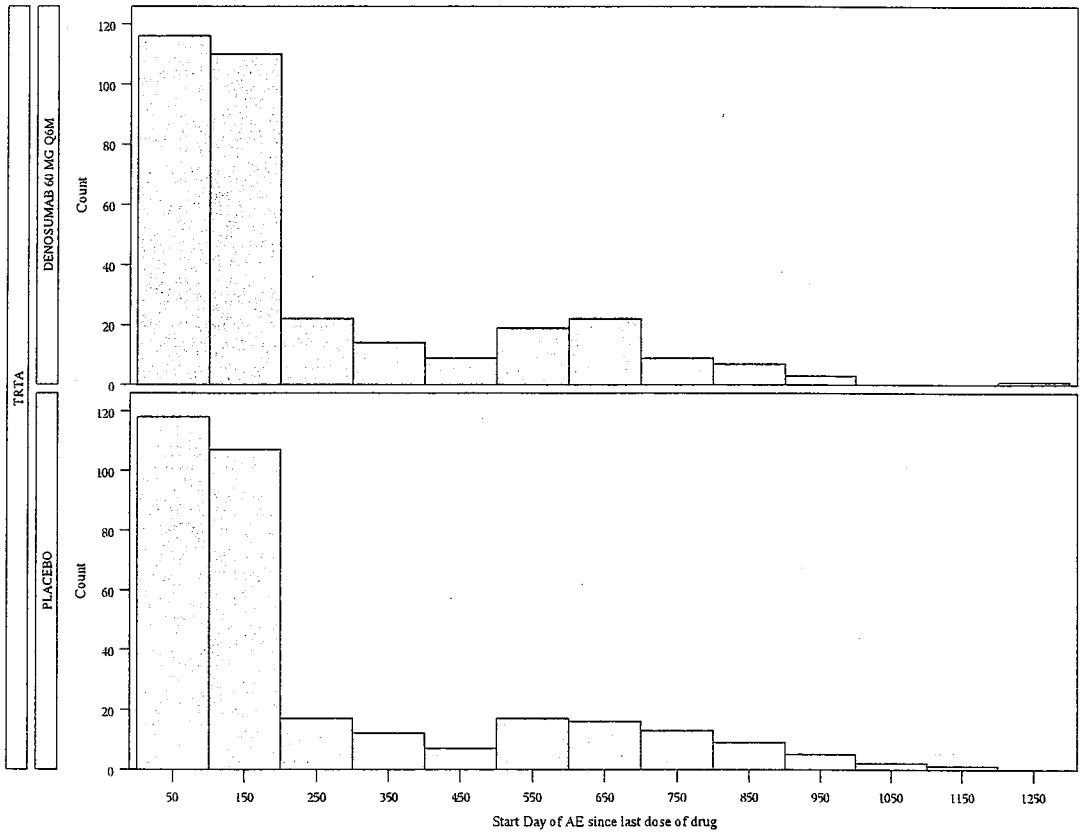

Figure 2: Infectious Event Counts since last dose of drug

Table 4: Distribution of Infection AEs

	Denosumab	Placebo
Baseline to Month 24	235	232
Month 25 to Month 48	108	96
Total	343	328

Serious infections

The number of subjects experiencing serious infectious adverse events by month 24 is shown in table 5. There appears to be an imbalance in serious adverse events between the denosumab and placebo groups: the two sided p value for Fisher's exact test is $p \approx 0.02$, and the risk ratio is $RR = 8.05$, with a 95% confidence interval of $(1.02, 63.63)$, obtained using exact methods.

Table 5: Subjects Experiencing a Serious Infection by Month 24

	Denosumab (%)	Placebo (%)
Serious Infection AE	8 (4.9)	1 (0.6)
No Serious Infection AE	156(95.1)	164 (99.4)
Total	164 (100)	165 (100)

The number of subjects experiencing serious infectious adverse events by month 36 is shown in Table 6. There still appears to be an imbalance in serious adverse events between the denosumab and placebo groups. However the two sided p value for Fisher's exact test is $p \approx 0.061$, and the risk ratio is $RR = 4.02$, with a 95% confidence interval of $(0.87, 18.66)$, which was obtained using exact methods.

Table 6: Subjects Experiencing an Infection by Month 36

	Denosumab (%)	Placebo (%)
Serious Infection AE	8 (4.9)	2 (1.2)
No Serious Infection AE	156 (95.1)	163(98.8)
Total	164 (100)	165 (100)

The number of subjects experiencing serious infectious adverse events by month 48 is shown in Table 7. The table does not differ from Table 6.

Table 7: Subjects Experiencing an Infection by Month 48

	Denosumab (%)	Placebo (%)
Serious Infection AE	8 (4.9)	2 (1.2)
No Serious Infection AE	156 (95.1)	163(98.8)
Total	164 (100)	165 (100)

Distribution of Serious Adverse Events

Figure 3 shows the count of serious infectious events versus the start date of the event. It may be observed that there were more serious adverse events (SAE) experienced in the denosumab group than in the placebo group (12 versus 2). See table 11 of the appendix for more details.

The 12 infection SAEs in the denosumab group were experienced by 8 subjects. Two denosumab subjects (subjects 20040132-102017 and 20040132-107072) experienced 2 infections SAEs each. One denosumab subject, subject 20040132-307019, experienced three SAEs, which were classified as infections: Pyelonephritis, Sepsis, and Urinary tract infection. These three events were reported between study days 605 and 607. Five denosumab subjects each experienced one SAE classified as an infection. Both treatment arms each reported one SAE of infection in the extension phase, months 25 to 48 of the trial, while 10 infection SAEs were reported in the initial phase of the trial.

Of the subjects who experienced an infection SAE, one denosumab subject, 20040132-12302, did not complete the initial 24 months of the study and was lost to follow up. Another denosumab subject, 20040132-307019 completed the initial 24 months of the trial, but did not enter the extension phase. Two denosumab subjects, 20040132-107072 and 20040132-124011, began the extension phase of the trial, but did not complete the extension phase. Subject 20040132-107072 fell, broke her hip and was moved to a nursing home. Subject 20040132-124011 was lost to follow up.

Trial Completion

Subject trial completion for the 24 month on-treatment phase of trial 20040132 is given in table 8, while table 9 deals with subjects who entered and completed the extension phase of the trial. Of the 164 denosumab subjects in the safety population, 142 completed the 24 month portion of the trial. Of the 165 placebo subjects in the safety population, 144 completed the 24 month portion of the trial. Of the subjects who completed the 24 month on treatment portion of the trial, 128 subjects in the denosumab arm and 128 in the placebo arm were were enrolled in the extension phase of the trial, lasting from months 25 to 48. Of the 128 subjects in the denosumab arm in the extension phase of the trial, 109 completed the full 48 months. Of the 128 subjects in the placebo arm in the extension phase of the trial, 114 completed the full 48 months.

Descriptive statistics for the number of days that subjects were on treatment, including the number of subjects (n), the mean, standard deviation (s) and the five number summary (minimum, first quartile (Q_1), median, third quartile (Q_3), and maximum), may be found in table 10. The mean time on treatment for placebo is lower than for denosumab, although this difference is not statistically significant ($p \approx 0.34$). The median values are quite comparable. Overall, there does not appear to be a significant difference in completion rates between arms at either 24 months or for the 48 month extension phase.

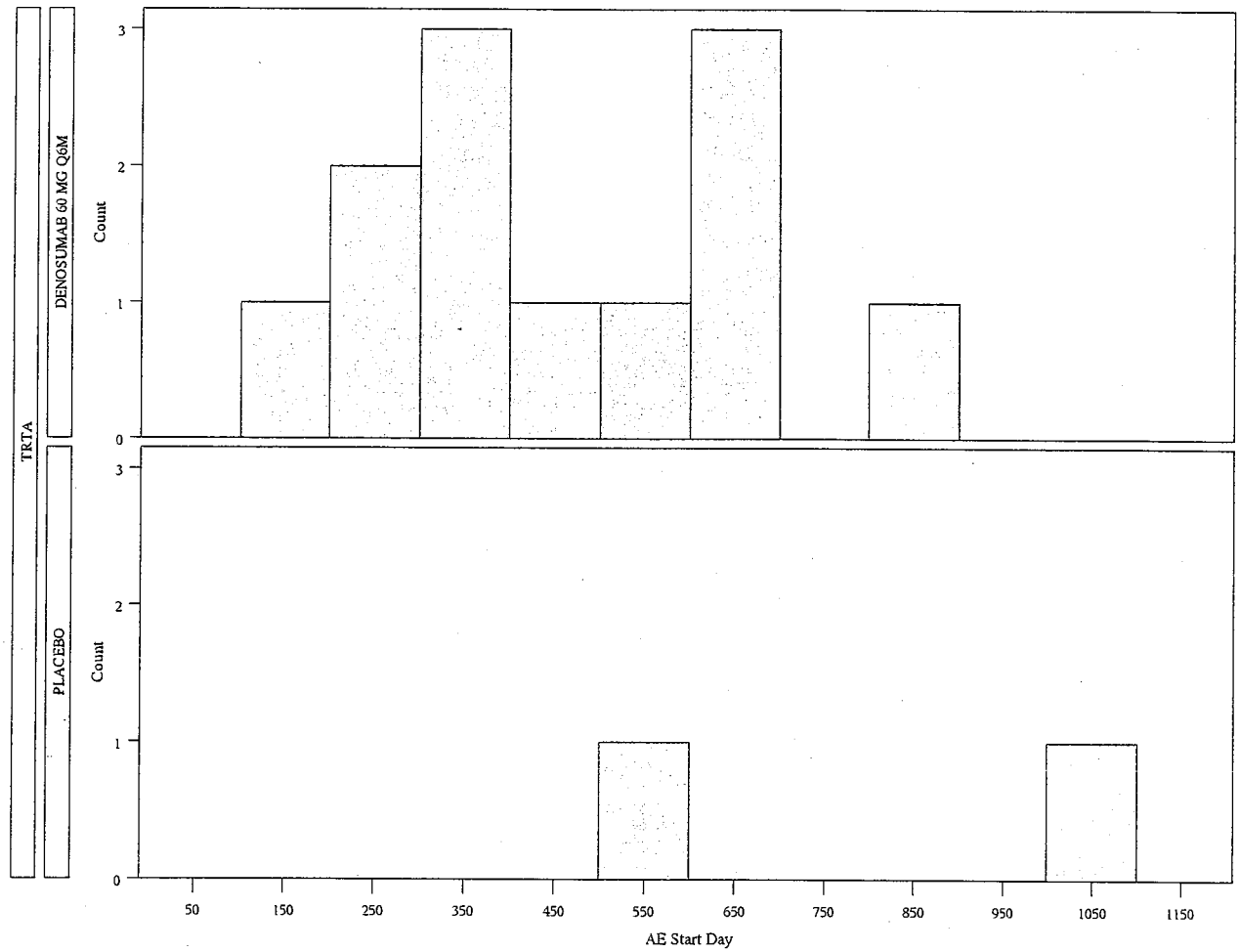

Figure 3: Start Dates of Infectious Events

Table 8: Subjects Completing Treatment Phase, Baseline to Month 24

	Denosumab (%)	Placebo (%)
Completed 24 Months	142 (86.6)	144 (87.3)
Did not complete 24 Months	22 (13.4)	21(12.7)
Total	164 (100)	165 (100)

Table 9: Subjects Completing Extension Phase, Month 24 to Month 48

	Denosumab (%)	Placebo (%)
Completed 48 Months	109 (85.2)	114 (89.1)
Did not complete 48 Months	19 (14.8)	14(10.9)
Total	128 (100)	128 (100)

Table 10: Descriptive Statistics for Number of Days on Treatment

Treatment	n	mean	s	min	Q_1	median	Q_3	max
Denosumab	164	701.1	123.8	75	724.5	731	742	843
Placebo	165	686.3	151.6	46	723	732	747	803

Discussion

Infections, in aggregate, appear to be balanced between the denosumab and placebo arms. Infections classified as serious adverse events appear to be imbalanced, with a marked majority of both serious adverse events and subjects experiencing those events occurring in the denosumab arm. When subjects discontinued treatment, denosumab subjects appear to evidence distributions similar to placebo subjects for serious infections and infections in aggregate. However, table 4 shows a marked decrease in the number of infections in months 25 to 48 from baseline to month 24. Although some of the this decrease can be undoubtedly attributed to the smaller sample participating in the study (128 versus 165 in placebo arm) and some to decrease may be anticipated due to survivorship effects, the number which might be naively expected is $232 \cdot 128/165 \approx 180$ rather than 96. Conclusions regarding a decrease in serious adverse events need to be tempered with concerns for potential under ascertainment in the extension phase of the trial.

Appendix

See table 11 on the next page.

Table 11: Serious Adverse Events for Infection

Unique Subject ID	Treatment	SAE	Trial Phase	Trial Day	Days since last dose	Completed 24 months	Completed 48 months*
20040132-102017	Denosumab	Diverticulitis	0-24 months	367	170	Yes	Yes
20040132-102017	Denosumab	Pneumonia	0-24 months	518	151	Yes	Yes
20040132-103048	Denosumab	Cellulitis	0-24 months	345	163	Yes	Yes
20040132-105011	Denosumab	Diverticulitis	0-24 months	209	13	Yes	Yes
20040132-107072	Denosumab	Pneumonia	0-24 months	361	178	Yes	No
20040132-107072	Denosumab	Pneumonia	25-48 months	848	307	Yes	No
20040132-123026	Denosumab	Pneumonia	0-24 months	176	5	No	
20040132-124011	Denosumab	Sepsis	0-24 months	484	114	Yes	No
20040132-302008	Denosumab	Urinary tract infection	0-24 months	605	53	Yes	Yes
20040132-302008	Denosumab	Pyelonephritis	0-24 months	607	55	Yes	Yes
20040132-302008	Denosumab	Sepsis	0-24 months	607	55	Yes	Yes
20040132-307019	Denosumab	Appendicitis	0-24 months	211	30	Yes	
20040132-103041	Placebo	Lobar pneumonia	0-24 months	512	121	Yes	Yes
20040132-103032	Placebo	Diverticulitis	25-48 months	1068	529	Yes	Yes

* A missing value indicates that the subject did not enroll in the 48 month extension phase

Signatures

Primary Statistical Reviewer:

Paul H. Schuette Sept. 14, 2009

Paul H. Schuette, PhD — date
Mathematical Statistician
Division of Biometrics VII

Secondary Statistical Reviewers:

Yute Wu 9/14/2009

Yu-te Wu, PhD — date
Mathematical Statistician
Division of Biometrics VII

G Rochester 9/14/2009

George Rochester, MA, PhD, RAC — date
Division Director
Division of Biometrics VII

U.S. Department of Health and Human Services

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Translational Science

Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

BLA Number	125331, 125320, 125332, and 125333
Drug Name:	denosumab (PROLIA)
Indication(s):	- Prevention of osteoporosis in postmenopausal women - Treatment of osteoporosis in postmenopausal women - Treatment and prevention of bone loss associated with hormone ablation therapy with breast cancer - Treatment and prevention of bone loss associated with hormone ablation therapy in patients with prostate cancer
Applicant:	Amgen Inc.
Date submitted:	December 19, 2009
PDUFA Date:	October 19, 2009
Date review completed	August 21, 2009
Review Priority:	Standard
Biometrics Division:	Quantitative Safety and Pharmacoepidemiology Division
Statistical Reviewer:	Leslie Kenna, Ph.D., Safety Reviewer
Secondary Reviewers:	Paul Schuette, Ph.D., Mathematical Statistician George Rochester, Ph.D., Acting Director
Medical Division:	Division of Reproductive and Urologic Products, and Division of Biologic Oncology Products
Clinical Team:	Vaishali B. Popat M.D., M.P.H, Adrienne Rothstein, Ph.D, Theresa Kehoe, M.D., Medical Officer, Team Leader, Division of Reproductive and Urologic Products Suzanne Demko, P.A.-C, Senior Clinical Analyst, Division of Biologic Oncology Products
Project Manager:	Celia Peacock, MPH, RD, Division of Reproductive and Urologic Products; Melanie Pierce, B.S., Division of Biologic Oncology Products

Keywords: serum calcium low, hypocalcemia, renal function, vitamin D, osteoporosis, bone loss, [redacted] cancer

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Leslie Kenna, Ph.D.
Safety Reviewer, Division of Biometrics VI

Date: August 21, 2009

Concurring Reviewer(s): Paul Schuette, Ph.D.
Mathematical Statistician, Division of Biometrics VI

C. George Rochester, Ph.D.
Lead Mathematical Statistician, Division of Biometrics VI

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

This review evaluates the incidence of adverse cardiovascular events reported during nine clinical trials of denosumab administered at a dose of 60 mg via the subcutaneous (SC) route once every six months (Q6M). Arms testing other doses and regimens of denosumab were included in Phase 1 and Phase 2 studies, but are not included in this safety evaluation since the sponsor only seeks marketing approval for the 60 mg Q6M dose at this time. The studies included in this analysis were of at least 12 months duration.

The data from nine studies suggest that the risk of bradyarrhythmia is approximately twice as high in subjects receiving denosumab than in subjects receiving placebo control. Additionally, the data suggest that the risk of events of ischaemic heart disease is approximately 1.3 to 1.8 times the risk in subjects receiving placebo control. There appeared to be no consistent effect of denosumab on events of myocardial infarction or any outcomes related to arrhythmia.

1.2 Statistical Issues and Findings

The goal of this review is to determine whether available data suggest that treatment with denosumab is associated with increased risk of adverse cardiovascular events. Adverse events were quantified with respect to subject incidence rate—the number of subjects reporting one or more occurrence of a given event divided by the total number of subjects receiving the treatment. Multiple occurrences of the same event were counted once per subject, and risk was quantified via computation of relative risk (RR), odds ratio (OR) and risk difference (RD).

An As-Treated analysis was performed using the safety population. Specifically, the analysis included subjects who received at least one dose of treatment and subjects were classified according to actual treatment received. The dataset included information on adverse event seriousness and severity, with severity graded as mild/1, moderate/2, severe/3, life-threatening/4, or fatal/5, and seriousness as a binary variable (serious vs. not serious). Serious is defined as in Sec. 312.32 ("IND safety reports") of 21 Code of Federal Regulations. Analyses were carried out to explore the following event characteristics: severity, seriousness, and time to event.

The cardiovascular adverse events from nine studies were analyzed using a classification system developed by the sponsor, and broad and narrow cardiovascular-related standardized MedDRA queries (SMQs). The sponsor developed a classification system to categorize various cardiovascular MedDRA Preferred Terms (PTs) into six categories: acute coronary syndromes, arrhythmia, congestive heart failure, death, other vascular disorders and stroke, and included a system for adjudicating the events themselves. An analysis of unadjudicated adverse event data was performed, as well.

Three sets of analyses were performed, based on the following groupings of MedDRA preferred terms: (1) The sponsor's groupings, (2) Broad search of MedDRA SMQ terms (listed in Appendix III), and (3) Narrow search of MedDRA SMQ terms (listed in Appendix IV). These approaches were applied to four ways of grouping the nine studies in the database: (1) analyze all studies separately, (2) pool the two largest pivotal studies (HALT and PMO indications), (3) pool the placebo-controlled studies (PMO indication), and (4) pool all controlled studies (PMO indication).

One approach to identifying adverse event reports for which there was an imbalance between the denosumab and control arms was to sort on the p-value associated with estimates of risk. In this context, a p-value is not used for valid inference, but, rather, as one criteria to sort events in terms of difference in incidence. Once subject incidence and risk was computed for each of the different sets of pooled data according to the various approaches described above for grouping MedDRA terms, events with a p-value of 0.10 were selected for futher evaluation.

The events identified via this approach were then placed in the context of the incidence of the same event at all severity levels, regardless of p-value. That is, if risk of "moderate bradycardia" was observed to occur with $p<0.10$, then risk estimates for mild, moderate, severe, life-threatening, serious and severe or worse bradycardia were added to the table, regardless of their associated p-value.

In addition, events of a serious nature were selected for futher evaluation.

Risk of cardiovascular events was computed separately for each of nine studies, as well as for the studies pooled according to whether they were large, pivotal studies (PMO and HALT indications), placebo-controlled (PMO indication), or controlled studies in the PMO population. A broad and narrow SMQ search strategy was used to group terms for the analysis. Thus, there were eight assessments performed by the reviewer, i.e. 2 MedDRA approaches (broad and narrow) for each of four ways of grouping data (all studies separately, large, pivotal studies pooled, placebo-controlled studies pooled, PMO studies pooled).

Bradyarrhytmia and ischaemic heart disease are the only signals that appear consistently in the analysis of the data from the nine studies of denosumab in PMO and HALT populations.

Bradyarrhythmia had a consistent signal according to the broad MedDRA search strategy. In the analysis of all PMO studies pooled, relative risk was estimated as 2.9 for moderate events and 1.7 for all worse severity levels. This trend was observed in the analysis of study 20030216 alone (RR=3.5), which appears to have heavily influenced the pooled analysis.

Severe ischaemic heart disease was associated with relative risk estimates greater than one in all eight analyses, with RR ranging from 1.7 to 2.0. There was a consistent estimate of relative risk greater than one across all severity levels for the placebo-

controlled and pooled [redacted]isk estimates ranging from 1.4 to 1.8 having p-values less than 0.05 were observed for all worse severity levels in the pooled placebo-controlled and PMO studies.

This review provides an exploratory statistical evaluation of adverse event reports. Ultimately, this information, along with clinical judgment will be used to determine the cardiovascular safety of denosumab.

2. INTRODUCTION

2.1 Class and Indication

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing individuals to an increased risk of fracture. Denosumab, a fully human monoclonal antibody which binds to and inhibits the action of receptor activator of nuclear factor κB (RANK) ligand, blocks the differentiation, activation, and survival of osteoclasts and thereby inhibits bone resorption. Denosumab has the potential to protect against bone loss and reduce the risk for fracture in disease settings in which bone loss occurs, such as postmenopausal osteoporosis (PMO) and bone loss associated with hormone ablation therapy (HALT).

2.2 Background on Drug Development

This marketing application includes thirty (30) clinical studies in normal volunteers and patients with osteoporosis (approximately 10,500 subjects), and in those with bone loss associated with hormone ablation therapy (approximately 1700 subjects), rheumatoid arthritis, or advanced cancer. The studies were performed between June 2001 and September 2008. Twelve studies were conducted in subjects with postmenopausal osteoporosis or low bone mass. Two studies were conducted in subjects with breast cancer or prostate cancer who had bone loss associated with hormone ablation therapy (aromatase inhibitor and androgen deprivation therapy, respectively). A third study is ongoing in subjects with breast cancer receiving aromatase inhibitor therapy. Nine additional studies, conducted in healthy subjects, provide biopharmaceutic and clinical pharmacology information as well as information on initial efficacy and tolerability of denosumab. The remaining studies were conducted in patient populations outside of the bone loss indications (i.e. inhibition of structural damage in subjects with rheumatoid arthritis, prevention of skeletal-related events in subjects with advanced cancer and bone metastases, and treatment of multiple myeloma).

2.3 Specific Studies Reviewed

The following nine studies contribute data to this review: protocols numbered 20030216, 20040132, 20050179, 20050234, 20050172, 20040135, 20040138, 20050141, and 20010223. These studies were selected since they enrolled the relevant PMO or HALT patient population, evaluated 60 mg denosumab dosed via the subcutaneous (SC) route once every six months (Q6M) for at least 12 months, and utilized randomization to treatment arm.

The PMO clinical development program is supported by two large, pivotal phase 3 studies (20030216 and 20040132). Study 20030216 is a three year, randomized, double-blind, placebo-controlled study in postmenopausal women with osteoporosis designed to determine whether denosumab treatment can reduce the incidence of new vertebral (primary endpoint), and nonvertebral and hip fractures (secondary endpoints) as compared with control. Study 20040132 is a randomized, double-blind, placebo-controlled study in postmenopausal women with low bone mass to determine whether denosumab treatment can prevent lumbar spine bone loss.

Supportive phase 2 and phase 3 studies in PMO have been completed, including Studies 20010223, 20050141, 20050179, 20050172, and 20050234. Study 20010223 is a phase 2, randomized, double-blind, placebo-controlled dose ranging study in postmenopausal women with low BMD. Studies 20050141 and 20050179 examine the effect of denosumab compared with alendronate on BMD and bone turnover markers (BTMs), and Study 20050234 examines the effect of denosumab on BMD and BTMs in women who switch from alendronate to denosumab therapy compared to women continuing to receive alendronate. Study 20050172 is a Phase 2, randomized, double-blind, placebo-controlled, dose-response study in Japanese women with PMO.

The HALT clinical development program is supported by two large, pivotal phase 3 studies (20040138 and 20040135). Study 20040138 was a randomized, double-blind, placebo-controlled study in men undergoing androgen deprivation therapy for nonmetastatic prostate cancer to determine the treatment effect of denosumab on lumbar spine BMD compared with control. Study 20040138 also included prespecified endpoints for new vertebral and any fracture risk reduction. Study 20040135 was a randomized, double-blind, placebo-controlled study in women undergoing aromatase inhibitor therapy for nonmetastatic breast cancer to determine the treatment effect of denosumab on lumbar spine BMD compared with control. The primary analyses for Study 20040138 and Study 20040135 were performed at 3 years and 2 years, respectively, once all subjects had the opportunity to complete the treatment phase. Both studies included an ongoing 2-year extension phase in which no investigational product was administered to characterize the safety profile after cessation of denosumab treatment. An open-label extension study of Study 20040138 has initiated (Study 20080537), and eligible subjects were offered the choice to enroll into the extension study rather than continue in the follow-up phase of Study 20040138.

Table 1 and Table 2 provide a summary of the design and objectives of the PMO and HALT population studies, respectively, included in this safety review. All of the studies enrolled a denosumab 60 mg SC arm and occured over a period of 12 months or longer. All nine studies included a control arm and were conducted in a relevant patient population.

Table 1. Features of PMO Studies Included in this Reviewer's Safety Analysis. Footnotes are on the following page.

	Objectives	Design	Test Product	Number Exposed	Key Entry Criteria	Duration
20030216	EFF (fracture), SAFE, TOL, BMD, PD, PK, bone histology, histomorphometry, fracture healing	Phase 3, RAND, DB, PC	DEN 60 mg SC Q6M or PLAC SC Q6M 6 doses total	3886 DEN 3876 PLAC	Women with PMO[1] Age: 60-90 yr	36 months
20040132	EFF (BMD), SAFE, TOL, PD	Phase 3, RAND, DB, PC	DEN 60 mg SC Q6M or PLAC SC Q6M 4 doses total	164 DEN 165 PLAC	Postmenopausal women with low BMD[2] Age: ≤ 90 yr	24 months treat 24 months off treatment extension
20050172	EFF (BMD), SAFE, TOL, dose selection, PK, PD	Phase 2, RAND, DB, PC, dose-response	DEN 60 mg[8] SC Q6M or PLAC SC Q6M 2 doses total	54 DEN 55 PLAC	Japanese women with PMO[3] Age: ≤ 80 yr	12 months
20010223	EFF (BMD), SAFE, TOL, dose selection	Phase 2, RAND, DB, PC, AC, dose-finding	DEN 60 mg[9, 10] SC Q6M or PLAC SC Q6M or ALEN 70 mg PO QW	47 DEN 46 PLAC 46 ALEN	Postmenopausal women with low BMD[4] Age: ≤ 80 yr	48 months
20050179	EFF (cortical thickness, BMD), PD, SAFE	Phase 2, RAND, DB, DD, PC, AC	DEN 60 mg SC Q6M (2 doses) plus PLAC for ALEN PO QW or PLAC for DEN SC Q6M (2 doses) plus ALEN 70 mg PO QW or PLAC for DEN SC Q6M (2 doses) plus PLAC for ALEN PO QW	83 DEN 82 ALEN 82 PLAC	Postmenopausal women with low BMD[5] Age: 50 to 70 yr	12 months
20050234	Comparative EFF (BMD), PD, SAFE, TOL	Phase 3b, RAND, DB, AC, DD, parallel-group	DEN 60 mg SC Q6M (2 doses) plus PLAC for ALEN PO QW or PLAC for DEN SC Q6M (2 doses) plus ALEN 70 mg PO QW	253 DEN 251 ALEN	Women with PMO[6] who received ALEN 70 mg QW or equivalent for ≥ 6 mo before screening Age: ≥ 55 yr	12 months
20050141	Comparative EFF (BMD), SAFE, TOL	Phase 3, RAND, DB, AC, DD, parallel group	DEN 60 mg SC Q6M (2 doses) plus PLAC for ALEN PO QW or PLAC for DEN SC Q6M (2 doses) plus ALEN 70 mg PO QW	594 DEN 595 ALEN	Postmenopausal women with low BMD[7]	12 months

AC=Active controlled, ALEN=Alendronate, BMD=Bone Mineral Density, DB=Double blind, DD=Double dummy, DEN=Denosumab, EFF=Efficacy, PC=Placebo controlled, PD=Pharmacodynamics, PK=Pharmacokinetics, PLAC=Placebo, PMO=Postmenopausal osteoporosis, RAND=randomized, Rx=Treatment, SAFE=Safety study, SC=Subcutaneous, Q6M=Every 6 months, QW=Every week, TOL=Tolerability study

Footnotes for Table 1 (on previous):

[1]PMO = -4.0 ≤ T-score < -2.5 at the lumbar spine or total hip or both

[2]BMD = -2.5 < T-score < -1.0 at the lumbar spine

[3]PMO = -4.0 ≤ T-score ≤ -2.5 for lumbar spine or -3.5 ≤ T-score ≤ -2.5 for total hip or femoral neck

[4]BMD = -4.0 ≤ T-score ≤ -1.8 for lumbar spine or -3.5 ≤ T-score ≤ -1.8 for total hip or femoral neck

[5]BMD = -3.0 ≤ T-score ≤ -2.0 at the lumbar spine or total hip

[6]PMO = -4.0 ≤ T-score ≤ -2.0 at the lumbar spine or total hip

[7]BMD = T-score ≤ -2.0 at the lumbar spine or total hip

[8]In addition, 14mg and 100 mg doses were tested, but data from these arms are not included in this safety analysis.

[9]In addition, an arm in which DEN 6 mg, 14 mg, or 30 mg was dosed SC Q3M was tested, but not included in this analysis.

[10]Doses of 14mg, 100 mg, or 210 mg were administered SC Q6M, but not included in this analysis.

Table 2. Features of HALT Studies Included in this Reviewer's Safety Analysis.

	Objectives	Design	Test Product	Number Exposed	Key Entry Criteria	Duration*
20040135	EFF (BMD), SAFE, PK	Phase 3, RAND, DB, PC	DEN 60 mg SC Q6M or PLAC SC Q6M (4 doses)	125 DEN 124 PLAC	Women with nonmetastatic breast cancer receiving aromatase inhibitor therapy with low bone mass; BMD criteria[1] Age: ≥ 18 yr	24 months treatment + 24-month safety follow-up
20040138	EFF (BMD, vertebral and any fracture incidence), SAFE, PK	Phase 3, RAND, DB, PC	DEN 60 mg SC Q6M or Placebo SC Q6M (6 doses)	731 DEN 725 PLAC	Men with nonmetastatic prostate cancer receiving androgen-deprivation therapy; subjects with BMD criteria[2]	36 months treatment + 24-month safety follow-up or 2-year extension

AC=Active controlled, ALEN=Alendronate, BMD=Bone Mineral Density, DB=Double blind, DD=Double dummy, DEN=Denosumab, EFF=Efficacy, PC=Placebo controlled, PD=Pharmacodynamics, PK=Pharmacokinetics, PLAC=Placebo, PMO=Postmenopausal osteoporosis, RAND=randomized, Rx=Treatment, SAFE=Safety study, SC=Subcutaneous, Q6M=Every 6 months, QW=Every week, TOL=Tolerability study

*Duration: Includes follow up

[1]BMD criteria: -2.5 ≤ BMD, T-score ≤ -1.0 at the lumbar spine, femoral neck, or total hip (with none < -2.5)

[2]BMD criteria: BMD T-score < -4.0 at lumbar spine, total hip, or femoral neck excluded For those < 70 yrs of age (but not those ≥ 70 yrs): history of osteoporotic fracture or BMD T-score < -1.0 at the lumbar spine, total hip, or femoral neck

The following studies were not included in this safety analysis because they enrolled only healthy subjects, had a small number of patients, were shorter than 12 months in duration

(b) (4)

[redacted]

3. DATA SOURCES

The sponsor provided all data and study reports in electronic format. The model for the data structure was described as consistent with CDISC Study Data Tabulation Model (SDTM) and Analysis Dataset model (ADaM) guidelines (www.cdisc.org).

Appendix V lists the study reports reviewed and provides the path to their location in the electronic document room and chapter location in Global Summit Review.

Since the AAE dataset only includes subjects who reported an adverse event, the ASLINFO and demographics (DM) datasets were needed to determine the appropriate count of subjects (denominator) exposed to treatment or control.

Adverse events were coded using terminology standardized in the Medical Dictionary for Regulatory Activities (MedDRA). Appendix VI lists the version of MedDRA utilized to code events in each of the nine studies reviewed. The Integrated Summary of Safety (ISS) dataset harmonized these versions into single dataset with MedDRA version 11.0.

4. METHODS

This review evaluates the incidence of adverse cardiovascular events reported during nine clinical trials of denosumab 60 mg administered via the subcutaneous route once every six months. The trials were not designed to detect a statistically significant difference in adverse events, thus, the data analytic approaches described in this review are considered exploratory.

The goal of this review is to determine whether available data suggest that treatment with denosumab is associated with adverse cardiovascular events.

Questions to be explored include:
• Do significantly more subjects experience adverse cardiovascular events in the denosumab treatment group compared to the control group?
• Is the severity of cardiovascular events greater in the denosumab treatment group compared to the control group?
• Is the seriousness of cardiovascular events greater in the denosumab treatment group compared to the control group?
• Is the time to occurrence of cardiovascular events in the denosumab treatment group shorter than in the control group?

Statistical Methodologies

The safety dataset integrates data from all subjects who received at least one dose of investigational product. Adverse events were graded according to severity, specifically into the categories of "Mild", "Moderate", "Severe", "Life-threatening" and "Fatal". They were also flagged according to whether they were of a serious nature, as defined in Sec. 312.32 ("IND safety reports") of 21 Code of Federal Regulations:

> Serious adverse drug experience: Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Rationale for Pooling Data
Data from the nine studies described in Section 2.1.3 and Section 2.2 of this review were reviewed individually and also pooled according to the following groupings of interest. Note that although some studies tested several doses of denosumab, only the 60 mg denosumab arm was included in the analysis.

Large, Pivotal Trial Data
The data from Study 20030216 and Study 20040138 were pooled for analysis since both were large, placebo-controlled large, pivotal trials of 36 months in duration. The pooled data from studies 20030216 and 20040138 will be referred to as the large, pivotal dataset, and covers the PMO and HALT populations.

Placebo-Controlled Studies in PMO
Data from the denosumab and placebo arms were pooled from Study 20030216, 20040132, 20050172, 20050179, and 20010223, as these represent the placebo-controlled studies in patients with PMO.

All Controlled PMO Studies in PMO
Data from the denosumab, placebo and alendronate arms were pooled from Study 20030216, 20040132, 20050172, 20050179, 20010223, 20050234, and 20050141, as these represent any controlled studies of denosumab in the PMO population.

Data from Study 20040135 and Study 20040138 were not pooled for analysis because they were conducted in different populations (i.e. male vs. female; different age groups; different illness).

This analysis accepts the Sponsor's records of adverse events. That is, no attempt was made to evaluate the case report forms for agreement between information in the patient's record and values recorded in the dataset.

Definition of Safety Population
The incidence of adverse events reported in subjects receiving a 60 mg dose of denosumab every six months (Q6M) was compared to that in subjects administered control treatment – placebo and/or alendronate 70 mg dosed orally once weekly (QW). An As-Treated approach was taken to the analysis—the safety population included all subjects who received at least one dose of treatment (i.e. members of the SAFETY=T population) and according to actual treatment received (i.e. the TRTA or EXTRT variable). The dataset included information on adverse event seriousness and severity (variable name: AESEV or AETOXGR). Seriousness was indicated by the variable named AESER. Severity was denoted with the variable AESEV (mild, moderate, severe, life-threatening, fatal) or AETOXGR (Grade 1-Grade 5).

Metrics
Adverse events were quantified in terms of subject incidence rate—the number of subjects reporting one or more occurrence of a given event divided by the total number of

subjects receiving the treatment. Multiple occurrences of same event were counted once per subject.

Relative risks (RR), odds ratios (OR) and risk differences (RD) were computed to quantify risk. Relative risk is the ratio of the probability of the event occurring in the experimental group versus in a control group. The odds ratio is the ratio of the odds of an event occurring in the experimental group to the odds it occurs in the control group. The risk difference computes the absolute change in risk attributable to experimental intervention and is calculated as risk in the experimental group minus risk in the control group. Risk differences allow for a risk estimate to be computed in the event that zero events occur in one of the arms since it involves taking differences, thus, does not involve division by zero.

P-values for risk estimates were computed and p-values for relative risk were used to prioritize/score adverse events. Since the nine studies analyzed were not designed for a causal analysis of safety, this use of a p-value is exploratory. Logistic regression was used to obtain two-sided p-values. When cell counts were less than or equal to 5, exact logistic regression was used to obtain the confidence interval and p-value of risk estimates. When cell counts were equal to zero, the point estimate was assigned as zero (no event in the denosumab group) but the confidence interval and p-value was computed using exact logistic regression.

In addition, time to event (i.e. SMQ category or one of the sponsor's six categories of adverse cardiovascular event) was computed. Time to event was not computed for individual preferred terms since the data were too sparse to support such an estimate.

MedDRA Term Search strategy

The reviewer performed an analysis of unadjudicated adverse event data. The unadjudicated data were examined since the sponsor only adjudicated adverse event data from two studies and it was of interest to evaluate outcomes from as many relevant trials as possible. In addition, adjudication has the potential to introduce subjectivity into data collection, thus, analysis of unadjudicated data seemed an important check to perform. Three sets of analyses were performed, based on the following groupings of MedDRA preferred terms: (1) the sponsor's groupings, (2) broad search of MedDRA SMQ terms listed in Appendix III, and (3) narrow search of MedDRA SMQ terms listed in Appendix IV.

For each of these three approaches to MedDRA term grouping, the following items were tabulated: the preferred term, the severity (i.e. AESEV or AETOXGR), the total number of events, the number of subjects that experienced at least one event, and the risk rate (at the subject level) for actual treatment received. These items were computed for all of the preferred terms separately, and with terms pooled under structured categories. RR, OR, RD and their corresponding 95% confidence intervals are provided.

MedDRA terms were also grouped according to System Organ Class (SOC), Higher Level Group Term (HLGT), High Level Term (HLT) and Preferred Term (PT) for each

of the three pooled datasets of interest: pooled large, pivotal trials, pooled placebo-controlled PMO trials, pooled placebo- or active- controlled trials.

5. RESULTS

Tabulations of subject incidence, risk and their associated p-values were generated by grouping reported adverse events according to broad SMQ, narrow SMQ and the sponsor's MedDRA preferred term grouping strategy. Events with a relative risk having an associated p-value of less than 0.10 were selected for further evaluation. Given that none of the nine studies were designed to evaluate the incidence of cardiovascular adverse events, this approach of ranking reports of adverse events by p-value is considered an exploratory analysis.

Table 3 shows a cross-trial comparison of relative risk estimates for events having at least one relative risk estimate associated with a p-value less than 0.10. Note that columns of the table correspond to the trial or pooled dataset for which the relative risk estimates were computed—the first nine columns correspond to using a broad SMQ search strategy and the remaining columns correspond to a narrow SMQ search strategy. Relative Risk estimates are reported unless the relative risk cannot be computed due to the occurrence of zero events. In such instances, the number of subjects in each arm with the event is reported instead of RR. Highlighted entries are associated with a p-value less than 0.10, while non-highlighted RR values are not associated with a p-value less than 0.10. Empty cells indicate that a particular event did not occur in that particular dataset employing the given SMQ strategy.

Table 3 shows that there were 24 different terms whose relative risk estimate was associated with a p-value less than 0.10: Arrhythmia related investigations, Bradyarrhythmias, Cardiac Arrhythmias, Cardiac arrhythmia terms, Cardiac Failure, Cardiomyopathy, Conduction Defects, Disorders of Sinus Node Function, Embolic and Thrombotic Events, Embolic and Thrombotic Events—Arterial, Embolic and Thrombotic Events—Unspecified, Embolic and Thrombotic Events—Venous, Gastrointestinal Haemorrhage, Gastrointestinal Perforation, Ulceration, etc., Haemodynamic oedema, effusions, etc., Haemorrhages, Haemorrhage Terms (excl lab), Hypertension, Ischaemic Heart Disease, Myocardial Infarction, Pulmonary Hypertension, Thrombophlebitis, Torsade de Pointes/QT Prolongation, and Toxic-septic shock conditions.

Note that more detailed tabulations and a discussion of the results is provided in Appendix VII. Tables A1 – A42 in Appendix VII provide event counts, risk estimates, confidence intervals and p-values for all individual studies and pooled datasets using broad SMQ, narrow SMQ and the sponsor's grouping of terms.

Table 3. Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison. Columns of the table correspond to the trial or pooled dataset on which the relative risk estimates were computed. The first nine columns correspond to using a broad SMQ search strategy and the remaining columns correspond to a narrow SMQ search strategy. Relative Risk estimates are reported unless it cannot be computed due to the occurrence of zero events. In such instances, the number of subjects in each arm with the event is reported instead of RR. Note that highlighted entries are associated with a p-value less than 0.10. Non-highlighted RR values are not associated with a p-value less than 0.10. Empty cells indicate that a particular event didn't occur in that particular dataset employing the given SMQ strategy.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Arrhythmia related investigations	Ser 1.08	Ser 0 Den 0 Plac	Ser 0 Den 0 Plac	Ser 1.32	Ser 0.99	Ser 0 Den 0 Alen	Ser 1.16	Ser 1.14	Ser 0.97									
	All 1.08	All 1.76	All 1.86	All 1.12	All 0.99	All 1.5	All 1.08	All 1.11	All 1.0									
	Mild 1.3	Mild 1.34	Mild 0.93	Mild 0.62	Mild 0.77	Mild 2.5	Mild 1.25	Mild 1.3	Mild 1.19									
	Fatal 0.3	Fatal 0 Den 0 Plac	Fatal 0 Den 0 Plac	Fatal 1.98	Fatal 1 Den 0 Alen	Fatal 0 Den 0 Alen	Fatal 0.69	Fatal 0.3	Fatal 0.33									

All = All severity levels pooled; DEN = Denosumab; Fatal = Fatal severity; LT = Life-threatening severity; Mild = Mild severity; Mod = Moderate severity; PLA = Placebo; Ser = Serious event; Sev = Severe severity; ≥Sev = Severe or worse severity

(Table 3 continued on the next page.)

Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Bradyarrhythmias	Ser 1.9	Ser 0 Den 0 Plac	Ser 1 Den 0 Plac	Ser 1.74	Ser 1 Den 0 Alen	Ser 1 Den 0 Alen	Ser 1.9	Ser 1.9	Ser 1.75									
	All 1.3	All 1.01	All 1 Den 0 Plac	All 1.82	All 2.0	All 1 Den 0 Alen	All 1.4	All 1.29	All 1.15									
	Mod 3.5	Mod 0 Den 0 Plac	Mod 0 Den 0 Plac	Mod 0.66	Mod 0 Den 1 Alen	Mod 0 Den 0 Alen	Mod 2.3	Mod 3.5	Mod 2.9									
	Sev 1.66	Sev 0 Den 0 Plac	Sev 1 Den 0 Plac	Sev 4.96	Sev 1 Den 0 Alen	Sev 1 Den 0 Alen	Sev 2.1	Sev 1.66	Sev 1.66									
	≥Sev 1.7	≥Sev 0 Den 0 Plac	≥Sev 1 Den 0 Plac	≥Sev 4.96	≥Sev 1 Den 0 Alen	≥Sev 1 Den 0 Alen	≥Sev 2.1	≥Sev 1.71	≥Sev 1.66									

All = All severity levels pooled; DEN = Denosumab; Fatal = Fatal severity; LT = Life-threatening severity; Mild = Mild severity; Mod = Moderate severity; PLA = Placebo; Ser = Serious event; Sev = Severe severity; ≥Sev = Severe or worse severity

(Table 3 continued on the next page.)

Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Cardiac Arrhythmias	Ser 1.11	Ser 0 Den 0 Plac	Ser 0.93	Ser 1.28	Ser 2.94	Ser 2.0	Ser 1.15	Ser 1.13	Ser 0.99									
	All 1.03	All 2.01	All 1.09	All 1.07	All 1.18	All 0.74	All 1.04	All 1.06	All 0.94									
	Sev 0.98	Sev 0 Den 1 Plac	Sev 2.79	Sev 2.0	Sev 1.96	Sev 0.98	Sev 1.16	Sev 0.96	Sev 0.85									
	Fatal 0.3	Fatal 0 Den 0 Plac	Fatal 0 Den 0 Plac	Fatal 2.0	Fatal 1 Den 0 Alen	Fatal 0 Den 0 Alen	Fatal 0.69	Fatal 0.3	Fatal 0.33									
Cardiac arrhythmia terms	Ser 1.18	Ser 0 Den 0 Plac	Ser 0.93	Ser 1.49	Ser 2 Den 0 Alen	Ser 2.0	Ser 1.25	Ser 1.25	Ser 1.05									
	All 0.97	All 2.52	All 0.31	All 1.21	All 1.72	All 0.49	All 1.01	All 1.01	All 0.87									
	Mild 0.83	Mild 2.52	Mild 0 Den 1 Plac	Mild 0.85	Mild 1.96	Mild 0.66	Mild 0.83	Mild 0.83	Mild 0.77									

All = All severity levels pooled; DEN = Denosumab; Fatal = Fatal severity; LT = Life-threatening severity; Mild = Mild severity; Mod = Moderate severity; PLA = Placebo; Ser = Serious event; Sev = Severe severity; ≥Sev = Severe or worse severity

(Table 3 continued on the next page.)

Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ											NARROW SMQ						
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Cardiac Failure	Ser 0.95	Ser 0 Den 0 Plac	Ser 0 Den 1 Plac	Ser 0.76	Ser 0 Den 0 Alen	Ser 1 Den 0 Alen	Ser 0.89	Ser 0.89	Ser 0.81	Ser 0.92		Ser 0 Den 1 Plac	Ser 0.74		Ser 1 Den 0 Alen	Ser 0.87	Ser 0.92	Ser 0.79
	All 1.13	All 0.56	All 1.33	All 0.95	All 1.32	All 1.57	All 1.09	All 1.09	All 0.99	All 1.14		All 0 Den 2 Plac	All 0.8		All 1 Den 0 Alen	All 1.06	All 1.14	All 0.96
	Mild 1.03	Mild 1.01	Mild 1.63	Mild 1.6	Mild 1.82	Mild 1.23	Mild 1.14	Mild 1.14	Mild 0.96	Mild 0.91		Mild 0 Den 0 Plac	Mild 2.5		Mild 0 Den 0 Alen	Mild 1.04	Mild 0.91	Mild 0.76
	Mod 1.3	Mod 0.25	Mod 0.62	Mod 0.31	Mod 0.50	Mod 0.98	Mod 1.01	Mod 1.01	Mod 1.03	Mod 1.43		Mod 0 Den 2 Plac	Mod 0.17		Mod 0 Den 0 Alen	Mod 1.22	Mod 1.43	Mod 1.19
	LT 0.6	LT 0 Den 0 Plac	LT 0 Den 0 Plac	LT 0.17	LT 0 Den 0 Alen	LT 1 Den 0 Alen	LT 0.36	LT 0.36	LT 0.66	LT 0.6		LT 0 Den 0 Plac	LT 0.17		LT 1 Den 0 Alen	LT 0.36	LT 0.6	LT 0.66

All = All severity levels pooled; DEN = Denosumab; Fatal = Fatal severity; LT = Life-threatening severity; Mild = Mild severity; Mod = Moderate severity; PLA = Placebo; Ser = Serious event; Sev = Severe severity; ≥Sev = Severe or worse severity

(Table 3 continued on the next page.)

Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Cardiomyopathy	Ser 1.01	Ser 0 Den 0 Plac	Ser 0 Den 1 Plac	Ser 1.22	Ser 0 Den 2 Alen	Ser 0 Den 0 Alen	Ser 1.08	Ser 1.03	Ser 0.86	Ser 2.5	1	Ser 0 Den 0 Plac	Ser 2.0	Ser 0 Den 1 Alen		Ser 2.33	Ser 2.5	Ser 2.08
	All 0.97	All 1.51	All 1.14	All 0.97	All 0.81	All 1.23	All 0.97	All 0.98	All 0.88	All 1.0		All 1 Den 0 Plac	All 0.99	All 0 Den 1 Alen		All 1.0	All 1.0	All 0.83
	Mod 0.95	Mod 1.01	Mod 0.93	Mod 0.69	Mod 0.66	Mod 0 Den 2 Alen	Mod 0.89	Mod 0.97	Mod 0.84	Mod 1.33		Mod 1 Den 0 Plac	Mod 0.66	Mod 0 Den 1 Alen		Mod 1.0	Mod 1.33	Mod 1.11
	Fatal 0.4	Fatal 0 Den 0 Plac	Fatal 0 Den 0 Plac	Fatal 1.79	Fatal 0 Den 0 Alen	Fatal 0 Den 0 Alen	Fatal 0.81	Fatal 0.36	Fatal 0.3	Fatal 1 Den 0 Plac		Fatal 0 Den 0 Plac	Fatal 0 Den 0 Plac	Fatal 0 Den 0 Alen		Fatal 1 Den 0 Plac	Fatal 1 Den 0 Plac	Fatal 1 Den 0 Plac
Conduction Defects	Ser 2.66	Ser 0 Den 0 Plac	Ser 1 Den 0 Plac	Ser 0.66	Ser 0 Den 0 Alen		Ser 1.66	Ser 2.66	Ser 2.22									
	All 1.1	All 1.01	All 1 Den 0 Plac	All 1.49	All 0.99		All 1.16	All 1.04	All 0.91									
	Sev 4.99	Sev 0 Den 0 Plac	Sev 1 Den 0 Plac	Sev 2.98	Sev 0 Den 0 Alen		Sev 4.0	Sev 4.99	Sev 4.16									

Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

Event	BROAD SMQ									NARROW SMQ								
	2003 0216	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Disorders of Sinus Node Function	Ser 1.57			Ser 2.48		Ser 1 Den 0 Alen	Ser 1.77	Ser 1.57	Ser 1.42									
	All 1.7			All 1.98		All 1 Den 0 Alen	All 1.8	All 1.8	All 1.58									
	Mod 3.7			Mod 0.99			Mod 2.6	Mod 3.7	Mod 3.1									
						Mod 0 Den 0 Alen												
Embolic and Thrombotic Events	Ser 1.14		Ser 2.79	Ser 1.17	Ser 0.25	Ser 0.98	Ser 1.15	Ser 1.14	Ser 0.96	Ser 1.1		Ser 2.8	Ser 1.27	Ser 0 Den 3 Alen	Ser 0 Den 0 Alen	Ser 1.15	Ser 1.09	Ser 0.91
	All 1.04		All 1.4	All 1.11	All 0.42	All 0.98	All 1.06	All 1.04	All 0.89	All 0.99		All 1.4	All 1.13	All 0.40	All 0.98	All 1.03	All 0.98	All 0.84
	Mod 0.93		Mod 0 Den 1 Plac	Mod 1.52	Mod 0.66	Mod 0.98	Mod 1.06	Mod 0.95	Mod 0.83	Mod 0.86		Mod 0 Den 1 Plac	Mod 2.1	Mod 0.50	Mod 0.98	Mod 1.07	Mod 0.86	Mod 0.76
	Sev 1.5		Sev 0.93	Sev 1.19	Sev 0 Den 1 Alen	Sev 0 Den 1 Alen	Sev 1.43	Sev 1.5	Sev 1.24	Sev 1.5		Sev 0.93	Sev 1.37	Sev 0 Den 1 Alen	Sev 0 Den 0 Alen	Sev 1.4	Sev 1.4	Sev 1.19

All = All severity levels pooled; DEN = Denosumab; Fatal = Fatal severity; LT = Life-threatening severity; Mild = Mild severity; Mod = Moderate severity; PLA = Placebo; Ser = Serious event; Sev = Severe severity; ≥Sev = Severe or worse severity

(Table 3 continued on the next page.)

Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Embolic and Thrombotic Events, Arterial	Ser 1.24		Ser 2.79	Ser 1.1	Ser 0 Den 2 Alen	Ser 0 Den 0 Alen	Ser 1.19	Ser 1.22	Ser 1.01	Ser 1.24		Ser 2.8	Ser 1.1	Ser 0 Den 2 Alen	Ser 0 Den 0 Alen	Ser 1.19	Ser 1.22	Ser 1.01
	All 1.22		All 2.79	All 1.11	All 0.99	All 0 Den 1 Alen	All 1.19	All 1.2	All 1.03	All 1.22		All 2.8	All 1.11	All 0.99	All 0 Den 1 Alen	All 1.19	All 1.2	All 1.03
	Sev 1.7		Sev 0.83	Sev 1.61	Sev 0 Den 0 Alen	Sev 0 Den 0 Alen	Sev 1.7	Sev 1.66	Sev 1.39	Sev 1.7		Sev 0.93	Sev 1.61	Sev 0 Den 0 Alen	Sev 0 Den 0 Alen	Sev 1.7	Sev 1.66	Sev 1.4
	LT 0.4		LT 2 Den 0 Plac	LT 0.58	LT 0 Den 0 Alen	LT 0 Den 0 Alen	LT 0.5	LT 0.4	LT 0.33	LT 0.4		LT 2 Den 0 Plac	LT 0.58	LT 0 Den 0 Alen	LT 0 Den 0 Alen	LT 0.5	LT 0.4	LT 0.33
Embolic and Thrombotic Events, Unspecified	Ser 1.32			Ser 0.93	Ser 0.99	Ser 0.98	Ser 1.2	Ser 1.35	Ser 1.17									
	All 1.29			All 0.84	All 0.50	All 0.98	All 1.15	All 1.31	All 1.12									
	Sev 1.8			Sev 0.99	Sev 0 Den 0 Alen	Sev 0 Den 1 Alen	Sev 1.52	Sev 1.8	Sev 1.45									
	≥Sev 1.6			≥Sev 0.86	≥Sev 0 Den 0 Alen	≥Sev 0.98	≥Sev 1.31	≥Sev 1.6	≥Sev 1.37									

Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMQ Controlled**
Embolic and Thrombotic Events, Venous	Ser 1.0		Ser 0 Den 0 Plac	Ser 2.73	Ser 0 Den 1 Alen	Ser 0 Den 0 Alen	Ser 1.26	Ser 1.0	Ser 0.83	Ser 1.0		Ser 0 Den 0 Plac	Ser 2.73	Ser 0 Den 1 Alen	Ser 0 Den 0 Alen	Ser 1.26	Ser 1.0	Ser 0.83
	All 0.75		All 0 Den 1 Plac	All 1.39	All 0 Den 3 Alen	All 1 Den 0 Alen	All 0.86	All 0.75	All 0.64	All 0.75		All 0 Den 1 Plac	All 1.39	All 0 Den 3 Alen	All 1 Den 0 Alen	All 0.86	All 0.75	All 0.64
	Mild 0.5		Mild 0 Den 0 Plac	Mild 0.5	Mild 0 Den 2 Alen	Mild 0 Den 0 Alen	Mild 0.5	Mild 0.5	Mild 0.42	Mild 0.5		Mild 0 Den 0 Plac	Mild 0.5	Mild 0 Den 2 Alen	Mild 0 Den 0 Alen	Mild 0.5	Mild 0.5	Mild 0.42
	Mod 0.59		Mod 0 Den 1 Plac	Mod 2.64	Mod 0 Den 0 Alen	Mod 1 Den 0 Alen	Mod 0.84	Mod 0.59	Mod 0.53	Mod 0.59		Mod 0 Den 1 Plac	Mod 2.64	Mod 0 Den 0 Alen	Mod 1 Den 0 Alen	Mod 0.84	Mod 0.59	Mod 0.53

All = All severity levels pooled; DEN = Denosumab; Fatal = Fatal severity; LT = Life-threatening severity; Mild = Mild severity; Mod = Moderate severity; PLA = Placebo; Ser = Serious event; Sev = Severe severity; ≥Sev = Severe or worse severity

(Table 3 continued on the next page.)

Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Gastrointestinal Haemorrhage	Ser 1.21	Ser 0 Den 0 Plac	Ser 1 Den 0 Plac	Ser 0.44	Ser 1 Den 0 Alen	Ser 0 Den 0 Alen	Ser 0.96	Ser 1.21	Ser 1.05									
	All 1.4	All 0.5	All 1.86	All 0.9	All 1.01	All 0.49	All 1.24	All 1.29	All 1.15									
	Mild 1.0	Mild 0.25	Mild 0.93	Mild 1.49	Mild 0 Den 4 Alen	Mild 0.98	Mild 1.11	Mild 0.94	Mild 0.81									
	Mod 2.1	Mod 1.01	Mod 0 Den 0 Plac	Mod 0.5	Mod 3 Den 0 Alen	Mod 0 Den 1 Alen	Mod 1.52	Mod 1.9	Mod 1.76									
Gastrointestinal Perforation, Ulceration, etc.	Ser 1.4	Ser 0 Den 0 Plac	Ser 1.86	Ser 0.47	Ser 0.99	Ser 0 Den 1 Alen	Ser 1.1	Ser 1.4	Ser 1.21									
	All 1.16	All 1.01	All 1.67	All 0.97	All 1.04	All 0.22	All 1.12	All 1.15	All 1.04									
	Mild 1.0	Mild 0.6	Mild 0.93	Mild 2.2	Mild 0.91	Mild 0.49	Mild 1.11	Mild 0.98	Mild 0.92									
	Mod 1.4	Mod 2.52	Mod 3 Den 0 Plac	Mod 0.78	Mod 1.2	Mod 0 Den 4 Alen	Mod 1.25	Mod 1.4	Mod 1.24									

All = All severity levels pooled; DEN = Denosumab; Fatal = Fatal severity; LT = Life-threatening severity; Mild = Mild severity; Mod = Moderate severity; PLA = Placebo; Ser = Serious event; Sev = Severe severity; ≥Sev = Severe or worse severity

(Table 3 continued on the next page.)

Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Haemodynamic oedema, effusions, etc.	Ser 1.63	Ser 0 Den 0 Plac	Ser 0 Den 0 Plac	Ser 1.16	Ser 0 Den 0 Alen	Ser 1 Den 0 Alen	Ser 1.47	Ser 1.63	Ser 1.44	Ser 1.63	Ser 0 Den 0 Plac	Ser 0 Den 0 Plac	Ser 1.16	Ser 0 Den 0 Alen	Ser 1 Den 0 Alen	Ser 1.47	Ser 1.63	Ser 1.44
	All 1.09	All 0.64	All 1.47	All 1.08	All 1.32	All 1.8	All 1.09	All 1.09	All 1.0	All 1.09	All 0.64	All 1.5	All 1.08	All 1.32	All 1.8	All 1.09	All 1.09	All 1.0
Haemorrhages	Mild 1.02 Ser 0.86	Mild 1.51 Ser 0 Den 0 Plac	Mild 1.34 Ser 1 Den 0 Plac	Mild 1.5 Ser 0.73	Mild 1.5 Ser 1 Den 0 Alen	Mild 1.38 Ser 0 Den 0 Alen	Mild 1.1 Ser 0.82	Mild 1.05 Ser 0.86	Mild 0.98 Ser 0.73	Mild 1.02 Ser 0.86	Mild 1.5 Ser 0 Den 0 Plac	Mild 1.34 Ser 1 Den 0 Plac	Mild 1.5 Ser 0.73	Mild 1.50 Ser 1 Den 0 Alen	Mild 1.38 Ser 0 Den 0 Alen	Mild 1.1 Ser 0.82	Mild 1.05 Ser 0.86	Mild 0.98 Ser 0.73
	All 0.99	All 0.36	All 1.46	All 0.91	All 1.12	All 0.53	All 0.97	All 0.95	All 0.86	All 0.99	All 0.38	All 1.33	All 0.92	All 0.89	All 0.53	All 0.98	All 0.96	All 0.87
	Mild 0.95	Mild 0.22	Mild 1.2	Mild 1.08	Mild 1.9	Mild 0.84	Mild 0.97	Mild 0.9	Mild 0.83	Mild 0.95	Mild 0.23	Mild 1.06	Mild 1.08	Mild 0.52	Mild 0.84	Mild 0.98	Mild 0.91	Mild 0.84
	Mod 1.09	Mod 1.01	Mod 2 Den 0 Plac	Mod 0.67	Mod 0.29	Mod 0.16	Mod 0.99	Mod 1.1	Mod 0.99	Mod 1.1	Mod 1.01	Mod 2 Den 0 Plac	Mod 0.7	Mod 3.45	Mod 0.16	Mod 1.01	Mod 1.12	Mod 1.0
	Sev 0.82	Sev 0.5	Sev 1 Den 0 Plac	Sev 0.78	Sev None	Sev 0 Den 0 Alen	Sev 0.81	Sev 0.75	Sev 0.62	Sev 0.82	Sev 0.5	Sev 1 Den 0 Plac	Sev 0.84	Sev 0 Den 0 Alen	Sev 0 Den 0 Alen	Sev 0.83	Sev 0.75	Sev 0.62

All = All severity levels pooled; DEN = Denosumab; Fatal = Fatal severity; LT = Life-threatening severity; Mild = Mild severity; Mod = Moderate severity; PLA = Placebo; Ser = Serious event; Sev = Severe severity; ≥Sev = Severe or worse severity

(Table 3 continued on the next page.)

Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Haemorrhage Terms (excl lab)	Ser 0.86	Ser None	Ser 1 Den 0 Plac	Ser 0.73	Ser 1 Den 0 Alen	Ser 0 Den 0 Alen	Ser 0.82	Ser 0.86	Ser 0.73	Ser 0.86	Ser 0 Den 0 Plac	Ser 1 Den 0 Plac	Ser 0.73	Ser 1 Den 0 Alen	Ser 0 Den 0 Alen	Ser 0.82	Ser 0.86	Ser 0.73
	All 0.99	All 0.36	All 1.46	All 0.92	All 1.12	All 0.53	All 0.98	All 0.95	All 0.87	All 0.99	All 0.38	All 1.33	All 0.92	All 0.89	All 0.53	All 0.98	All 0.96	All 0.87
	Mild 0.96	Mild 0.22	Mild 1.2	Mild 1.08	Mild 1.9	Mild 0.84	Mild 0.98	Mild 0.9	Mild 0.83	Mild 0.95	Mild 0.23	Mild 1.06	Mild 1.08	Mild 0.52	Mild 0.84	Mild 0.98	Mild 0.91	Mild 0.84
	Mod 1.1	Mod 1.01	Mod 2 Den 0 Plac	Mod 0.7	Mod 0.29	Mod 0.16	Mod 1.01	Mod 1.12	Mod 1.0	Mod 1.1	Mod 1.01	Mod 2 Den 0 Plac	Mod 0.7	Mod 3.45	Mod 0.16	Mod 1.01	Mod 1.12	Mod 1.0
	Sev 0.82	Sev 0.5	Sev 1 Den 0 Plac	Sev 0.84	Sev 0 Den 0 Alen	Sev 0 Den 0 Alen	Sev 0.83	Sev 0.75	Sev 0.62	Sev 0.82	Sev 0 Den 0 Plac	Sev 1 Den 0 Plac	Sev 0.84	Sev 0 Den 0 Alen	Sev 0 Den 0 Alen	Sev 0.83	Sev 0.75	Sev 0.62
Hypertension	Ser 0.93	Ser 0 Den 0 Plac	Ser 0 Den 0 Plac	Ser 0.57	Ser 0 Den 1 Alen	Ser 1 Den 0 Alen	Ser 0.86	Ser 0.93	Ser 0.8	Ser 0.93	Ser 0 Den 0 Plac	Ser 0 Den 0 Plac	Ser 0.57	Ser 0 Den 1 Alen	Ser 1 Den 0 Alen	Ser 0.86	Ser 0.93	Ser 0.8
	All 0.99	All 0.4	All 0.58	All 1.06	All 0.61	All 1.07	All 0.99	All 0.98	All 0.86	All 0.99	All 0.4	All 0.58	All 1.06	All 1.64	All 1.07	All 0.99	All 0.98	All 0.86
	Mod 0.97	Mod 0.25	Mod 0 den 5 plac	Mod 0.82	Mod 0.51	Mod 0.98	Mod 0.95	Mod 0.96	Mod 0.83	Mod 0.97	Mod 0.25	Mod 0 den 5 plac	Mod 0.82	Mod 1.96	Mod 0.98	Mod 0.95	Mod 0.96	Mod 0.83

Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Ischaemic Heart Disease	Ser 1.4	Ser 0 Den 0 Plac	Ser 1.86	Ser 0.8	Ser 0.33	Ser 0.98	Ser 1.18	Ser 1.4	Ser 1.18	Ser 1.4	Ser 0 Den 0 Plac	Ser 1.86	Ser 0.8	Ser 0.33	Ser 0.98	Ser 1.18	Ser 1.4	Ser 1.18
	All 1.14	All 0.34	All 1.86	All 1.01	All 0.59	All 0.33	All 1.11	All 1.13	All 0.96	All 1.15	All 0.34	All 1.86	All 0.99	All 0.59	All 0.33	All 1.11	All 1.13	All 0.96
	Sev 2.0	Sev 0 Den 1 Plac	Sev 0.93	Sev 1.28	Sev 0.50	Sev 0 Den 0 Alen	Sev 1.8	Sev 1.8	Sev 1.55	Sev 2.0	Sev 0 Den 1 Plac	Sev 0.93	Sev 1.28	Sev 0.50	Sev 0 Den 0 Alen	Sev 1.8	Sev 1.8	Sev 1.6
	≥Sev 1.7	≥Sev 0 Den 1 Plac	≥Sev 1.86	≥Sev 0.89	≥Sev 0.50	≥Sev 1 Den 0 Alen	≥Sev 1.4	≥Sev 1.6	≥Sev 1.4	≥Sev 1.7	≥Sev 0 Den 1 Plac	≥Sev 1.86	≥Sev 0.89	≥Sev 0.50	≥Sev 1 Den 0 Alen	≥Sev 1.4	≥Sev 1.6	≥Sev 1.4

All = All severity levels pooled; DEN = Denosumab; Fatal = Fatal severity; LT = Life-threatening severity; Mild = Mild severity; Mod = Moderate severity; PLA = Placebo; Ser = Serious event; Sev = Severe severity; ≥Sev = Severe or worse severity

(Table 3 continued on the next page.)

Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Myocardial Infarction	Ser 1.42		Ser 2 Den 0 Plac	Ser 0.8	Ser 0 Den 1 Alen		Ser 1.13	Ser 1.38	Ser 1.15	Ser 1.42		Ser 2 Den 0 Plac	Ser 0.8	Ser 0 Den 1 Alen		Ser 1.13	Ser 1.4	Ser 1.15
	All 1.36		All 2 Den 0 Plac	All 0.88	All 0.99		All 1.14	All 1.32	All 1.13	All 1.41		All 2 Den 0 Plac	All 0.88	All 0.99		All 1.16	All 1.36	All 1.16
	Mild 0		Mild 0 Den 0 Plac	Mild 0.5	Mild 0 Den 0 Alen		Mild 0.2	Mild 0 Den 3 Pla	Mild 0 Den 3 Pla	Mild 0 Den 2 Pla		Mild 0 Den 0 Plac	Mild 0 Den 1 Plac	Mild 0 Den 0 Alen		Mild 0 Den 3 Plac	Mild 0 Den 2 Plac	Mild 0 Den 2 Plac
	Sev 2.5		Sev 1 Den 0 Plac	Sev 2.48	Sev 0 Den 0 Alen		Sev 2.5	Sev 2.3	Sev 1.9	Sev 2.5		Sev 1 Den 0 Plac	Sev 2.48	Sev 0 Den 0 Alen		Sev 2.5	Sev 2.3	Sev 1.9
	≥Sev 1.5		≥Sev 2 Den 0 Plac	≥Sev 0.83	≥Sev 0 Den 0 Alen		≥Sev 1.18	≥Sev 1.48	≥Sev 1.23	≥Sev 1.5		≥Sev 2 Den 0 Plac	≥Sev 0.83	≥Sev 0 Den 0 Alen		≥Sev 1.18	≥Sev 1.5	≥Sev 1.23

All = All severity levels pooled; DEN = Denosumab; Fatal = Fatal severity; LT = Life-threatening severity; Mild = Mild severity; Mod = Moderate severity; PLA = Placebo; Ser = Serious event; Sev = Severe severity; ≥Sev = Severe or worse severity

(Table 3 continued on the next page.)

Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Pulmonary Hypertension	Ser 1.55	Ser 0 Den 0 Plac	Ser 0 Den 0 Plac	Ser 3.3	Ser 0 Den 0 Alen	Ser 0 Den 0 Alen	Ser 2.0	Ser 1.55	Ser 1.29	Ser 1 Den 0 Plac			Ser 0 Den 0 Plac			Ser 1 Den 0 Plac	Ser 1 Den 0 Plac	Ser 1 Den 0 Plac
	All 0.91	All 0 Den 2 Plac	All 1.3	All 1.09	All 0.99	All 1.48	All 0.96	All 0.91	All 0.81	All 1.5			All 0.33			All 1.0	All 1.5	All 1.25
	Mod 0.79	Mod 0 Den 1 Plac	Mod 2.79	Mod 0.76	Mod 1.96	Mod 0 Den 1 Alen	Mod 0.78	Mod 0.79	Mod 0.68	Mod 2 Den 0 Plac			Mod 0.99			Mod 3.0	Mod 2 Den 0 Plac	Mod 2 Den 0 Plac
	≥Sev 2.0	≥Sev 0 Den 0 Plac	≥Sev 0 Den 0 Plac	≥Sev 1.32	≥Sev 0 Den 0 Alen	≥Sev 1 Den 0 Alen	≥Sev 1.7	≥Sev 2.0	≥Sev 1.77	≥Sev 2 Den 0 Plac			≥Sev 0 Den 1 Plac			≥Sev 2.0	≥Sev 2 Den 0 Plac	≥Sev 2 Den 0 Plac

All = All severity levels pooled; DEN = Denosumab; Fatal = Fatal severity; LT = Life-threatening severity; Mild = Mild severity; Mod = Moderate severity; PLA = Placebo; Ser = Serious event; Sev = Severe severity; ≥Sev = Severe or worse severity

(Table 3 continued on the next page.)

Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Thrombophlebitis	Ser 2.33		Ser 0 Den 0 Plac	Ser 1.49	Ser 0 Den 1 Alen	Ser 0 Den 0 Alen	Ser 2.0	Ser 2.33	Ser 1.94	Ser 3.0			Ser 0 Den 1 Plac		Ser 0 Den 0 Alen	Ser 1.5	Ser 3.0	Ser 2.5
	All 1.06		All 0 Den 1 Plac	All 0.99	All 0.33	All 1 Den 0 Alen	All 1.05	All 1.08	All 0.93	All 0.6			All 0 Den 2 Plac		All 1 Den 0 Alen	All 0.53	All 0.6	All 0.55
	Mod 0.91		Mod 0 Den 1 Plac	Mod 1.19	Mod 1 Den 0 Alen	Mod 1 Den 0 Alen	Mod 0.95	Mod 0.94	Mod 0.83	Mod 0.37			Mod 0 Den 1 Plac		Mod 1 Den 0 Alen	Mod 0.33	Mod 0.37	Mod 0.42
	Sev 2.6		Sev 0 Den 0 Plac	Sev 0.6	Sev 0 Den 1 Alen	Sev 0 Den 0 Alen	Sev 1.59	Sev 2.6	Sev 2.16	Sev 3 Den 0 Plac			Sev 0 Den 1 Plac		Sev 0 Den 0 Alen	Sev 3.0	Sev 3 Den 0 Plac	Sev 3 Den 0 Plac
	≥Sev 2.6		≥Sev 0 Den 0 Plac	≥Sev 0.79	≥Sev 0 Den 1 Alen	≥Sev 0 Den 0 Alen	≥Sev 1.69	≥Sev 2.6	≥Sev 2.16	≥Sev 3 Den 0 Plac			≥Sev 0 Den 1 Plac		≥Sev 0 Den 0 Alen	≥Sev 3.0	≥Sev 3 Den 0 Plac	≥Sev 3 Den 0 Plac

All = All severity levels pooled; DEN = Denosumab; Fatal = Fatal severity; LT = Life-threatening severity; Mild = Mild severity; Mod = Moderate severity; PLA = Placebo; Ser = Serious event; Sev = Severe severity; ≥Sev = Severe or worse severity

(Table 3 continued on the next page.)

Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Torsade de Pointes/QT Prolongation	Ser 1.03	Ser 0 Den 0 Plac	Ser 0 Den 0 Plac	Ser 1.45	Ser 1 Den 0 Alen	Ser 0 Den 0 Alen	Ser 1.16	Ser 1.06	Ser 0.91	Ser 2 Den 0 Plac			Ser 0.99			Ser 3.0	Ser 2 Den 0 Plac	Ser 2 Den 0 Plac
	All 0.92	All 2.01	All 2.79	All 1.39	All 0.99	All 0.98	All 1.0	All 0.96	All 0.88	All 2.0			All 2.0			All 2.0	All 2.0	All 1.66
	Mod 0.74	Mod 2 Den 0 Plac	Mod 1 Den 0 Plac	Mod 0.99	Mod 1.5	Mod 0.98	Mod 0.77	Mod 0.76	Mod 0.71	Mod 1 Den 1 Plac			Mod 1 Den 0 Plac			Mod 2.0	Mod 1.0	Mod 0.83
	Fatal 0.3	Fatal 0 Den 0 Plac	Fatal 0 Den 0 Plac	Fatal 1.98	Fatal 1 Den 0 Alen	Fatal 0 Den 0 Alen	Fatal 0.69	Fatal 0.3	Fatal 0.33	Fatal 0 Den 0 Plac			Fatal 0 Den 0 Plac			Fatal 0 Den 0 Plac	Fatal 0 Den 0 Plac	Fatal 0 Den 0 Plac

All = All severity levels pooled; DEN = Denosumab; Fatal = Fatal severity; LT = Life-threatening severity; Mild = Mild severity; Mod = Moderate severity; PLA = Placebo; Ser = Serious event; Sev = Severe severity; ≥Sev = Severe or worse severity

(Table 3 continued on the next page.)

Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Toxic-septic shock conditions	Ser 1.16		Ser 1 Den 0 Plac	Ser 0.76	Ser 0 Den 1 Alen		Ser 0.96	Ser 1.16	Ser 0.97	Ser 3.0			Ser 0 den 4 plac			Ser 0.6	Ser 3.0	Ser 2 Den 0 Plac
	All 1.09		All 0.93	All 0.84	All 0.50		All 0.97	All 1.04	All 0.9	All 1.66			All 0 den 4 plac			All 0.71	All 1.66	All 1.66
	Mod 1.75		Mod 0 Den 0 Plac	Mod 0.87	Mod 0.99		Mod 1.16	Mod 1.75	Mod 1.66	Mod 0 Den 1 Plac			Mod 0 Den 0 Plac			Mod 0 Den 1 Plac	Mod 0 Den 1 Plac	Mod 0.83
	≥Sev 0.84		≥Sev 1 Den 0 Plac	≥Sev 0.63	≥Sev 0 Den 0 Alen		≥Sev 0.75	≥Sev 0.84	≥Sev 0.7	≥Sev 3.0			≥Sev 0 den 4 plac			≥Sev 3 Den 5 Plac	≥Sev 3 Den 1 Plac	≥Sev 1 Den 0 Plac

All = All severity levels pooled; DEN = Denosumab; Fatal = Fatal severity; LT = Life-threatening severity; Mild = Mild severity; Mod = Moderate severity; PLA = Placebo; Ser = Serious event; Sev = Severe severity; ≥Sev = Severe or worse severity

Of the 24 terms in Table 3 having at least one relative risk estimate associated with a p-value less than 0.10, relative risk estimates were close to 1.0 or scattered below and above 1.0, thus, not consistently suggesting an imbalance in incidence, for the following terms: arrhythmia related investigations, cardiac arrhythmias, cardiac arrhythmia terms, cardiac failure, cardiomyopathy, embolic and thrombotic events, embolic and thrombotic events—arterial, embolic and thrombotic events—unspecified, embolic and thrombotic events—venous, Haemodynamic oedema, effusions, etc., Haemorrhages, Haemorrhage Terms (excl lab), Hypertension, Torsade de Pointes/QT Prolongation and Toxic-septic shock conditions.

There appears to be an imbalance in the incidence of gastrointestinal haemorrrhage and gastrointestinal perforation, ulceration, etc. in trial 20030216 (see Table A1 in Appendix VII). The relative risk estimate for serious events of gastrointestinal perforation, ulceration, etc. in Study 20030216 was 1.4 (56 denosumab, 40 placebo) and associated with a p-value of 0.10. The relative risk of gastrointestinal haemorrhage across all levels of severity was 1.38 (69 denosumab, 50 placebo) and associated with a p-value of 0.08. In addition, the relative risk for moderate severity gastrointestinal haemorrages was 2.1 (31 denosumab, 15 placebo) in study 20030216, with a p-value of 0.018. In contrast, gastrointestinal haemorrhage and gastrointestinal perforation, ulceration, etc. was associated with a relative risk of 0.47 (9 denosumab, 19 placebo) for serious events in study 20040138, with a p-value of 0.054. Study 20040138 is a study in cancer patients, while 20030216 was conducted in the PMO population.

There appears to be an imbalance in the incidence of ischaemic heart disease in study 20030216 (see Table A1). The relative risk for serious or severe events of ischaemic heart disease was 1.4 (106 denosumab, 75 placebo) and 2.0 (68 denosumab, 34 placebo), respectively, with corresponding p-values of 0.02 and 0.002. However, no other trial suggests an imbalance in the incidence of ischemic heart disease.

There appears to be an imbalance in the incidence of myocardial infarction events in study 20030216. The relative risk for severe events of myocardial infarction was 2.5 (25 denosumab, 10 placebo), and associated p-value of 0.01. However, no other trial suggests an imbalance in the incidence of myocardial infarction.

There appears to be an imbalance in the incidence of thrombophlebitis in study 20030216. The relative risk for serious events of thrombophlebitis was 2.3 (14 denosumab, 6 placebo), and associated with a p-value of 0.07. However, no other trial suggests an imbalance in the incidence of thrombophlebitis.

The data suggest an imbalance in the incidence of bradyarrhythmias. In study 20030216, the relative risk for serious and moderate events was 1.9 (19 denosumab, 10 placebo) and 3.5 (14 denosumab, 4 placebo), respectively, with corresponding p-values of 0.095 and 0.03. Table A7 shows that the relative risk for serious, moderate, severe and severe or worse bradyarrhythmia events was 2.0 or greater in the analysis of the pooled large, pivotal trial data set, and associated with p-values ranging from 0.06 to 0.09. The relative risk for serious, all, and severe events in study 20040138 was 1.7, 1.8, and 5.0,

respectively, although none of these estimates was associated with a p-value less than 0.10.

The data suggest that there may have been an imbalance in the incidence of conduction defects. Table 3 shows that in study 20030216, the relative risk for serious and severe conduction defects was 2.7 and 5.0, respectively, although none of these estimates were associated with a p-value less than 0.10. In study 20040138, relative risk for all and severe events was 1.5 and 3.0, respectively, although none were associated with a p-value less than 0.10. Table A7 shows that in the pooled large, pivotal dataset, relative risk for severe events was 4.0 (8 denosumab, 2 placebo), with an associated p-value of 0.109.

The data suggest that there may have been an imbalance in disorders of sinus node function. Table A1 shows that in study 20030216, the relative risk for serious, all and moderate disorders of sinus node function was 1.6, 1.7, and 3.7 respectively, however, only moderate severity was associated with a p-value less than 0.10 (p=0.057). Table 3 shows that in study 20040138, relative risk for serious and all events was 2.5 and 2.0, respectively, although none were associated with a p-value less than 0.10. Table A7 shows that in the pooled large, pivotal dataset, relative risk for all and moderate events was 1.76 (23 denosumab, 13 placebo) and 2.6 (13 denosumab, 5 placebo), respectively, with associated p-values of 0.097 and 0.096.

The data suggest that there may have been an imbalance in the incidence of pulmonary hypertension. Table A4 shows that in study 20040138, the relative risk for serious events was 3.3 (10 denosumab, 3 placebo) and associated with a p-value of 0.09. Table 3 shows that the relative risk for serious events was 1.6 in study 20030216, although it was not associated with a p-value less than 0.10. Table A1 shows that the relative risk for severe or worse events was 2.0 (16 denosumab, 8 placebo) in study 20030216 and associated with a p-value of 0.10. Table A7 shows that in the pooled large, pivotal trial dataset, the relative risk for serious and severe or worse events was 2.0 (24 denosumab, 12 placebo) and 1.7 (24 denosumab, 14 placebo), respectively, with associated p-values of 0.05 and 0.106.

Based on the cross-study comparison of events in Table 3, this review will focus on the following adverse events:
•Conduction defects (child of "bradyarrhythmias (incl conduction defects and disorders of sinus node function) (SMQ)" which is a child of "cardiac arrhythmias (SMQ)")
•Disorders of sinus node function (child of "bradyarrhythmias (incl conduction defects and disorders of sinus node function) (SMQ)" which is a child of "cardiac arrhythmias (SMQ)")
•Bradyarrhythmia (child of "cardiac arrhythmias (SMQ)")
•Pulmonary hypertension

Table 4 tallies subjects experiencing conduction defects by Preferred Term in the pooled large, pivotal trial dataset. The greatest imbalance of subjects was in 'Atrioventricular block complete', with eight subjects receiving denosumab and four subjects receiving

placebo. In addition, 'Bundle branch block right" had imbalance, as the event was recorded in eleven subjects receiving denosumab and seven receiving placebo.

Table 4. Conduction defects (SMQ): Number of Subjects in the Large Pivotal Studies with One or More Events According to a Broad MedDRA Classification of Preferred Terms. Analysis conducted on a pooled dataset combining large, pivotal studies 20030216 and 20040138.

	Denosumab 60 mg Q6M	**Placebo**
Atrioventricular block	1	2
Atrioventricular block complete	8	4
Atrioventricular block first degree	2	1
Atrioventricular block second degree	1	1
Bifascicular block	0	1
Bundle branch block	0	3
Bundle branch block left	6	6
Bundle branch block right	11	7
Electrocardiogram repolarisation abnormality	2	0
Trifascicular block	0	1
Wolff-Parkinson-White syndrome	1	0

Table 5 tallies subjects experiencing conduction defects by Preferred Term in the pooled placebo-controlled PMO studies dataset. It shows little imbalance in the incidence of conduction defects.

Table 5. Conduction defects (SMQ): Number of Subjects in the Placebo-Controlled PMO Studies with One or More Events According to a Broad MedDRA Classification of Preferred Terms. Analysis conducted on a pooled dataset combining studies 20030216, 20040132, 20050172, 20050179 and 20010223.

	Denosumab 60 mg Q6M	**Placebo**
Atrioventricular block	1	1
Atrioventricular block complete	5	3
Atrioventricular block first degree	0	2
Atrioventricular block second degree	1	1
Bifascicular block	0	1
Bundle branch block	0	2
Bundle branch block left	6	6
Bundle branch block right	10	7
Electrocardiogram repolarisation abnormality	2	0
Wolff-Parkinson-White syndrome	1	0

Table 6 tallies subjects experiencing disorders of sinus node function by Preferred Term in the pooled large, pivotal trials dataset. It shows that the greatest imbalance of subjects was in 'Sick sinus syndrome', with sixteen subjects receiving denosumab and five subjects receiving placebo.

Table 6. Disorders of sinus node function (SMQ): Number of Subjects in the Large Pivotal Studies with One or More Events According to a Broad MedDRA Classification of Preferred Terms. Analysis conducted on a pooled dataset combining large, pivotal studies 20030216 and 20040138.

	Denosumab 60 mg Q6M	Placebo
Sick sinus syndrome	16	5
Sinus arrhythmia	2	1
Sinus bradycardia	5	7

Table 7 tallies subjects experiencing disorders of sinus node function by Preferred Term in the pooled placebo-controlled PMO studies dataset. It shows the greatest imbalance for the incidence of sick sinus syndrome.

Table 7. Disorders of sinus node function (SMQ): Number of Subjects in the Placebo-Controlled PMO Studies: One or More Events According to a Broad MedDRA Classification of Preferred Terms. Analysis conducted on a pooled dataset combining studies 20030216, 20040132, 20050172, 20050179 and 20010223.

	Denosumab 60 mg Q6M	Placebo
Sick sinus syndrome	11	4
Sinus arrhythmia	2	0
Sinus bradycardia	5	6

Table 8 tallies subjects experiencing Bradyarrhythmias by Preferred Term in the pooled large, pivotal studies dataset. It shows that the greatest imbalance of subjects was in 'Sick sinus syndrome', with sixteen subjects receiving denosumab and five subjects receiving placebo.

Table 8. Bradyarrhythmias (incl conduction defects and disorders of sinus node function) (SMQ): Number of Subjects in the Large Pivotal Studies with One or More Events According to a Broad MedDRA Classification of Preferred Terms. Analysis conducted on a pooled dataset combining large, pivotal studies 20030216 and 20040138.

	Denosumab 60 mg Q6M	Placebo
Bradyarrhythmia	0	1
Bundle branch block left	6	6
Bundle branch block right	11	7
Electrocardioagram repolarisation abnormality	2	0
Sick sinus syndrome	16	5
Sinus arrhythmia	2	1
Sinus bradycardia	5	7
Trifascicular block	0	1
Wolff-Parkinson-White syndrome	1	0

Table 9 tallies subjects experiencing Bradyarrhythmias by Preferred Term in the pooled placebo-controlled studies dataset. It shows the largest discrepany for sick sinus syndrome.

Table 9. Bradyarrhythmias (incl conduction defects and disorders of sinus node function) (SMQ): Number of Subjects in the Placebo-Controlled PMO Studies with One or More Events According to a Broad MedDRA Classification of Preferred Terms. Analysis conducted on a pooled dataset combining studies 20030216, 20040132, 20050172, 20050179 and 20010223.

	Denosumab 60 mg Q6M	**Placebo**
Bradyarrhythmia	0	1
Bundle branch block left	6	6
Bundle branch block right	10	7
Electrocardioagram repolarisation abnormality	2	0
Sick sinus syndrome	11	4
Sinus arrhythmia	2	0
Sinus bradycardia	5	6
Wolff-Parkinson-White syndrome	1	0

Table 10 tallies subjects experiencing Pulmonary Hypertension by Preferred Term. It shows little imbalance in the incidence of pulmonary hypertension.

Table 10. Pulmonary Hypertension (SMQ): Number of Subjects in the Large Pivotal Studies with One or More Events According to a Broad MedDRA Classification of Preferred Terms. Analysis conducted on a pooled dataset combining large, pivotal studies 20030216 and 20040138.

	Denosumab 60 mg Q6M	**Placebo**
Carotid pulse decreased	0	1
Dyspnoea	125	136
Emphysema	17	16
Hepatic cirrhosis	3	2
Pulmonary infarction	0	1

Table 11 tallies subjects experiencing Pulmonary Hypertension by Preferred Term in the pooled placebo controlled PMO studies dataset. It shows little imbalance in the Preferred Terms comprising pulmonary hypertension.

Table 11. Pulmonary Hypertension (SMQ): Number of Subjects in the Placebo-Controlled PMO Studies with One or More Events According to a Broad MedDRA Classification of Preferred Terms. Analysis conducted on a pooled dataset combining studies 20030216, 20040132, 20050172, 20050179 and 20010223.

	Denosumab 60 mg Q6M	Placebo
Carotid pulse decreased	0	1
Dyspnoea	94	106
Emphysema	13	13
Hepatic cirrhosis	1	2
Pulmonary infarction	0	1

There is no narrow SMQ grouping of adverse events for bradyarrhythmia, conduction defects or disorders of sinus node function. Table 12 shows a tally of subjects experiencing Pulmonary Hypertension by Preferred Term using narrow SMQ grouping on the pooled large, pivotal trials dataset. It shows little imbalance in the incidence of pulmonary hypertension.

Table 12. Pulmonary Hypertension (SMQ): Number of Subjects in the Large Pivotal Studies with One or More Events According to a Narrow MedDRA Classification of Preferred Terms. Analysis conducted on a pooled dataset combining large, pivotal studies 20030216 and 20040138.

	Denosumab 60 mg Q6M	Placebo
Pulmonary arterial hypertension	0	1
Pulmonary hypertension	6	5
Right atrial dilatation	0	1
Right ventricular failure	1	0

Table 13 tallies subjects experiencing Pulmonary Hypertension by Preferred Term on the pooled placebo-controlled PMO trial dataset. It shows little imbalance in the Preferred Terms comprising pulmonary hypertension.

Table 13. Pulmonary Hypertension (SMQ): Number of Subjects in the Large Pivotal Studies with One or More Events According to a Narrow MedDRA Classification of Preferred Terms. Analysis conducted on a pooled dataset combining studies 20030216, 20040132, 20050172, 20050179 and 20010223.

	Denosumab 60 mg Q6M	Placebo
Pulmonary arterial hypertension	0	1
Pulmonary hypertension	5	2
Right atrial dilatation	0	1
Right ventricular failure	1	0

The lists of preferred terms above are areas where one can statistically assess the imbalance.

Analysis by MedDRA System Organ Class Hierarchy
To increase the likelihood of detecting potential signals, an alternative analysis of the data was performed. Adverse events were grouped according to MedDRA hierarchy. That is, in addition to evaluating results by SMQ, adverse events were analyzed by their System Organ Class (SOC), Higher Level Group Term (HLGT), Higher Level Term (HLT) and Preferred Term (PT).

Table 14, Table 15, and Table 16 show the groupings by HLGT, HLT and PT for events with a p-value less than 0.10 associated with their event counts and relative risk estimate for the pooled large, pivotal trial dataset. Table 17 shows that no signal (i.e. no $p<0.10$) was apparent at the SOC level.

At the HLGT level, the relative risk for pleural disorders was 1.9 (25 denosumab, 13 placebo, with a 95% confidence interval of 0.98 to 3.74 and a p-value of 0.052. The relative risk for administration site reactions was 3.3 (10 denosumab, 3 placebo), with a 95% confidence interval of 0.91 to 12.1, and a p-value of 0.053.

At the HLT level, two categories had relative risk estimates associated with a p-value less than 0.10: pneumothorax and pleural effusions NEC, and circulatory collapse and shock. Pneumothorax and pleural effusions was associated with a relative risk of 1.92 (25 denosumab, 13 placebo), with a 95% confidence interval of 0.98 to 3.7 and $p = 0.052$. Circulatory collapse and shock was associated with a relative risk of 3.0 (9 denosumab, 3 placebo), with a 95% confidence interval of 0.81 to 11.0 and $p=0.084$.

At the PT level, cardiac failure (RR=1.43 (0.96,2.13); $p=0.073$), pleural effusion (RR=2.3 (1.09,4.8); $p=0.024$), essential hypertension (RR=2.37 (1.04, 5.4); $p=0.035$), sick sinus syndrome (RR=3.2 (1.17, 8.7); $p=0.017$), and orthostatic hypotension (RR=3.0 (0.96, 9.26); $p=0.046$) were associated with a p-value less than 0.10. Event counts are provided in Table 14. Four events were associated with zero events in the placebo group and one or more events in the denosumab group: aortic dilatation (3 denosumab events), dilatation atrial (3 denosumab events), lower gastrointestinal haemorrhage (3 denosumab events), and pulse absent (3 denosumab events).

Table 14. HLGT Grouping of Events for the Pooled Large, Pivotal Trial Dataset: Events with Relative Risk Estimates Having a P-value Less than 0.10.

HLGT	Arm	Number of Events	RR	p-value	95% Confidence Interval for RR
Coronary artery disorders	DEN	307	1.16	0.064	(0.99, 1.36)
	PLA	262			
Pleural disorders	DEN	25	1.92	0.052	(0.98, 3.74)
	PLA	13			
Administration site reactions	DEN	10	3.32	0.053	(0.91, 12.1)
	PLA	3			
Infections - pathogen unspecified	DEN	1	0.17	0.070	(0.02, 1.38)
	PLA	6			

Table 15. HLT Grouping of Events for the Pooled Large, Pivotal Trial Dataset: Events with Relative Risk Estimates Having a P-value Less than 0.10.

HLT	Arm	Number of Events	RR	p-value	95% Confidence Interval for RR
Pneumothorax and pleural effusions NEC	DEN	25	1.92	0.052	(0.98, 3.74)
	PLA	13			
Cardiac disorders NEC	DEN	3	0.30	0.051	(0.082, 1.09)
	PLA	10			
Circulatory collapse and shock	DEN	9	3.0	0.084	(0.81, 11.0)
	PLA	3			
Eye injuries NEC	DEN	2	0.22	0.034	(0.048, 1.0)
	PLA	9			
Arterial inflammations*	DEN	0	0	0.062	NA
	PLA	4			

*One arm is associated with zero events
Den = Denosumab
Pla = Placebo

Table 16. PT Grouping of Events for the Pooled Large, Pivotal Trial Dataset: Events with Relative Risk Estimates Having a P-value Less than 0.10.

PT	Arm	Number of Events	RR	p-value	95% Confidence Interval for RR
Oedema peripheral	DEN	242	1.19	0.063	(0.99, 1.43)
	PLA	203			
Cardiac failure	DEN	59	1.43	0.073	(0.96, 2.13)
	PLA	41			
Pleural effusion	DEN	23	2.29	0.024	(1.09, 4.81)
	PLA	10			
Essential hypertension	DEN	19	2.37	0.035	(1.04, 5.40)
	PLA	8			
Sick sinus syndrome	DEN	16	3.19	0.017	(1.17, 8.70)
	PLA	5			
Orthostatic hypotension	DEN	12	2.99	0.046	(0.96, 9.26)
	PLA	4			
Periorbital haematoma	DEN	2	0.22	0.034	(0.048, 1.02)
	PLA	9			
Cardiomegaly	DEN	2	0.25	0.065	(0.053, 1.17)
	PLA	8			
Cardiac disorder	DEN	1	0.17	0.070	(0.02, 1.38)
	PLA	6			
Sinus tachycardia*	DEN	0	0	NA	NA
	PLA	5			
Temporal arteritis*	DEN	0	0	NA	NA
	PLA	4			
Aortic dilatation*	DEN	3	NA	NA	NA
	PLA	0			
Bundle branch block*	DEN	0	0	NA	NA
	PLA	3			
Dilatation atrial*	DEN	3	NA	NA	NA
	PLA	0			
Haemorrhagic stroke*	DEN	0	0	NA	NA
	PLA	3			
Lower gastrointestinal haemmorhage*	DEN	3	NA	NA	NA
	PLA	0			
Pulse absent*	DEN	3	NA	NA	NA
	PLA	0			
Vascular pseudo aneurysm*	DEN	0	0	NA	NA
	PLA	3			

*One arm is associated with zero events
Den = Denosumab
Pla = Placebo

Table 17. SOC Grouping of Cardiac and Vascular Events for the Pooled Large, Pivotal Trial Dataset.

SOC	Arm	Number of Events	RR	p-value	95% Confidence Interval for RR
Cardiac disorders	DEN	948	1.06	0.15	(0.98, 1.15)
	PLA	881			
Vascular disorders	DEN	1222	0.993	0.84	(0.93, 1.06)
	PLA	1222			

Table 18, Table 19 and Table 20 show the groupings by HLGT, HLT and PT for events with a p-value less than 0.10 associated with relative risk estimates for the pooled placebo-controlled PMO trials dataset.

At the HLGT level, the relative risk estimate for administration site reactions and reproductive tract disorders NEC were associated with a p-value of 0.03 and 0.08, respectively. The relative risk for administrative site reactions was 3.66 (95% CI: 1.0, 13.1) with a p-value of 0.032. The relative risk for reproductive tract disorders NEC was 3.0 (95% CI: 0.81,11.1) with a p-value of 0.084. Event counts are provided in Table 18.

Table 18. HLGT Grouping of Events for the Pooled Placebo-ControlledTrials Dataset: Events with Relative Risk Estimates Having a P-value Less than 0.10.

HLGT	Arm	Number of Events	RR	p-value	95% Confidence Interval for RR
Coronary artery disorders	Den	244	1.18	0.069	(0.99, 1.42)
	Pla	205			
Administration site reactions	Den	11	3.66	0.032	(1.0, 13.1)
	Pla	3			
Reproductive tract disorders NEC	Den	9	3.0	0.084	(0.81, 11.05)
	Pla	3			

Den = Denosumab
Pla = Placebo

At the HLT level, the following had relative risk estimates greater than 1.0 that were associated with a p-value less than 0.10: myocardial disorders NEC (RR=1.83 (0.81,3.7); p = 0.087), reproductive tract disorders NEC (excl neoplasms) (RR=3.0 (0.81, 11.0); p=0.084), and injection and infusion site reactions (RR=4.5 (0.97, 20.8); p=0.035). Event counts are provided in Table 19.

Table 19. HLT Grouping of Events for the Pooled Placebo-ControlledTrials Dataset: Events with Relative Risk Estimates Having a P-value Less than 0.10.

HLT	Arm	Number of Events	RR	p-value	95% Confidence Interval for RR
Myocardial disorders NEC	Den	22	1.83	0.087	(0.91, 3.7)
	Pla	12			
Reproductive tract disorders NEC (excl neoplasms)	Den	9	3.0	0.084	(0.81, 11.0)
	Pla	3			
Injection and infusion site reactions	Den	9	4.5	0.035	(0.97, 20.8)
	Pla	1			
Eye injuries NEC	Den	2	0.25	0.065	(0.053, 1.17)
	Pla	8			
Cardiac disorders NEC	Den	1	0.12	0.021	(0.016, 1.0)
	Pla	8			
Arterial inflammations*	Den	0	0	0.062	NA
	Pla	4			

*One arm is associated with zero events
Den = Denosumab
Pla = Placebo

At the PT level, tachycardia (RR=1.56 (0.94,2.6); p=0.08), essential hypertension (RR=2.37 (1.04, 5.4); p=0.03), aortic stenosis (RR=2.6 (0.93,7.3); p=0.06), acute myocardial infarction (RR=2.39 (0.84, 6.8); p=0.09), sick sinus syndrome (RR=2.74 (0.87, 8.6); p=0.07), pleural effusion (RR=3.33 (0.92, 12.1); p=0.05), and genital haemorrhage (RR=3.0 (0.81, 11.0); p=0.08). Event counts are provided in Table 20.

Table 20. PT Grouping of Events for the Pooled Placebo-ControlledTrials Dataset: Events with Relative Risk Estimates Having a P-value Less than 0.10.

PT	Arm	Number of Events	RR	p-value	95% Confidence Interval for RR
Haematoma	Den	38	0.68	0.06	(0.45, 1.0)
	Pla	56			
Tachycardia	Den	39	1.56	0.08	(0.94, 2.6)
	Pla	25			
Hot flush	Den	22	0.61	0.06	(0.36, 1.0)
	Pla	36			
Hypotension	Den	22	0.61	0.06	(0.36, 1.0)
	Pla	36			
Essential hypertension	Den	19	2.37	0.03	(1.0, 5.4)
	Pla	8			
Aortic stenosis	Den	13	2.59	0.06	(0.93, 7.3)
	Pla	5			
Acute myocardial infarction	Den	12	2.39	0.09	(0.84, 6.8)
	Pla	5			
Sick sinus syndrome	Den	11	2.74	0.07	(0.87, 8.6)
	Pla	4			
Pleural effusion	Den	10	3.33	0.05	(0.92, 12.1)
	Pla	3			
Genital haemorrhage	Den	9	3.0	0.08	(0.81, 11.0)
	Pla	3			
Periorbital haematoma	Den	2	0.25	0.06	(0.05, 1.17)
	Pla	8			
Cardiac disorder*	Den	0	0	0.03	NA
	Pla	5			
Sinus tachycardia*	Den	0	0	0.03	NA
	Pla	5			
Temporal arteritis*	Den	0	0	0.06	NA
	Pla	4			

*One arm is associated with zero events
Den = Denosumab
Pla = Placebo

Table 21 shows that cardiac disorders and vascular disorders SOCs were not associated with relative risk estimates having a p-value less than 0.10.

Table 21. SOC Grouping of Events for the Pooled Placebo-ControlledTrials Dataset.

SOC	Arm	Number of Events	RR	p-value	95% Confidence Interval for RR
Cardiac disorders	Den	792	1.07	0.13	(0.98, 1.18)
	Pla	729			
Vascular disorders	Den	1074	0.98	0.50	(0.91, 1.05)
	Pla	1096			

Den = Denosumab
Pla = Placebo

Table 22, Table 23, Table 24 and Table 25 show the groupings by SOC, HLGT, HLT and PT for events with a p-value less than 0.10 for the pooled placebo- or active- controlled PMO trials dataset.

Table 22 shows that the relative risk for vascular disorders is less than 1.0, which does not suggest a signal at the SOC level.

Table 22. SOC Grouping of Events for the Pooled Placebo- or Active-ControlledTrials Dataset.

SOC	Arm	Number of Events	RR	p-value	95% Confidence Interval for RR
Cardiac disorders	Den	819	0.93	0.14	(0.85, 1.02)
	Pla	729			
Vascular disorders	Den	1133	0.86	.000045	(0.80, 0.92)
	Pla	1096			

Den = Denosumab
Pla = Placebo

At the HLGT level, only administration site reactions were associated with relative risk greater than one (RR=3.0; 11 denosumab, 3 placebo; p-value=0.072).

Table 23. HLGT Grouping of Events for the Pooled Placebo- or Active-ControlledTrials Dataset: Events with Relative Risk Estimates Having a P-value Less than 0.10.

HLGT	Arm	Number of Events	RR	p-value	95% Confidence Interval for RR
Vascular hypertensive disorders	Den	706	0.86	0.0015	(0.78, 0.94)
	Pla	686			
Joint disorders	Den	71	0.75	0.070	(0.54, 1.0)
	Pla	79			
Cardiac valve disorders	Den	58	0.73	0.078	(0.51, 1.0)
	Pla	66			
Vascular haemorrhagic disorders	Den	47	0.67	0.041	(0.46, 0.99)
	Pla	58			
Administration site reactions	Den	11	3.0	0.072	(0.85, 10.9)
	Pla	3			

Den = Denosumab
Pla = Placebo

Table 24 shows that at the HLT level, there was no suggestion of increased risk.

Table 24. HLT Grouping of Events for the Pooled Placebo- or Active-ControlledTrials Dataset: Events with Relative Risk Estimates Having a P-value Less than 0.10.

HLT	Arm	Number of Events	RR	p-value	95% Confidence Interval for RR
Vascular hypertensive disorders NEC	Den	692	0.86	0.0023	(0.78, 0.95)
	Pla	669			
Haemorrhages NEC	Den	47	0.67	0.041	(0.46, 0.99)
	Pla	58			
Vascular hypotensive disorders	Den	31	0.64	0.062	(0.40, 1.03)
	Pla	40			
Cardiac valve disorders NEC	Den	3	0.31	0.077	(0.08, 1.17)
	Pla	8			
Eye injuries NEC	Den	2	0.21	0.051	(0.04, 0.98)
	Pla	8			
Cardiac disorders NEC	Den	1	0.10	0.014	(0.01, 0.83)
	Pla	8			
Arterial inflammations*	Den	0	0	0.042	NA
	Pla	4			

*One arm is associated with zero events
Den = Denosumab
Pla = Placebo

Table 25 shows that at the PT level, there was no suggestion of increased risk.

Table 25. PT Grouping of Events for the Pooled Placebo- or Active-ControlledTrials Dataset: Events with Relative Risk Estimates Having a P-value Less than 0.10.

PT	Arm	Number of Events	RR	p-value	95% Confidence Interval for RR
Hypertension	Den	669	0.84	.00066	(0.76, 0.93)
	Pla	660			
Haematoma	Den	41	0.61	0.014	(0.41, 0.91)
	Pla	56			
Hypotension	Den	23	0.53	0.015	(0.31, 0.89)
	Pla	36			
Extrasystoles	Den	20	0.57	0.051	(0.32, 1.0)
	Pla	29			
Cardiac Failure Congestive	Den	16	0.58	0.087	(0.31, 1.1)
	Pla	23			
Periorbital haematoma	Den	2	0.21	0.051	(0.04, 0.98)
	Pla	8			
Cardiac disorder*	Den	0	0	0.019	NA
	Pla	5			
Sinus tachycardia*	Den	0	0	0.019	NA
	Pla	5			
Temporal arteritis*	Den	0	0	0.042	NA
	Pla	4			
Vascular pseudoaneurysm*	Den	0	0	0.093	NA
	Pla	3			

*One arm is associated with zero events
Den = Denosumab
Pla = Placebo

According to this MedDRA SOC analysis, it appears that administration site reactions are the only consistent signal in the trials.

6. DISCUSSION

This report describes three approaches to grouping MedDRA terms for analyzing cardiovascular adverse events – the sponsor's approach, SMQ term grouping, and MedDRA SOC grouping. It considers adjudicated and non-adjudicated data.

Risk of cardiovascular events was computed separately for each of nine studies, as well as for the studies pooled according to whether they were large pivotal studies, placebo-controlled, or controlled studies in the PMO population. A broad and narrow MedDRA search strategy was used to group terms for the analysis. Thus, there were eight assessments performed by the reviewer, i.e. 2 MedDRA approaches (broad and narrow) for each of four ways of grouping data (all studies separately, large, pivotal studies pooled, placebo-controlled studies pooled, PMO studies pooled).

Given that the SMQ grouping was developed by a panel of experts representing different viewpoints, the results of that grouping holds more weight in this review. In addition, the analysis of non-adjudicated data is of greater interest since it permits the use of data from more studies and does not rely on an unvetted grouping of MedDRA terms.

An analysis of the adverse event data by SMQ suggested an imbalance in conduction defects, disorders of sinus node function, bradyarrhythmia and pulmonary hypertension. The Preferred Terms comprising these SMQs were explored in greater detail to determine the source of the imbalance.

The relative risk for conduction defects estimated in each pooled dataset explored (pooled large, pivotal trails, pooled placebo-controlled PMO trials, pooled placebo- or active-controlled PMO trials) ranged from 1.66-2.66 for serious events, although none of these RR estimates was associated with $p<0.10$. The relative risk for severe events was greater than or equal to 4.0, with $p<0.10$ for the pooled large, pivotal trial dataset. The relative risk estimate was close to 1.0 when data from all severity levels were pooled.

The imbalance in conduction defects was due to events of atrioventricular block complete (8 subjects denosumab, 4 subjects placebo) and bundle branch block right (11 subjects denosumab vs 7 subjects placebo) in the pooled large, pivotal trials dataset. Similarly, in the pooled placebo-controlled PMO study dataset, atrioventricular block complete (5 denosumab vs. 3 placebo) and bundle branch block right (10 denosumab vs. 7 placebo) were associated with the imbalance in conduction defects.

The relative risk for disorders of sinus node function estimated in each pooled dataset explored ranged from 1.42-1.77 for serious events, although none of these estimates were associated with $p<0.10$. The analysis of all severity levels grouped together in the pooled large, pivotal trials dataset yielded a relative risk estimate of 1.8, and was associated with $p<0.10$. Moderately severe disorders of sinus node function had relative risk estimates ranging from 2.7-3.7 in all of the pooled datasets explored, and these estimates were associated with $p<0.10$.

The imbalance in disorders of sinus node function are due to reports of sick sinus syndrome—16 denosumab vs. 5 placebo in the pooled large, pivotal trial dataset, and 11 denosumab vs. 4 placebo in the pooled placebo-controlled PMO trial dataset.

The relative risk for serious events of bradyarrhythmia was 1.9 for the pooled large, pivotal trial dataset, as well as the pooled placebo-controlled PMO trial dataset. Each of these estimates of RR was associated with $p<0.10$. Relative risk for moderate events in all pooled datasets explored ranged from 2.3-3.5, and were associated with $p<0.10$. Relative risk for severe events in the pooled large, pivotal trial dataset was 2.1, and associated with $p<0.10$.

Bradyarrhythmia is a parent SMQ for conduction defects and disorders of sinus node function. When examined at the preferred term level, it was apparent that the terms associated with the imbalance in conduction defects and disorders of sinus node function were driving the imbalance in bradyarrhythmia, specifically, atrioventricular block complete, bundle branch block right and sick sinus syndrome.

The relative risk for serious events of pulmonary hypertension was 2.0 in the pooled large, pivotal trial dataset, and associated with a $p<0.10$. The relative risk for events of a severe or worse nature ranged from 1.7-2.0 in the pooled large, pivotal and pooled placebo-controlled datasets, and were associated with $p<0.10$.

The analysis of preferred terms in pulmonary hypertension showed that in the narrow SMQ terms list, pulmonary hypertension was observed in 5 subjects receiving denosumab and 2 receiving placebo.

7. CONCLUSION

Bradyarrhytmia and ischaemic heart disease are the only signals that appear consistently in this exploratory analysis of the data from the nine studies of denosumab in PMO and HALT populations.

Bradyarrhythmia had a consistent signal according to the broad MedDRA search strategy. In the analysis of all PMO studies pooled, relative risk was estimated as 2.9 for moderate events and 1.7 for all worse severity levels. This trend was observed in the analysis of study 20030216 alone (RR=3.5), which appears to have heavily influenced the pooled analysis. Figure 1 shows this graphically in a Forest Plot of odds ratio estimates in each of the nine trials evaluated.

Severe ischaemic heart disease was associated with relative risk estimates greater than one in several analyses, with RR ranging from 1.7 to 2.0. There was a consistent estimate of relative risk greater than one across all severity levels for the placebo-controlled and pooled PMO studies. Relative risk estimates ranging from 1.4 to 1.8 having p-values less than 0.10 were observed for all worse severity levels in the pooled placebo-controlled and PMO studies. Figure 2 shows this graphically in a Forest Plot of odds ratio estimates in each of the nine trials evaluated.

This exploratory result will be discussed with the review team to evaluate clinical relevance.

Figure 1. Forest Plot of Odds Ratio for Bradyarrhythmias: Serious Adverse Events.

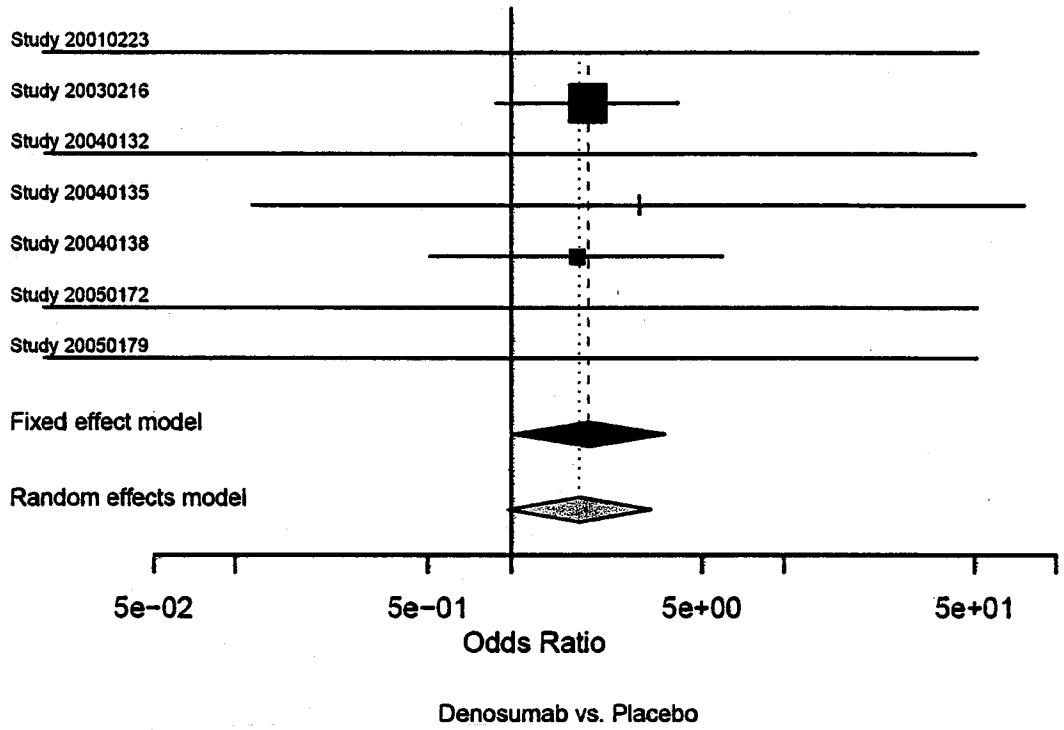
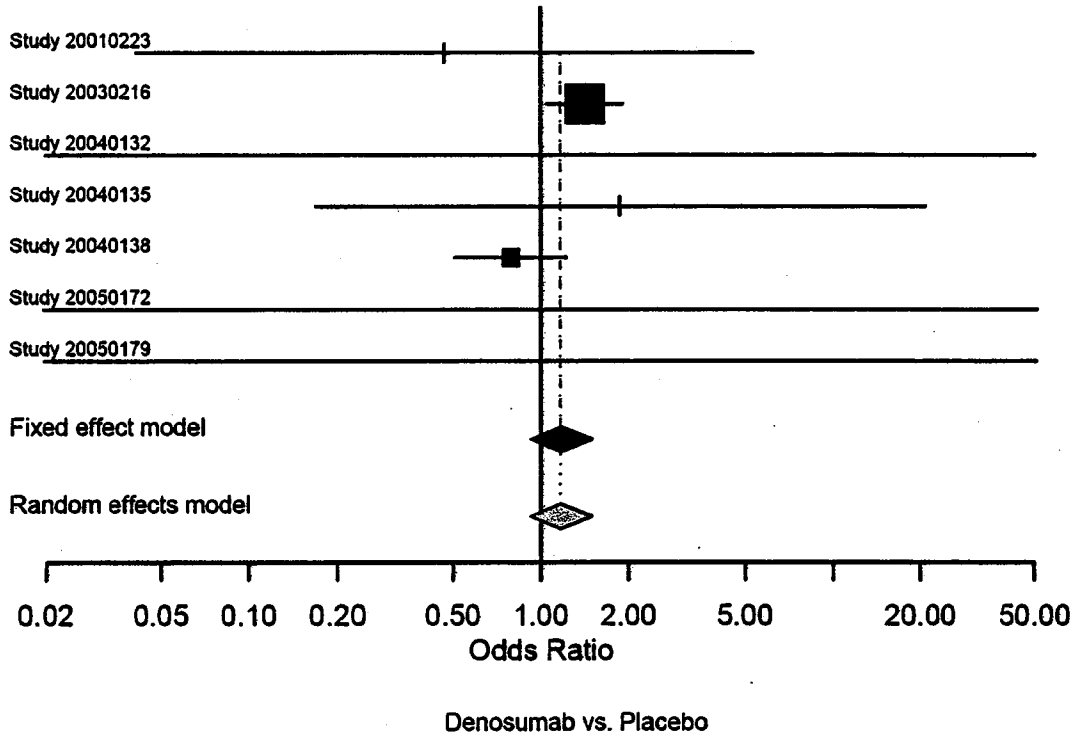


Figure 2. Forest Plot of Odds Ratio for Ischaemic Heart Disease: Serious Adverse Events.



APPENDICES

Appendix I Sponsor's Procedure for Adjudicating Adverse Events

The sponsor's procedure for adjudicating cardiovascular adverse events in studies 20030216 and 20040138 is described in this section.

An adjudication committee was formed to define and apply standard criteria for consistent, independent, and unbiased review of serious adverse event (SAE) reports. The adjudication committee (i.e. the San Francisco Coordinating Center; SFCC) adjudicated any serious adverse cardiovascular events in Study 20030216 and 20040138 that were sent to the SFCC by the sponsor. The SFCC was blinded to treatment arm.

The sponsor received all Serious Adverse Event (SAE) reports consistent with their global SAE reporting processes. The sponsor's Safety team screened all SAE Reports for deaths and potential cardiovascular (CV) events according to predefined MedDRA preferred terms approved by the SFCC. The sponsor was blinded to treatment arm while screening the SAEs. All SAEs matching predefined MedDRA preferred terms within those categories were sent to SFCC for review and adjudication.

Two cardiologists from the SFCC blindly reviewed and independently assessed events to determine an adjudicated diagnosis according to the event definitions classification criteria. An Event Specialist compared adjudication forms from each assigned cardiologist to determine if the classification was concordant or discordant. If the codes were discordant, the case was sent to a third Cardiologist for review. Cases which were concordant in two of the three adjudications were reviewed by a Physician Adjudicator to determine if the case warranted holding for discussion or if the case should be considered complete and the majority decision reflected on a Final Decision Summary Form. The Oncologist, upon the request of a Cardiologist, assessed deaths that occurred in the Study 20040138 to determine if they were cancer-related.

Only events confirmed positive by the adjudication committee to meet cardiovascular event definition criteria were included in the sponsor's analysis. In addition, each non-fatal event code that had a corresponding fatal event code within the same event category (ACS, stroke, other vascular event, arrhythmia, or CHF) and with the same serious adverse event number and the same date of onset was flagged and excluded from the analysis. Only the corresponding fatal event was included in the sponsor's analysis.

The sponsor analyzed time to first adjudicated positive cardiovascular event using a Cox proportional hazards model stratifying by study with treatment group and the baseline cardiovascular risk level as the independent variable (defined in Appendix II).

Appendix II Criteria for determining baseline cardiovascular risk

A total cardiovascular risk assessment score was computed for each subject at baseline by summing the points from each individual risk factor based on the modified Raloxifene Use for the Heart (RUTH) criteria used in the Multiple Outcomes of Raloxifene (MORE) study as listed in the table provided below. Subjects with a total cardiovascular risk assessment score of ≥4 points were considered at high risk for cardiovascular events, and subjects with <4 points were considered at low risk for cardiovascular events.

Modified RUTH Criteria for Defining a Population at High-Risk for Cardiovascular Events.

Cardiovascular risk factor	Points
Prior myocardial infarction, percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) surgery	4
Diabetes mellitus	3
Age ≥70 years	2
Age 65-69 years	1
Former/current smoker[a]	1
Hypertension[a]	1
High cholesterol[a]	1

RUTH = Raloxifene Use for the Heart

[a]An extra point is added if all 3 criteria "former/current smoker", "hypertension", and "high cholesterol" were met (i.e. yielding a total of 4 points).

Appendix III Details on Reviewer's Broad MedDRA SMQ Search Strategy

- Cardiac arrhythmias (SMQ)
  - Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias) (SMQ)
  - Bradyarrhythmias (incl conduction defects and disorders of sinus node function) (SMQ)
    - Conduction defects (SMQ)
    - Disorders of sinus node function (SMQ)
  - Tachyarrhythmias (incl supraventricular and ventricular tachyarrhythmias) (SMQ)
    - Supraventricular tachyarrhythmias (SMQ)
    - Ventricular tachyarrhythmias (SMQ)
  - Congenital and neonatal arrhythmias (SMQ)
  - Arrhythmia related investigations, signs and symptoms (SMQ)
- Cardiac Failure (SMQ)
- Cardiomyopathy (SMQ)
- Cerebrovascular disorders (SMQ)
  - Central nervous system haemorrhages and cerebrovascular accidents (SMQ)
    - Haemorrhagic cerebrovascular conditions (SMQ)
    - Ischaemic cerebrovascular conditions (SMQ)
- Embolic and thrombotic events (SMQ)
  - Embolic and thrombotic event, arterial (SMQ)
  - Embolic and thrombotic event, venous (SMQ)
  - Embolic and thrombotic event, vessel type unspecified and mixed arterial venous (SMQ)
- Gastrointestinal perforation, ulceration, haemorrhage or obstruction (SMQ)
  - Gastrointestinal haemorrhage (SMQ)
- Haemodynamic oedema, effusions and fluid overload (SMQ)
- Haemolytic disorders (SMQ)
- Haemorrhages (SMQ)
  - Haemorrhage laboratory terms (SMQ)
  - Haemorrhage terms (excl laboratory terms) (SMQ)
- Hypertension (SMQ)
- Ischaemic heart disease (SMQ)
  - Myocardial infarction (SMQ)
- Pulmonary hypertension (SMQ)
- Shock (SMQ)
  - Anaphylactic/anaphylactoid shock conditions (SMQ)
  - Hypoglycaemic and neurogenic shock conditions (SMQ)
  - Hypovolaemic shock conditions (SMQ)
  - Shock-associated circulatory or cardiac conditions (excl torsade de pointes) (SMQ)
  - Torsade de pointes, shock-associated conditions (SMQ)
  - Toxic-septic shock conditions (SMQ)
- Thrombophlebitis (SMQ)
- Torsade de pointes / QT prolongation (SMQ)

Appendix IV Details on Reviewer's Narrow MedDRA SMQ Search Strategy

Cardiac Failure (SMQ)
Cardiomyopathy (SMQ)
Cerebrovascular disorders (SMQ)
  Central nervous system haemorrhages and cerebrovascular accidents (SMQ)
    Haemorrhagic cerebrovascular conditions (SMQ)
    Ischaemic cerebrovascular conditions (SMQ)
Embolic and thrombotic events (SMQ)
  Embolic and thrombotic event, arterial (SMQ)
  Embolic and thrombotic event, venous (SMQ)
Haemodynamic oedema, effusions and fluid overload (SMQ)
Haemolytic disorders (SMQ)
Haemorrhages (SMQ)
  Haemorrhage laboratory terms (SMQ)
  Haemorrhage terms (excl laboratory terms) (SMQ)
Hypertension (SMQ)
Ischaemic heart disease (SMQ)
  Myocardial infarction (SMQ)
Pulmonary hypertension (SMQ)
Shock (SMQ)
  Anaphylactic/anaphylactoid shock conditions (SMQ)
  Hypoglycaemic and neurogenic shock conditions (SMQ)
  Hypovolaemic shock conditions (SMQ)
  Shock-associated circulatory or cardiac conditions (excl torsade de pointes) (SMQ)
  Torsade de pointes, shock-associated conditions (SMQ)
  Toxic-septic shock conditions (SMQ)
Thrombophlebitis (SMQ)
Torsade de pointes / QT prolongation (SMQ)

Appendix V Location of Data and Reports Utilized in this Review

Description	Location
Adverse Events Analysis Data	**5.3.5.3 iss – Integrated Summary of Safety** cbsap58\M\eCTD_Submissions\STN125320\0000\m5\datasets\iss\analysis**aae.xpt**
Cardiovascular Events Analysis Data	**5.3.5.3 iss – Integrated Summary of Safety** cbsap58\M\eCTD_Submissions\STN125320\0000\m5\datasets\iss\analysis**acecv.xpt**
Subject Level Information Analysis Data	**5.3.5.3 iss – Integrated Summary of Safety** cbsap58\M\eCTD_Submissions\STN125320\0000\m5\datasets\iss\analysis**aslinfo.xpt**
Clinical Overview	**2.5 Clinical Overview** cbsap58\M\eCTD_Submissions\STN125320\0000\m2\25-clin-over**clinical-overview.pdf**
Reviewer's Guide to Data Conventions	**5.3.5.3.25.3.3 Analysis Data Definition** cbsap58\M\eCTD_Submissions\STN125320\0000\m5\datasets\iss\analysis\ **crtreviewersguide.pdf**
CV Event Adjudication Manual of Operations	**Section 5.3.5.3.28 Integrated analysis of safety – integrated summary of safety report** cbsap58\M\eCTD_Submissions\STN125320\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pmo\5353-rep-analys-data-more-one-stud\iss**cv-manual-procedures.pdf**
Definitions and links to ADaM datasets	**5.3.5.3.25.3.3 Analysis Data Definition** cbsap58\M\eCTD_Submissions\STN125320\0000\m5\datasets\iss\analysis**define.xml**
Statistical Analysis Plan for the Summary of Safety	**5.3.5.3.12 Statistical Methods Interim Analysis Plan** cbsap58\M\eCTD_Submissions\STN125320\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pmo\5353-rep-analys-data-more-one-stud\iss**isap.pdf**
Integrated Analysis of Safety	**Section 5.3.5.3.28 Integrated analysis of safety – integrated summary of safety report** cbsap58\M\eCTD_Submissions\STN125320\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pmo\5353-rep-analys-data-more-one-stud**iss.pdf**
MedDRA coding conventions	**Section 5.3.5.3.28 Integrated analysis of safety – integrated summary of safety report** cbsap58\M\eCTD_Submissions\STN125320\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pmo\5353-rep-analys-data-more-one-stud\iss**medra-coding-guidelines.pdf**
Synopses of individual studies	**Section 2.7.6 Synopses of Individual Studies** cbsap58\M\eCTD_Submissions\STN125320\0000\m2\27-clin-sum**synopses-indiv-studies.pdf**
Summary of Clinical Safety	**Section 2.7.4 Summary of Clinical Safety** cbsap58\M\eCTD_Submissions\STN125320\0000\m2\27-clin-sum**summary-clin-safety-pdf**

Appendix VI MedDRA Version Utilized in Each Clinical Trial Reviewed.

Note that the Integrated Summary of Safety dataset harmonized version on MedDRA version 11.0.

Study	MedDRA version
20030216	11.0
20040132	9.0
20040135	9.0
20040138	11.0
20050172	10.0
20050179	10.0
20050234	10.0
20010223	9.0
20050141	10.0

Appendix VII Additional Details on Reviewer's Analysis

Broad Search Criteria: All Studies Analyzed Separately

Table A1 and Table A2 list the adverse cardiovascular events for which a p-value associated with relative risk estimates is equal to or less than 0.10 for at least one severity level when a broad MedDRA SMQ search strategy was employed to analyze each of the nine studies separately.

The events identified were placed in the context with the same event of all severity levels, regardless of statistical significance. That is, if risk of "moderate bradycardia" was observed to occur with p<0.10, then the risk estimates for mild, moderate, severe, life-threatening, serious and severe or worse bradycardia were added to the table regardless of whether they occurred with p<0.10.

Table A1 shows the estimated relative risk for moderate bradyarrhythmia was 3.5 (p=0.031) in subjects receiving denosumab in study 20030216. Relative risk estimates were all greater than one for severe (RR=1.66), life-threatening (RR=2.0), serious (RR=1.9) and severe (RR=1.71) bradyarrhythmia, but none of these estimates were associated with a p-value less than 0.10. No subject experienced a fatal bradyarrhythmia in study 20030216. The relative risk for moderate disorders of sinus node function was 3.66 (p=0.057). The relative risk of serious events was 1.57, but this estimate was associated with a p-value of 0.348. Relative risk was unity for severe events (RR=1). The relative risk (RR=1.52) for severe embolic and thrombotic events had a p-value of less than 0.05 (p=0.018), but the relative risk of mild, moderate, life-threatening or fatal events was unity. There was a statistically significant (p=0.032) relative risk of 1.73 for severe arterial embolic and thrombotic events, but estimated relative risk for the fatal (RR=1.28) and serious (RR=1.24) categories was not associated with a p-value less than 0.05. The relative risk of having an arterial embolic or thrombotic event of category severe or worse was 1.32 with a p-value of 0.179.

The relative risk for moderate gastrointestinal haemorrhage was 2.0 (p=0.018). Although no other level of gastrointestinal haemorrhage severity was associated with a p-value less than 0.10, there was trend toward relative risk greater than unity for the severe (RR=1.33) and serious (RR=1.21) categories. One subject experienced a fatal gastrointestinal haemorrhage in study 20030216, and that subject received denosumab.

P-values less than 0.10 were observed for severe (RR=2.0, p=0.0007), severe or worse (RR=1.72, p=0.002), and serious (RR=1.41, p=0.021) ischaemic heart disease events in subjects receiving denosumab in study 20030216. In this study, 9 subjects receiving denosumab and 7 receiving placebo had a fatal event, yielding a relative risk of 1.28 (p=0.62). The relative risk of severe myocardial infarction was 2.5 (p=0.011). The relative risk of life-threatening or fatal events was approximately unity. The relative risk of serious events was 1.52, but this was associated with a p-value of 0.147.

Table A2 shows the relative risk for severe cardiac arrhythmias was 1.52 (p=0.056), however, no other level of arrhythmia severity was associated with a p-value less than

0.10 in study 20040138. The estimated relative risk for fatal cardiac arrhythmias was 1.98 (p=0.507), and for serious cardiac arrhythmias 1.28 (p=0.323). Although one estimate of relative risk was associated with a p-value less than 0.10 for one category of severity for each of the following adverse events – cardiac failure, gastrointestinal perforation, or haemodynamic oedema – estimates of relative risk were above and below unity for the remaining severity levels.

Table A1. Broad Search Criteria With All Studies Analyzed Separately: Study 20030216 Results.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=3886) n	Placebo Exposed Subjects (N=3876) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
Arrhythmia related investigations								
	All pooled	206	191	1.08	(0.89, 1.3)	3.73	(-6.07, 13.5)	0.455
	Mild/1	125	96	1.3	(1.0, 1.7)	7.40	(0.0020, 15)	0.05
	Moderate/2	66	75	0.88	(0.6, 1.2)	-2.37	(-8.31, 3.58)	0.435
	Severe/3	20	19	1.05	(0.6, 2.0)	0.245	(-2.90, 3.39)	0.879
	Life-threatening/4	5	1	4.99	(0.6, 43)	1.03	(-0.207, 2.3)	0.219
	Fatal/5	3	10	0.3	(0.08, 1.1)	-1.81	(-3.6, 0.012)	0.057
	≥Severe/3	28	30	0.93	(0.56, 1.6)	-0.535	(-4.37, 3.30)	0.785
	Serious	38	35	1.08	(0.69, 1.7)	0.749	(-3.55, 5.04)	0.733
Bradyarrhythmias								
	All pooled	38	29	1.31	(0.81, 2.1)	2.30	(-1.82, 6.41)	0.274
	Mild/1	14	21	0.66	(0.34, 1.3)	-1.82	(-4.80, 1.17)	0.233
	Moderate/2	14	4	3.49	(1.2, 10.6)	2.57	(0.433, 4.71)	0.031
	Severe/3	10	6	1.66	(0.60, 4.6)	1.03	(-0.99, 3.04)	0.319
	Life-threatening/4	2	1	1.99	(0.18, 22)	0.257	(-0.617, 1.1)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	12	7	1.71	(0.67, 4.3)	1.28	(-0.916, 3.5)	0.253
	Serious	19	10	1.9	(0.88, 4.1)	2.31	(-0.404, 5.0)	0.095
Cardiac Arrhythmias								
	All pooled	377	365	1.03	(0.90, 1.18)	2.85	(-10.2, 15.9)	0.6699
	Mild/1	205	189	1.08	(0.89, 1.31)	3.99	(-5.77, 13.8)	0.4231
	Moderate/2	155	149	1.04	(0.83, 1.29)	1.45	(-7.19, 10.1)	0.7428
	Severe/3	50	51	0.98	(0.66, 1.44)	-0.291	(-5.33, 4.75)	0.9099
	Life-threatening/4	7	5	1.4	(0.44, 4.40)	0.511	(-1.24, 2.26)	0.7742
	Fatal/5	3	10	0.3	(0.08, 1.09)	-1.81	(-3.6, 0.012)	0.0569
	≥Severe/3	60	64	0.94	(0.66, 1.33)	-1.07	(-6.65, 4.51)	0.7065
	Serious	97	87	1.11	(0.84, 1.48)	2.52	(-4.25, 9.28)	0.4664
Cardiac Failure								
	All pooled	268	236	1.13	(0.96, 1.34)	8.08	(-2.88, 19.0)	0.1487
	Mild/1	140	135	1.03	(0.82, 1.30)	1.20	(-7.03, 9.42)	0.7755
	Moderate/2	116	90	1.29	(0.98, 1.69)	6.63	(-0.52, 13.8)	0.0692
	Severe/3	26	24	1.08	(0.62, 1.88)	0.499	(-3.06, 4.06)	0.7836
	Life-threatening/4	3	5	0.6	(0.14, 2.50)	-0.518	(-1.95, 0.91)	0.5071
	Fatal/5	6	8	0.75	(0.26, 2.15)	-0.520	(-2.41, 1.37)	0.5893
	≥Severe/3	33	36	0.91	(0.57, 1.46)	-0.796	(-4.97, 3.38)	0.7088
	Serious	39	41	0.95	(0.61, 1.47)	-0.542	(-5.04, 3.95)	0.8132
Cardiomyopathy								
	All pooled	358	368	0.97	(0.84, 1.11)	-2.82	(-15.8, 1.0.1)	0.6699
	Mild/1	194	185	1.05	(0.86, 1.27)	2.19	(-7.40, 11.8)	0.6539
	Moderate/2	156	163	0.95	(0.77, 1.18)	-1.91	(-10.7, 6.92)	0.6718
	Severe/3	43	42	1.02	(0.67, 1.56)	0.229	(-4.40, 4.86)	0.9226
	Life-threatening/4	5	5	1	(0.29, 3.44)	-0.00332	(-1.60, 1.59)	1
	Fatal/5	4	11	0.36	(0.12, 1.14)	-1.81	(-3.76, 0.15)	0.0762
	≥Severe/3	50	57	0.87	(0.60, 1.28)	-1.84	(-7.03, 3.35)	0.4872
	Serious	67	66	1.01	(0.72, 1.42)	0.214	(-5.56, 5.99)	0.9422

(Table A1 is continued on the next page.)

Table A1 (continued from the previous page). Broad Search Criteria With All Studies Analyzed Separately: Study 20030216 Results.

Disorders of Sinus Node Function								
	All pooled	17	10	1.7	(0.78, 3.7)	1.79	(-0.824, 4.4)	0.179
	Mild/1	2	3	0.66	(0.11, 4.0)	-0.259	(-1.39, 0.87)	0.687
	Moderate/2	11	3	3.66	(1.02, 13)	2.06	(0.171, 3.94)	0.057
	Severe/3	5	5	1	(0.29, 3.4)	-0.0033	(-1.60, 1.59)	1
	Life-threatening/4	1	0	_	N.A.	0.257	(-0.25, 0.76)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	6	5	1.2	(0.37, 3.92)	0.254	(-1.42, 1.93)	1
	Serious	11	7	1.57	(0.61, 4.04)	1.02	(-1.11, 3.16)	0.348
Embolic and thrombotic events								
	All pooled	184	176	1.04	(0.85, 1.28)	1.94	(-7.41, 11.3)	0.684
	Mild/1	41	45	0.91	(0.60, 1.38)	-1.06	(-5.72, 3.60)	0.656
	Moderate/2	59	63	0.93	(0.66, 1.33)	-1.07	(-6.61, 4.46)	0.7044
	Severe/3	79	52	1.52	(1.07, 2.14)	6.91	(1.19, 12.6)	0.018
	Life-threatening/4	15	17	0.88	(0.44, 1.76)	-0.526	(-3.38, 2.33)	0.718
	Fatal/5	13	14	0.93	(0.44, 1.97)	-0.267	(-2.89, 2.35)	0.842
	≥Severe/3	101	81	1.24	(0.93, 1.66)	5.09	(-1.64, 11.8)	0.138
	Serious	128	112	1.14	(0.89, 1.46)	4.04	(-3.66, 11.7)	0.304
Embolic and thrombotic events, arterial								
	All pooled	93	76	1.22	(0.90, 1.65)	4.32	(-2.17, 10.8)	0.192
	Mild/1	18	16	1.12	(0.57, 2.20)	0.504	(-2.43, 3.44)	0.737
	Moderate/2	25	22	1.13	(0.64, 2.01)	0.757	(-2.69, 4.21)	0.667
	Severe/3	40	23	1.73	(1.04, 2.89)	4.36	(0.370, 8.35)	0.032
	Life-threatening/4	4	10	0.4	(0.13, 1.27)	-1.55	(-3.44, 0.34)	0.118
	Fatal/5	9	7	1.28	(0.48, 3.44)	0.510	(-1.51, 2.53)	0.620
	≥Severe/3	53	40	1.32	(0.88, 1.99)	3.32	(-1.52, 8.16)	0.179
	Serious	67	54	1.24	(0.87, 1.77)	3.31	(-2.20, 8.82)	0.239
Embolic and thrombotic events, unspecified								
	All pooled	70	54	1.29	(0.91, 1.84)	4.08	(-1.50, 9.66)	0.1516
	Mild/1	17	15	1.13	(0.57, 2.26)	0.505	(-2.35, 3.36)	0.7286
	Moderate/2	23	19	1.21	(0.66, 2.21)	1.02	(-2.25, 4.28)	0.5415
	Severe/3	28	16	1.75	(0.95, 3.22)	3.08	(-0.26, 6.42)	0.071
	Life-threatening/4	6	3	1.99	(0.50, 7.97)	0.770	(-0.74, 2.28)	0.5076
	Fatal/5	3	4	0.75	(0.17, 3.34)	-0.260	(-1.60, 1.08)	0.7261
	≥Severe/3	37	23	1.6	(0.96, 2.69)	3.59	(-0.31, 7.48)	0.0712
	Serious	49	37	1.32	(0.86, 2.02)	3.06	(-1.59, 7.72)	0.1973

(Table A1 is continued on the next page.)

Table A1 (continued from the previous page). Broad Search Criteria With All Studies Analyzed Separately: Study 20030216 Results.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=3886) n	Placebo Exposed Subjects (N=3876) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
Gastrointestinal haemorrhage								
	All pooled	69	50	1.38	(0.96, 1.98)	4.86	(-0.61, 10.3)	0.082
	Mild/1	27	27	1	(0.59, 1.70)	-0.0179	(-3.72, 3.68)	0.992
	Moderate/2	31	15	2.06	(1.11, 3.81)	4.11	(0.695, 7.52)	0.018
	Severe/3	12	9	1.33	(0.56, 3.15)	0.766	(-1.54, 3.08)	0.516
	Life-threatening/4	1	1	1	(0.06, 15.9)	-0.00066	(-0.72, 0.71)	1
	Fatal/5	1	0	_	N.A.	0.257	(-0.25, 0.76)	1
	≥Severe/3	14	10	1.4	(0.62, 3.14)	1.02	(-1.45, 3.49)	0.417
	Serious	23	19	1.21	(0.66, 2.21)	1.02	(-2.25, 4.28)	0.542
Gastrointestinal perforation, ulceration, etc.								
	All pooled	195	168	1.16	(0.95, 1.42)	6.84	(-2.56, 16.2)	0.1538
	Mild/1	86	86	1	(0.74, 1.34)	-0.0571	(-6.61, 6.49)	0.9864
	Moderate/2	87	64	1.36	(0.98, 1.87)	5.88	(-0.27, 12.0)	0.0609
	Severe/3	36	27	1.33	(0.81, 2.19)	2.30	(-1.69, 6.29)	0.2592
	Life-threatening/4	2	3	0.66	(0.11, 3.98)	-0.259	(-1.39, 0.87)	0.687
	Fatal/5	1	1	1	(0.06, 15.9)	-0.00066	(-0.72, 0.71)	1
	≥Severe/3	38	30	1.26	(0.78, 2.03)	2.04	(-2.11, 6.18)	0.3352
	Serious	56	40	1.4	(0.93, 2.09)	4.09	(-0.83, 9.0)	0.103
Ischaemic heart disease								
	All pooled	198	173	1.14	(0.94, 1.39)	6.32	(-3.17, 15.8)	0.192
	Mild/1	61	65	0.94	(0.66, 1.32)	-1.07	(-6.70, 4.55)	0.709
	Moderate/2	93	77	1.2	(0.89, 1.62)	4.07	(-2.44, 10.6)	0.221
	Severe/3	68	34	1.99	(1.32, 3.00)	8.73	(3.67, 13.8)	.0007
	Life-threatening/4	11	8	1.37	(0.55, 3.41)	0.767	(-1.43, 2.96)	0.494
	Fatal/5	9	7	1.28	(0.48, 3.44)	0.510	(-1.51, 2.53)	0.620
	≥Severe/3	83	48	1.72	(1.21, 2.45)	8.97	(3.25, 14.7)	0.002
	Serious	106	75	1.41	(1.05, 1.89)	7.93	(1.22, 14.6)	0.021
Myocardial Infarction								
	All pooled	41	30	1.36	(0.85, 2.18)	2.81	(-1.42, 7.05)	0.193
	Mild/1	0	3	0	N.A.	-0.774	(-1.65, 0.10)	0.125
	Moderate/2	5	3	1.66	(0.40, 6.95)	0.513	(-0.91, 1.94)	0.726
	Severe/3	25	10	2.49	(1.20, 5.18)	3.85	(0.875, 6.83)	0.011
	Life-threatening/4	6	7	0.85	(0.29, 2.54)	-0.262	(-2.08, 1.56)	0.778
	Fatal/5	8	7	1.14	(0.41, 3.14)	0.253	(-1.70, 2.21)	0.800
	≥Severe/3	37	24	1.54	(0.92, 2.57)	3.33	(-0.60, 7.26)	0.097
	Serious	40	28	1.42	(0.88, 2.30)	3.07	(-1.08, 7.21)	0.147
Pulmonary Hypertension								
	All pooled	121	132	0.91	(0.72, 1.17)	-2.92	(-10.8, 4.98)	0.4691
	Mild/1	63	62	1.01	(0.72, 1.44)	0.216	(-5.38, 5.82)	0.9397
	Moderate/2	53	67	0.79	(0.55, 1.13)	-3.65	(-9.14, 1.84)	0.1928
	Severe/3	15	8	1.87	(0.79, 4.41)	1.80	(-0.62, 4.21)	0.1455
	Life-threatening/4	1	0	_	N.A.	0.257	(-0.25, 0.76)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	16	8	1.99	(0.85, 4.66)	2.05	(-0.42, 4.52)	0.1033
	Serious	14	9	1.55	(0.67, 3.58)	1.28	(-1.14, 3.70)	0.2993

(Table A1 is continued on the next page.)

Table A1. (continued from the previous page). Broad Search Criteria With All Studies Analyzed Separately: Study 20030216 Results.

Thrombophlebitis								
	All pooled	65	61	1.06	(0.75, 1.50)	0.989	(-4.63, 6.61)	0.7303
	Mild/1	25	26	0.96	(0.55, 1.66)	-0.275	(-3.87, 3.32)	0.881
	Moderate/2	31	34	0.91	(0.56, 1.48)	-0.795	(-4.85, 3.26)	0.7009
	Severe/3	13	5	2.59	(0.93, 7.27)	2.06	(-0.083, 4.2)	0.0959
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	13	5	2.59	(0.93, 7.27)	2.06	(-0.083, 4.2)	0.0959
	Serious	14	6	2.33	(0.90, 6.05)	2.05	(-0.20, 4.31)	0.0742
Torsade de Pointes / QT Prolongation								
	All pooled	95	103	0.92	(0.70, 1.21)	-2.13	(-9.14, 4.89)	0.5523
	Mild/1	41	37	1.11	(0.71, 1.72)	1.00	(-3.43, 5.44)	0.6572
	Moderate/2	34	46	0.74	(0.47, 1.15)	-3.12	(-7.61, 1.38)	0.1738
	Severe/3	16	13	1.23	(0.59, 2.55)	0.763	(-1.95, 3.48)	0.5815
	Life-threatening/4	5	2	2.49	(0.48, 12.8)	0.771	(-0.56, 2.11)	0.4529
	Fatal/5	3	10	0.3	(0.08, 1.09)	-1.81	(-3.6, 0.012)	0.0569
	≥Severe/3	24	25	0.96	(0.55, 1.67)	-0.274	(-3.80, 3.25)	0.8789
	Serious	31	30	1.03	(0.63, 1.70)	0.237	(-3.69, 4.17)	0.9057

Table A2. Broad Search Criteria With All Studies Analyzed Separately: Study 20040132 Results.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=164) n	Placebo Exposed Subjects (N=165) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
Haemorrhages								
	All pooled	6	17	0.36	(0.14, 0.88)	-66.4	(-121, -11.9)	0.0181
	Mild/1	3	14	0.22	(0.06, 0.74)	-66.6	(-114, -19.3)	0.0106
	Moderate/2	2	2	1.01	(0.14, 7.06)	0.0739	(-23.6, 23.8)	1
	Severe/3	1	2	0.5	(0.05, 5.49)	-6.02	(-26.5, 14.5)	1
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	1	2	0.5	(0.05, 5.49)	-6.02	(-26.5, 14.5)	1
	Serious	0	0	_	N.A.	_	N.A.	.
Haemorrhage Terms (excl lab)								
	All pooled	6	17	0.36	(0.14, 0.88)	-66.4	(-121, -11.9)	0.0181
	Mild/1	3	14	0.22	(0.06, 0.74)	-66.6	(-114, -19.3)	0.0106
	Moderate/2	2	2	1.01	(0.14, 7.06)	0.0739	(-23.6, 23.8)	1
	Severe/3	1	2	0.5	(0.05, 5.49)	-6.02	(-26.5, 14.5)	1
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	1	2	0.5	(0.05, 5.49)	-6.02	(-26.5, 14.5)	1
	Serious	0	0	_	N.A.	_	N.A.	.
Hypertension								
	All pooled	6	15	0.4	(0.16, 1.01)	-54.3	(-107, -1.89)	0.0439
	Mild/1	4	7	0.57	(0.17, 1.93)	-18.0	(-56.8, 20.7)	0.5418
	Moderate/2	2	8	0.25	(0.05, 1.17)	-36.3	(-73, 0.054)	0.104
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	_	N.A.	_	N.A.	.

Table A3. Broad Search Criteria With All Studies Analyzed Separately: Study 20040135 Results.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=129) n	Placebo Exposed Subjects (N=120) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
Hypertension								
	All pooled	5	8	0.58	(0.20, 1.73)	-27.9	(-83.6, 27.8)	0.3982
	Mild/1	4	5	0.74	(0.20, 2.71)	-10.7	(-57.3, 36.0)	0.7419
	Moderate/2	0	5	0	N.A.	-41.7	(-77.4, -5.9)	0.0249
	Severe/3	1	0	_	N.A.	7.75	(-7.38, 22.9)	1
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	1	0	_	N.A.	7.75	(-7.38, 22.9)	1
	Serious	0	0	_	N.A.	_	N.A.	.

Table A4. Broad Search Criteria With All Studies Analyzed Separately: Study 20040138 Results.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=731) n	Placebo Exposed Subjects (N=725) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
Cardiac Arrhythmias								
	All pooled	70	65	1.07	(0.77, 1.47)	6.10	(-23.7, 35.9)	0.688
	Mild/1	17	21	0.8	(0.43, 1.51)	-5.71	(-22.1, 10.7)	0.494
	Moderate/2	29	32	0.9	(0.55, 1.47)	-4.47	(-25.1, 16.1)	0.671
	Severe/3	22	11	1.98	(0.97, 4.06)	14.9	(-0.33, 30.2)	0.056
	Life-threatening/4	5	8	0.62	(0.20, 1.89)	-4.19	(-13.9, 5.48)	0.420
	Fatal/5	6	3	1.98	(0.50, 7.90)	4.07	(-3.97, 12.1)	0.507
	≥Severe/3	32	21	1.51	(0.88, 2.60)	14.8	(-4.40, 34.0)	0.131
	Serious	36	28	1.28	(0.79, 2.07)	10.6	(-10.4 , 31.7)	0.323
Cardiac failure								
	All pooled	77	80	0.95	(0.71, 1.28)	-5.01	(-36.9, 26.9)	0.758
	Mild/1	50	31	1.6	(1.03, 2.47)	25.6	(2.15, 49.1)	0.033
	Moderate/2	11	35	0.31	(0.16, 0.61)	-33.2	(-51.2, -15)	.0003
	Severe/3	12	14	0.85	(0.40, 1.83)	-2.89	(-16.5, 10.7)	0.677
	Life-threatening/4	1	6	0.17	(0.02, 1.37)	-6.91	(-14.0, 0.21)	0.069
	Fatal/5	5	2	2.48	(0.48, 12.7)	4.08	(-3.01, 11.2)	0.452
	≥Severe/3	18	22	0.81	(0.44, 1.50)	-5.72	(-22.5, 11.1)	0.504
	Serious	13	17	0.76	(0.37, 1.55)	-5.66	(-20.3, 8.93)	0.447
Cardiomyopathy								
	All pooled	100	102	0.97	(0.75, 1.26)	-3.89	(-39.4, 31.6)	0.83
	Mild/1	41	41	0.99	(0.65, 1.51)	-0.464	(-24.1, 23.2)	0.9694
	Moderate/2	34	49	0.69	(0.45, 1.05)	-21.1	(-44.9, 2.74)	0.0829
	Severe/3	25	18	1.38	(0.76, 2.50)	9.37	(-8.00, 26.7)	0.2909
	Life-threatening/4	6	8	0.74	(0.26, 2.13)	-2.83	(-12.9, 7.20)	0.5805
	Fatal/5	9	5	1.79	(0.60, 5.30)	5.42	(-4.59, 15.4)	0.4217
	≥Severe/3	39	31	1.25	(0.79, 1.98)	10.6	(-11.4, 32.6)	0.3448
	Serious	38	31	1.22	(0.77, 1.93)	9.22	(-12.6, 31.0)	0.4075
Gastrointestinal perforation, ulceration, etc.								
	All pooled	37	38	0.97	(0.62, 1.50)	-1.80	(-24.5, 20.9)	0.877
	Mild/1	20	9	2.2	(1.01, 4.81)	14.9	(0.635, 29.3)	0.041
	Moderate/2	11	14	0.78	(0.36, 1.71)	-4.26	(-17.6, 9.09)	0.531
	Severe/3	7	14	0.5	(0.20, 1.22)	-9.73	(-22.0, 2.52)	0.119
	Life-threatening/4	0	0	–	N.A.	–	N.A.	.
	Fatal/5	1	1	0.99	(0.06, 15.8)	-0.0113	(-3.82, 3.79)	1
	≥Severe/3	8	15	0.53	(0.23, 1.24)	-9.75	(-22.6, 3.07)	0.136
	Serious	9	19	0.47	(0.21, 1.03)	-13.9	(-28, 0.216)	0.054
Haemodynamic oedema, effusions, etc.								
	All pooled	83	76	1.08	(0.81, 1.45)	8.72	(-23.3, 40.7)	0.594
	Mild/1	54	36	1.49	(0.99, 2.24)	24.2	(-0.47, 48.9)	0.055
	Moderate/2	24	34	0.7	(0.42, 1.17)	-14.1	(-34.2, 6.03)	0.17
	Severe/3	7	7	0.99	(0.35, 2.81)	-0.0792	(-10.1, 9.95)	0.988
	Life-threatening/4	2	2	0.99	(0.14, 7.02)	-0.0226	(-5.40, 5.35)	1
	Fatal/5	0	0	–	N.A.	–	N.A.	.
	≥Severe/3	9	9	0.99	(0.40, 2.48)	-0.102	(-11.5, 11.2)	0.986
	Serious	7	6	1.16	(0.39, 3.43)	1.30	(-8.36, 11.0)	0.792

(Table A4 is continued on the next page.)

Table A4 (continued from the previous page). Broad Search Criteria With All Studies Analyzed Separately: Study 20040138 Results.

Pulmonary Hypertension

All pooled	45	41	1.09	(0.72, 1.64)	5.01	(-19.2, 29.2)	0.6853
Mild/1	21	14	1.49	(0.76, 2.90)	9.42	(-6.30, 25.1)	0.2408
Moderate/2	20	26	0.76	(0.43, 1.35)	-8.50	(-26.5, 9.47)	0.3537
Severe/3	6	6	0.99	(0.32, 3.06)	-0.0679	(-9.36, 9.22)	0.9886
Life-threatening/4	2	0	_	N.A.	2.74	(-1.05, 6.52)	0.4997
Fatal/5	1	0	_	N.A.	1.37	(-1.31, 4.05)	1
≥Severe/3	8	6	1.32	(0.46, 3.79)	2.67	(-7.35, 12.7)	0.6019
Serious	10	3	3.31	(0.91, 12.0)	9.54	(-0.088, 19)	0.0909

Table A5. Broad Search Criteria With All Studies Analyzed Separately: Study 20040141 Results.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=593) n	Alen-dronate Exposed Subjects (N=586) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
Gastrointestinal Haemorrhage								
	All pooled	4	4	4	4	0.0806	(-9.29, 9.45)	1
	Mild/1	0	4	0	0	6.83	(0.16, 13.5)	0.0607
	Moderate/2	3	0	3	3	-5.06	(-10.8, 0.65)	0.2494
	Severe/3	0	0	0	0	_	N.A.	.
	Life-threatening/4	1	0	1	1	-1.69	(-4.99, 1.62)	1
	Fatal/5	0	0	0	0	_	N.A.	.
	≥Severe/3	1	0	1	1	-1.69	(-4.99, 1.62)	1
	Serious	1	0	1	1	-1.69	(-4.99, 1.62)	1
Haemorrhages								
	All pooled	18	20	1.12	(0.60, 2.10)	3.78	(-16.4 , 23.9)	0.7136
	Mild/1	10	19	1.92	(0.90, 4.10)	15.6	(-2.13, 33.3)	0.0846
	Moderate/2	7	2	0.29	(0.06, 1.39)	-8.39	(-18.3, 1.50)	0.1781
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	1	0	_	N.A.	-1.69	(-4.99, 1.62)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	1	0	_	N.A.	-1.69	(-4.99, 1.62)	1
	Serious	1	0	_	N.A.	-1.69	(-4.99, 1.62)	1
Haemorrhage Terms (excl lab)								
	All pooled	18	20	1.12	(0.60, 2.10)	3.78	(-16.4, 23.9)	0.7136
	Mild/1	10	19	1.92	(0.90, 4.10)	15.6	(-2.13, 33.3)	0.0846
	Moderate/2	7	2	0.29	(0.06, 1.39)	-8.39	(-18.3, 1.50)	0.1781
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	1	0	_	N.A.	-1.69	(-4.99, 1.62)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	1	0	_	N.A.	-1.69	(-4.99, 1.62)	1
	Serious	1	0	_	N.A.	-1.69	(-4.99, 1.62)	1
Hypertension								
	All pooled	28	17	0.61	(0.34, 1.11)	-18.2	(-40.0, 3.61)	0.1028
	Mild/1	19	11	0.59	(0.28, 1.22)	-13.3	(-31.2, 4.67)	0.148
	Moderate/2	10	5	0.51	(0.17, 1.47)	-8.33	(-21.1, 4.43)	0.2988
	Severe/3	0	1	0	N.A.	1.71	(-1.64, 5.05)	0.497
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	1	0	N.A.	1.71	(-1.64, 5.05)	0.497
	Serious	0	1	0	N.A.	1.71	(-1.64, 5.05)	0.497

Table A6. Broad Search Criteria With All Studies Analyzed Separately: Study 20050234 Results.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=253) n	Alen-dronate (N=249) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
Gastrointestinal Perforation, Ulceration, etc.								
	All pooled	2	9	0.22	(0.05, 1.00)	-28.2	(-54, -2.6)	0.0353
	Mild/1	2	4	0.49	(0.09, 2.66)	-8.16	(-27.2, 10.9)	0.4471
	Moderate/2	0	4	0	N.A.	-16.1	(-32, -0.45)	0.0598
	Severe/3	0	1	0	N.A.	-4.02	(-11.9, 3.84)	0.496
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	1	0	N.A.	-4.02	(-11.9, 3.84)	0.496
	Serious	0	1	0	N.A.	-4.02	(-11.9, 3.84)	0.496
Haemorrhages								
	All pooled	7	13	0.53	(0.22, 1.31)	-24.5	(-58.8, 9.69)	0.1598
	Mild/1	6	7	0.84	(0.29, 2.47)	-4.40	(-32.2, 23.4)	0.7565
	Moderate/2	1	6	0.16	(0.02, 1.35)	-20.1	(-40.7, 0.41)	0.0666
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	_	N.A.	_	N.A.	.
Haemorrhage Terms (excl lab)								
	All pooled	7	13	0.53	(0.22, 1.31)	-0.245	(-58.8, 9.69)	0.1598
	Mild/1	6	7	0.84	(0.29, 2.47)	-4.40	(-32.2, 23.4)	0.7565
	Moderate/2	1	6	0.16	(0.02, 1.35)	-0.201	(-40.7, 0.41)	0.0666
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	_	N.A.	_	N.A.	.

Table A7 shows the tabulation of cardiovascular adverse events having at one relative risk estimate associated with a p-value of less than 0.10 when a broad MedDRA SMQ search strategy was employed to a pooled dataset consisting of the two large, pivotal studies.

According to this analysis, the relative risk for serious bradyarrhythmia events was 1.85 (p=0.0587). In addition, p-values were less than 0.10 for several other severity categories (Moderate: RR=2.28, p=0.06; Severe: RR=2.14, p=0.09; Severe or worse: RR=2.12, p=0.0729). However, no one suffered a fatal bradyarrhythmia in either of the two large, pivotal studies.

Although severe embolic and thrombotic events in the large, pivotal studies were associated with a relative risk of 1.43 (p=0.02), relative risk estimates for the remaining severity categories approached unity. Likewise, only severe arterial embolic and thrombotic events in the large, pivotal studies were associated with a p-value less than 0.10 for a relative risk greater than unity (RR=1.7; p=0.02). Severe events of ischaemic heart disease in the large, pivotal studies were associated with a relative risk of 1.76

(p=0.001), and severe or worse events were associated with a relative risk of 1.35 (p=0.03). However, the relative risk was not consistently estimated above one for the remaining severity categories. Severe events of myocardial infarction in the large, pivotal studies were associated with a relative risk of 2.49 (p=0.003), however, there does not appear to be a consistent estimate of relative risk greater than one across the other categories of myocardial infarction severity. Serious events of pulmonary hypertension were associated with a relative risk of 2.0 (p=0.05) in the large, pivotal studies. There was a trend toward increased relative risk of pulmonary hypertension events for other severity categories (Severe events: RR=1.49; Severe events or worse: RR=1.71), however, none of these were associated with a p-value less than 0.10.

Kaplan-Meier estimates were computed for instances in which the p-value was less than 0.10. The upper graph on each plot shows the Kaplan-Meier estimators for the greatment groups, along with equal-precision 95% confidence bands. P-values are obtained using the log rank test.

Table A7. Broad Search Criteria With Two Large, pivotal Studies (20030216 and 20040138) Pooled.

Adverse Event Grouping	Severity	Denosumab Subjects (N=4617)	Placebo Subjects (N=4601)	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
		n	n					
Arrhythmia Related Investigations								
	All pooled	242	223	1.08	(0.91, 1.29)	3.95	(-4.99, 12.9)	0.3866
	Mild/1	130	104	1.25	(0.97, 1.61)	5.55	(-0.87, 12.0)	0.0901
	Moderate/2	77	88	0.87	(0.64, 1.18)	-2.45	(-7.86, 2.96)	0.3753
	Severe/3	32	25	1.28	(0.76, 2.15)	1.50	(-1.70, 4.70)	0.3592
	Life-threatening/4	7	6	1.16	(0.39, 3.46)	0.212	(-1.32, 1.74)	0.7862
	Fatal/5	9	13	0.69	(0.30, 1.61)	-0.876	(-2.87, 1.12)	0.3887
	≥Severe/3	48	43	1.11	(0.74, 1.68)	1.05	(-2.99, 5.09)	0.61
	Serious	58	50	1.16	(0.79, 1.68)	1.70	(-2.70, 6.09)	0.4495
Bradyarrhythmia								
	All pooled	49	35	1.4	(0.91, 2.15)	3.01	(-0.87, 6.88)	0.1289
	Mild/1	18	23	0.78	(0.42, 1.44)	-1.10	(-3.82, 1.62)	0.4273
	Moderate/2	16	7	2.28	(0.94, 5.53)	1.94	(-0.091, 4.0)	0.0614
	Severe/3	15	7	2.14	(0.87, 5.23)	1.73	(-0.26, 3.72)	0.0892
	Life-threatening/4	2	1	1.99	(0.18, 22.0)	0.216	(-0.52, 0.95)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	17	8	2.12	(0.91, 4.90)	1.94	(-0.18, 4.06)	0.0729
	Serious	26	14	1.85	(0.97, 3.54)	2.59	(-0.093, 5.3)	0.0587
Cardiac Failure								
	All pooled	345	316	1.09	(0.94, 1.26)	6.04	(-4.49, 16.6)	0.2608
	Mild/1	190	166	1.14	(0.93, 1.40)	5.07	(-2.79, 12.9)	0.2063
	Moderate/2	127	125	1.01	(0.79, 1.29)	0.339	(-6.32, 7.00)	0.9205
	Severe/3	38	38	1	(0.64, 1.56)	-0.0286	(-3.72, 3.66)	0.9879
	Life-threatening/4	4	11	0.36	(0.12, 1.14)	-1.52	(-3.17, 0.12)	0.0761
	Fatal/5	11	10	1.1	(0.47, 2.58)	0.209	(-1.74, 2.16)	0.8333
	≥Severe/3	51	58	0.88	(0.60, 1.27)	-1.56	(-5.97, 2.85)	0.4885
	Serious	52	58	0.89	(0.62, 1.30)	-1.34	(-5.78, 3.09)	0.5526
Conduction Defects								
	All pooled	28	24	1.16	(0.68, 2.00)	0.848	(-2.21, 3.91)	0.5866
	Mild/1	16	19	0.84	(0.43, 1.63)	-0.664	(-3.18, 1.85)	0.6042
	Moderate/2	3	3	1	(0.20, 4.93)	-0.00226	(-1.04, 1.04)	1
	Severe/3	8	2	3.99	(0.85, 18.8)	1.30	(-0.044, 2.6)	0.1092
	Life-threatening/4	1	1	1	(0.06, 15.9)	-0.00075	(-0.60, 0.60)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	9	3	2.99	(0.81, 11.0)	1.30	(-0.17, 2.77)	0.1457
	Serious	10	6	1.66	(0.60, 4.57)	0.862	(-0.84, 2.56)	0.3203
Disorders of Sinus Node Function								
	All pooled	23	13	1.76	(0.89, 3.48)	2.16	(-0.39, 4.70)	0.097
	Mild/1	4	4	1	(0.25, 3.98)	-0.00301	(-1.21, 1.20)	1
	Moderate/2	13	5	2.59	(0.92, 7.26)	1.73	(-0.072, 3.5)	0.0959
	Severe/3	7	5	1.4	(0.44, 4.39)	0.429	(-1.04, 1.90)	0.7743
	Life-threatening/4	1	0	_	N.A.	0.217	(-0.21, 0.64)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	8	5	1.59	(0.52, 4.87)	0.646	(-0.89, 2.18)	0.5808
	Serious	16	9	1.77	(0.78, 4.00)	1.51	(-0.61, 3.63)	0.1636

(Table A7 is continued on the next page.)

Table A7 (continued from the previous page). Broad Search Criteria With Two Pivotal Studies (20030216 and 20040138) Pooled.

Embolic and thrombotic events								
	All pooled	251	236	1.06	(0.89, 1.26)	3.07	(-6.06, 12.2)	0.5099
	Mild/1	46	51	0.9	(0.60, 1.34)	-1.12	(-5.29, 3.05)	0.5978
	Moderate/2	85	80	1.06	(0.78, 1.43)	1.02	(-4.39, 6.44)	0.7112
	Severe/3	103	72	1.43	(1.06, 1.92)	6.66	(1.09, 12.2)	0.0191
	Life-threatening/4	26	32	0.81	(0.48, 1.36)	-1.32	(-4.55, 1.91)	0.4216
	Fatal/5	21	24	0.87	(0.49, 1.56)	-0.668	(-3.51, 2.18)	0.6455
	≥Severe/3	142	124	1.14	(0.90, 1.45)	3.81	(-3.03, 10.6)	0.2752
	Serious	181	157	1.15	(0.93, 1.42)	5.08	(-2.59, 12.8)	0.1944
Embolic and thrombotic events, arterial								
	All pooled	130	109	1.19	(0.92, 1.53)	4.47	(-2.02, 11.0)	0.1773
	Mild/1	20	18	1.11	(0.59, 2.09)	0.420	(-2.20, 3.04)	0.7532
	Moderate/2	37	28	1.32	(0.81, 2.15)	1.93	(-1.49, 5.34)	0.2686
	Severe/3	53	31	1.7	(1.10, 2.65)	4.74	(0.865, 8.62)	0.0166
	Life-threatening/4	11	22	0.5	(0.24, 1.03)	-2.40	(-4.84, 0.04)	0.0538
	Fatal/5	13	14	0.93	(0.44, 1.97)	-0.227	(-2.43, 1.98)	0.8401
	≥Severe/3	77	67	1.15	(0.83, 1.58)	2.12	(-2.95, 7.18)	0.4128
	Serious	98	82	1.19	(0.89, 1.59)	3.40	(-2.24, 9.05)	0.2377
Embolic and thrombotic events, venous								
	All pooled	51	59	0.86	(0.59, 1.25)	-1.78	(-6.21, 2.66)	0.4321
	Mild/1	8	16	0.5	(0.21, 1.16)	-1.74	(-3.83, 0.34)	0.1003
	Moderate/2	21	25	0.84	(0.47, 1.49)	-0.885	(-3.76, 1.99)	0.5465
	Severe/3	21	18	1.16	(0.62, 2.18)	0.636	(-2.01, 3.29)	0.638
	Life-threatening/4	7	4	1.74	(0.51, 5.95)	0.647	(-0.76, 2.06)	0.5486
	Fatal/5	1	3	0.33	(0.03, 3.19)	-0.435	(-1.29, 0.42)	0.3741
	≥Severe/3	28	24	1.16	(0.68, 2.00)	0.848	(-2.21, 3.91)	0.5866
	Serious	33	26	1.26	(0.76, 2.11)	1.50	(-1.76, 4.75)	0.3677
Ischaemic heart disease								
	All pooled	254	228	1.11	(0.93, 1.32)	5.46	(-3.63, 14.5)	0.2391
	Mild/1	72	71	1.01	(0.73, 1.40)	0.163	(-4.88, 5.21)	0.9495
	Moderate/2	110	94	1.17	(0.89, 1.53)	3.39	(-2.61, 9.40)	0.268
	Severe/3	90	51	1.76	(1.25, 2.47)	8.41	(3.40, 13.4)	0.001
	Life-threatening/4	22	25	0.88	(0.50, 1.55)	-0.669	(-3.58, 2.24)	0.6522
	Fatal/5	13	14	0.93	(0.44, 1.97)	-0.227	(-2.43, 1.98)	0.8401
	≥Severe/3	118	87	1.35	(1.03, 1.78)	6.65	(0.631, 12.7)	0.0304
	Serious	143	121	1.18	(0.93, 1.50)	4.67	(-2.13, 11.5)	0.1786
Myocardial infarction								
	All pooled	65	57	1.14	(0.80, 1.62)	1.69	(-2.98, 6.35)	0.4778
	Mild/1	1	5	0.2	(0.02, 1.71)	-0.870	(-1.91, 0.17)	0.1243
	Moderate/2	8	6	1.33	(0.46, 3.83)	0.429	(-1.16, 2.02)	0.5972
	Severe/3	35	14	2.49	(1.34, 4.62)	4.54	(1.57, 7.50)	0.0027
	Life-threatening/4	13	20	0.65	(0.32, 1.30)	-1.53	(-3.97, 0.91)	0.2184
	Fatal/5	12	14	0.85	(0.40, 1.84)	-0.444	(-2.61, 1.72)	0.6879
	≥Severe/3	57	48	1.18	(0.81, 1.73)	1.91	(-2.42, 6.24)	0.3868
	Serious	61	54	1.13	(0.78, 1.62)	1.48	(-3.06, 6.01)	0.5234

(Table A7 is continued on the next page.)

Table A7 (continued from the previous page). Broad Search Criteria With Two Pivotal Studies (20030216 and 20040138) Pooled.

Pulmonary hypertension								
	All pooled	166	173	0.96	(0.78, 1.18)	-1.65	(-9.33, 6.04)	0.6745
	Mild/1	84	76	1.1	(0.81, 1.50)	1.68	(-3.66, 7.01)	0.538
	Moderate/2	73	93	0.78	(0.58, 1.06)	-4.40	(-9.83, 1.03)	0.1121
	Severe/3	21	14	1.49	(0.76, 2.94)	1.51	(-1.00, 4.02)	0.2399
	Life-threatening/4	3	0	_	N.A.	0.650	(-0.085, 1.4)	0.2499
	Fatal/5	1	0	_	N.A.	0.217	(-0.208,0.64)	1
	≥Severe/3	24	14	1.71	(0.88, 3.30)	2.16	(-0.46, 4.77)	0.1063
	Serious	24	12	1.99	(1.00, 3.98)	2.59	(0.046, 5.13)	0.0462
Thrombophlebitis								
	All pooled	75	71	1.05	(0.76, 1.45)	0.813	(-4.28, 5.91)	0.7546
	Mild/1	26	27	0.96	(0.56, 1.64)	-0.237	(-3.32, 2.85)	0.8804
	Moderate/2	37	39	0.95	(0.60, 1.48)	-0.463	(-4.15, 3.23)	0.806
	Severe/3	16	10	1.59	(0.72, 3.51)	1.29	(-0.87, 3.46)	0.2422
	Life-threatening/4	1	0	_	N.A.	0.217	(-0.21, 0.64)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	17	10	1.69	(0.78, 3.70)	1.51	(-0.70, 3.71)	0.1802
	Serious	20	10	1.99	(0.93, 4.25)	2.16	(-0.17, 4.48)	0.0689

Table A8 shows the tabulation of cardiovascular adverse events for which at least one severity level was associated relative risk having a p-value less than 0.10 when a broad MedDRA SMQ search strategy was employed to a pooled dataset consisting of all placebo-controlled studies.

Moderate bradyarrhythmia was associated with a relative risk of 3.49 (p=0.03). There was a consistent pattern of relative risk estimates greater than one for all other higher levels of severity (Severe: RR=1.66; Life-threatening: RR=2.0; Severe or worse: RR=1.7; Serious: RR=1.9), however, none of these increases were associated with a p-value less than 0.10.

The estimate of relative risk for moderate disorders of sinus node function was 3.66 (p=0.057). Relative risk estimates were greater than one for severe or worse (RR=1.2) and serious (RR=1.6) disorders of sinus node function, however none of these levels of severity were associated with a p-value less than 0.10. Severe embolic and thrombotic events were associated with a relative risk of 1.49 (p=0.02), but relative risk estimates associated with all other severity categories were not consistently greater than one. Likewise, severe arterial embolic and thrombotic events were associated with a relative risk of 1.7 (p=0.05), but relative risk observed across the other severity categories was unity.

Relative risk associated with events of moderate gastroinstestinal haemorrhage was 1.9 (p=0.02), but the relative risk estimates for other levels of severity were not very different from one and were not associated with a p-value less than 0.10. Likewise, only relative risk of moderate gastrointestinal perforation (RR=1.4, p=0.03) was associated with a p-value less than 0.10.

When all of the placebo-controlled studies were pooled, relative risk of [illegible], p=0.002), severe or worse (RR=1.62, p=0.006), and serious (RR=1.39, p=0.03) events of ischaemic heart disease were associated with a p-value less than 0.10. There was also a trend toward higher risk for life threatening (RR=1.37, p=0.494) and fatal (RR=1.28, p=0.620) events. The relative risk for severe myocardial infarction (RR=2.27, p=0.02) was associated with a p-value less than 0.10, and there was a trend toward relative risk greater than one for events of a severe or worse nature (RR=1.48, p=0.129) and for serious events (RR=1.38, p=0.187).

Table A8. Broad Search Criteria With Placebo Controlled Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223) Pooled.

Adverse Event Grouping	Severity	Denosumab Subjects n	Denosumab Subjects N=4604 % (n/N)	Placebo Subjects n	Placebo Subjects N=4224 % (n/N)	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	P value
Arrhythmia related investigations										
	All pooled	223	5.27	201	4.76	1.11	(0.92, 1.3)	5.0	(-4.23, 14)	0.285
	Mild/1	137	3.24	104	2.46	1.31	(1.02, 1.7)	7.73	(0.64, 14.8)	0.033
	Moderate/2	71	1.68	78	1.85	0.91	(0.66, 1.3)	-1.70	(-7.3, 3.9)	0.552
	Severe/3	20	0.47	20	0.47	1	(0.54, 1.9)	-0.012	(-2.9, 2.9)	0.993
	Life-threatening/4	5	0.12	1	0.02	4.99	(0.58 , 43)	0.945	(-0.19, 2.1)	0.219
	Fatal/5	3	0.07	10	0.24	0.3	(0.08, 1.1)	-1.66	(-3.3, .011)	0.057
	≥Severe/3	28	0.66	31	0.73	0.9	(0.54, 1.5)	-0.728	(-4.3, 2.82)	0.688
	Serious	40	0.95	35	0.83	1.14	(0.73, 1.8)	1.16	(-2.8, 5.16)	0.570
Brady-arrhythmia										
	All pooled	40	0.95	31	0.73	1.29	(0.81, 2.1)	2.11	(-1.78, 6.0)	0.288
	Mild/1	16	0.38	23	0.54	0.69	(0.37, 1.3)	-1.67	(-4.6, 1.22)	0.258
	Moderate/2	14	0.33	4	0.09	3.49	(1.2, 10.6)	2.36	(0.40, 4.3)	0.031
	Severe/3	10	0.24	6	0.14	1.66	(0.60, 4.6)	0.941	(-0.91, 2.8)	0.319
	Life-threatening/4	2	0.05	1	0.02	1.99	(0.18 , 22)	0.236	(-0.57, 1.0)	1
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	12	0.28	7	0.17	1.71	(0.67, 4.3)	1.18	(-0.84, 3.2)	0.253
	Serious	19	0.45	10	0.24	1.9	(0.88, 4.1)	2.12	(-0.37, 4.6)	0.096
Cardiac Arrhythmias										
	All pooled	404	9.55	381	9.03	1.06	(0.93, 1.2)	5.20	(-7.2, 17.6)	0.410
	Mild/1	225	5.32	202	4.79	1.11	(0.92, 1.3)	5.31	(-4.0 , 14.6)	0.265
	Moderate/2	162	3.83	153	3.62	1.06	(0.85, 1.3)	2.03	(-6.0, 10.1)	0.622
	Severe/3	50	1.18	52	1.23	0.96	(0.65, 1.4)	-0.505	(-5.2, 4.2)	0.832
	Life-threatening/4	7	0.17	5	0.12	1.4	(0.44, 4.4)	0.47	(-1.1, 2.07)	0.774
	Fatal/5	3	0.07	10	0.24	0.3	(0.08, 1.1)	-1.66	(-3.3, .011)	0.057
	≥Severe/3	60	1.42	65	1.54	0.92	(0.65, 1.3)	-1.22	(-6.4, 3.92)	0.642
	Serious	99	2.34	87	2.06	1.13	(0.85, 1.5)	2.78	(-3.5, 9.0)	0.383
Cardio-myopathy										
	All pooled	372	8.79	379	8.98	0.98	(0.85, 1.1)	-1.89	(-14, 10.2)	0.760
	Mild/1	202	4.77	196	4.64	1.03	(0.85, 1.3)	1.30	(-7.7, 10.3)	0.778
	Moderate/2	161	3.8	165	3.91	0.97	(0.79, 1.2)	-1.05	(-9.3, 7.2)	0.803
	Severe/3	44	1.04	43	1.02	1.02	(0.67, 1.6)	0.210	(-4.1, 4.5)	0.924
	Life-threatening/4	5	0.12	5	0.12	1	(0.29, 3.4)	-.0031	(-1.5, 1.5)	1
	Fatal/5	4	0.09	11	0.26	0.36	(0.12, 1.1)	-1.66	(-3.5, 0.13)	0.076
	≥Severe/3	51	1.21	58	1.37	0.88	(0.60, 1.3)	-1.69	(-6.5, 3.1)	0.491
	Serious	68	1.61	66	1.56	1.03	(0.73, 1.4)	0.432	(-4.9, 5.8)	0.874

(Table A8 is continued on the next page.)

Table A8 (continued from the previous page). Broad Search Criteria With Placebo Controlled Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223) Pooled.

Disorders of Sinus Node Function										
	All pooled	18	0.43	10	0.24	1.8	(0.83, 3.9)	1.88	(-0.56, 4.3)	0.132
	Mild/1	3	0.07	3	0.07	1	(0.20, 4.9)	-.0019	(-1.1, 1.13)	1
	Moderate/2	11	0.26	3	0.07	3.66	(1.02, 13)	1.89	(0.16, 3.62)	0.057
	Severe/3	5	0.12	5	0.12	1	(0.29, 3.4)	-.0031	(-1.5, 1.5)	1
	Life-threatening/4	1	0.02	0	0	_	N.A.	0.236	(-0.23, 0.7)	1
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	6	0.14	5	0.12	1.2	(0.37, 3.9)	0.233	(-1.3, 1.8)	1
	Serious	11	0.26	7	0.17	1.57	(0.61, 4.0)	0.941	(-1.0, 2.9)	0.348
Embolic and Thrombotic Events										
	All pooled	185	4.37	177	4.19	1.04	(0.85, 1.3)	1.78	(-6.9, 10.4)	0.686
	Mild/1	41	0.97	45	1.07	0.91	(0.60, 1.4)	-0.973	(-5.3, 3.3)	0.656
	Moderate/2	60	1.42	63	1.49	0.95	(0.67, 1.4)	-0.748	(-5.9, 4.4)	0.774
	Severe/3	79	1.87	53	1.26	1.49	(1.05, 2.1)	6.11	(8.28, 11.4)	0.024
	Life-threatening/4	15	0.35	17	0.4	0.88	(0.44, 1.8)	-0.483	(-3.1, 2.1)	0.718
	Fatal/5	13	0.31	14	0.33	0.93	(0.44, 2.0)	-0.245	(-2.7, 2.2)	0.842
	≥Severe/3	101	2.39	82	1.94	1.23	(0.92, 1.6)	4.44	(-1.8, 10.6)	0.161
	Serious	129	3.05	113	2.68	1.14	(0.89, 1.5)	3.71	(-3.4 , 10.8)	0.306
Embolic and Thrombotic Events, arterial										
	All pooled	93	2.2	77	1.82	1.2	(0.89, 1.6)	3.73	(-2.3, 9.72)	0.222
	Mild/1	18	0.43	16	0.38	1.12	(0.57, 2.2)	0.463	(-2.2, 3.16)	0.737
	Moderate/2	25	0.59	22	0.52	1.13	(0.64, 2.0)	0.695	(-2.5, 3.9)	0.667
	Severe/3	40	0.95	24	0.57	1.66	(1.00, 2.8)	3.77	(0.072, 7.5)	0.046
	Life-threatening/4	4	0.09	10	0.24	0.4	(0.13, 1.3)	-1.42	(-3.2, 0.31)	0.118
	Fatal/5	9	0.21	7	0.17	1.28	(0.48, 3.4)	0.468	(-1.4, 2.32)	0.620
	≥Severe/3	53	1.25	41	0.97	1.29	(0.86, 1.9)	2.81	(-1.7, 7.28)	0.218
	Serious	67	1.58	55	1.3	1.22	(0.85, 1.7)	2.80	(-2.3, 7.9)	0.280
Embolic and Thrombotic Events, Unsp										
	All pooled	71	1.68	54	1.28	1.31	(0.92, 1.9)	3.98	(-1.2, 9.1)	0.129
	Mild/1	17	0.4	15	0.36	1.13	(0.57, 2.3)	0.463	(-2.2, 3.1)	0.729
	Moderate/2	24	0.57	19	0.45	1.26	(0.69, 2.3)	1.17	(-1.9, 4.2)	0.450
	Severe/3	28	0.66	16	0.38	1.75	(0.95, 3.2)	2.83	(-0.24, 5.9)	0.071
	Life-threatening/4	6	0.14	3	0.07	1.99	(0.5, 8.0)	0.707	(-0.68 , 2.1)	0.508
	Fatal/5	3	0.07	4	0.09	0.75	(0.17, 3.3)	-0.239	(-1.5, 0.99)	0.726
	≥Severe/3	37	0.87	23	0.54	1.6	(0.96, 2.7)	3.29	(-0.28, 6.9)	0.071
	Serious	50	1.18	37	0.88	1.35	(0.88, 2.1)	3.05	(-1.3, 7.4)	0.165

(Table A8 is continued on the next page.)

Table A8 (continued from the previous page). Broad Search Criteria With Placebo Controlled Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223) Pooled.

Adverse Event Grouping	Severity	Denosumab Subjects n	Denosumab Subjects N=4604 % (n/N)	Placebo Subjects n	Placebo Subjects N=4224 % (n/N)	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	P value
Gastro-intestinal haemorrhage										
	All pooled	74	1.75	57	1.35	1.29	(0.92, 1.8)	3.98	(-1.3, 9.3)	0.138
	Mild/1	31	0.73	33	0.78	0.94	(0.57, 1.5)	-0.493	(-4.2, 3.2)	0.794
	Moderate/2	33	0.78	17	0.4	1.94	(1.1, 3.5)	3.77	(0.50, 7.04)	0.024
	Severe/3	12	0.28	9	0.21	1.33	(0.56, 3.2)	0.703	(-1.4, 2.8)	0.516
	Life-threatening/4	1	0.02	1	0.02	1	(0.06, 16)	-0.0006	(-0.7, 0.7)	1
	Fatal/5	1	0.02	0	0	_	N.A.	0.236	(-0.23, 0.7)	1
	≥Severe/3	14	0.33	10	0.24	1.4	(0.62, 3.1)	0.939	(-1.3, 3.2)	0.417
	Serious	23	0.54	19	0.45	1.21	(0.66, 2.2)	0.933	(-2.06, 3.9)	0.542
Gastro-intestinal perforation, ulceration, etc.										
	All pooled	220	5.2	191	4.52	1.15	(0.95, 1.4)	6.73	(-2.43, 16)	0.15
	Mild/1	104	2.46	106	2.51	0.98	(0.75, 1.3)	-0.538	(-7.2, 6.1)	0.874
	Moderate/2	94	2.22	67	1.59	1.4	(1.03, 1.9)	6.34	(0.51, 12.2)	0.033
	Severe/3	39	0.92	29	0.69	1.34	(0.83, 2.2)	2.35	(-1.5, 6.15)	0.228
	Life-threatening/4	2	0.05	3	0.07	0.66	(0.11, 4.0)	-0.238	(-1.3, 0.80)	0.687
	Fatal/5	1	0.02	1	0.02	1	(0.06, 16)	-.0006	(-0.7, 0.66)	1
	≥Severe/3	41	0.97	32	0.76	1.28	(0.81, 2.0)	2.11	(-1.8, 6.05)	0.295
	Serious	56	1.32	40	0.95	1.4	(0.93, 2.1)	3.76	(-0.76, 8.3)	0.103
Ischaemic heart disease										
	All pooled	203	4.8	179	4.24	1.13	(0.93, 1.4)	5.56	(-3.3, 0.14)	0.219
	Mild/1	62	1.47	66	1.56	0.94	(0.66, 1.3)	-0.986	(-6.19, 4.2)	0.711
	Moderate/2	97	2.29	80	1.9	1.21	(0.90, 1.6)	3.97	(-2.1, 10.1)	0.203
	Severe/3	68	1.61	37	0.88	1.83	(1.23, 2.7)	7.30	(2.58, 12.0)	0.002
	Life-threatening/4	11	0.26	8	0.19	1.37	(0.55, 3.4)	0.704	(-1.3, 2.7)	0.494
	Fatal/5	9	0.21	7	0.17	1.28	(0.48, 3.4)	0.468	(-1.4, 2.3)	0.620
	≥Severe/3	83	1.96	51	1.21	1.62	(1.15, 2.3)	7.5	(2.21, 12.9)	0.006
	Serious	107	2.53	77	1.82	1.39	(1.04, 1.9)	7.04	(0.82, 13.3)	0.027
Myocardial infarction										
	All pooled	41	0.97	31	0.73	1.32	(0.83, 2.1)	2.34	(-1.6, 6.3)	0.241
	Mild/1	0	0	3	0.07	0	N.A.	-0.711	(-1.5, .009)	0.125
	Moderate/2	5	0.12	3	0.07	1.66	(0.40, 7.0)	0.471	(-0.84, 1.8)	0.726
	Severe/3	25	0.59	11	0.26	2.27	(1.12, 4.6)	3.30	(0.53, 6.08)	0.020
	Life-threatening/4	6	0.14	7	0.17	0.85	(0.29, 2.5)	-0.241	(-1.9, 1.4)	0.778
	Fatal/5	8	0.19	7	0.17	1.14	(0.41, 3.1)	0.232	(-1.6, 2.0)	0.8
	≥Severe/3	37	0.87	25	0.59	1.48	(0.89, 2.5)	2.82	(-0.82, 6.5)	0.129
	Serious	40	0.95	29	0.69	1.38	(0.85, 2.2)	2.58	(-1.25, 6.4)	0.187

(Table A8 is continued on the next page.)

Table A8 (continued from the previous page). Broad Search Criteria With Placebo Controlled Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223) Pooled.

Pulmonary Hypertension										
	All pooled	122	2.88	134	3.17	0.91	(0.7 , 1.2)	-2.92	(-10.2 , 4.4)	0.434
	Mild/1	63	1.49	63	1.49	1	(0.7 , 1.4)	-0.039	(-5.2, 5.1)	0.988
	Moderate/2	54	1.28	68	1.61	0.79	(0.56, 1.1)	-3.35	(-8.4, 1.74)	0.197
	Severe/3	15	0.35	8	0.19	1.87	(0.79, 4.4)	1.65	(-0.57, 39)	0.146
	Life-threatening/4	1	0.02	0	0	_	N.A.	0.236	(-.23, 0.70)	1
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	16	0.38	8	0.19	1.99	(0.85, 4.7)	1.89	(-0.38 , 4.2)	0.103
	Serious	14	0.33	9	0.21	1.55	(0.67, 3.6)	1.18	(-1.04 , 3.4)	0.299
Thrombo-phlebitis										
	All pooled	66	1.56	61	1.45	1.08	(0.76, 1.5)	1.14	(-4.04, 6.3)	0.666
	Mild/1	25	0.59	26	0.62	0.96	(0.55, 1.7)	-0.252	(-3.6, 3.05)	0.881
	Moderate/2	32	0.76	34	0.81	0.94	(0.58, 1.5)	-0.49	(-4.25, 3.4)	0.797
	Severe/3	13	0.31	5	0.12	2.59	(0.93, 7.3)	1.89	(-.077, 3.9)	0.096
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	13	0.31	5	0.12	2.59	(0.93, 7.3)	1.89	(-.077, 3.9)	0.096
	Serious	14	0.33	6	0.14	2.33	(0.90, 6.1)	1.89	(-0.18, 4.0)	0.074
Torsade de Pointes / QT Prolongation										
	All pooled	101	2.39	105	2.49	0.96	(0.73, 1.3)	-1.01	(-7.6, 5.56)	0.763
	Mild/1	45	1.06	38	0.9	1.18	(0.77, 1.8)	1.63	(-2.57, 5.8)	0.447
	Moderate/2	36	0.85	47	1.11	0.76	(0.50, 1.2)	-2.63	(-6.8, 1.58)	0.221
	Severe/3	16	0.38	13	0.31	1.23	(0.59, 2.6)	0.701	(-1.8, 3.19)	0.582
	Life-threatening/4	5	0.12	2	0.05	2.49	(0.48, 13)	0.708	(-0.52, 1.9)	0.453
	Fatal/5	3	0.07	10	0.24	0.3	(0.08, 1.1)	-1.66	(-3.3, .011)	0.057
	≥Severe/3	24	0.57	25	0.59	0.96	(0.55, 1.7)	-0.252	(-3.5, 2.99)	0.879
	Serious	32	0.76	30	0.71	1.06	(0.65, 1.8)	0.454	(-3.2, 4.09)	0.807

Table A9 shows the results of the analysis of a dataset in which all PMO studies (placebo and active controlled) were pooled and analyzed using broad MedDRA SMQ criteria.

Moderate bradyarrhythmia was associated with a relative risk of 2.9 (p=0.058). Relative risk for additional severity categories was greater than one (Severe: RR=1.66; Life-threatening: RR=1.66, p=1; Severe or worse: RR=1.66, p=0.267; Serious: RR=1.75, p=0.141), however none of these estimates were associated with a p-value less than 0.10. Moderate gastrointestinal haemorrhage was associated with a relative risk of 1.76 (p=0.05), but relative risk estimates among the remaining severity levels was not consistently greater than one.

Severe ischaemic heart disease was associated with a relative risk of 1.55 (p=0.03). Risk estimates were greater than one in other severity categories (Life-threatening: RR=1.25, p=0.628; Severe or worse: RR=1.39, p=0.063; Serious: RR=1.18, p=0.269), but none were associated with a p-value less than 0.10.

Table A9. Broad Search Criteria With All Controlled PMO Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223, 20050234, and 20050141) Pooled.

Adverse Event Grouping	Severity	Denosumab Subjects	Denosumab Subjects N=5451	Placebo Subjects	Placebo Subjects N=4224	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	P value
		n	% (n/N)	n	% (n/N)					
Arrhythmia Related Investigations										
	All pooled	242	4.77	201	4.76	1	(0.83, 1.2)	0.0375	(-8.7, 8.7)	0.993
	Mild/1	149	2.93	104	2.46	1.19	(0.93, 1.5)	4.70	(-1.9, 11.3)	0.165
	Moderate/2	77	1.52	78	1.85	0.82	(0.60, 1.1)	-3.32	(-8.6, 1.96)	0.214
	Severe/3	20	0.39	20	0.47	0.83	(0.45, 1.5)	-0.80	(-3.5, 1.89)	0.558
	Life-threatening/4	5	0.1	1	0.02	4.16	(0.49, 36)	0.748	(-0.23, 1.7)	0.231
	Fatal/5	4	0.08	10	0.24	0.33	(0.10, 1.1)	-1.58	(-3.2, .076)	0.061
	≥Severe/3	29	0.57	31	0.73	0.78	(0.47, 1.3)	-1.63	(-4.9, 1.67)	0.327
	Serious	41	0.81	35	0.83	0.97	(0.62, 1.5)	-0.218	(-3.9, 3.46)	0.908
Brady-arrhythmias										
	All pooled	43	0.85	31	0.73	1.15	(0.73, 1.8)	1.1	(-2.5, 4.73)	0.544
	Mild/1	17	0.33	23	0.54	0.61	(0.33, 1.2)	-2.10	(-4.8, 0.63)	0.123
	Moderate/2	14	0.28	4	0.09	2.91	(0.96, 8.8)	1.81	(0.094, 3.5)	0.058
	Severe/3	12	0.24	6	0.14	1.66	(0.62, 4.4)	0.942	(-0.81, 2.7)	0.304
	Life-threatening/4	2	0.04	1	0.02	1.66	(0.15, 18)	0.157	(-.56, 0.87)	1
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	14	0.28	7	0.17	1.66	(0.67, 4.1)	1.10	(-0.80, 3.0)	0.267
	Serious	21	0.41	10	0.24	1.75	(0.82, 3.7)	1.77	(-0.53, 4.1)	0.141
Cardiac Arrhythmias										
	All pooled	432	8.51	381	9.03	0.94	(0.83, 1.1)	-5.19	(-16.7, 6.4)	0.378
	Mild/1	242	4.77	202	4.79	1	(0.83, 1.2)	-0.199	(-8.9, 8.5)	0.964
	Moderate/2	171	3.37	153	3.62	0.93	(0.75, 1.2)	-2.57	(-10.1, 4.9)	0.501
	Severe/3	53	1.04	52	1.23	0.85	(0.58, 1.2)	-1.88	(-6.2, 2.5)	0.392
	Life-threatening/4	7	0.14	5	0.12	1.16	(0.37, 3.7)	0.194	(-1.3, 1.65)	1
	Fatal/5	4	0.08	10	0.24	0.33	(0.10, 1.1)	-1.58	(-3.2, .076)	0.061
	≥Severe/3	64	1.26	65	1.54	0.82	(0.58, 1.2)	-2.80	(-7.6, 2.02)	0.251
	Serious	104	2.05	87	2.06	0.99	(0.75, 1.3)	-0.131	(-5.9, 5.66)	0.965
Cardiac Arrhythmia Terms										
	All pooled	221	4.35	210	4.98	0.87	(0.73, 1.1)	-6.23	(-14.9 , 2.4)	0.155
	Mild/1	102	2.01	110	2.61	0.77	(0.59, 1.0)	-5.97	(-12, 0.19)	0.055
	Moderate/2	99	1.95	81	1.92	1.02	(0.76, 1.4)	0.306	(-5.31, 5.9)	0.915
	Severe/3	34	0.67	32	0.76	0.88	(0.55, 1.4)	-0.886	(-4.3, 2.6)	0.613
	Life-threatening/4	3	0.06	4	0.09	0.62	(0.14, 2.8)	-0.357	(-1.5, 0.79)	0.709
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	37	0.73	34	0.81	0.9	(0.57, 1.4)	-0.769	(-4.34, 2.8)	0.672
	Serious	68	1.34	54	1.28	1.05	(0.73, 1.5)	0.598	(-4.04, 5.2)	0.801

(Table A9 is continued on the next page.)

Table A9 (continued from the previous page). Broad Search Criteria With All Controlled PMO Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223, 20050234, and 20050141) Pooled.

Cardio-myopathy										
	All pooled	400	7.88	379	8.98	0.88	(0.77, 1.0)	-11.0	(-22, 0.035)	0.056
	Mild/1	223	4.39	196	4.64	0.95	(0.78, 1.1)	-2.52	(-11.0, 6.0)	0.560
	Moderate/2	167	3.29	165	3.91	0.84	(0.68, 1.0)	-6.20	(-13.8, 1.4)	0.109
	Severe/3	44	0.87	43	1.02	0.85	(0.56, 1.3)	-1.52	(-5.5, 2.44)	0.448
	Life-threatening/4	6	0.12	5	0.12	1	(0.30, 3.3)	-0.003	(-1.41, 1.4)	1
	Fatal/5	4	0.08	11	0.26	0.3	(0.1, 0.95)	-1.82	(-3.5,-.098)	0.037
	≥Severe/3	52	1.02	58	1.37	0.75	(0.51, 1.1)	-3.50	(-8.0, 0.97)	0.120
	Serious	68	1.34	66	1.56	0.86	(0.61, 1.2)	-2.25	(-7.1, 2.7)	0.366
Disorders of Sinus Node Function										
	All pooled	19	0.37	10	0.24	1.58	(0.74, 3.4)	1.37	(-0.86, 3.6)	0.237
	Mild/1	3	0.06	3	0.07	0.83	(0.17, 4.1)	-0.120	(-1.2, 0.93)	1
	Moderate/2	11	0.22	3	0.07	3.05	(.85, 10.9)	1.46	(-0.055,3.0)	0.105
	Severe/3	6	0.12	5	0.12	1	(0.30, 3.3)	-0.003	(-1.4, 1.4)	1
	Life-threatening/4	1	0.02	0	0	_	N.A.	0.197	(-.19, 0.58)	1
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	7	0.14	5	0.12	1.16	(0.37, 3.7)	0.194	(-1.3, 1.65)	1
	Serious	12	0.24	7	0.17	1.42	(0.56, 3.6)	0.705	(-1.1, 2.5)	0.454
Embolic and Thrombotic Events, Arterial										
	All pooled	95	1.87	77	1.82	1.03	(0.76, 1.4)	0.466	(-5.03, 6.0)	0.868
	Mild/1	19	0.37	16	0.38	0.99	(0.51, 1.9)	-0.049	(-2.55, 2.5)	0.969
	Moderate/2	26	0.51	22	0.52	0.98	(0.56, 1.7)	-0.092	(-3.02, 2.8)	0.951
	Severe/3	40	0.79	24	0.57	1.39	(0.84, 2.3)	2.19	(-1.13 , 5.5)	0.203
	Life-threatening/4	4	0.08	10	0.24	0.33	(0.10, 1.1)	-1.58	(-3.2,0.076)	0.061
	Fatal/5	9	0.18	7	0.17	1.07	(0.40, 2.9)	0.114	(-1.57, 1.8)	0.895
	≥Severe/3	53	1.04	41	0.97	1.07	(0.72, 1.6)	0.724	(-3.35, 4.8)	0.728
	Serious	67	1.32	55	1.3	1.01	(0.71, 1.4)	0.164	(-4.48, 4.8)	0.945
Embolic and Thrombotic Events, Venous										
	All pooled	38	0.75	49	1.16	0.64	(0.42, 1.0)	-4.13	(-8.1,-0.12)	0.040
	Mild/1	7	0.14	14	0.33	0.42	(0.17, 1.0)	-1.94	(-4.0, .074)	0.050
	Moderate/2	14	0.28	22	0.52	0.53	(0.27, 1.0)	-2.46	(-5.06,0.15)	0.058
	Severe/3	15	0.3	13	0.31	0.96	(0.46, 2.0)	-0.126	(-2.37, 2.1)	0.912
	Life-threatening/4	5	0.1	4	0.09	1.04	(0.28, 3.9)	0.037	(-1.23, 1.3)	1
	Fatal/5	1	0.02	3	0.07	0.28	(0.03, 2.7)	-0.514	(-1.4, 0.38)	0.336
	≥Severe/3	21	0.41	19	0.45	0.92	(0.49, 1.7)	-0.366	(-3.05, 2.3)	0.788
	Serious	22	0.43	22	0.52	0.83	(0.46, 1.5)	-0.88	(-3.7, 1.95)	0.538

(Table A9 is continued on the next page.)

Table A9 (continued from the previous page). Broad Search Criteria With All Controlled PMO Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223, 20050234, and 20050141) Pooled.

Gastro-intestinal haemorrhage										
	All pooled	79	1.56	57	1.35	1.15	(0.82, 1.6)	2.05	(-2.8, 6.92)	0.412
	Mild/1	32	0.63	33	0.78	0.81	(0.50, 1.3)	-1.52	(-4.95, 1.9)	0.382
	Moderate/2	36	0.71	17	0.4	1.76	(0.99, 3.1)	3.06	(.066, 6.06)	0.051
	Severe/3	12	0.24	9	0.21	1.11	(0.47, 2.6)	0.231	(-1.7, 2.16)	0.815
	Life-threatening/4	2	0.04	1	0.02	1.66	(0.15, 18)	0.157	(-.56, 0.87)	1
	Fatal/5	1	0.02	0	0	_	N.A.	0.197	(-.19, 0.58)	1
	≥Severe/3	15	0.3	10	0.24	1.25	(0.56, 2.8)	0.585	(-1.5, 2.68)	0.588
	Serious	24	0.47	19	0.45	1.05	(0.58, 1.9)	0.225	(-2.5, 2.99)	0.874
Haemorrhages										
	All pooled	289	5.69	278	6.59	0.86	(0.74, 1.0)	-8.95	(-19, 0.88)	0.073
	Mild/1	165	3.25	166	3.93	0.83	(0.67, 1.0)	-6.83	(-14.5,0.79)	0.077
	Moderate/2	111	2.19	93	2.2	0.99	(0.76, 1.3)	-0.174	(-6.16, 5.8)	0.955
	Severe/3	24	0.47	32	0.76	0.62	(0.37, 1.0)	-2.85	(-6.1, 0.37)	0.077
	Life-threatening/4	3	0.06	1	0.02	2.49	(0.26, 24)	0.354	(-0.46, 1.2)	0.631
	Fatal/5	5	0.1	6	0.14	0.69	(0.21, 2.3)	-0.437	(-1.9, 0.99)	0.561
	≥Severe/3	32	0.63	38	0.9	0.7	(0.44, 1.1)	-2.70	(-6.3, 0.89)	0.134
	Serious	45	0.89	51	1.21	0.73	(0.49, 1.1)	-3.22	(-7.4, 0.96)	0.126
Haemorrhage Terms (excl lab)										
	All pooled	289	5.69	276	6.54	0.87	(0.74, 1.0)	-8.48	(-18.3, 1.3)	0.089
	Mild/1	165	3.25	165	3.91	0.83	(0.67, 1.0)	-6.60	(-14.2, 1.0)	0.087
	Moderate/2	111	2.19	92	2.18	1	(0.76, 1.3)	0.063	(-5.90, 6.0)	0.983
	Severe/3	24	0.47	32	0.76	0.62	(0.37, 1.1)	-2.85	(-6.08, 3.7)	0.077
	Life-threatening/4	3	0.06	1	0.02	2.49	(0.26, 24)	0.354	(-0.46, 1.2)	0.631
	Fatal/5	5	0.1	6	0.14	0.69	(0.21, 2.3)	-0.437	(-1.9, 0.99)	0.561
	≥Severe/3	32	0.63	38	0.9	0.7	(0.44, 1.1)	-2.70	(-6.3, 0.89)	0.134
	Serious	45	0.89	51	1.21	0.73	(0.49, 1.1)	-3.22	(-7.4, 0.96)	0.126
Hypertension										
	All pooled	746	14.69	719	17.03	0.86	(.79,0.95)	-23.4	(-38, -8.5)	0.002
	Mild/1	377	7.42	349	8.27	0.9	(0.78, 1.0)	-8.44	(-19.4, 2.6)	0.131
	Moderate/2	383	7.54	385	9.12	0.83	(.72,0.95)	-15.8	(-27, -4.5)	0.006
	Severe/3	34	0.67	39	0.92	0.72	(0.46, 1.2)	-2.54	(-6.2, 1.11)	0.166
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	1	0.02	0	0	_	N.A.	0.197	(-0.19,-.58)	1
	≥Severe/3	35	0.69	39	0.92	0.75	(0.47, 1.2)	-2.35	(-6.02, 1.3)	0.205
	Serious	29	0.57	30	0.71	0.8	(0.48, 1.3)	-1.40	(-4.7, 1.88)	0.399
Ischaemic heart disease										
	All pooled	207	4.08	179	4.24	0.96	(0.79, 1.2)	-1.64	(-9.8, 6.51)	0.693
	Mild/1	63	1.24	66	1.56	0.79	(0.56, 1.1)	-3.23	(-8.05, 1.6)	0.185
	Moderate/2	98	1.93	80	1.9	1.02	(0.76, 1.4)	0.346	(-5.24, 5.9)	0.904
	Severe/3	69	1.36	37	0.88	1.55	(1.04, 2.3)	4.82	(0.57, 9.07)	0.029
	Life-threatening/4	12	0.24	8	0.19	1.25	(0.51, 3.1)	0.468	(-1.4, 2.34)	0.628
	Fatal/5	9	0.18	7	0.17	1.07	(0.40, 2.9)	0.114	(-1.57, 1.8)	0.895
	≥Severe/3	85	1.67	51	1.21	1.39	(0.98, 2.0)	4.66	(-0.17, 9.5)	0.063
	Serious	109	2.15	77	1.82	1.18	(0.88, 1.6)	3.22	(-2.45, 8.9)	0.269

(*Table A9 is continued on the next page.*)

Table A9 (continued from the previous page). Broad Search Criteria With All Controlled PMO Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223, 20050234, and 20050141) Pooled.

Myocardial Infarction										
	All pooled	42	0.83	31	0.73	1.13	(0.71, 1.8)	0.927	(-2.66, 4.5)	0.614
	Mild/1	0	0	3	0.07	0	N.A.	-0.711	(-1.5, .093)	0.094
	Moderate/2	6	0.12	3	0.07	1.66	(0.42, 6.6)	0.471	(-0.77, 1.7)	0.524
	Severe/3	25	0.49	11	0.26	1.89	(0.93, 3.8)	2.32	(-0.15, 4.8)	0.073
	Life-threatening/4	6	0.12	7	0.17	0.71	(0.24, 2.1)	-0.477	(-2.0, 1.1)	0.540
	Fatal/5	8	0.16	7	0.17	0.95	(0.34, 2.6)	-0.083	(-1.7, 1.56)	0.921
	≥Severe/3	37	0.73	25	0.59	1.23	(0.74, 2.0)	1.36	(-1.9, 4.65)	0.421
	Serious	40	0.79	29	0.69	1.15	(0.71, 1.9)	1.01	(-2.47, 4.5)	0.573
Pulmonary Hypertension										
	All pooled	131	2.58	134	3.17	0.81	(0.64, 1.0)	-5.95	(-13, 0.91)	0.086
	Mild/1	69	1.36	63	1.49	0.91	(0.65, 1.3)	-1.34	(-6.2, 3.5)	0.587
	Moderate/2	56	1.1	68	1.61	0.68	(0.48, 1.0)	-5.08	(-9.8,-0.32)	0.033
	Severe/3	15	0.3	8	0.19	1.56	(0.66, 3.7)	1.06	(-0.93, 3.1)	0.306
	Life-threatening/4	2	0.04	0	0	_	N.A.	0.394	(-0.15, 0.9)	0.504
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	17	0.33	8	0.19	1.77	(0.76, 4.1)	1.45	(-0.61, 3.5)	0.178
	Serious	14	0.28	9	0.21	1.29	(0.56, 3.0)	0.625	(-1.38, 2.6)	0.546
Torsade de Pointes / QT Prolongation										
	All pooled	111	2.19	105	2.49	0.88	(0.68, 1.1)	-3.02	(-9.2, 3.17)	0.336
	Mild/1	50	0.98	38	0.9	1.09	(0.72, 1.7)	0.844	(-3.09, 4.8)	0.676
	Moderate/2	40	0.79	47	1.11	0.71	(0.46, 1.1)	-3.26	(-7.3, 0.73)	0.104
	Severe/3	16	0.32	13	0.31	1.02	(0.49, 2.1)	0.071	(-2.2, 2.34)	0.951
	Life-threatening/4	5	0.1	2	0.05	2.08	(0.40, 11)	0.511	(-0.57, 1.59)	0.467
	Fatal/5	4	0.08	10	0.24	0.33	(0.10, 1.0)	-1.58	(-3.2, .076)	0.061
	≥Severe/3	25	0.49	25	0.59	0.83	(0.48, 1.4)	-1.00	(-4.01,2.01)	0.512
	Serious	33	0.65	30	0.71	0.91	(0.56, 1.5)	-0.609	(-4.0, 2.75)	0.722

Table A10, A11, A12, A13, A14 and A15 show the results of the analysis of all studies separately using narrow MedDRA SMQ search criteria.

In Study 20030216, severe embolic and thrombotic arterial events were associated with a relative risk of 1.73 (p=0.03), and relative risk estimates tended to be greater than one for the remaining severity levels (Fatal: RR=1.38, p=0.620; Severe or worse: RR=1.32, p=0.179; Serious: RR=1.24, p=0.239). Estimates of relative risk for severe (RR=2.0, p=0.0007), severe or worse (RR=1.72, p=0.002), and serious (RR=1.41, p=0.02) ischaemic heart disease was associated with p-values less than 0.10. There was a trend toward increased risk of life-threatening (RR=1.37, p=0.494) and fatal (RR=1.28, p=0.62) events, although these estimates were not associated with p-values less than 0.10. Severe myocardial infarction was associated with a relative risk of 2.5 (p=0.01). Events of severe or worse and severe myocardial infarction events (RR=1.54 and 1.42, respectively) were associated with relative risk estimates greater than one, however, these events were not associated with a p-value less than 0.10 (p=0.097 and 0.147, respectively).

Table A10. ~~Narrow Search Criteria~~ With All Studies Analyzed Separately: Study 20030216.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=3886) n	Placebo Exposed Subjects (N=3876) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	P value
Embolic and thrombotic events								
	All pooled	124	125	0.99	(0.77, 1.26)	-0.34	(-8.18, 7.50)	0.9322
	Mild/1	25	30	0.83	(0.49, 1.41)	-1.31	(-5.04, 2.43)	0.4926
	Moderate/2	38	44	0.86	(0.56, 1.33)	-1.57	(-6.12, 2.98)	0.4979
	Severe/3	53	36	1.47	(0.96, 2.24)	4.35	(-0.38, 9.09)	0.0718
	Life-threatening/4	9	14	0.64	(0.28, 1.48)	-1.30	(-3.71, 1.12)	0.2936
	Fatal/5	10	10	1	(0.42, 2.39)	-0.00664	(-2.26, 2.25)	0.9954
	≥Severe/3	69	59	1.17	(0.83, 1.65)	2.53	(-3.13, 8.20)	0.3807
	Serious	84	76	1.1	(0.81, 1.50)	2.01	(-4.31, 8.33)	0.5335
Embolic and thrombotic events, arterial								
	All pooled	93	76	1.22	(0.90, 1.65)	4.32	(-2.17, 10.8)	0.192
	Mild/1	18	16	1.12	(0.57, 2.20)	0.504	(-2.43, 3.44)	0.737
	Moderate/2	25	22	1.13	(0.64, 2.01)	0.757	(-2.69, 4.21)	0.667
	Severe/3	40	23	1.73	(1.04, 2.89)	4.36	(0.370, 8.35)	0.032
	Life-threatening/4	4	10	0.4	(0.13, 1.27)	-1.55	(-3.44, 0.34)	0.118
	Fatal/5	9	7	1.28	(0.48, 3.44)	0.510	(-1.51, 2.53)	0.620
	≥Severe/3	53	40	1.32	(0.88, 1.99)	3.32	(-1.52, 8.16)	0.179
	Serious	67	54	1.24	(0.87, 1.77)	3.31	(-2.20, 8.82)	0.239
Ischaemic heart disease								
	All pooled	198	172	1.15	(0.94, 1.40)	6.58	(-2.90, 16.1)	0.174
	Mild/1	61	64	0.95	(0.67, 1.35)	-0.814	(-6.42, 4.79)	0.776
	Moderate/2	93	77	1.2	(0.89, 1.62)	4.07	(-2.44, 10.6)	0.221
	Severe/3	68	34	1.99	(1.32, 3.00)	8.73	(3.67, 13.8)	.0007
	Life-threatening/4	11	8	1.37	(0.55, 3.41)	0.767	(-1.43, 2.96)	0.494
	Fatal/5	9	7	1.28	(0.48, 3.44)	0.510	(-1.51, 2.53)	0.620
	≥Severe/3	83	48	1.72	(1.21, 2.45)	8.97	(3.25, 14.7)	0.002
	Serious	106	75	1.41	(1.05, 1.89)	7.93	(1.22, 14.6)	0.021
Myocardial infarction								
	All pooled	41	29	1.41	(0.88, 2.26)	3.07	(-1.14, 7.27)	0.153
	Mild/1	0	2	0	N.A.	-0.516	(-1.23, 0.20	0.249
	Moderate/2	5	3	1.66	(0.40, 6.95)	0.513	(-0.91, 1.94)	0.726
	Severe/3	25	10	2.49	(1.20, 5.18)	3.85	(0.875, 6.83)	0.011
	Life-threatening/4	6	7	0.85	(0.29, 2.54)	-0.262	(-2.08, 1.56)	0.778
	Fatal/5	8	7	1.14	(0.41, 3.14)	0.253	(-1.70, 2.21)	0.80
	≥Severe/3	37	24	1.54	(0.92, 2.57)	3.33	(-0.60, 7.26)	0.097
	Serious	40	28	1.42	(0.88, 2.30)	3.07	(-1.08, 7.21)	0.147

Table A11. Narrow Search Criteria With All Studies Analyzed Separately: Study 20040132.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=3886) n	Placebo Exposed Subjects (N=3876) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	P value
Haemorrhages								
	All pooled	6	16	0.38	(0.15, 0.94)	-60.4	(-11.4, -6.9)	0.0284
	Mild/1	3	13	0.23	(0.07, 0.80)	-60.5	(-10.6,-14.6)	0.0183
	Moderate/2	2	2	1.01	(0.14, 7.06)	0.0739	(-23.6, 23.8)	1
	Severe/3	1	2	0.5	(0.05, 5.49)	-6.02	(-26.5, 14.5)	1
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	1	2	0.5	(0.05, 5.49)	-6.02	(-26.5, 14.5)	1
	Serious	0	0	_	N.A.	_	N.A.	.
Haemorrhage Terms (excl lab)								
	All pooled	6	16	0.38	(0.15, 0.94)	-60.4	(-11.4,-6.87)	0.0284
	Mild/1	3	13	0.23	(0.07, 0.80)	-60.5	(-106, -14.6)	0.0183
	Moderate/2	2	2	1.01	(0.14, 7.06)	0.0739	(-23.6, 23.8)	1
	Severe/3	1	2	0.5	(0.05, 5.49)	-6.02	(-26.5, 14.5)	1
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	1	2	0.5	(0.05, 5.49)	-6.02	(-26.5, 14.5)	1
	Serious	0	0	_	N.A.	_	N.A.	.
Hypertension								
	All pooled	6	15	0.4	(0.16, 1.01)	-54.3	(-107, -1.89)	0.0439
	Mild/1	4	7	0.57	(0.17, 1.93)	-18.0	(-56.8, 20.7)	0.5418
	Moderate/2	2	8	0.25	(0.05, 1.17)	-36.3	(-73.1, 0.54)	0.104
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	_	N.A.	_	N.A.	.

Table A12. Narrow Search Criteria With All Studies Analyzed Separately: Study 20040135.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=129) n	Placebo Exposed Subjects (N=120) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	P value
Hypertension								
	All pooled	5	8	0.58	(0.20, 1.73)	-27.9	(-83.6, 27.8)	0.3982
	Mild/1	4	5	0.74	(0.20, 2.71)	-10.7	(-57.3, 36.0)	0.7419
	Moderate/2	0	5	0	N.A.	-41.7	(-77.4,-5.91)	0.0249
	Severe/3	1	0	_	N.A.	7.75	(-7.38, 22.9)	1
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	1	0	_	N.A.	7.75	(-7.38, 22.9)	1
	Serious	0	0	_	N.A.	_	N.A.	.

In Study 20040138, moderate embolic and thrombotic events were associated with a relative risk of 2.1 (p=0.059), but results were mixed for the remaining severity categories. Likewise, mild haemodynamic oedema and effusions were associated with a relative risk of 1.5 (p=0.055), but risk was approximately unity for the remaining categories of severity.

Note that none of the cardiovascular adverse events in the following studies were associated with a relative risk having a p-value less than 0.10: Study 20010223 (smallest p-value: 0.1278), Study 20040132 (smallest p-value: 0.4985), Study 20040135 (smallest p-value: 0.258), Study 20050141 (smallest p-value: 0.0846), Study 20050172 (smallest p-value: 0.3632), Study 20050179 (smallest p-value: 0.2424), Study 20050234 (smallest p-value: 0.23).

Table A13. Narrow Search Criteria With All Studies Analyzed Separately: Study 20040138.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=731) n	Placebo Exposed Subjects (N=725) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
Cardiac Failure								
	All pooled	21	26	0.8	(0.45, 1.41)	-7.13	(-25.3, 11.0)	0.4412
	Mild/1	5	2	2.48	(0.48, 12.7)	4.08	(-3.01, 11.2)	0.452
	Moderate/2	1	6	0.17	(0.02, 1.37)	-6.91	(-14.0, 0.21)	0.0686
	Severe/3	9	11	0.81	(0.34, 1.95)	-2.86	(-14.8, 9.10)	0.6392
	Life-threatening/4	1	6	0.17	(0.02, 1.37)	-6.91	(-14.0, 0.21)	0.0686
	Fatal/5	5	2	2.48	(0.48, 12.7)	4.08	(-3.01, 11.2)	0.452
	≥Severe/3	15	19	0.78	(0.40, 1.53)	-5.69	(-21.2, 9.83)	0.4725
	Serious	12	16	0.74	(0.35, 1.56)	-5.65	(-19.8, 8.46)	0.4323
Embolic and thrombotic events								
	All pooled	49	43	1.13	(0.76, 1.68)	7.72	(-17.3, 32.7)	0.545
	Mild/1	3	4	0.74	(0.17, 3.31)	-1.41	(-8.52, 5.70)	0.725
	Moderate/2	19	9	2.09	(0.95, 4.60)	13.6	(-0.49, 27.6)	0.059
	Severe/3	18	13	1.37	(0.68, 2.78)	6.69	(-8.12, 21.5)	0.3764
	Life-threatening/4	9	12	0.74	(0.32, 1.75)	-4.24	(-16.5, 8.01)	0.498
	Fatal/5	4	7	0.57	(0.17, 1.93)	-4.18	(-13.1, 4.72)	0.384
	≥Severe/3	30	32	0.93	(0.57, 1.51)	-3.10	(-23.8, 17.6)	0.770
	Serious	41	32	1.27	(0.81, 1.99)	11.9	(-10.5, 34.3)	0.296
Haemo-dynamic oedema, effusions, etc.								
	All pooled	83	76	1.08	(0.81, 1.45)	8.72	(-23.3, 40.7)	0.594
	Mild/1	54	36	1.49	(0.99, 2.24)	24.2	(-0.47, 48.9)	0.055
	Moderate/2	24	34	0.7	(0.42, 1.17)	-14.1	(-34.2, 6.03)	0.17
	Severe/3	7	7	0.99	(0.35, 2.81)	-0.0792	(-10.1, 9.95)	0.988
	Life-threatening/4	2	2	0.99	(0.14, 7.02)	-0.0226	(-5.40, 5.35)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	9	9	0.99	(0.40, 2.48)	-0.102	(-11.5, 11.2)	0.986
	Serious	7	6	1.16	(0.39, 3.43)	1.30	(-8.36, 11.0)	0.792
Toxic-septic shock conditions								
	All pooled	0	4	0	N.A.	-5.52	(-10.9,-0.13)	0.0612
	Mild/1	0	0	_	N.A.	_	N.A.	.
	Moderate/2	0	0	_	N.A.	_	N.A.	.
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	3	0	N.A.	-4.14	(-8.81, 0.54)	0.1232
	Fatal/5	0	1	0	N.A.	-1.38	(-4.08, 1.32)	0.4979
	≥Severe/3	0	4	0	N.A.	-5.52	(-10.9,-0.13)	0.0612
	Serious	0	4	0	N.A.	-5.52	(-10.9,-0.13)	0.0612

Table A14. Narrow Search Criteria With All Studies Analyzed Separately: Study 20050141.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=593) n	Alendronate Exposed Subjects (N=586) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
Haemorrhages								
	All pooled	18	20	1.12	(0.60, 2.10)	3.78	(-16.4, 23.9)	0.7136
	Mild/1	10	19	1.92	(0.90, 4.10)	15.6	(-2.13, 33.3)	0.0846
	Moderate/2	7	2	0.29	(0.06, 1.39)	-8.39	(-18.3, 1.50)	0.1781
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	1	0	_	N.A.	-1.69	(-4.99, 1.62)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	1	0	_	N.A.	-1.69	(-4.99, 1.62)	1
	Serious	1	0	_	N.A.	-1.69	(-4.99, 1.62)	1
Haemorrhage Terms (excl lab)								
	All pooled	18	20	1.12	(0.60, 2.10)	3.78	(-16.4, 23.9)	0.7136
	Mild/1	10	19	1.92	(0.90, 4.10)	15.6	(-2.13, 33.3)	0.0846
	Moderate/2	7	2	0.29	(0.06, 1.39)	-8.39	(-18.3, 1.50)	0.1781
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	1	0	_	N.A.	-1.69	(-4.99, 1.62)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	1	0	_	N.A.	-1.69	(-4.99, 1.62)	1
	Serious	1	0	_	N.A.	-1.69	(-4.99, 1.62)	1
Hypertension								
	All pooled	28	17	0.61	(0.34, 1.11)	-18.2	(-40.0, 3.61)	0.1028
	Mild/1	19	11	0.59	(0.28, 1.22)	-13.3	(-31.2, 4.67)	0.148
	Moderate/2	10	5	0.51	(0.17, 1.47)	-8.33	(-21.1, 4.43)	0.2988
	Severe/3	0	1	0	N.A.	1.71	(-1.64, 5.05)	0.497
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	1	0	N.A.	1.71	(-1.64, 5.05)	0.497
	Serious	0	1	0	N.A.	1.71	(-1.64, 5.05)	0.497

Table A15. Narrow Search Criteria With All Studies Analyzed Separately: Study 20050234.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=253) n	Alendronate Exposed Subjects (N=249) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
Haemorrhages								
	All pooled	7	13	0.53	(0.22, 1.31)	-24.5	(-58.8, 9.69)	0.1598
	Mild/1	6	7	0.84	(0.29, 2.47)	-4.40	(-32.2, 23.4)	0.7565
	Moderate/2	1	6	0.16	(0.02, 1.35)	-20.1	(-40.7, 0.41)	0.0666
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	_	N.A.	_	N.A.	.
Haemorrhage Terms (excl lab)								
	All pooled	7	13	0.53	(0.22, 1.31)	-24.5	(-58.8, 9.69)	0.1598
	Mild/1	6	7	0.84	(0.29, 2.47)	-4.40	(-32.2, 23.4)	0.7565
	Moderate/2	1	6	0.16	(0.02, 1.35)	-20.1	(-40.7, 0.41)	0.0666
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	_	N.A.	_	N.A.	.

Table A16 shows the results of a cardiovascular adverse event analysis using narrow MedDRA SMQ search criteria in a pooled dataset of the two large, pivotal trials, Study 20030216 and 20040138.

The relative risk for severe embolic and thrombotic events was 1.44 (p=0.05), however, the relative risk for events in all other severity categories was approximately one. Likewise, only severe arterial embolic and thrombotic events was associated with a relative risk of 1.7 (p=0.02); the relative risk of events in the remaining severity categories approached one. Severe ischaemic heart disease was associated with a relative risk of 1.76 (p=0.001), and severe or worse events were associated with a relative risk of 1.35 (p=0.03). However, the relative risk for fatal and life-threatening ischaemic heart disease was approximately equal to one. Relative risk for severe myocardial infarction was 2.5 (p=0.003), however, a relative risk greater than one was not observed in the other categories of severity.

Table A16. Narrow [redacted] rge, pivotal Studies (20030216 and 20040138) Pooled.

Adverse Event Grouping	Severity	Denosumab Subjects (N=4617)	Placebo Subjects (N=4601)	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
		n	n					
Cardiac Failure								
	All pooled	107	101	1.06	(0.81, 1.38)	1.22	(-4.84, 7.29)	0.6925
	Mild/1	25	24	1.04	(0.59, 1.81)	0.199	(-2.77, 3.17)	0.8957
	Moderate/2	44	36	1.22	(0.79, 1.89)	1.71	(-2.08, 5.49)	0.3774
	Severe/3	31	31	1	(0.61, 1.64)	-0.0233	(-3.36, 3.31)	0.9891
	Life-threatening/4	4	11	0.36	(0.12, 1.14)	-1.52	(-3.17, 0.12)	0.0761
	Fatal/5	11	10	1.1	(0.47, 2.58)	0.209	(-1.74, 2.16)	0.8333
	≥Severe/3	44	51	0.86	(0.58, 1.28)	-1.55	(-5.68, 2.57)	0.46
	Serious	49	56	0.87	(0.60, 1.28)	-1.56	(-5.89, 2.77)	0.4808
Embolic and thrombotic events								
	All pooled	173	168	1.03	(0.83, 1.26)	0.956	(-6.75, 8.66)	0.8078
	Mild/1	28	34	0.82	(0.50, 1.35)	-1.33	(-4.66, 2.01)	0.4364
	Moderate/2	57	53	1.07	(0.74, 1.55)	0.826	(-3.61, 5.26)	0.7148
	Severe/3	71	49	1.44	(1.01, 2.07)	4.73	(0.103, 9.35)	0.0452
	Life-threatening/4	18	26	0.69	(0.38, 1.26)	-1.75	(-4.57, 1.06)	0.2223
	Fatal/5	14	17	0.82	(0.41, 1.66)	-0.663	(-3.03, 1.70)	0.5827
	≥Severe/3	99	91	1.08	(0.82, 1.44)	1.66	(-4.14, 7.46)	0.5739
	Serious	125	108	1.15	(0.89, 1.49)	3.60	(-2.81, 10.0)	0.2708
Embolic and thrombotic events, arterial								
	All pooled	130	109	1.19	(0.92, 1.53)	4.47	(-2.02, 11.0)	0.1773
	Mild/1	20	18	1.11	(0.59, 2.09)	0.420	(-2.20, 3.04)	0.7532
	Moderate/2	37	28	1.32	(0.81, 2.15)	1.93	(-1.49, 5.34)	0.2686
	Severe/3	53	31	1.7	(1.10, 2.65)	4.74	(0.865, 8.62)	0.0166
	Life-threatening/4	11	22	0.5	(0.24, 1.03)	-2.40	(-4.84, 0.04)	0.0538
	Fatal/5	13	14	0.93	(0.44, 1.97)	-0.227	(-2.43, 1.98)	0.8401
	≥Severe/3	77	67	1.15	(0.83, 1.58)	2.12	(-2.95, 7.18)	0.4128
	Serious	98	82	1.19	(0.89, 1.59)	3.40	(-2.24, 9.05)	0.2377
Embolic and thrombotic events, venous								
	All pooled	51	59	0.86	(0.59, 1.25)	-1.78	(-6.21, 2.66)	0.4321
	Mild/1	8	16	0.5	(0.21, 1.16)	-1.74	(-3.83, 0.34)	0.1003
	Moderate/2	21	25	0.84	(0.47, 1.49)	-0.885	(-3.76, 1.99)	0.5465
	Severe/3	21	18	1.16	(0.62, 2.18)	0.636	(-2.01, 3.29)	0.638
	Life-threatening/4	7	4	1.74	(0.51, 5.95)	0.647	(-0.76, 2.06)	0.5486
	Fatal/5	1	3	0.33	(0.03, 3.19)	-0.435	(-1.29, 0.42)	0.3741
	≥Severe/3	28	24	1.16	(0.68, 2.00)	0.848	(-2.21, 3.91)	0.5866
	Serious	33	26	1.26	(0.76, 2.11)	1.50	(-1.76, 4.75)	0.3677
Ischaemic heart disease								
	All pooled	252	226	1.11	(0.93, 1.32)	5.46	(-3.59, 14.5)	0.2371
	Mild/1	70	69	1.01	(0.73, 1.41)	0.165	(-4.81, 5.14)	0.9483
	Moderate/2	110	94	1.17	(0.89, 1.53)	3.39	(-2.61, 9.40)	0.268
	Severe/3	90	51	1.76	(1.25, 2.47)	8.41	(3.40, 13.4)	0.001
	Life-threatening/4	22	25	0.88	(0.50, 1.55)	-0.669	(-3.58, 2.24)	0.6522
	Fatal/5	13	14	0.93	(0.44, 1.97)	-0.227	(-2.43, 1.98)	0.8401
	≥Severe/3	118	87	1.35	(1.03, 1.78)	6.65	(0.631, 12.7)	0.0304
	Serious	143	121	1.18	(0.93, 1.50)	4.67	(-2.13, 11.5)	0.1786

(Table A16 is continued on the next page.)

Table A16 (continued from the previous page). Narrow Search Criteria With Two Large, pivotal Studies (20030216 and 20040138) Pooled.

Myocardial infarction								
	All pooled	64	55	1.16	(0.81, 1.66)	1.91	(-2.70, 6.52)	0.4172
	Mild/1	0	3	0	N.A.	-0.652	(-1.4, 0.086)	0.1243
	Moderate/2	8	6	1.33	(0.46, 3.83)	0.429	(-1.16, 2.02)	0.5972
	Severe/3	35	14	2.49	(1.34, 4.62)	4.54	(1.57, 7.50)	0.0027
	Life-threatening/4	13	20	0.65	(0.32, 1.30)	-1.53	(-3.97, 0.91)	0.2184
	Fatal/5	12	14	0.85	(0.40, 1.84)	-0.444	(-2.61, 1.72)	0.6879
	≥Severe/3	57	48	1.18	(0.81, 1.73)	1.91	(-2.42, 6.24)	0.3868
	Serious	61	54	1.13	(0.78, 1.62)	1.48	(-3.06, 6.01)	0.5234
Thrombophlebitis								
	All pooled	9	17	0.53	(0.24, 1.18)	-1.75	(-3.91, 0.42)	0.1141
	Mild/1	4	7	0.57	(0.17, 1.94)	-0.655	(-2.07, 0.76)	0.3866
	Moderate/2	3	9	0.33	(0.09, 1.23)	-1.31	(-2.78, 0.17)	0.0915
	Severe/3	3	1	2.99	(0.31, 28.7)	0.432	(-0.42, 1.28)	0.6249
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	3	1	2.99	(0.31, 28.7)	0.432	(-0.42, 1.28)	0.6249
	Serious	3	2	1.49	(0.25, 8.94)	0.215	(-0.74, 1.17)	1

Table A17 shows the result of an analysis of placebo-controlled trials using narrow MedDRA SMQ search criteria to evaluate the risk for cardiovascular adverse events.

Severe arterial embolic and thrombotic events were associated with a relative risk of 1.66 (p=0.05). The relative risk for fatal (RR=1.28), severe or worse (RR=1.29) and serious (RR=1.22) events were all greater than one, however, none of these estimates were associated with a p-value less than 0.10. Estimates of relative risk for severe (RR=1.83, p=0.002), severe or worse (RR=1.62, p=0.006), and serious (RR=1.39, p=0.03) ischaemic heart disease were all greater than one. Life-threatening (RR=1.37) and fatal (RR=1.28) events were also associated with a relative risk estimate greater than one, however these estimates did not have a p-value less than 0.10.

Relative risk for severe myocardial infarction was greater than one (RR=2.27, p=0.02). Myocardial infarction events of a severe or worse nature (RR=1.48) and events of a serious nature (RR=1.38) also had relative risk estimates greater than one, but these estimates were not associated with a p-value less than 0.10. Events of a life-threatening or fatal nature were associated with relative risk estimates approaching unity.

Table A17. Narrow Search Criteria With Placebo Controlled Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223) Pooled.

Adverse Event Grouping	Severity	Denosumab Subjects n	Denosumab Subjects N=4232 % (n/N)	Placebo Subjects n	Placebo Subjects N=4221 % (n/N)	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	P value
Embolic and thrombotic events										
	All pooled	124	2.93	126	2.99	0.98	(0.77, 1.3)	-0.55	(-7.8, 6.7)	0.881
	Mild/1	25	0.59	30	0.71	0.83	(0.49, 1.4)	-1.20	(-4.63, 2.2)	0.493
	Moderate/2	38	0.9	44	1.04	0.86	(0.56, 1.3)	-1.44	(-5.6, 2.73)	0.498
	Severe/3	53	1.25	37	0.88	1.43	(0.94, 2.2)	3.76	(-0.62, 8.1)	0.092
	Life-threatening/4	9	0.21	14	0.33	0.64	(0.28, 1.5)	-1.19	(-3.4, 1.03)	0.294
	Fatal/5	10	0.24	10	0.24	1	(0.42, 2.4)	-0.006	(-2.08, 2.1)	0.995
	≥Severe/3	69	1.63	60	1.42	1.15	(0.81, 1.6)	2.09	(-3.14, 7.3)	0.433
	Serious	84	1.98	77	1.82	1.09	(0.80, 1.5)	1.61	(-4.2, 7.43)	0.589
Embolic and thrombotic events, arterial										
	All pooled	93	2.2	77	1.82	1.2	(0.89, 1.62)	3.73	(-2.25, 9.72)	0.222
	Mild/1	18	0.43	16	0.38	1.12	(0.57, 2.20)	0.463	(-2.24, 3.16)	0.737
	Moderate/2	25	0.59	22	0.52	1.13	(0.64, 2.01)	0.695	(-2.47, 3.87)	0.667
	Severe/3	40	0.95	24	0.57	1.66	(1.00, 2.75)	3.77	(0.072, 7.46)	0.046
	Life-threatening/4	4	0.09	10	0.24	0.4	(0.13, 1.27)	-1.42	(-3.16, 0.31)	0.118
	Fatal/5	9	0.21	7	0.17	1.28	(0.48, 3.44)	0.468	(-1.38, 2.32)	0.620
	≥Severe/3	53	1.25	41	0.97	1.29	(0.86, 1.93)	2.81	(-1.66, 7.28)	0.218
	Serious	67	1.58	55	1.3	1.22	(0.85, 1.73)	2.80	(-2.28, 7.89)	0.280
Ischaemic heart disease										
	All pooled	201	4.75	178	4.22	1.13	(0.92, 1.37)	5.33	(-3.50, 14.1)	0.237
	Mild/1	62	1.47	65	1.54	0.95	(0.67, 1.34)	-0.749	(-5.94, 4.44)	0.777
	Moderate/2	95	2.24	80	1.9	1.18	(0.88, 1.59)	3.50	(-2.57, 9.56)	0.259
	Severe/3	68	1.61	37	0.88	1.83	(1.23, 2.73)	7.30	(2.58, 12.0)	0.002
	Life-threatening/4	11	0.26	8	0.19	1.37	(0.55, 3.41)	0.704	(-1.31, 2.72)	0.494
	Fatal/5	9	0.21	7	0.17	1.28	(0.48, 3.44)	0.468	(-1.38, 2.32)	0.620
	≥Severe/3	83	1.96	51	1.21	1.62	(1.15, 2.29)	7.53	(2.21, 12.9)	0.006
	Serious	107	2.53	77	1.82	1.39	(1.04, 1.85)	7.04	(0.823, 13.3)	0.027
Myocardial infarction										
	All pooled	41	0.97	30	0.71	1.36	(0.85, 2.18)	2.58	(-1.31, 6.47)	0.194
	Mild/1	0	0	2	0.05	0	N.A.	-0.474	(-1.13, 0.18)	0.249
	Moderate/2	5	0.12	3	0.07	1.66	(0.40, 6.95)	0.471	(-0.84, 1.78)	0.726
	Severe/3	25	0.59	11	0.26	2.27	(1.12, 4.60)	3.30	(0.527, 6.08)	0.020
	Life-threatening/4	6	0.14	7	0.17	0.85	(0.29, 2.54)	-0.241	(-1.91, 1.43)	0.778
	Fatal/5	8	0.19	7	0.17	1.14	(0.41, 3.14)	0.232	(-1.56, 2.03)	0.8
	≥Severe/3	37	0.87	25	0.59	1.48	(0.89, 2.45)	2.82	(-0.82, 6.46)	0.129
	Serious	40	0.95	29	0.69	1.38	(0.85, 2.21)	2.58	(-1.25, 6.42)	0.187

Table A18 shows the results of the application of narrow MedDRA SMQ search criteria applied to a dataset of all PMO studies pooled.

Here, severe ischaemic heart disease was the only adverse event associated with a p-value less than 0.10 (RR=1.55, p=0.03). There was no clear trend with regard to risk estimates of any other severity category for ischaemic heart disease.

Table A18. Narrow Search Criteria With All Controlled PMO Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223, 20050234, 20050141) Pooled.

Adverse Event Grouping	Severity	Denosumab Subjects n	Denosumab Subjects N=5078 % (n/N)	Placebo Subjects n	Placebo Subjects N=4221 % (n/N)	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	P value
Embolic and Thrombotic Events, Arterial										
	All pooled	95	1.87	77	1.82	1.03	(0.76, 1.4)	0.466	(-5.0, 6.0)	0.868
	Mild/1	19	0.37	16	0.38	0.99	(0.51, 1.9)	-0.049	(-2.55, 2.5)	0.969
	Moderate/2	26	0.51	22	0.52	0.98	(0.56, 1.7)	-0.092	(-3.0, 2.8)	0.951
	Severe/3	40	0.79	24	0.57	1.39	(0.84, 2.3)	2.19	(-1.13, 5.5)	0.203
	Life-threatening/4	4	0.08	10	0.24	0.33	(0.10, 1.1)	-1.58	(-3.2,0.076)	0.061
	Fatal/5	9	0.18	7	0.17	1.07	(0.40, 2.9)	0.114	(-1.57, 1.8)	0.895
	≥Severe/3	53	1.04	41	0.97	1.07	(0.72, 1.6)	0.724	(-3.35, 4.8)	0.728
	Serious	67	1.32	55	1.3	1.01	(0.71, 1.4)	0.164	(-4.48, 4.8)	0.945
Embolic and Thrombotic Events, Venous										
	All pooled	38	0.75	49	1.16	0.64	(0.42, 1.0)	-4.13	(-8.1,-0.12)	0.040
	Mild/1	7	0.14	14	0.33	0.42	(0.17, 1.0)	-1.94	(-4.0,0.074)	0.050
	Moderate/2	14	0.28	22	0.52	0.53	(0.27, 1.0)	-2.46	(-5.06,0.15)	0.058
	Severe/3	15	0.3	13	0.31	0.96	(0.46, 2.0)	-0.126	(-2.37,2.12)	0.912
	Life-threatening/4	5	0.1	4	0.09	1.04	(0.28, 3.9)	0.037	(-1.23, 1.3)	1
	Fatal/5	1	0.02	3	0.07	0.28	(0.03, 2.7)	-0.514	(-1.4, 0.38)	0.336
	≥Severe/3	21	0.41	19	0.45	0.92	(0.49, 1.7)	-0.366	(-3.05, 2.3)	0.788
	Serious	22	0.43	22	0.52	0.83	(0.46, 1.5)	-0.880	(-3.7, 1.95)	0.538
Haemorrhages										
	All pooled	287	5.65	273	6.47	0.87	(0.74, 1.0)	-8.16	(-17.9 , 1.6)	0.10
	Mild/1	163	3.21	162	3.84	0.84	(0.68, 1.0)	-6.28	(-13.8,1.28)	0.101
	Moderate/2	111	2.19	92	2.18	1	(0.76, 1.3)	0.063	(-5.9, 6.03)	0.983
	Severe/3	24	0.47	32	0.76	0.62	(0.37, 1.0)	-2.85	(-6.1, 0.37)	0.077
	Life-threatening/4	3	0.06	1	0.02	2.49	(0.26, 24)	0.354	(-0.46, 1.2)	0.631
	Fatal/5	5	0.1	6	0.14	0.69	(0.21, 2.3)	-0.437	(-1.9, 0.99)	0.561
	≥Severe/3	32	0.63	38	0.9	0.7	(0.44, 1.1)	-2.70	(-6.3, 0.89)	0.134
	Serious	45	0.89	51	1.21	0.73	(0.49, 1.1)	-3.22	(-7.4, 0.96)	0.126
Haemorrhage Terms (excl lab)										
	All pooled	287	5.65	273	6.47	0.87	(0.74, 1.0)	-8.16	(-17.9, 1.6)	0.10
	Mild/1	163	3.21	162	3.84	0.84	(0.68, 1.0)	-6.28	(-13.8, 1.3)	0.101
	Moderate/2	111	2.19	92	2.18	1	(0.76, 1.3)	0.063	(-5.9, 6.03)	0.983
	Severe/3	24	0.47	32	0.76	0.62	(0.37, 1.1)	-2.85	(-6.1, 0.37)	0.077
	Life-threatening/4	3	0.06	1	0.02	2.49	(0.26, 24)	0.354	(-0.46, 1.2)	0.631
	Fatal/5	5	0.1	6	0.14	0.69	(0.21, 2.3)	-0.437	(-1.9, 0.99)	0.561
	≥Severe/3	32	0.63	38	0.9	0.7	(0.44, 1.1)	-2.70	(-6.3, 0.89)	0.134
	Serious	45	0.89	51	1.21	0.73	(0.49, 1.1)	-3.22	(-7.4, 0.96)	0.126

(Table A18 continued on the next page.)

Table A18 (continued from the previous page). Narrow Search Criteria With All Controlled PMO Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223, 20050234, 20050141) Pooled.

Hypertension										
	All pooled	746	14.69	719	17.03	0.86	(0.79, 1.0)	-23.4	(-38.4,-8.5)	0.002
	Mild/1	377	7.42	349	8.27	0.9	(0.78, 1.0)	-8.44	(-19.4, 2.6)	0.131
	Moderate/2	383	7.54	385	9.12	0.83	(0.72, 1.0)	-15.8	(-27, -4.5)	0.006
	Severe/3	34	0.67	39	0.92	0.72	(0.46, 1.2)	-2.54	(-6.2, 1.11)	0.166
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	1	0.02	0	0	_	N.A.	0.197	(-0.19,0.58)	1
	≥Severe/3	35	0.69	39	0.92	0.75	(0.47, 1.2)	-2.35	(-6.0, 1.33)	0.205
	Serious	29	0.57	30	0.71	0.8	(0.48, 1.3)	-1.40	(-4.7, 1.88)	0.399
Ischaemic heart disease										
	All pooled	205	4.04	178	4.22	0.96	(0.79, 1.17)	-1.80	(-9.93, 6.33)	0.664
	Mild/1	63	1.24	65	1.54	0.81	(0.57, 1.14)	-2.99	(-7.80, 1.81)	0.218
	Moderate/2	96	1.89	80	1.9	1	(0.74, 1.34)	-0.0478	(-5.61, 5.52)	0.987
	Severe/3	69	1.36	37	0.88	1.55	(1.04, 2.31)	4.82	(0.574, 9.07)	0.029
	Life-threatening/4	12	0.24	8	0.19	1.25	(0.51, 3.05)	0.468	(-1.40, 2.34)	0.628
	Fatal/5	9	0.18	7	0.17	1.07	(0.40, 2.87)	0.114	(-1.57, 1.80)	0.895
	≥Severe/3	85	1.67	51	1.21	1.39	(0.98, 1.96)	4.66	(-0.17, 9.48)	0.063
	Serious	109	2.15	77	1.82	1.18	(0.88, 1.57)	3.22	(-2.45, 8.90)	0.269
Myocardial Infarction										
	All pooled	42	0.83	30	0.71	1.16	(0.73, 1.9)	1.16	(-2.39, 4.7)	0.524
	Mild/1	0	0	2	0.05	0	N.A.	-0.474	(-1.1, 0.18)	0.206
	Moderate/2	6	0.12	3	0.07	1.66	(0.42, 6.6)	0.471	(-0.77, 1.7)	0.524
	Severe/3	25	0.49	11	0.26	1.89	(0.93, 3.8)	2.32	(-0.15, 4.8)	0.073
	Life-threatening/4	6	0.12	7	0.17	0.71	(0.24, 2.1)	-0.477	(-2.0, 1.07)	0.540
	Fatal/5	8	0.16	7	0.17	0.95	(0.34, 2.6)	-0.083	(-1.73, 1.6)	0.921
	≥Severe/3	37	0.73	25	0.59	1.23	(0.74, 2.0)	1.36	(-1.93, 4.7)	0.421
	Serious	40	0.79	29	0.69	1.15	(0.71, 1.9)	1.01	(-2.5, 4.5)	0.573
Shock-associated Circulatory or Cardiac Conditions										
	All pooled	20	0.39	18	0.43	0.92	(0.49, 1.7)	-0.326	(-2.94, 2.3)	0.806
	Mild/1	5	0.1	2	0.05	2.08	(0.4, 10.7)	0.511	(-0.57, 1.6)	0.467
	Moderate/2	0	0	3	0.07	0	N.A.	-0.711	(-1.5,0.093)	0.094
	Severe/3	3	0.06	0	0	_	N.A.	0.591	(-0.08, 1.3)	0.256
	Life-threatening/4	5	0.1	2	0.05	2.08	(0.4, 10.7)	0.511	(-0.57, 1.6)	0.467
	Fatal/5	9	0.18	11	0.26	0.68	(0.28, 1.6)	-0.834	(-2.76, 1.1)	0.388
	≥Severe/3	15	0.3	13	0.31	0.96	(0.46, 2.0)	-0.126	(-2.4, 2.12)	0.912
	Serious	15	0.3	13	0.31	0.96	(0.46, 2.0)	-0.126	(-2.4, 2.12)	0.912

Table A19, A20 and A21 show the results of applying the sponsor's Preferred Term grouping strategy to each of the nine studies separately.

In study 20030216, severe (RR=1.87, p=0.001), severe or worse (RR=1.53, p=0.01), and serious (RR=1.33, p=0.04) events of acute coronary syndromes/all preferred terms pooled were associated with a relative risk greater than one and a p-value less than 0.10. Relative risk for life-threatening events was also greater than one (RR=1.38, p=0.494), but was not associated with a p-value less than 0.10. Severe acute coronary syndomes/acute myocardial infarction was associated with a relative risk of 4.5 (p=0.065). The relative risk estimates associated with the remaining categories of acute coronary

syndromes/myocardial infarction severity, however, were not consistently greater than one. Serious acute coronary syndromes/angina pectoris was associated with a relative risk of 1.83 (p=0.04). There was a trend toward relative risk estimates greater than one for severe (RR=1.8, p=0.11) and severe or worse (RR=1.75, p=0.118) events, but they were not associated with p-values less than 0.10. Mild arrhythmia/bradycardia was associated with a relative risk of 4.65 (p=0.01), but relative risk was not consistently greater than one for the remaining severity categories. Relative risk for moderate arrhythmia/tachycardia was 2.49 (p=0.05), but relative risk estimates were not greater than one for the remaining severity levels. Relative risk for severe events of other vascular disorders/All PTs was 1.65 (p=0.055). There was no a consistent trend toward relative risk estimates greater than one for the remaining severity categories and none were associated with a p-value less than 0.10. Risk difference for serious vascular disorders/skin ulcers was 0.00154 (p=0.031). The risk difference had to be computed since six (6) serious events were observed in the denosumab arm, but zero (0) in the control arm. The relative risk for severe events was 5.0, but this was not associated with a p-value less than 0.10 (p=0.219).

In study 20040138, the relative risk for severe arrhythmia/all PTs was 1.98 (p=0.056). There was a consistent trend of relative risk estimates greater than one for the remaining categories of severity, with RR=1.32 for fatal arrhythmia, RR=1.46 for severe or worse arrhythmia, and RR=1.2 for serious arrhythmia. None of these estimates, however, were associated with a p-value less than 0.10, with p=1, p=0.167 and p=0.463, respectively. Relative risk for mild congestive heart failure with all preferred terms pooled was1.61 (p=0.01), however, there was no consistent trend with respect to relative risk for the remaining severity categories. Relative risk for mild congestive heart failure/oedema peripheral was 1.65 (p=0.04), however, relative risk for the remaining severity categories was not greater than one. The risk difference of life-threatening vascular disorders with all terms pooled was 0.0109 (p=0.008). Risk difference had to be computed since there were eight events in the denosumab arm and zero in the control arm. Severe or worse (RR=1.37, p=0.376) and serious (RR=1.53, p=0.227) vascular disorders had relative risk estimates greater than one, but none were associated with p-values less than 0.10.

Note that the following studies did not have any events with a significant p-value: Study 20010223 (smallest p-value: 0.5754), Study 20040132 24 months (smallest p-value: 0.1421), Study 20040135 (smallest p-value: 0.116), Study 20050141 (smallest p-value: 0.374), Study 20050172 (smallest p-value: 0.6179), Study 20050179 (smallest p-value: 0.497, Study 20050234 (smallest p-value: 0.2486).

Table A19. Sponsor's Search Criteria With All Studies Analyzed Separately: Study 20030216.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=3886) n	Placebo Exposed Subjects (N=3876) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	P value
Acute coronary syndromes: All PTs								
	All pooled	232	209	1.11	(0.92, 1.33)	5.78	(-4.52, 16.1)	0.271
	Mild/1	80	86	0.93	(0.69, 1.25)	-1.60	(-8.04, 4.84)	0.626
	Moderate/2	104	85	1.22	(0.92, 1.62)	4.83	(-2.02, 11.7)	0.167
	Severe/3	73	39	1.87	(1.27, 2.75)	8.72	(3.42, 14.0)	0.001
	Life-threatening/4	11	8	1.37	(0.55, 3.41)	0.767	(-1.43, 2.96)	0.494
	Fatal/5	10	13	0.77	(0.34, 1.75)	-0.781	(-3.20, 1.64)	0.527
	≥Severe/3	89	58	1.53	(1.10, 2.12)	7.94	(1.88, 14.0)	0.010
	Serious	111	83	1.33	(1.01, 1.77)	7.15	(0.208, 14.1)	0.044
Acute coronary syndromes: Acute myocardial infarction								
	All pooled	12	5	2.39	(0.84, 6.79)	1.80	(-0.28, 3.88)	0.143
	Mild/1	0	0	_	N.A.	_	N.A.	.
	Moderate/2	2	0	_	N.A.	0.515	(-0.20, 1.23)	0.500
	Severe/3	9	2	4.49	(0.97, 20.8)	1.80	(0.128, 3.47)	0.065
	Life-threatening/4	0	2	0	N.A.	-0.516	(-1.23, 0.20)	0.249
	Fatal/5	1	1	1	(0.06, 15.9)	-0.0007	(-0.72, 0.71)	1
	≥Severe/3	10	5	1.99	(0.68, 5.83)	1.28	(-0.67, 3.24)	0.301
	Serious	12	5	2.39	(0.84, 6.79)	1.80	(-0.28, 3.88)	0.143
Acute coronary syndromes: Angina pectoris								
	All pooled	101	87	1.16	(0.87, 1.54)	3.54	(-3.29, 10.4)	0.310
	Mild/1	39	33	1.18	(0.74, 187)	1.52	(-2.74, 5.79)	0.484
	Moderate/2	54	45	1.2	(0.81, 1.77)	2.29	(-2.71, 7.28)	0.370
	Severe/3	20	11	1.81	(0.87, 3.78)	2.31	(-0.50, 5.11)	0.107
	Life-threatening/4	1	1	1	(0.06, 15.9)	-0.0007	(-0.72, 0.71)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	21	12	1.75	(0.86, 3.54)	2.31	(-0.59, 5.20)	0.118
	Serious	33	18	1.83	(1.03, 3.24)	3.85	(0.26, 7.44)	0.036
Acute coronary syndromes: Cardiac disorder								
	All pooled	0	5	0	N.A.	-1.29	(-2.4, -0.16)	0.031
	Mild/1	0	4	0	N.A.	-1.03	(-2.0,-0.021)	0.0621
	Moderate/2	0	1	0	N.A.	-0.258	(-0.76, 0.25)	0.4994
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	_	N.A.	_	N.A.	.

(Table A19 is continued on the next page.)

Table A19 (continued from the previous page). Sponsor's [redacted] Studies Analyzed Separately: Study 20030216.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=3886) n	Placebo Exposed Subjects (N=3876) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	P value
Other vascular disorders: All PTs								
	All pooled	179	162	1.1	(0.90, 1.36)	4.27	(-4.85, 0.13)	0.359
	Mild/1	71	76	0.93	(0.68, 1.28)	-1.34	(-7.40, 4.73)	0.67
	Moderate/2	76	68	1.11	(0.81, 1.54)	2.01	(-3.99, 8.02)	0.511
	Severe/3	38	23	1.65	(0.98, 2.76)	3.84	(-0.082, 7.8)	0.055
	Life-threatening/4	7	6	1.16	(0.39, 3.46)	0.253	(-1.57, 2.07)	0.785
	Fatal/5	2	3	0.66	(0.11, 3.98)	-0.259	(-1.39, 0.87)	0.687
	≥Severe/3	46	30	1.53	(0.97, 2.42)	4.10	(-0.28, 8.48)	0.067
	Serious	50	38	1.31	(0.86, 2.00)	3.06	(-1.65, 7.77)	0.203
Other vascular disorder: Aortic Aneurysm								
	All pooled	6	8	0.75	(0.26, 2.15)	-0.520	(-2.41, 1.37)	0.5893
	Mild/1	1	1	1	(0.06, 15.9)	-0.00066	(-0.72, 0.71)	1
	Moderate/2	5	3	1.66	(0.40, 6.95)	0.513	(-0.91, 1.94)	0.7264
	Severe/3	0	4	0	N.A.	-1.03	(-2.0,-0.021)	0.0621
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	4	0	N.A.	-1.03	(-2.0,-0.021)	0.0621
	Serious	1	5	0.2	(0.02, 1.71)	-1.03	(-2.3, 0.20)	0.1244
Other vascular disorder: Aortic stenosis								
	All pooled	13	5	2.59	(0.93, 7.27)	2.06	(-0.083, 4.2)	0.0959
	Mild/1	8	4	1.99	(0.60, 6.62)	1.03	(-0.72, 2.77)	0.3873
	Moderate/2	3	0	_	N.A.	0.772	(-0.10, 1.65)	0.2499
	Severe/3	2	1	1.99	(0.18, 22.0)	0.257	(-0.62, 1.13)	1
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	2	1	1.99	(0.18, 22.0)	0.257	(-0.62, 1.13)	1
	Serious	3	0	_	N.A.	0.772	(-0.10, 1.65)	0.2499
Other vascular disorders: Skin ulcer								
	All pooled	34	28	1.21	(0.74, 1.99)	1.53	(-2.43, 5.49)	0.450
	Mild/1	15	16	0.94	(0.46, 1.89)	-0.268	(-3.07, 2.54)	0.852
	Moderate/2	19	14	1.35	(0.68, 2.70)	1.28	(-1.62, 4.17)	0.387
	Severe/3	5	1	4.99	(0.58, 42.7)	1.03	(-0.21, 2.26)	0.219
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	5	1	4.99	(0.58, 42.7)	1.03	(-0.21, 2.26)	0.219
	Serious	6	0	_	N.A.	1.54	(0.310, 2.78)	0.031

(Table A19 is continued on the next page.)

Table A19 (continued from the previous page). Sponsor's Search Criteria With All Studies Analyzed Separately: Study 20030216.

Stroke: Cerebral Thrombosis								
	All pooled	3	5	0.6	(0.14, 2.50)	-0.518	(-1.95, 0.91)	0.5071
	Mild/1	1	0	_	N.A.	0.257	(-0.25, 0.76)	1
	Moderate/2	0	4	0	N.A.	-1.03	(-2.0,-0.021)	0.0621
	Severe/3	2	1	1.99	(0.18, 22.0)	0.257	(-0.62, 1.13)	1
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	2	1	1.99	(0.18, 22.0)	0.257	(-0.62, 1.13)	1
	Serious	3	3	1	(0.20, 4.94)	-0.0020	(-1.24, 1.23)	1
Acute coronary syndromes: Myocardial Ischaemia								
	All pooled	37	31	1.19	(0.74, 1.91)	1.52	(-2.62, 5.67)	0.4714
	Mild/1	14	20	0.7	(0.35, 1.38)	-1.56	(-4.50, 1.38)	0.2989
	Moderate/2	16	11	1.45	(0.67, 3.12)	1.28	(-1.34, 3.90)	0.3385
	Severe/3	5	1	4.99	(0.58, 42.7)	1.03	(-0.21, 2.3)	0.2186
	Life-threatening/4	1	0	_	N.A.	0.257	(-0.25, 0.76)	1
	Fatal/5	1	0	_	N.A.	0.257	(-0.25, 0.76)	1
	≥Severe/3	7	1	6.98	(0.86, 56.7)	1.54	(0.12, 2.97)	0.0702
	Serious	12	5	2.39	(0.84, 6.79)	1.80	(-0.28, 3.9)	0.143
Arrhythmia: Bradycardia								
	All pooled	18	12	1.5	(0.72, 3.10)	1.54	(-1.22, 4.30)	0.276
	Mild/1	14	3	4.65	(1.34, 16.2)	2.83	(0.75, 4.91)	0.013
	Moderate/2	2	5	0.4	(0.08, 2.06)	-0.775	(-2.11, 0.56)	0.288
	Severe/3	3	4	0.75	(0.17, 3.34)	-0.260	(-1.60, 1.08)	0.726
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	3	4	0.75	(0.17, 3.34)	-0.260	(-1.60, 1.08)	0.726
	Serious	4	3	1.33	(0.30, 5.94)	0.255	(-1.08, 1.59)	1
Arrhythmia: Sick Sinus Syndrome								
	All pooled	11	4	2.74	(0.87, 8.61)	1.80	(-0154, 3.75)	0.1181
	Mild/1	1	1	1	(0.06, 15.9)	-0.00066	(-0.72, 0.71)	1
	Moderate/2	7	1	6.98	(0.86, 56.7)	1.54	(0.12, 2.97)	0.0702
	Severe/3	4	3	1.33	(0.30, 5.94)	0.255	(-1.08, 1.59)	1
	Life-threatening/4	1	0	_	N.A.	0.257	(-0.25, 0.76)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	5	3	1.66	(0.40, 6.95)	0.513	(-0.91, 1.94)	0.7264
	Serious	9	4	2.24	(0.69, 7.28)	1.28	(-0.53, 3.1)	0.2664
Arrhythmia: Sinus tachycardia								
	All pooled	0	5	0	N.A.	-1.29	(-2.4, -0.16)	0.031
	Mild/1	0	4	0	N.A.	-1.03	(-2.0,-0.021)	0.0621
	Moderate/2	0	1	0	N.A.	-0.258	(-0.76, 0.25)	0.4994
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	_	N.A.	_	N.A.	.

(Table A19 is continued on the next page.)

Table A19 (continued from the previous page). Sponsor's Search Criteria With All Studies Analyzed Separately: Study 20030216.

Arrhythmia: Supraventricular tachycardia								
	All pooled	9	9	1	(0.40, 2.5)	-0.006	(-2.15, 2.13)	0.9956
	Mild/1	0	6	0	N.A.	-1.55	(-2.79,-0.31)	0.0155
	Moderate/2	6	3	1.99	(0.50, 7.97)	0.77	(-0.74, 2.28)	0.5076
	Severe/3	3	2	1.5	(0.25, 8.95)	0.256	(-0.87, 1.38)	1
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	3	2	1.5	(0.25, 8.95)	0.256	(-0.87, 1.38)	1
	Serious	7	2	3.49	(0.73, 16.8)	1.29	(-0.23, 2.80)	0.1794
Arrhythmia: Tachycardia								
	All pooled	38	24	1.58	(0.95, 2.63)	3.59	(-0.37, 7.55)	0.076
	Mild/1	25	17	1.47	(0.79, 2.71)	2.05	(-1.22, 5.31)	0.219
	Moderate/2	15	6	2.49	(0.97, 6.42)	2.31	(0.0027, 4.6)	0.050
	Severe/3	0	2	0	N.A.	-0.516	(-1.23, 0.20)	0.250
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	2	0	N.A.	-0.516	(-1.23, 0.20)	0.249
	Serious	1	1	1	(0.06, 15.9)	-0.0007	(-0.72, 0.71)	1
Congestive Heart Failure: Cardiac Failure Congestive								
	All pooled	16	23	0.69	(0.37, 1.31)	-1.82	(-4.96, 1.33)	0.2577
	Mild/1	1	7	0.14	(0.02, 1.16)	-1.55	(-3.0, -0.12)	0.0387
	Moderate/2	11	9	1.22	(0.51, 2.94)	0.509	(-1.75, 2.76)	0.6585
	Severe/3	5	7	0.71	(0.23, 2.24)	-0.519	(-2.27, 1.23)	0.5803
	Life-threatening/4	0	1	0	N.A.	-0.258	(-0.76, 0.25)	0.4994
	Fatal/5	0	1	0	N.A.	-0.258	(-0.76, 0.25)	0.4994
	≥Severe/3	5	9	0.55	(0.19, 1.65)	-1.04	(-2.92, 0.85)	0.3007
	Serious	10	13	0.77	(0.34, 1.75)	-0.781	(-3.20, 1.64)	0.527
Congestive Heart Failure: Oedema								
	All pooled	3	8	0.37	(0.10, 1.41)	-1.29	(-2.97, 0.38)	0.1452
	Mild/1	0	4	0	N.A.	-1.03	(-2.0,-0.021)	0.0621
	Moderate/2	3	4	0.75	(0.17, 3.34)	-0.260	(-1.6, 1.08)	0.7261
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	_	N.A.	_	N.A.	.
Congestive Heart Failure: Oedema Peripheral								
	All pooled	189	155	1.22	(0.99, 1.50)	8.65	(-0.51, 17.8)	0.0642
	Mild/1	121	105	1.15	(0.89, 1.49)	4.05	(-3.43, 11.5)	0.2889
	Moderate/2	74	56	1.32	(0.93, 1.86)	4.59	(-1.11, 10.3)	0.1147
	Severe/3	4	4	1	(0.25, 3.99)	-0.0027	(-1.43, 1.43)	1
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	4	4	1	(0.25, 3.99)	-0.0027	(-1.43, 1.43)	1
	Serious	3	0	_	N.A.	0.772	(-0.10, 1.65)	0.2499

Table A20. Sponsor's Search Criteria With All Studies Analyzed Separately: Study 20040138.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=731) n	Placebo Exposed Subjects (N=725) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
Acute Coronary Syndromes: Angina Pectoris								
	All pooled	17	8	2.11	(0.92, 4.85)	12.2	(-1.09, 25.5)	0.0727
	Mild/1	5	3	1.65	(0.40, 6.89)	2.70	(-4.88, 10.3)	0.7258
	Moderate/2	10	4	2.48	(0.78, 7.87)	8.16	(-1.84, 18.2)	0.1775
	Severe/3	3	1	2.98	(0.31, 28.5)	2.72	(-2.64, 8.09)	0.6245
	Life-threatening/4	2	1	1.98	(0.18, 21.8)	1.36	(-3.29, 6.01)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	4	2	1.98	(0.36, 10.8)	2.71	(-3.86, 9.28)	0.6869
	Serious	4	4	0.99	(0.25, 3.95)	-0.0453	(-7.64, 7.55)	1
Acute Coronary Syndromes: Chest Pain								
	All pooled	8	10	0.79	(0.31, 2.00)	-2.85	(-14.2, 8.51)	0.6228
	Mild/1	3	3	0.99	(0.20, 4.90)	-0.034	(-6.62, 6.55)	1
	Moderate/2	5	6	0.83	(0.25, 2.70)	-1.44	(-10.3, 7.46)	0.7727
	Severe/3	0	1	0	N.A.	-1.38	(-4.08, 1.32)	0.4979
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	1	0	N.A.	-1.38	(-4.08, 1.32)	0.4979
	Serious	0	4	0	N.A.	-5.52	(-10.9,-0.13)	0.0612
Acute Coronary Syndromes: Coronary Artery Disease								
	All pooled	15	17	0.88	(0.44, 1.74)	-2.93	(-18.0, 12.1)	0.7031
	Mild/1	2	0	_	N.A.	2.74	(-1.05, 6.52)	0.4997
	Moderate/2	2	7	0.28	(0.06, 1.36)	-6.92	(-15.0, 1.14)	0.107
	Severe/3	9	8	1.12	(0.43, 2.88)	1.28	(-9.76, 12.3)	0.8205
	Life-threatening/4	2	2	0.99	(0.14, 7.02)	-0.0226	(-5.40, 5.35)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	11	10	1.09	(0.47, 2.55)	1.25	(-11.0, 13.5)	0.8409
	Serious	9	11	0.81	(0.34, 1.95)	-2.86	(-14.8, 9.10)	0.6392
Acute Coronary Syndromes: Myocardial Ischaemia								
	All pooled	5	7	0.71	(0.23, 2.22)	-2.82	(-12.1, 6.48)	0.578
	Mild/1	2	1	1.98	(0.18, 21.8)	1.36	(-3.29, 6.01)	1
	Moderate/2	2	3	0.66	(0.11, 3.95)	-1.40	(-7.42, 4.61)	0.6858
	Severe/3	1	1	0.99	(0.06, 15.8)	-0.011	(-3.82, 3.79)	1
	Life-threatening/4	0	2	0	N.A.	-2.76	(-6.58, 1.06)	0.2478
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	1	3	0.33	(0.03, 3.17)	-2.77	(-8.16, 2.62)	0.3724
	Serious	0	6	0	N.A.	-8.28	(-14.9, -1.7)	0.0151

(Table A20 is continued on the next page.)

Table A20 (continued from previous page). Sponsor's Search Criteria With All Studies Analyzed Separately: Study 20040138.

Arrhythmia: All PTs								
	All pooled	69	66	9.1	(0.75, 1.43)	3.36	(-26.4, 33.2)	0.825
	Mild/1	17	22	3.03	(0.41, 1.43)	-7.09	(-23.7, 9.50)	0.402
	Moderate/2	29	32	4.41	(0.55, 1.47)	-4.47	(-25.1, 16.1)	0.671
	Severe/3	22	11	1.52	(0.97, 4.06)	14.9	(-0.33, 30.2)	0.056
	Life-threatening/4	5	8	1.1	(0.20, 1.89)	-4.19	(-13.9, 5.48)	0.420
	Fatal/5	4	3	0.41	(0.30, 5.89)	1.33	(-5.77, 8.44)	1
	≥Severe/3	31	21	2.9	(0.85, 2.52)	13.4	(-5.60, 32.5)	0.167
	Serious	35	29	4	(0.74, 1.94)	7.88	(-13.2, 28.9)	0.463
Congestive heart failure: All PTs								
	All pooled	108	106	14.62	(0.79, 1.29)	1.54	(-34.8, 37.9)	0.934
	Mild/1	65	40	5.52	(1.10, 2.36)	33.7	(7.25, 60.2)	0.013
	Moderate/2	28	57	7.86	(0.31, 0.76)	-40.3	(-64.3,-16.3)	0.001
	Severe/3	19	20	2.76	(0.51, 1.75)	-1.59	(-18.2, 15.0)	0.851
	Life-threatening/4	3	7	0.97	(0.11, 1.64)	-5.55	(-14.0, 2.94)	0.223
	Fatal/5	9	3	0.41	(0.81, 11.0)	8.17	(-1.09, 17.4)	0.144
	≥Severe/3	30	29	4	(0.62 1.69)	1.04	(-19.2, 21.3)	0.920
	Serious	27	21	2.9	(0.73, 2.23)	7.97	(-10.4, 26.3)	0.394
Congestive heart failure: Oedema peripheral								
	All pooled	53	48	6.62	(0.75, 1.60)	6.30	(-19.8, 32.4)	0.636
	Mild/1	40	24	3.31	(1.01, 2.71)	21.6	(0.61, 0.43)	0.044
	Moderate/2	10	23	3.17	(0.21, 0.90)	-18.0	(-33.3,-2.76)	0.021
	Severe/3	3	3	0.41	(0.20, 4.90)	-0.034	(-6.62, 6.55)	1
	Life-threatening/4	0	0	0	N.A.	_	N.A.	.
	Fatal/5	0	0	0	N.A.	_	N.A.	.
	≥Severe/3	3	3	0.41	(0.20, 4.90)	-0.034	(-6.62, 6.55)	1
	Serious	1	2	0.28	(0.05, 5.46)	-1.39	(-6.05, 3.27)	0.623
Congestive Heart Failure: Pulmonary Oedema								
	All pooled	0	4	0	N.A.	-5.52	(-10.9,-0.13)	0.0612
	Mild/1	0	0	_	N.A.	_	N.A.	.
	Moderate/2	0	0	_	N.A.	_	N.A.	.
	Severe/3	0	2	0	N.A.	-2.76	(-6.58, 1.06)	0.2478
	Life-threatening/4	0	2	0	N.A.	-2.76	(-6.58, 1.06)	0.2478
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	4	0	N.A.	-5.52	(-10.9,-0.13)	0.0612
	Serious	0	3	0	N.A.	-4.14	(-8.81, 0.54)	0.1232
Other vascular disorders: All PTs								
	All pooled	50	48	6.62	(0.70, 1.51)	2.19	(-23.5, 27.9)	0.867
	Mild/1	23	22	3.03	(0.58, 1.84)	1.12	(-16.7, 18.9)	0.902
	Moderate/2	18	17	2.34	(0.55, 2.02)	1.18	(-14.6, 16.9)	0.884
	Severe/3	13	12	1.66	(0.49, 2.34)	1.23	(-12.1, 14.6)	0.856
	Life-threatening/4	8	0	0	N.A.	10.9	(3.40, 18.5)	0.008
	Fatal/5	1	1	0.14	(0.06, 15.8)	-0.0113	(-3.82, 3.79)	1
	≥Severe/3	18	13	1.79	(0.68, 2.78)	6.69	(-8.12, 21.5)	0.376
	Serious	20	13	1.79	(0.76, 3.04)	9.43	(-5.84, 24.7)	0.227

(Table A20 is continued on the next page.)

Table A20 (continued from previous page). Sponsor's Search Criteria With All Studies Analyzed Separately: Study 20040138.

Stroke: All PTs								
	All pooled	40	36	1.1	(0.71, 1.71)	5.06	(-17.8, 27.9)	0.664
	Mild/1	6	6	0.99	(0.32, 3.06)	-0.068	(-9.36, 9.22)	0.9886
	Moderate/2	18	13	1.37	(0.68, 2.78)	6.69	(-8.12, 21.5)	0.3764
	Severe/3	13	14	0.92	(0.44, 1.95)	-1.53	(-15.4, 12.3)	0.8291
	Life-threatening/4	1	6	0.17	(0.02, 1.37)	-6.91	(-14.0, 0.21)	0.0686
	Fatal/5	7	3	2.31	(0.60, 8.91)	5.44	(-3.03, 13.9)	0.3421
	≥Severe/3	20	23	0.86	(0.48, 1.56)	-4.36	(-21.8, 13.0)	0.6228
	Serious	30	24	1.24	(0.73, 2.10)	7.94	(-11.5, 27.3)	0.423

Table A21. Sponsor's Search Criteria With All Studies Analyzed Separately: Study 20050141.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=593) n	Alendronate Exposed Subjects (N=586) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
Acute Coronary Syndromes: All PTs								
	All pooled	8	16	0.49	(0.21, 1.15)	-13.8	(-29.9, 2.32)	0.0931
	Mild/1	4	6	0.66	(0.19, 2.32)	-3.49	(-14.0, 6.99)	0.5449
	Moderate/2	2	8	0.25	(0.05, 1.16)	-10.3	(-20.8, 0.21)	0.0629
	Severe/3	1	2	0.49	(0.04, 5.43)	-1.73	(-7.49, 4.04)	0.6225
	Life-threatening/4	0	0	–	N.A.	–	N.A.	.
	Fatal/5	1	0	–	N.A.	1.69	(-1.62, 4.99)	1
	≥Severe/3	2	2	0.99	(0.14, 6.99)	-0.0403	(-6.68, 6.60)	1
	Serious	2	4	0.49	(0.09, 2.69)	-3.45	(-11.6, 4.68)	0.4494
Acute Coronary Syndromes: Chest Pain								
	All pooled	2	10	0.2	(0.04, 0.90)	-13.7	(-25.2,-2.21)	0.0211
	Mild/1	1	4	0.25	(0.03, 2.20)	-5.14	(-12.6, 2.30)	0.2152
	Moderate/2	1	6	0.16	(0.02, 1.36)	-8.55	(-17.3, 0.24)	0.068
	Severe/3	0	0	–	N.A.	–	N.A.	.
	Life-threatening/4	0	0	–	N.A.	–	N.A.	.
	Fatal/5	0	0	–	N.A.	–	N.A.	.
	≥Severe/3	0	0	–	N.A.	–	N.A.	.
	Serious	0	1	0	N.A.	-1.71	(-5.05, 1.64)	0.497

Table A22 shows the results of an analysis of data pooled from the two large, pivotal studies when analyzed according to the sponsor's categorization of MedDRA preferred terms.

The estimate of relative risk for severe acute coronary syndromes / all PTs pooled was 1.62 (p=0.0035). Estimates of relative risk were not consistently greater than one for the remaining levels of severity. The estimate of risk difference for severe acute coronary syndromes / acute coronary syndromes was 1.30 (p=0.03). The risk difference had to be computed because zero subjects receiving placebo had an event, but six subjects receiving denosumab reported an event. Relative risk for severe or worse (RR=3.5, p=0.1795) and serious (RR=2.33, p=0.3435) acute coronary syndromes were greater than one, but they were not associated with p-values less than 0.10. Estimates of relative risk for angina pectoris were associated with p-values less than 0.10 for several categories of

severity—severe angina was observed with a relative risk of 1.91 (p=0.0639); severe or worse angina had a relative risk of 1.78 (p=0.0794) and serious angina had a relative risk of 1.68 (p=0.0517). Mild bradycardia was associated with a relative risk of 5.0 (p=0.0075), but no other severity category was associated with a p-value less than 0.10. Sick sinus syndrome had a relative risk of 3.19 for all severity levels pooled (p=0.03). Relative risk for sick sinus syndrome was greater than one for all severity levels (Mild: RR=2.0, p=1; Moderate: RR=4.5, p=0.065; Severe: RR=2.0, p=0.5076; Severe or worse: RR=2.33, p=0.3435; Serious: RR=2.79, p=0.0633), but none were associated with a p-value less than 0.10. Vascular disorders/All PTs events of grade severe or worse were associated with a relative risk of 1.48 (p=0.043) and of grade life-threatening were associated with a relative risk of 2.49 (p=0.05). Relative risk for severe events was 1.45 (p=0.0859) and for serious events was 1.37 (p=0.0855). Risk difference for serious skin ulcers was 1.3 (p=0.0312). Risk difference is reported because there were zero events in the placebo group, and six events in the denosumab arm. Relative risk for severe events was greater than one (RR=5.0, p=0.2186), but the associated p-value was not less than 0.10.

Table A22. Sponsor's Search Criteria With Two Large, pivotal Studies (20030278 and 20040138) Pooled.

Adverse Event Grouping	Severity	Denosumab Subjects (N=4617) n	Placebo Subjects (N=4601) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
Acute coronary syndromes: All PTs								
	All pooled	298	270	1.1	(0.94, 1.29)	5.86	(-3.95, 15.7)	0.242
	Mild/1	94	95	0.99	(0.74, 1.31)	-0.288	(-6.07, 5.50)	0.9222
	Moderate/2	126	106	1.18	(0.92, 1.53)	4.25	(-2.14, 10.6)	0.1925
	Severe/3	94	58	1.62	(1.17, 2.23)	7.75	(2.56, 12.9)	0.0035
	Life-threatening/4	22	25	0.88	(0.50, 1.55)	-0.669	(-3.58, 2.24)	0.6522
	Fatal/5	18	22	0.82	(0.44, 1.52)	-0.883	(-3.57, 1.80)	0.519
	≥Severe/3	127	100	1.27	(0.98, 1.64)	5.77	(-0.55, 12.1)	0.0738
	Serious	151	135	1.11	(0.89, 1.40)	3.36	(-3.71, 10.4)	0.3517
Acute coronary syndromes: Acute coronary syndrome								
	All pooled	8	3	2.66	(0.71, 10.0)	1.08	(-0.33, 2.49)	0.2263
	Mild/1	0	1	0	N.A.	-0.217	(-0.64, 0.21)	0.4991
	Moderate/2	1	0	_	N.A.	0.217	(-0.21, 0.64)	1
	Severe/3	6	0	_	N.A.	1.30	(0.26, 2.34)	0.0312
	Life-threatening/4	1	2	0.5	(0.05, 5.49)	-0.218	(-0.96, 0.52)	0.6243
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	7	2	3.49	(0.72, 16.8)	1.08	(-0.19, 2.36)	0.1795
	Serious	7	3	2.33	(0.60, 8.99)	0.864	(-0.48, 2.21)	0.3435
Acute Coronary Syndromes: Angina Pectoris								
	All pooled	118	95	1.24	(0.95, 1.62)	4.91	(-1.22, 11.0)	0.1167
	Mild/1	44	36	1.22	(0.79, 1.89)	1.71	(-2.08, 5.49)	0.3774
	Moderate/2	64	49	1.3	(0.90, 1.88)	3.21	(-1.28, 7.70)	0.1611
	Severe/3	23	12	1.91	(0.95, 3.83)	2.37	(-0.14, 4.88)	0.0639
	Life-threatening/4	3	2	1.49	(0.25, 8.94)	0.215	(-0.74, 1.17)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	25	14	1.78	(0.93, 3.42)	2.37	(-0.28, 5.02)	0.0794
	Serious	37	22	1.68	(0.99, 2.84)	3.23	(-0.022, 6.5)	0.0517
Acute Coronary Syndromes: Cardiac Disorder								
	All pooled	1	6	0.17	(0.02, 1.38)	-1.09	(-2.2, 0.038)	0.0698
	Mild/1	0	4	0	N.A.	-0.869	(-1.7,-0.018)	0.062
	Moderate/2	1	1	1	(0.06, 15.9)	-0.00075	(-0.60, 0.60)	1
	Severe/3	0	1	0	N.A.	-0.217	(-0.64, 0.21)	0.4991
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	1	0	N.A.	-0.217	(-0.64, 0.21)	0.4991
	Serious	0	1	0	N.A.	-0.217	(-0.64, 0.21)	0.4991

(Table A22 is continued on the next page.)

Table A22 (continued from the previous page). Sponsor's Search Criteria With Two Large, pivotal Studies (20030216 and 20040138) Pooled.

Acute Coronary Syndromes: Coronary Artery Stenosis								
	All pooled	5	1	4.98	(0.58, 42.6)	0.866	(-0.17, 1.91)	0.2186
	Mild/1	1	0	_	N.A.	0.217	(-0.21, 0.64)	1
	Moderate/2	0	0	_	N.A.	_	N.A.	.
	Severe/3	3	1	2.99	(0.31, 28.7)	0.432	(-0.42, 1.28)	0.6249
	Life-threatening/4	1	0	_	N.A.	0.217	(-0.21, 0.64)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	4	1	3.99	(0.45, 35.7)	0.649	(-0.30, 1.60)	0.3749
	Serious	5	0	_	N.A.	1.08	(0.13, 2.03)	0.0624
Arrhythmia: Bradycardia								
	All pooled	26	16	1.62	(0.87, 3.01)	2.15	(-0.59, 4.90)	0.1247
	Mild/1	15	3	4.98	(1.44, 17.20)	2.60	(0.797, 4.4)	0.0075
	Moderate/2	7	7	1	(0.35, 2.84)	-0.0053	(-1.60, 1.58)	0.9948
	Severe/3	5	6	0.83	(0.25, 2.72)	-0.221	(-1.63, 1.19)	0.7739
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	5	6	0.83	(0.25, 2.72)	-0.221	(-1.63, 1.19)	0.7739
	Serious	8	6	1.33	(0.46, 3.83)	0.429	(-1.16, 2.02)	0.5972
Arrhythmia: Sick sinus syndrome								
	All pooled	16	5	3.19	(1.17, 8.70)	2.38	(0.435, 4.32)	0.0264
	Mild/1	2	1	1.99	(0.18, 22.0)	0.216	(-0.52, 0.95)	1
	Moderate/2	9	2	4.48	(0.97, 20.7)	1.51	(0.107, 2.92)	0.0653
	Severe/3	6	3	1.99	(0.50, 7.96)	0.648	(-0.63, 1.92)	0.5076
	Life-threatening/4	1	0	_	N.A.	0.217	(-0.21, 0.64)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	7	3	2.33	(0.60, 8.99)	0.864	(-0.48, 2.21)	0.3435
	Serious	14	5	2.79	(1.01, 7.74)	1.95	(0.096, 3.80)	0.0633
Arrhythmia: Sinus tachycardia								
	All pooled	0	5	0	N.A.	-1.09	(-2.0, -0.14)	0.0309
	Mild/1	0	4	0	N.A.	-0.869	(-1.7,-0.018)	0.062
	Moderate/2	0	1	0	N.A.	-0.217	(-0.64, 0.21)	0.4991
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	_	N.A.	_	N.A.	.
Arrhythmia: Supraventricular tachycardia								
	All pooled	9	9	1	(0.40, 2.51)	-0.0068	(-1.81, 1.80)	0.9941
	Mild/1	0	6	0	N.A.	-1.30	(-2.4, -0.26)	0.0154
	Moderate/2	6	3	1.99	(0.50, 7.96)	0.648	(-0.63, 1.92)	0.5076
	Severe/3	3	2	1.49	(0.25, 8.94)	0.215	(-0.74, 1.17)	1
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	3	2	1.49	(0.25, 8.94)	0.215	(-0.74, 1.17)	1
	Serious	7	2	3.49	(0.72, 16.8)	1.08	(-0.19, 2.36)	0.1795

(Table A22 is continued on the next page.)

Table A22 (continued from the previous page). Sponsor's Search Criteria With Two Large, pivotal Studies (20030216 and 20040138) Pooled.

Arrhythmia: Syncope								
	All pooled	81	81	1	(0.73, 1.35)	-0.0610	(-5.43, 5.30)	0.9822
	Mild/1	37	32	1.15	(0.72, 1.85)	1.06	(-2.46, 4.58)	0.5554
	Moderate/2	27	40	0.67	(0.41, 1.09)	-2.85	(-6.31, 0.62)	0.1078
	Severe/3	18	14	1.28	(0.64, 2.57)	0.856	(-1.54, 3.26)	0.4849
	Life-threatening/4	2	1	1.99	(0.18, 21.97)	0.216	(-0.52, 0.95)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	20	15	1.33	(0.68, 2.59)	1.07E-03	(-1.44, 3.58)	0.4029
	Serious	22	18	1.22	(0.65, 2.27)	8.53E-04	(-1.83, 3.54)	0.5334
Arrhythmia: Tachycardia								
	All pooled	39	29	1.34	(0.83, 2.16)	2.14E-03	(-1.35, 5.64)	0.229
	Mild/1	26	20	1.3	(0.72, 2.32)	1.28E-03	(-1.59, 4.16)	0.3815
	Moderate/2	15	7	2.14	(0.87, 5.23)	1.73E-03	(-0.26, 3.72)	0.0892
	Severe/3	0	2	0	N.A.	-0.435	(-1.04, 0.17)	0.2491
	Life-threatening/4	0	1	0	N.A.	-0.217	(-0.64, 0.21)	0.4991
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	3	0	N.A.	-0.652	(-1.39, .086)	0.1243
	Serious	1	2	0.5	(0.05, 5.49)	-0.218	(-0.96, 0.52)	0.6243
Congestive Heart Failure: All PTs								
	All pooled	482	455	1.06	(0.93, 1.19)	5.51	(-6.83, 17.8)	0.3818
	Mild/1	270	232	1.16	(0.98, 1.38)	8.06	(-1.21, 17.3)	0.0883
	Moderate/2	188	202	0.93	(0.76, 1.13)	-3.18	(-11.4, 5.03)	0.4476
	Severe/3	56	51	1.09	(0.75, 1.60)	1.04	(-3.33, 5.42)	0.6397
	Life-threatening/4	7	15	0.47	(0.19, 1.14)	-1.74	(-3.74, 0.25)	0.0862
	Fatal/5	17	15	1.13	(0.56, 2.26)	0.422	(-1.98, 2.82)	0.7306
	≥Severe/3	77	78	0.98	(0.72, 1.34)	-0.275	(-5.53, 4.97)	0.9181
	Serious	83	77	1.07	(0.79, 1.46)	1.24	(-4.09, 6.57)	0.6481
Congestive Heart Failure: Cardiac Failure								
	All pooled	59	41	1.43	(0.96, 2.13)	3.87	(-0.36, 8.10)	0.0731
	Mild/1	17	11	1.54	(0.72, 3.28)	1.29	(-0.96, 3.54)	0.26
	Moderate/2	27	18	1.49	(0.82, 2.71)	1.94	(-0.91, 4.78)	0.1824
	Severe/3	13	7	1.85	(0.74, 4.63)	1.29	(-0.60, 3.19)	0.1818
	Life-threatening/4	1	2	0.5	(0.05, 5.49)	-0.218	(-0.96, 0.52)	0.6243
	Fatal/5	3	6	0.5	(0.12, 1.99)	-0.654	(-1.93, 0.62)	0.3427
	≥Severe/3	17	15	1.13	(0.56, 2.26)	0.422	(-1.98, 2.82)	0.7306
	Serious	20	17	1.17	(0.61, 2.24)	0.637	(-1.94, 3.22)	0.6287
Congestive Heart Failure: Cardiac Failure Congestive								
	All pooled	29	41	0.7	(0.44, 1.13)	-2.63	(-6.17, 0.92)	0.1459
	Mild/1	5	9	0.55	(0.19, 1.65)	-0.873	(-2.46, 0.72)	0.3006
	Moderate/2	12	14	0.85	(0.40, 1.84)	-0.444	(-2.61, 1.72)	0.6879
	Severe/3	12	16	0.75	(0.35, 1.58)	-0.878	(-3.13, 1.37)	0.4435
	Life-threatening/4	0	4	0	N.A.	-0.869	(-1.72,-.018)	0.062
	Fatal/5	1	1	1	(0.06, 15.9)	-0.00075	(-0.60, 0.60)	1
	≥Severe/3	13	21	0.62	(0.31, 1.23)	-1.75	(-4.22, 0.73)	0.1662
	Serious	16	23	0.69	(0.37, 1.31)	-1.53	(-4.18, 1.12)	0.2567

(Table A22 is continued on the next page.)

Table A22 (continued from the previous page). Sponsor's Search Criteria With Two Large, pivotal Studies (20030216 and 20040138) Pooled.

Congestive Heart Failure: Cardiomegaly								
	All pooled	2	8	0.25	(0.05, 1.17)	-1.31	(-2.65, 0.04)	0.0648
	Mild/1	1	4	0.25	(0.03, 2.23)	-0.653	(-1.60, 0.30)	0.2178
	Moderate/2	0	3	0	N.A.	-0.652	(-1.39,0.086)	0.1243
	Severe/3	1	1	1	(0.06, 15.9)	-0.00075	(-0.60, 0.60)	1
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	1	1	1	(0.06, 15.9)	-0.00075	(-0.60, 0.60)	1
	Serious	0	1	0	N.A.	-0.217	(-0.64, 0.21)	0.4991
Congestive Heart Failure: Dyspnoea								
	All pooled	125	136	0.92	(0.72, 1.16)	-2.48	(-9.26, 4.29)	0.472
	Mild/1	62	55	1.12	(0.78, 1.61)	1.47	(-3.10, 6.04)	0.5271
	Moderate/2	60	79	0.76	(0.54, 1.06)	-4.17	(-9.15, 0.80)	0.1001
	Severe/3	13	11	1.18	(0.53, 2.63)	0.425	(-1.66, 2.51)	0.689
	Life-threatening/4	2	0	_	N.A.	0.433	(-0.17, 1.03)	0.4999
	Fatal/5	1	0	_	N.A.	0.217	(-0.21, 0.64)	1
	≥Severe/3	16	11	1.45	(0.67, 3.12)	1.07	(-1.13, 3.28)	0.3398
	Serious	19	11	1.72	(0.82, 3.61)	1.72	(-0.60, 4.05)	0.1461
Congestive Heart Failure: Oedema								
	All pooled	6	13	0.46	(0.17, 1.21)	-1.53	(-3.38, 0.33)	0.1063
	Mild/1	3	6	0.5	(0.12, 1.99)	-0.654	(-1.93, 0.62)	0.3427
	Moderate/2	3	7	0.43	(0.11, 1.65)	-0.872	(-2.22, 0.47)	0.2255
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	_	N.A.	_	N.A.	.
Congestive Heart Failure: Oedema Peripheral								
	All pooled	242	203	1.19	(0.99, 1.43)	8.29	(-0.45, 17.0)	0.0632
	Mild/1	161	129	1.24	(0.99, 1.56)	6.83	(-0.29, 14.0)	0.0602
	Moderate/2	84	79	1.06	(0.78, 1.44)	1.02	(-4.36, 6.40)	0.7093
	Severe/3	7	7	1	(0.35, 2.84)	-0.0053	(-1.60, 1.58)	0.9948
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	7	7	1	(0.35, 2.84)	-0.0053	(-1.60, 1.58)	0.9948
	Serious	4	2	1.99	(0.37, 10.9)	0.432	(-0.61, 1.47)	0.6874

(Table A22 is continued on the next page.)

Table A22 (continued from the previous page): Sponsor's Search Criteria With Two Large, pivotal Studies (20030216 and 20040138) Pooled.

Adverse Event Grouping	Severity	Denosumab Subjects (N=4617)	Placebo Subjects (N=4601)	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
		n	n					
Other vascular disorders: All PTs								
	All pooled	229	210	1.09	(0.91, 1.30)	3.96	(-4.74, 12.7)	0.3724
	Mild/1	94	98	0.96	(0.72, 1.26)	-0.940	(-6.77, 4.89)	0.752
	Moderate/2	94	85	1.1	(0.82, 1.47)	1.89	(-3.75, 7.52)	0.5119
	Severe/3	51	35	1.45	(0.95, 2.23)	3.44	(-0.48, 7.36)	0.0859
	Life-threatening/4	15	6	2.49	(0.97, 6.42)	1.94	(.00013, 3.9)	0.0502
	Fatal/5	3	4	0.75	(0.17, 3.34)	-0.220	(-1.34, 0.91)	0.726
	≥Severe/3	64	43	1.48	(1.01, 2.18)	4.52	(0.145, 8.89)	0.043
	Serious	70	51	1.37	(0.96, 1.96)	4.08	(-0.57, 8.72)	0.0855
Other vascular disorders: Aortic aneurysm								
	All pooled	12	17	0.7	(0.34, 1.47)	-1.10	(-3.38, 1.19)	0.3476
	Mild/1	4	4	1	(0.25, 3.98)	-0.00301	(-1.21, 1.20)	1
	Moderate/2	6	7	0.85	(0.29, 2.54)	-0.222	(-1.75, 1.31)	0.7766
	Severe/3	1	6	0.17	(0.02, 1.38)	-1.09	(-2.21,0.038)	0.0698
	Life-threatening/4	1	0	_	N.A.	0.217	(-0.21, 0.64)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	2	6	0.33	(0.07, 1.64)	-0.871	(-2.07, 0.33)	0.1788
	Serious	3	8	0.37	(0.10, 1.41)	-1.09	(-2.50, 0.32)	0.1451
Other vascular disorders: Skin ulcer								
	All pooled	40	29	1.37	(0.85, 2.21)	2.36	(-1.16, 5.88)	0.1886
	Mild/1	18	16	1.12	(0.57, 2.20)	0.421	(-2.05, 2.90)	0.7388
	Moderate/2	22	15	1.46	(0.76, 2.81)	1.50	(-1.08, 4.09)	0.2532
	Severe/3	5	1	4.98	(0.58, 42.6)	0.866	(-0.17, 1.91)	0.2186
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	5	1	4.98	(0.58, 42.6)	0.866	(-0.17, 1.91)	0.2186
	Serious	6	0	_	N.A.	1.30	(0.26, 2.34)	0.0312
Other vascular disorders: Thrombophlebitis								
	All pooled	9	17	0.53	(0.24, 1.18)	-1.75	(-3.91, 0.42)	0.1141
	Mild/1	4	7	0.57	(0.17, 1.94)	-0.655	(-2.07, 0.76)	0.3866
	Moderate/2	3	9	0.33	(0.09, 1.23)	-1.31	(-2.78, 0.17)	0.0915
	Severe/3	3	1	2.99	(0.31, 28.7)	0.432	(-0.42, 1.28)	0.6249
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	3	1	2.99	(0.31, 28.7)	0.432	(-0.42, 1.28)	0.6249
	Serious	3	2	1.49	(0.25, 8.94)	0.215	(-0.74, 1.17)	1
Stroke: Cerebral Thrombosis								
	All pooled	3	5	0.6	(0.14, 2.50)	-0.437	(-1.64, 0.77)	0.5069
	Mild/1	1	0	_	N.A.	0.217	(-0.21, 0.64)	1
	Moderate/2	0	4	0	N.A.	-0.869	(-1.72,-.018)	0.062
	Severe/3	2	1	1.99	(0.18, 22.0)	0.216	(-0.52, 0.95)	1
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	2	1	1.99	(0.18, 22.0)	0.216	(-0.52, 0.95)	1
	Serious	3	3	1	(0.20, 4.93)	-0.00226	(-1.04, 1.04)	1

Table A23 shows the results of the analysis of a dataset in which all placebo-controlled studies were pooled and analyzed using the sponsor's grouping of MedDRA terms.

Acute coronary events were associated with a relative risk greater than one for events of grade severe (RR=1.76, p=0.003), severe or worse (RR=1.47, p=0.018) and serious (RR=1.31, p=0.054). Events of grade life-threatening had a relative risk of 1.37, but were not associated with a p-value less than 0.10 (p=0.494). Relative risk for serious angina pectoris was 1.73 (p=0.053). Severe angina was associated with a relative risk of 1.53 (p=0.225), but its p-value was not less than 0.10. Relative risk for mild bradycardia was 5.0 (p=0.008), but the remaining severity levels were not consistently associated with relative risk estimates greater than one. Relaitve risk for moderate tachycardia was 2.66 (p=0.03), but the remaining severity levels for tachycardia were not associated with a relative risk estimate greater than one. Severe vascular disorders – all PTs pooled was associated with a relative risk of 1.65 (p=0.055) and severe or worse vascular disorders were associated with a relative risk of 1.53 (p=0.067). However, the remaining categories of severity were not associated with consistent estimates of relative risk greater than one. The estimate of risk difference for serious skin ulcers was 1.42 (p=0.031). Risk difference had to be computed since there were zero events in the placebo arm and six events in the treatment arm. Relative risk for severe skin ulcers was 5.0 (p=0.219), but the associated p-value was not less than 0.10.

Table A23. Sponsor's Search Criteria With Placebo Controlled Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223) Pooled.

Adverse Event Grouping	Severity	Deno-sumab Subjects N=4232 n	Deno-sumab Subjects % (n/N)	Placebo Subjects N=4221 n	Placebo Subjects % (n/N)	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	P value
Acute coronary syndromes: All PTs										
	All pooled	242	5.72	219	5.19	1.1	(0.92, 1.3)	5.30	(-4.4, 15.0)	0.283
	Mild/1	84	1.98	90	2.13	0.93	(0.69, 1.3)	-1.47	(-7.5, 4.58)	0.633
	Moderate/2	109	2.58	91	2.16	1.19	(0.91, 1.6)	4.20	(-2.3, 10.7)	0.204
	Severe/3	74	1.75	42	1	1.76	(1.21, 2.6)	7.54	(2.58, 12.5)	0.003
	Life-threatening/4	11	0.26	8	0.19	1.37	(0.55, 3.4)	0.704	(-1.31, 2.7)	0.494
	Fatal/5	10	0.24	13	0.31	0.77	(0.34, 1.8)	-0.717	(-2.9, 1.50)	0.527
	≥Severe/3	90	2.13	61	1.45	1.47	(1.07, 2.0)	6.81	(1.17, 12.5)	0.018
	Serious	112	2.65	85	2.01	1.31	(0.99, 1.7)	6.33	(-0.10,12.8)	0.054
Acute coronary syndromes: Acute myocardial infarction										
	All pooled	12	0.28	5	0.12	2.39	(0.84, 6.8)	1.65	(-0.26 , 3.6)	0.143
	Mild/1	0	0	0	0	_	N.A.	_	N.A.	.
	Moderate/2	2	0.05	0	0	_	N.A.	0.473	(-0.18 , 1.1)	0.500
	Severe/3	9	0.21	2	0.05	4.49	(0.97, 21)	1.65	(0.12, 3.19)	0.065
	Life-threatening/4	0	0	2	0.05	0	N.A.	-0.474	(-1.1, 0.18)	0.249
	Fatal/5	1	0.02	1	0.02	1	(0.06, 16)	-.0006	(-0.66, .66)	1
	≥Severe/3	10	0.24	5	0.12	1.99	(0.68, 5.8)	1.18	(-0.62, 3.0)	0.301
	Serious	12	0.28	5	0.12	2.39	(0.84, 6.8)	1.65	(-0.26, 3.6)	0.143
Acute coronary syndromes: Angina pectoris										
	All pooled	103	2.43	91	2.16	1.13	(0.85,1.5)	2.78	(-3.6, 9.16)	0.394
	Mild/1	40	0.95	33	0.78	1.21	(0.76, 1.9)	1.63	(-2.3, 5.58)	0.417
	Moderate/2	55	1.3	48	1.14	1.14	(0.78, 1.7)	1.62	(-3.05, 6.3)	0.496
	Severe/3	20	0.47	13	0.31	1.53	(0.76,3.1)	1.65	(-1.01, 4.3)	0.225
	Life-threatening/4	1	0.02	1	0.02	1	(0.06, 16)	-.0006	(-0.66, .66)	1
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	21	0.5	14	0.33	1.5	(0.76,2.9)	1.65	(-1.09,4.38)	0.239
	Serious	33	0.78	19	0.45	1.73	(0.99, 3.0)	3.30	(-0.035,6.6)	0.053

(Table A23 continued on the next page.)

Table A23 (continued from the previous page). Sponsor's Search Criteria With Placebo Controlled Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223) Pooled.

Acute coronary syndromes: Cardiac disorder										
	All pooled	0	0	5	0.12	0	N.A.	-1.18	(-2.2,-0.15)	0.031
	Mild/1	0	0	4	0.09	0	N.A.	-0.95	(-1.9,-.019)	0.062
	Moderate/2	0	0	1	0.02	0	N.A.	-0.24	(-0.70,0.23)	0.499
	Severe/3	0	0	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	0	0	_	N.A.	_	N.A.	.
Acute coronary syndromes: Myocardial ischaemia										
	All pooled	37	0.87	31	0.73	1.19	(0.74, 1.9)	1.40	(-2.41, 5.2)	0.472
	Mild/1	14	0.33	20	0.47	0.7	(0.35, 1.4)	-1.43	(-4.1, 1.3)	0.299
	Moderate/2	16	0.38	11	0.26	1.45	(0.67, 3.1)	1.17	(-1.23, 3.6)	0.339
	Severe/3	5	0.12	1	0.02	4.99	(0.58, 43)	0.945	(-0.19 , 2.1)	0.219
	Life-threatening/4	1	0.02	0	0	_	N.A.	0.236	(-0.23 , 0.7)	1
	Fatal/5	1	0.02	0	0	_	N.A.	0.236	(-0.23, 0.7)	1
	≥Severe/3	7	0.17	1	0.02	6.98	(0.86, 57)	1.42	(0.11, 2.7)	0.070
	Serious	12	0.28	5	0.12	2.39	(0.84, 6.8)	1.65	(-0.26, 3.6)	0.143
Arrhythmia Bradycardia										
	All pooled	19	0.45	12	0.28	1.58	(0.77, 3.3)	1.65	(-0.93,4.22)	0.210
	Mild/1	15	0.35	3	0.07	4.99	(1.4, 17.2)	2.83	(0.87, 4.80)	0.008
	Moderate/2	2	0.05	5	0.12	0.4	(0.08, 2.0)	-0.712	(-1.94,0.52)	0.288
	Severe/3	3	0.07	4	0.09	0.75	(0.17,3.3)	-0.239	(-1.47,0.99)	0.726
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	3	0.07	4	0.09	0.75	(0.17,3.3)	-0.239	(-1.47,0.99)	0.726
	Serious	4	0.09	3	0.07	1.33	(0.30,5.9)	0.234	(-0.99,1.46)	1
Arrhythmia Sick Sinus Syndrome										
	All pooled	11	0.26	4	0.09	2.74	(0.87, 8.6)	1.65	(-0.14, 3.4)	0.118
	Mild/1	1	0.02	1	0.02	1	(0.06, 16	-.0006	(-0.66,0.66)	1
	Moderate/2	7	0.17	1	0.02	6.98	(0.86, 57)	1.42	(0.11, 2.73)	0.070
	Severe/3	4	0.09	3	0.07	1.33	(0.30, 5.9)	0.234	(-0.99, 1.5)	1
	Life-threatening/4	1	0.02	0	0	_	N.A.	0.236	(-0.23,0.70)	1
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	5	0.12	3	0.07	1.66	(0.40, 7.0	0.471	(-0.84, 1.8)	0.726
	Serious	9	0.21	4	0.09	2.24	(0.69, 7.3	1.18	(-0.49, 2.9)	0.267

(Table A23 is continued on the next page.)

Table A23 (continued from the previous page). Sponsor's Search Criteria With Placebo Controlled Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223) Pooled.

Arrhythmia Supra-ventricular tachycardia										
	All pooled	9	0.21	9	0.21	1	(0.40, 2.5)	-.0055	(-2.0, 2.0)	1.0
	Mild/1	0	0	6	0.14	0	N.A.	-1.42	(-2.6,-0.29)	0.016
	Moderate/2	6	0.14	3	0.07	1.99	(0.50, 8.0	0.707	(-0.68, 2.1)	0.508
	Severe/3	3	0.07	2	0.05	1.5	(0.25, 9.0	0.235	(-0.8, 1.27)	1
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	3	0.07	2	0.05	1.5	(0.25, 9.0	0.235	(-0.80, 1.3)	1
	Serious	7	0.17	2	0.05	3.49	(0.73, 17	1.18	(-0.21, 2.6)	0.180
Arrhythmia Tachycardia										
	All pooled	40	0.95	25	0.59	1.6	(0.97,2.6)	3.53	(-0.19,7.25)	0.063
	Mild/1	26	0.61	18	0.43	1.44	(0.79,2.6)	1.88	(-1.19,4.95)	0.230
	Moderate/2	16	0.38	6	0.14	2.66	(1.04,6.8)	2.36	(0.19, 4.53)	0.033
	Severe/3	0	0	2	0.05	0	N.A.	-0.474	(-1.13,0.18)	0.249
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	2	0.05	0	N.A.	-0.474	(-1.13,0.18)	0.249
	Serious	1	0.02	1	0.02	1	(0.06, 16)	-.0006	(-0.66,0.66)	1
Congestive Heart Failure: Cardiac Failure Congestive										
	All pooled	16	0.38	23	0.54	0.69	(0.37, 1.3)	-1.67	(-4.6, 1.22)	0.258
	Mild/1	1	0.02	7	0.17	0.14	(0.02, 1.2)	-1.42	(-2.7,-0.11)	0.039
	Moderate/2	11	0.26	9	0.21	1.22	(0.51, 2.9)	0.47	(-1.6, 2.54)	0.659
	Severe/3	5	0.12	7	0.17	0.71	(0.23, 2.2)	-0.48	(-2.08,1.13)	0.580
	Life-threatening/4	0	0	1	0.02	0	N.A.	-0.24	(-0.70,0.23)	0.499
	Fatal/5	0	0	1	0.02	0	N.A.	-0.24	(-0.70,0.23)	0.499
	≥Severe/3	5	0.12	9	0.21	0.55	(0.19, 1.7)	-0.95	(-2.68,0.78)	0.301
	Serious	10	0.24	13	0.31	0.77	(0.34, 1.8)	-0.72	(-2.94,1.50)	0.527
Congestive Heart Failure: Rales										
	All pooled	8	0.19	2	0.05	3.99	(0.85, 19)	1.42	(-0.048,2.9)	0.109
	Mild/1	5	0.12	2	0.05	2.49	(0.48, 13)	0.71	(-0.52,1.93)	0.453
	Moderate/2	3	0.07	0	0	_	N.A.	0.71	(-0.093,1.5)	0.250
	Severe/3	0	0	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	0	0	_	N.A.	_	N.A.	.

(Table A23 is continued on the next page.)

Table A23 (continued from the previous page). Sponsor's Search Criteria With Placebo Controlled Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223) Pooled.

Adverse Event Grouping	Severity	Deno-sumab Subjects n	Deno-sumab Subjects N=4232 % (n/N)	Placebo Subjects n	Placebo Subjects N=4221 % (n/N)	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	P value
Other vascular disorders: All PTs										
	All pooled	180	4.25	166	3.93	1.08	(0.88,1.3)	3.21	(-5.24,11.7)	0.457
	Mild/1	72	1.7	78	1.85	0.92	(0.67,1.3)	-1.47	(-7.09,4.16)	0.610
	Moderate/2	76	1.8	70	1.66	1.08	(0.78, 1.5)	1.37	(-4.18,6.93)	0.628
	Severe/3	38	0.9	23	0.54	1.65	(0.98,2.8)	3.53	(-0.077,7.1)	0.055
	Life-threatening/4	7	0.17	6	0.14	1.16	(0.39,3.5)	0.233	(-1.44,1.90)	0.785
	Fatal/5	2	0.05	3	0.07	0.66	(0.11, 4.0)	-0.238	(-1.28,0.80)	0.687
	≥Severe/3	46	1.09	30	0.71	1.53	(0.97, 2.4)	3.76	(-0.26,7.78)	0.067
	Serious	50	1.18	38	0.9	1.31	(0.86, 2.0)	2.81	(-1.51,7.14)	0.203
Other vascular disorders: Aortic aneurysm										
	All pooled	6	0.14	9	0.21	0.66	(0.24, 1.9)	-0.714	(-2.51,1.08)	0.435
	Mild/1	1	0.02	1	0.02	1	(0.06, 16)	-.0006	(-0.66,0.66)	1
	Moderate/2	5	0.12	4	0.09	1.25	(0.34, 4.6)	0.234	(-1.2, 1.6)	1
	Severe/3	0	0	4	0.09	0	N.A.	-0.948	(-1.9,-.019)	0.062
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	4	0.09	0	N.A.	-0.948	(-1.9,-.019)	0.062
	Serious	1	0.02	5	0.12	0.2	(0.02, 1.7)	-0.948	(-2.1, 0.19)	0.124
Other vascular disorders: Aortic stenosis										
	All pooled	13	0.31	5	0.12	2.59	(0.93, 7.3)	1.89	(-0.077,3.9)	0.096
	Mild/1	8	0.19	4	0.09	1.99	(0.60, 6.6)	0.943	(-0.66, 2.6)	0.387
	Moderate/2	3	0.07	0	0	_	N.A.	0.709	(-0.093,1.5)	0.250
	Severe/3	2	0.05	1	0.02	1.99	(0.18, 22)	0.236	(-0.57,1.04)	1
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	2	0.05	1	0.02	1.99	(0.18, 22)	0.236	(-0.57,1.04)	1
	Serious	3	0.07	0	0	_	N.A.	0.709	(-0.093,1.5)	0.250

(Table A23 is continued on the next page.)

Table A23 (continued from the previous page). Sponsor's Search Criteria With Placebo Controlled Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223) Pooled.

Other vascular disorders: Skin ulcer										
	All pooled	34	0.8	28	0.66	1.21	(0.74,2.0)	1.40	(-2.24,5.04)	0.451
	Mild/1	15	0.35	16	0.38	0.94	(0.46, 1.9)	-0.246	(-2.82,2.33)	0.852
	Moderate/2	19	0.45	14	0.33	1.35	(0.68, 2.7)	1.17	(-1.49,3.83)	0.387
	Severe/3	5	0.12	1	0.02	4.99	(0.58, 43)	0.945	(-0.19,2.08)	0.219
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	5	0.12	1	0.02	4.99	(0.58, 43)	0.945	(-0.19,2.08)	0.219
	Serious	6	0.14	0	0	_	N.A.	1.42	(0.28, 2.55)	0.031
Stroke: Cerebral Thrombosis										
	All pooled	3	0.07	5	0.12	0.6	(0.14, 2.5)	-0.476	(-1.8, 0.84)	0.507
	Mild/1	1	0.02	0	0	_	N.A.	0.236	(-0.23,0.70)	1
	Moderate/2	0	0	4	0.09	0	N.A.	-0.948	(-1.9,-.019)	0.062
	Severe/3	2	0.05	1	0.02	1.99	(0.18, 22)	0.236	(-0.57,1.04)	1
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	2	0.05	1	0.02	1.99	(0.18, 22)	0.236	(-0.57,1.04)	1
	Serious	3	0.07	3	0.07	1	(0.20, 4.9)	-.0019	(-1.1, 1.1)	1

Table A24 shows the results of the analysis of all PMO studies pooled and analyzed according to the sponsor's grouping of MedDRA terms

Severe acute coronary syndromes was associated with a relative risk of 1.5 (p=0.04), however, there was no consistent trend with respect to relative risk estimates for the remaining severity levels. Mild bradycardia was associated with a relative risk of 4.16 (p=0.02), but there was no consistent trend with regard to relative risk estimates for the remaining severity levels. Risk difference for serious skin ulcers was 1.18 (p=0.035). Serious skin ulcers were associated with a relative risk of 4.16 (p=0.231), but the associated p-value was not less than 0.10.

Table A24. Sponsor's Search Criteria With All Controlled PMO Studies (20050216, 20040132 24 month, 20050172, 20050179, 20010223, 20050234, 20050141) Pooled.

Adverse Event Grouping	Severity	Denosumab Subjects n	Denosumab Subjects N=5451 % (n/N)	Placebo Subjects n	Placebo Subjects N=4224 % (n/N)	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	P value
Acute coronary syndromes: All PTs										
	All pooled	254	5	219	5.19	0.96	(0.81, 1.15)	-1.86	(-10.8, 7.12)	0.684
	Mild/1	91	1.79	90	2.13	0.84	(0.63, 1.12)	-3.40	(-9.09, 2.28)	0.237
	Moderate/2	111	2.19	91	2.16	1.01	(0.77, 1.33)	0.30	(-5.65, 6.25)	0.921
	Severe/3	75	1.48	42	1	1.48	(1.02, 2.16)	4.82	(0.35, 9.29)	0.038
	Life-threatening/4	12	0.24	8	0.19	1.25	(0.51, 3.05)	0.468	(-1.40, 2.34)	0.628
	Fatal/5	11	0.22	13	0.31	0.7	(0.32, 1.57)	-0.914	(-3.02, 1.19)	0.387
	≥Severe/3	93	1.83	61	1.45	1.27	(0.92, 1.75)	3.86	(-1.29, 9.02)	0.146
	Serious	115	2.26	85	2.01	1.12	(0.85, 1.48)	2.51	(-3.38, 8.40)	0.406
Acute coronary syndromes: Cardiac Disorder										
	All pooled	0	0	5	0.12	0	N.A.	-1.18	(-2.2,-0.15)	0.019
	Mild/1	0	0	4	0.09	0	N.A.	-0.95	(-1.9,-.019)	0.042
	Moderate/2	0	0	1	0.02	0	N.A.	-0.24	(-0.70,0.23)	0.454
	Severe/3	0	0	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	0	0	_	N.A.	_	N.A.	.
Acute coronary syndromes: Myocardial ischaemia										
	All pooled	37	0.73	31	0.73	0.99	(0.62, 1.6)	-0.058	(-3.5, 3.42)	0.974
	Mild/1	14	0.28	20	0.47	0.58	(0.29, 1.2)	-1.98	(-4.5, 0.54)	0.115
	Moderate/2	16	0.32	11	0.26	1.21	(0.56, 2.6)	0.55	(-1.6, 2.72)	0.627
	Severe/3	5	0.1	1	0.02	4.16	(0.49, 36)	0.75	(-0.23, 1.7)	0.231
	Life-threatening/4	1	0.02	0	0	_	N.A.	0.20	(-0.19,0.58)	1
	Fatal/5	1	0.02	0	0	_	N.A.	0.20	(-0.19,0.58)	1
	≥Severe/3	7	0.14	1	0.02	5.82	(0.72, 47)	1.14	(0.02, 2.3)	0.078
	Serious	12	0.24	5	0.12	1.99	(0.70, 5.7)	1.18	(-0.05, 2.9)	0.227
Arrhythmia: Bradycardia										
	All pooled	19	0.37	12	0.28	1.32	(0.64, 2.7)	0.899	(-1.43,3.22)	0.454
	Mild/1	15	0.3	3	0.07	4.16	(1.2, 14.4)	2.24	(0.55, 3.94)	0.016
	Moderate/2	2	0.04	5	0.12	0.33	(0.06, 1.7)	-0.791	(-2.0, 0.38)	0.257
	Severe/3	3	0.06	4	0.09	0.62	(0.14, 2.8)	-0.357	(-1.5, 0.79)	0.709
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	3	0.06	4	0.09	0.62	(0.14, 2.8)	-0.357	(-1.5, 0.79)	0.709
	Serious	4	0.08	3	0.07	1.11	(0.25, 5.0)	0.077	(-1.0, 1.2)	1

(Table A24 continued on the next page.)

Table A24 (continued from the previous page). Sponsor's Search Criteria With All Controlled PMO Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223, 20050234, 20050141) Pooled.

Arrhythmia: Extrasystoles										
	All pooled	21	0.41	29	0.69	0.6	(0.34, 1.1)	-2.73	(-5.8, 0.32)	0.073
	Mild/1	17	0.33	20	0.47	0.71	(0.37, 1.4)	-1.39	(-4.0, 1.22)	0.289
	Moderate/2	4	0.08	10	0.24	0.33	(0.10, 1.1)	-1.58	(-3.2, .076)	0.061
	Severe/3	0	0	1	0.02	0	N.A.	-0.237	(-.07, 0.23)	0.454
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	1	0.02	0	N.A.	-0.237	(-0.70,0.23)	0.454
	Serious	0	0	0	0	_	N.A.	_	N.A.	.
Arrhythmia: Sick Sinus Syndrome										
	All pooled	12	0.24	4	0.09	2.49	(0.80, 7.7)	1.42	(-0.21, 3.0)	0.132
	Mild/1	1	0.02	1	0.02	0.83	(0.05, 13)	-0.040	(-0.64,0.56)	1
	Moderate/2	7	0.14	1	0.02	5.82	(0.72, 47)	1.14	(0.02, 2.3)	0.080
	Severe/3	5	0.1	3	0.07	1.39	(0.33, 5.8)	0.274	(-0.91, 1.5)	0.736
	Life-threatening/4	1	0.02	0	0	_	N.A.	0.197	(-0.19,0.58)	1
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	6	0.12	3	0.07	1.66	(0.42, 6.6)	0.471	(-0.77, 1.7)	0.524
	Serious	10	0.2	4	0.09	2.08	(0.65, 6.6)	1.02	(-0.51 2.55)	0.285
Arrhythmia: Sinus Bradycardia										
	All pooled	5	0.1	6	0.14	0.69	(0.21, 2.3)	-0.437	(-1.9 , 0.99)	0.561
	Mild/1	2	0.04	2	0.05	0.83	(0.12, 5.9)	-0.080	(-0.93,0.77)	1
	Moderate/2	3	0.06	2	0.05	1.25	(0.21, 7.5)	0.12	(-0.82 , 1.1)	1
	Severe/3	0	0	2	0.05	0	N.A.	-0.474	(-1.1, 0.18)	0.206
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	2	0.05	0	N.A.	-0.474	(-1.1, 0.18)	0.206
	Serious	0	0	3	0.07	0	N.A.	-0.711	(-1.5, .093)	0.094
Arrhythmia: Sinus Tachycardia										
	All pooled	1	0.02	5	0.12	0.17	(0.02, 1.4)	-0.988	(-2.1, 0.12)	0.098
	Mild/1	1	0.02	4	0.09	0.21	(0.02, 1.9)	-0.751	(-1.8, 0.26)	0.184
	Moderate/2	0	0	1	0.02	0	N.A.	-0.237	(-0.70,0.23)	0.454
	Severe/3	0	0	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	0	0	_	N.A.	_	N.A.	.
Arrhythmia: Supra-ventricular Tachycardia										
	All pooled	9	0.18	9	0.21	0.83	(0.33, 2.1)	-0.360	(-2.17,1.45)	0.694
	Mild/1	0	0	6	0.14	0	N.A.	-1.42	(-2.6,-0.29)	0.009
	Moderate/2	6	0.12	3	0.07	1.66	(0.42, 6.6)	0.471	(-0.77, 1.7)	0.524
	Severe/3	3	0.06	2	0.05	1.25	(0.21, 7.5)	0.117	(-0.82, 1.1)	1
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	3	0.06	2	0.05	1.25	(0.21, 7.5)	0.117	(-0.82, 1.1)	1
	Serious	7	0.14	2	0.05	2.91	(0.60, 14)	0.905	(-0.31, 2.1)	0.196

(Table A24 continued on the next page.)

Table A24 (continued from the previous page). Sponsor's Search Criteria With All Controlled PMO Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223, 20050234, 20050141) Pooled.

Arrhythmia: Tachy-arrhythmia										
	All pooled	1	0.02	3	0.07	0.28	(0.03, 2.7)	-0.514	(-1.41,0.38)	0.336
	Mild/1	1	0.02	0	0	_	N.A.	0.197	(-0.19,0.58)	1
	Moderate/2	0	0	1	0.02	0	N.A.	-0.237	(-0.70,0.23)	0.454
	Severe/3	0	0	1	0.02	0	N.A.	-0.237	(-0.70,0.23)	0.454
	Life-threatening/4	0	0	1	0.02	0	N.A.	-0.237	(-0.70,0.23)	0.454
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	2	0.05	0	N.A.	-0.474	(-1.1, 0.18)	0.206
	Serious	0	0	3	0.07	0	N.A.	-0.711	(-1.5, .093)	0.094
Arrhythmia: Tachycardia										
	All pooled	42	0.83	25	0.59	1.4	(0.85, 2.3)	2.35	(-1.1, 5.8)	0.183
	Mild/1	27	0.53	18	0.43	1.25	(0.69, 2.3)	1.05	(-1.8, 3.9)	0.467
	Moderate/2	17	0.33	6	0.14	2.36	(0.93, 6.0)	1.93	(-.027, 3.9)	0.063
	Severe/3	0	0	2	0.05	0	N.A.	-0.474	(-1.1, 0.18)	0.206
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	2	0.05	0	N.A.	-0.474	(-1.1, 0.18)	0.206
	Serious	1	0.02	1	0.02	0.83	(0.05, 13)	-0.040	(-0.64,0.56)	1
Congestive Heart Failure: Cardiac Failure										
	All pooled	53	1.04	38	0.9	1.16	(0.77, 1.8)	1.43	(-2.6, 5.4)	0.484
	Mild/1	16	0.32	11	0.26	1.21	(0.56, 2.6)	0.545	(-1.6, 2.7)	0.627
	Moderate/2	27	0.53	17	0.4	1.32	(0.72, 2.4)	1.29	(-1.5, 4.1)	0.367
	Severe/3	11	0.22	7	0.17	1.31	(0.51, 3.4)	0.508	(-1.3, 2.3)	0.579
	Life-threatening/4	0	0	1	0.02	0	N.A.	-0.237	(-0.70,0.23)	0.454
	Fatal/5	1	0.02	5	0.12	0.17	(0.02, 1.4)	-0.988	(-2.1, 0.12)	0.098
	≥Severe/3	12	0.24	13	0.31	0.77	(0.35, 1.7)	-0.717	(-2.9, 1.4)	0.506
	Serious	16	0.32	15	0.36	0.89	(0.44, 1.8)	-0.403	(-2.8, 2.0)	0.737
Congestive Heart Failure: Cardiac Failure Chronic										
	All pooled	5	0.1	8	0.19	0.52	(0.17, 1.6)	-0.911	(-2.5, 0.66)	0.274
	Mild/1	2	0.04	3	0.07	0.55	(0.09, 3.3)	-0.317	(-1.3, 0.66)	0.664
	Moderate/2	3	0.06	4	0.09	0.62	(0.14, 2.8)	-0.357	(-1.5, 0.79)	0.709
	Severe/3	1	0.02	1	0.02	0.83	(0.05, 13)	-0.040	(-0.64,0.56)	1
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	1	0.02	1	0.02	0.83	(0.05, 13)	-0.040	(-0.64,0.56)	1
	Serious	1	0.02	5	0.12	0.17	(0.02, 1.4)	-0.988	(-2.1 , 0.12)	0.098

(Table A24 continued on the next page.)

Table A24 (continued from the previous page). Sponsor's Search Criteria With All Controlled PMO Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223, 20050234, 20050141) Pooled.

Congestive Heart Failure: Cardiac Failure Congestive										
	All pooled	16	0.32	23	0.54	0.58	(0.31, 1.1)	-2.30	(-5.0, 0.41)	0.088
	Mild/1	1	0.02	7	0.17	0.12	(0.01, 1.0)	-1.46	(-2.8,-0.18)	0.027
	Moderate/2	11	0.22	9	0.21	1.02	(0.42, 2.5)	0.0340	(-1.9, 1.9)	0.972
	Severe/3	5	0.1	7	0.17	0.59	(0.19, 1.9)	-0.674	(-2.2, 0.83)	0.398
	Life-threatening/4	0	0	1	0.02	0	N.A.	-0.237	(-0.70, .23)	0.454
	Fatal/5	0	0	1	0.02	0	N.A.	-0.237	(-0.70, .23)	0.454
	≥Severe/3	5	0.1	9	0.21	0.46	(0.15, 1.4)	-1.15	(-2.8, 0.49)	0.184
	Serious	10	0.2	13	0.31	0.64	(0.28, 1.5)	-1.11	(-3.2, 0.96)	0.283
Congestive Heart Failure: Dyspnoea										
	All pooled	101	1.99	106	2.51	0.79	(0.60, 1.0)	-5.22	(-11.3,0.86)	0.089
	Mild/1	53	1.04	46	1.09	0.96	(0.65, 1.4)	-0.461	(-4.7, 3.7)	0.829
	Moderate/2	48	0.95	58	1.37	0.69	(0.47, 1.0)	-4.29	(-8.7, 0.12)	0.052
	Severe/3	9	0.18	6	0.14	1.25	(0.44, 3.5)	0.351	(-1.3, 2.0)	0.675
	Life-threatening/4	2	0.04	0	0	_	N.A.	0.394	(-0.15, .94)	0.504
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	11	0.22	6	0.14	1.52	(0.56, 4.1)	0.745	(-0.97 , 2.5)	0.403
	Serious	11	0.22	8	0.19	1.14	(0.46, 2.8)	0.271	(-1.6, 2.1)	0.773
Other vascular disorders: Aortic Aneurysm										
	All pooled	6	0.12	9	0.21	0.55	(0.20, 1.6)	-0.951	(-2.6, 0.73)	0.255
	Mild/1	1	0.02	1	0.02	0.83	(0.05, 13)	-0.040	(-0.64, .56)	1
	Moderate/2	5	0.1	4	0.09	1.04	(0.28, 3.9)	0.037	(-1.2, 1.3)	1
	Severe/3	0	0	4	0.09	0	N.A.	-0.948	(-1.9,-.019)	0.042
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	4	0.09	0	N.A.	-0.948	(-1.9,-.019)	0.042
	Serious	1	0.02	5	0.12	0.17	(0.02, 1.4)	-0.988	(-2.1, 0.12)	0.098
Other vascular disorders: Skin ulcer										
	All pooled	34	0.67	28	0.66	1.01	(0.61, 1.66)	0.0621	(-3.26, 3.38)	0.971
	Mild/1	15	0.3	16	0.38	0.78	(0.39, 1.57)	-0.837	(-3.22, 1.54)	0.486
	Moderate/2	19	0.37	14	0.33	1.13	(0.57, 2.25)	0.425	(-1.99, 2.84)	0.732
	Severe/3	5	0.1	1	0.02	4.16	(0.49, 35.6)	0.748	(-0.23, 1.73)	0.231
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	5	0.1	1	0.02	4.16	(0.49, 35.6)	0.748	(-0.23, 1.73)	0.231
	Serious	6	0.12	0	0	_	N.A.	1.18	(0.237, 2.13)	0.035

(Table A24 continued on the next page.)

Table A24 (continued from previous page). Sponsor's Search Criteria With All Controlled PMO Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223, 20050234, 20050141) Pooled.

Other vascular disorders: Vascular Pseudo-aneurysm										
	All pooled	0	0	3	0.07	0	N.A.	-0.711	(-1.5, .093)	0.094
	Mild/1	0	0	0	0	_	N.A.	_	N.A.	.
	Moderate/2	0	0	2	0.05	0	N.A.	-0.474	(-1.1, 0.18)	0.206
	Severe/3	0	0	1	0.02	0	N.A.	-0.237	(-0.70,0.23)	0.454
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	1	0.02	0	N.A.	-0.237	(-0.70,0.23)	0.454
	Serious	0	0	2	0.05	0	N.A.	-0.474	(-1.1, 0.18)	0.206
Stroke: Cerebral Thrombosis										
	All pooled	3	0.06	5	0.12	0.5	(0.12, 2.1)	-0.594	(-1.8, 0.64)	0.481
	Mild/1	1	0.02	0	0	_	N.A.	0.197	(-0.19, .58)	1
	Moderate/2	0	0	4	0.09	0	N.A.	-0.948	(-1.9,-.019)	0.042
	Severe/3	2	0.04	1	0.02	1.66	(0.15, 18)	0.157	(-0.56,0.87)	1
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	2	0.04	1	0.02	1.66	(0.15, 18)	0.157	(-0.56,0.87)	1
	Serious	3	0.06	3	0.07	0.83	(0.17, 4.1)	-0.120	(-1.2, 0.93)	1
Stroke: Vertebro-basilar insufficiency										
	All pooled	11	0.22	12	0.28	0.76	(0.34, 1.7)	-0.677	(-2.7, 1.4)	0.513
	Mild/1	6	0.12	6	0.14	0.83	(0.27, 2.6)	-0.240	(-1.7, 1.2)	0.748
	Moderate/2	4	0.08	7	0.17	0.47	(0.14, 1.6)	-0.871	(-2.3, 0.58)	0.243
	Severe/3	1	0.02	2	0.05	0.42	(0.04, 4.6)	-0.277	(-1.0, 0.49)	0.594
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	1	0.02	2	0.05	0.42	(0.04, 4.6)	-0.277	(-1.0, 0.49)	0.594
	Serious	3	0.06	8	0.19	0.31	(0.08, 1.2)	-1.30	(-2.8, 0.17)	0.077

Table A25 shows the events in Study 20030216 with whose relative risk estimate is associated with a p-value less than 0.10 when analyzed using the sponsor's grouping of preferred terms.

Table A25. Events in Study 20030216 with Relative Risk Estimates Associated with a P-value Less Than 0.10: Analyzed Using the Sponsor's Grouping of Preferred Terms. Note that in instances in which relative risk cannot be computed due to entries of zero, the number of subjects with the event are reported instead of RR.

Events with Relative Risk Having p<0.10	Severity	Risk*	p-value
Acute coronary syndromes: All PTs	Severe	1.9	0.001
	≥Severe	1.5	0.01
Acute coronary syndromes: Acute myocardial infarction	Severe	4.5	0.065
Acute coronary syndromes: Angina pectoris	Severe	1.8	0.107
	Serious	1.8	0.036
Acute coronary syndromes: Cardiac disorder**	All	0 DEN 5 PLA	0.031
	Mild	0 DEN 4 PLA	0.062
Acute coronary syndromes: Myocardial Ischaemia	≥Severe	7.0	0.0702
Arrhythmia: Bradycardia	Mild	4.7	0.013
Arrhythmia: Sick Sinus Syndrome	Moderate	7.0	0.070
Arrhythmia: Sinus tachycardia**	All pooled	0 DEN 5 PLA	0.031
	Mild	0 DEN 4 PLA	0.062
Arrhythmia: Supraventricular tachycardia**	Mild	0 DEN 6 PLA	0.016
Arrhythmia: Tachycardia	All pooled	1.6	0.076
	Moderate	2.5	0.050
Congestive Heart Failure: Cardiac Failure Congestive	Mild	0.14	0.039
Congestive Heart Failure: Oedema**	Mild	0 DEN 4 PLA	0.062
Congestive Heart Failure: Oedema Peripheral	All pooled	1.22	0.064
Other vascular disorders: All PTs	Severe	1.7	0.055
	≥Severe	1.5	0.067
Other vascular disorder: Aortic Aneurysm**	Severe	0 DEN 4 PLA	0.062
	≥Severe	0 DEN 4 PLA	0.062
Other vascular disorder: Aortic stenosis	All pooled	2.6	0.096
Other vascular disorders: Skin ulcer**	Serious	6 DEN 0 PLA	0.031
Stroke: Cerebral Thrombosis**	Moderate	0 DEN 4 PLA	0.052

*Relative Risk estimates are reported, unless otherwise noted.
**Relative risk cannot be computed due to entries of zero, therefore the number of subjects with the event are reported instead of RR.
All = All severity levels pooled, DEN = Denosumab, LT = Life-threatening severity, PLA = Placebo

Table A26 shows the events in individual studies whose relative risk estimate is associated with a p-value less than 0.10 when analyzed using the sponsor's grouping of preferred terms.

Table A26. Events with Relative Risk Estimates Associated with a P-value Less Than 0.10: Analyzed Using the Sponsor's Grouping of Preferred Terms. Note that in instances in which relative risk cannot be computed due to entries of zero, the number of subjects with the event are reported instead of RR.

Study	Events with Relative Risk Having p<0.10	Severity	Risk*	p-value
20040138	Acute Coronary Syndromes: Angina Pectoris	All pooled	2.1	0.073
20040138	Acute Coronary Syndromes: Chest Pain**	Serious	0 DEN 4 PLA	0.061
20040138	Acute Coronary Syndromes: Coronary Artery Disease	Moderate	0.28	0.107
20040138	Acute Coronary Syndromes: Myocardial Ischaemia**	Serious	0 DEN 6 PLA	0.015
20040138	Arrhythmia: All PTs	Severe	1.5	0.056
20040138	Congestive heart failure: All PTs	Mild	4.4	0.013
		Moderate	7.9	0.001
20040138	Congestive heart failure: Oedema peripheral	Mild	3.3	0.044
		Moderate	3.2	0.021
20040138	Congestive Heart Failure: Pulmonary Oedema**	All	0 DEN 4 PLA	0.0612
		≥Severe	0 DEN 4 PLA	0.0612
20040138	Other vascular disorders: All PTs**	LT	8 DEN 0 PLA	0.008
20040138	Stroke: All PTs	LT	0.17	0.069
20050141	Acute Coronary Syndromes: All PTs	All	0.49	0.093
		Moderate	0.25	0.063
20050141	Acute Coronary Syndromes: Chest Pain	All	0.2	0.021
		Moderate	0.16	0.068

*Relative Risk estimates are reported, unless otherwise noted.
**Relative risk cannot be computed due to entries of zero, therefore the number of subjects with the event are reported instead of RR.
All = All severity levels pooled
DEN = Denosumab
LT = Life-threatening severity
PLA = Placebo

Table A27 shows the events in the pooled large, pivotal studies dataset whose relative risk estimate is associated with a p-value less than 0.10 when analyzed using the sponsor's grouping of preferred terms.

Table A27. Events in the Pooled Large, pivotal Dataset with Relative Risk Estimates Associated with a P-value Less Than 0.10: Analyzed Using the Sponsor's Grouping of Preferred Terms. Note that in instances in which relative risk cannot be computed due to entries of zero, the number of subjects with the event are reported instead of RR.

Events with Relative Risk Having p<0.10	Severity	Risk*	p-value
Acute coronary syndromes: All PTs	Severe	1.6	0.004
	≥ Severe	1.3	0.074
Acute coronary syndromes: Acute coronary syndrome**	Severe	6 DEN 0 PLA	0.031
Acute Coronary Syndromes: Angina Pectoris	Severe	1.9	0.064
	≥ Severe	1.8	0.079
	Serious	1.7	0.052
Acute Coronary Syndromes: Cardiac Disorder**	All	0.17	0.070
	Mild	0 DEN 4 PLA	0.062
Acute Coronary Syndromes: Coronary Artery Stenosis**	Serious	5 DEN 0 PLA	0.062
Arrhythmia: Bradycardia	Mild	5.0	0.0075
Arrhythmia: Sick sinus syndrome	All	3.2	0.026
	Moderate	4.5	0.065
	Serious	2.8	0.063
Arrhythmia: Sinus tachycardia**	All	0 DEN 5 PLA	0.031
	Mild	0 DEN 4 PLA	0.062
Arrhythmia: Supraventricular tachycardia**	Mild	0 DEN 6 PLA	0.015
Arrhythmia: Syncope	Moderate	0.67	0.108
Arrhythmia: Tachycardia	Moderate	2.1	0.089
Congestive Heart Failure: All PTs	Mild	1.2	0.088
	LT	0.47	0.086
Congestive Heart Failure: Cardiac Failure	All	1.4	0.073
Congestive Heart Failure: Cardiac Failure Congestive**	LT	0 DEN 4 PLA	0.062
Congestive Heart Failure: Cardiomegaly	All	0.25	0.0648
Congestive Heart Failure: Dyspnoea	Moderate	0.76	0.100
Congestive Heart Failure: Oedema	All	0.46	0.106
Congestive Heart Failure: Oedema Peripheral	All	1.2	0.063
	Mild	1.2	0.060
Other vascular disorders: All PTs	Severe	1.5	0.086
	LT	2.5	0.050
	≥Severe	1.5	0.043
	Serious	1.4	0.086
Other vascular disorders: Aortic aneurysm	Severe	0.17	0.070
Other vascular disorders: Skin ulcer**	Serious	6 DEN 0 PLA	0.031
Other vascular disorders: Thrombophlebitis	Moderate	0.33	0.092
Stroke: Cerebral Thrombosis**	Moderate	0 DEN 4 PLA	0.062

*Relative Risk estimates are reported, unless otherwise noted.
**Relative risk cannot be computed due to entries of zero, therefore the number of subjects with the event are reported instead of RR.
All = All severity levels pooled, DEN = Denosumab, LT = Life-threatening severity, PLA = Placebo

Table A28 shows the events in the pooled placebo-controlled studies dataset whose relative risk estimate is associated with a p-value less than 0.10 when analyzed using the sponsor's grouping of preferred terms.

Table A28. Events in the Pooled Placebo-Controlled PMO Dataset with Relative Risk Estimates Associated with a P-value Less Than 0.10: Analyzed Using the Sponsor's Grouping of Preferred Terms. Note that in instances in which relative risk cannot be computed due to entries of zero, the number of subjects with the event are reported instead of RR.

Events with Relative Risk Having p<0.10	Severity	Risk*	p-value
Acute coronary syndromes: All PTs	Severe	1.8	0.003
	≥Severe	1.3	0.054
Acute coronary syndromes: Acute myocardial infarction	Severe	4.5	0.065
Acute coronary syndromes: Angina pectoris	Serious	1.7	0.053
Acute coronary syndromes: Cardiac disorder**	All	0 DEN 5 PLA	0.031
	Mild	0 DEN 4 PLA	0.062
Acute coronary syndromes: Myocardial ischaemia	≥Severe	7.0	0.070
Arrhythmia: Bradycardia	Mild	5.0	0.008
Arrhythmia: Sick Sinus Syndrome	Moderate	7.0	0.070
Arrhythmia: Supraventricular tachycardia**	Mild	0 DEN 6 PLA	0.016
Arrhythmia: Tachycardia	All	1.6	0.063
	Moderate	2.7	0.033
Congestive Heart Failure: Cardiac Failure Congestive	Mild	0.14	0.039
Congestive Heart Failure: Rales	All	4.0	0.109
Other vascular disorders: All PTs	Severe	1.7	0.055
	≥Severe	1.5	0.067
Other vascular disorders: Aortic aneurysm**	Severe	0 DEN 4 PLA	0.062
	≥Severe	0 DEN 4 PLA	0.062
Other vascular disorders: Aortic stenosis	All	2.6	0.096
Other vascular disorders: Skin ulcer**	Serious	6 DEN 0 PLA	0.031
Stroke: Cerebral Thrombosis**	Moderate	0 DEN 4 PLA	0.062

*Relative Risk estimates are reported, unless otherwise noted.
**Relative risk cannot be computed due to entries of zero, therefore the number of subjects with the event are reported instead of RR.
All = All severity levels pooled
DEN = Denosumab
LT = Life-threatening severity
PLA = Placebo

Table A29 shows the events in the pooled placebo- or active- controlled PMO studies dataset whose relative risk estimate is associated with a p-value less than 0.10 when analyzed using the sponsor's grouping of preferred terms.

Table A29. Events in the Pooled Any-Controlled PMO Dataset with Relative Risk Estimates Associated with a P-value Less Than 0.10: Analyzed Using the Sponsor's Grouping of Preferred Terms. Note that in instances in which relative risk cannot be computed due to entries of zero, the number of subjects with the event are reported instead of RR.

Events with Relative Risk Having p<0.10	Severity	Risk*	p-value
Acute coronary syndromes: All PTs	Severe	1.5	0.038
Acute coronary syndromes: Cardiac Disorder**	All	0 DEN 5 PLA	0.019
	Mild	0 DEN 4 PLA	0.042
Acute coronary syndromes: Myocardial ischaemia	≥Severe	5.8	0.078
Arrhythmia: Bradycardia	Mild	4.2	0.016
Arrhythmia: Extrasystoles	All	0.6	0.073
	Moderate	0.33	0.061
Arrhythmia: Sick Sinus Syndrome	Moderate	5.8	0.080
Arrhythmia: Sinus Bradycardia**	Serious	0 DEN 3 PLA	0.094
Arrhythmia: Sinus Tachycardia	All	0.17	0.098
Arrhythmia: Supraventricular Tachycardia**	Mild	0 DEN 6 PLA	0.009
Arrhythmia: Tachyarrhythmia**	Serious	0 DEN 3 PLA	0.094
Arrhythmia: Tachycardia	Moderate	2.4	0.063
Congestive Heart Failure: Cardiac Failure	Fatal	0.17	0.098
Congestive Heart Failure: Cardiac Failure Chronic	Serious	0.17	0.098
Congestive Heart Failure: Cardiac Failure Congestive	All	0.58	0.088
	Mild	0.12	0.027
Congestive Heart Failure: Dyspnoea	All	0.79	0.089
	Moderate	0.69	0.052
Other vascular disorders: Aortic Aneurysm**	Severe	0 DEN 4 PLA	0.042
	≥Severe	0 DEN 4 PLA	0.042
	Serious	0.17	0.098
Other vascular disorders: Skin ulcer**	Serious	6 DEN 0 PLA	0.035
Other vascular disorders: Vascular Pseudo-aneurysm**	All	0 DEN 3 PLA	0.094
Stroke: Cerebral Thrombosis**	Moderate	0 DEN 4 PLA	0.042
Stroke: Vertebrobasilar insufficiency	Serious	0.42	0.077

*Relative Risk estimates are reported, unless otherwise noted.
**Relative risk cannot be computed due to entries of zero, therefore the number of subjects with the event are reported instead of RR.
All = All severity levels pooled
DEN = Denosumab
LT = Life-threatening severity
PLA = Placebo

Table A30 shows the serious, life-threatening and fatal events whose relative risk estimate is associated with a p-value less than 0.10 using broad SMQ criteria.

Table A30. Events Recorded as Serious, Life-Threatening or Fatal Having a Relative Risk Associated with a P-value of Less Than 0.10: Broad SMQ Criteria.

Analysis	Events with Relative Risk Having p<0.10	Severity	Risk*	p-value
Study 20030216	Arrhythmia Related Investigations	Fatal	0.3	0.057
Study 20030216	Bradyarrhythmias	Serious	1.9	0.095
Study 20030216	Cardiac Arrhythmias	Fatal	0.3	0.057
Study 20030216	Cardiomyopathy	Fatal	0.36	0.076
Study 20030216	Gastrointestinal Perforation, Ulceration, etc.	Serious	1.4	0.103
Study 20030216	Ischaemic Heart Disease	Serious	1.4	0.021
Study 20030216	Thrombophlebitis	Serious	2.3	0.074
Study 20030216	Torsade de Pointes/QT Prolongation	Fatal	0.3	0.057
Study 20040138	Cardiac Failure	LT	0.17	0.069
Study 20040138	Gastrointestinal Perforation, ulceration, etc.	Serious	0.47	0.054
Study 20040138	Pulmonary Hypertension	Serious	3.3	0.091
Pool large, pivotal studies	Bradyarrhythmia	Serious	1.9	0.059
Pool large, pivotal studies	Cardiac Failure	LT	0.36	0.076
Pool large, pivotal studies	Embolic and Thrombotic Events, Arterial	LT	0.5	0.054
Pool large, pivotal studies	Pulmonary Hypertension	Serious	2.0	0.046
Pool large, pivotal studies	Thrombophlebitis	Serious	2.0	0.069
Pool placebo-controlled	Arrhythmia related investigations	Fatal	0.3	0.057
Pool placebo-controlled	Bradyarrhythmia	Serious	1.9	0.096
Pool placebo-controlled	Cardiac arrhythmias	Fatal	0.3	0.057
Pool placebo-controlled	Cardiomyopathy	Fatal	0.36	0.076
Pool placebo-controlled	Gastrointestinal Perforation, Ulceration, etc.	Serious	1.4	0.103
Pool placebo-controlled	Ischaemic Heart Disease	Serious	1.4	0.027
Pool placebo-controlled	Thrombophlebitis	Serious	2.3	0.074
Pool placebo-controlled	Torsade de Pointes / QT Prolongation	Fatal	0.3	0.057
Pool any controlled	Arrhythmia related investigations	Fatal	0.33	0.061
Pool any controlled	Cardiac arrhythmias	Fatal	0.33	0.061
Pool any controlled	Cardiomyopathy	Fatal	0.3	0.037
Pool any controlled	Embolic and Thrombotic Events, Arterial	LT	0.33	0.061
Pool any controlled	Torsade de Pointes / QT Prolongation	Fatal	0.33	0.061

*Relative Risk estimates are reported, unless otherwise noted.
LT = Life-threatening

In each of the following studies, no cardiovascular adverse event was associated with a relative risk having a p-value less than 0.05: Study 20010223 (smallest p-value: 0.1278), Study 20040132 (smallest p-value: 0.1421), Study 20040135 (smallest p-value: 0.248), Study 20050141 (smallest p-value: 0.0846), Study 20050172 (smallest p-value: 0.243), Study 20050179 (smallest p-value: 0.2102), Study 20050234 (smallest p-value: 0.23).

Table A31 shows the serious, life-threatening and fatal events whose relative risk estimate is associated with a p-value less than 0.10 using narrow SMQ criteria.

Table A31. Events Recorded as Serious, Life-Threatening or Fatal Having a Relative Risk Associated with a P-value of Less Than 0.10: Narrow SMQ Criteria. Note that in instances in which relative risk cannot be computed due to entries of zero, the number of subjects with the event are reported instead of RR.

Analysis	Events with Relative Risk Having p<0.10	Severity	Risk*	p-value
Study 20030216	Ischaemic Heart Disease	Serious	1.4	0.021
Study 20040138	Cardiac Failure	LT	0.17	0.069
Study 20040138	Toxic-septic shock conditions**	Serious	0 DEN 4 PLA	0.061
Pool large, pivotal studies	Cardiac Failure	LT	0.36	0.076
Pool large, pivotal studies	Embolic and Thrombotic Events, Arterial	LT	0.5	0.054
Pool placebo-controlled	Ischaemic Heart Disease	Serious	1.4	0.027
Pool any controlled	Embolic and Thrombotic Events, Arterial	LT	0.33	0.061

*Relative Risk estimates are reported, unless otherwise noted.
**Relative risk cannot be computed due to entries of zero, therefore the number of subjects with the event are reported instead of RR.
DEN = Denosumab
LT = Life-threatening
PLA = Placebo

Table A32 shows the serious, life-threatening and fatal events whose relative risk estimate is associated with a p-value less than 0.10 using the Sponsor's preferred term grouping.

Table A32. Events Recorded as Serious, Life-Threatening or Fatal Having a Relative Risk Associated with a P-value of Less Than 0.10: Sponsor's Preferred Term Grouping. Note that in instances in which relative risk cannot be computed due to entries of zero, the number of subjects with the event are reported instead of RR.

Analysis	Events with Relative Risk Having p<0.10	Severity	Risk*	p-value
Study 20030216	Acute coronary syndromes: Angina pectoris	Serious	1.8	0.036
Study 20030216	Other vascular disorders: Skin ulcer**	Serious	6 DEN 0 PLA	0.031
Study 20040138	Acute Coronary Syndromes: Chest Pain**	Serious	0 DEN 4 PLA	0.061
Study 20040138	Acute Coronary Syndromes: Myocardial Ischaemia**	Serious	0 DEN 6 PLA	0.015
Study 20040138	Other vascular disorders: All PTs**	LT	8 DEN 0 PLA	0.008
Study 20040138	Stroke: All PTs	LT	0.17	0.069
Pool large, pivotal studies	Acute Coronary Syndromes: Angina Pectoris	Serious	1.7	0.052
Pool large, pivotal studies	Acute Coronary Syndromes: Coronary Artery Stenosis**	Serious	5 DEN 0 PLA	0.0624
Pool large, pivotal studies	Arrhythmia: Sick sinus syndrome	Serious	2.8	0.063
Pool large, pivotal studies	Congestive Heart Failure: All PTs	LT	0.47	0.086
Pool large, pivotal studies	Congestive Heart Failure: Cardiac Failure Congestive**	LT	0 DEN 4 PLA	0.062
Pool large, pivotal studies	Congestive Heart Failure: All PTs	LT	0.47	0.086
Pool large, pivotal studies	Congestive Heart Failure: Cardiac Failure Congestive**	LT	0 DEN 4 PLA	0.062
Pool large, pivotal studies	Other vascular disorders: All PTs	LT	2.5	0.050
Pool large, pivotal studies	Other vascular disorders: All PTs	Serious	1.4	0.086
Pool large, pivotal studies	Other vascular disorders: Skin ulcer**	Serious	6 DEN 0 PLA	0.031
Pool placebo-controlled	Acute coronary syndromes: Angina pectoris	Serious	1.7	0.053
Pool placebo-controlled	Other vascular disorders: Skin ulcer**	Serious	6 DEN 0 PLA	0.031
Pool any controlled	Arrhythmia: Sinus Bradycardia**	Serious	0 DEN 3 PLA	0.094
Pool any controlled	Arrhythmia: Tachyarrhythmia**	Serious	0 DEN 3 PLA	0.094
Pool any controlled	Congestive Heart Failure: Cardiac Failure	Fatal	0.17	0.098
Pool any controlled	Congestive Heart Failure: Cardiac Failure Chronic	Serious	0.17	0.098
Pool any controlled	Other vascular disorders: Aortic Aneurysm	Serious	0.17	0.098
Pool any controlled	Other vascular disorders: Skin ulcer**	Serious	6 DEN 0 PLA	0.035
Pool any controlled	Stroke: Vertebrobasilar insufficiency	Serious	0.42	0.077

*Relative Risk estimates are reported, unless otherwise noted.

**Relative risk cannot be computed due to entries of zero, therefore the number of subjects with the event are reported instead of RR.

DEN = Denosumab

LT = Life-threatening

PLA = Placebo

Table A33 shows the events for which relative risk was associated with a p-value less than 0.10 when all severity levels were pooled in the broad SMQ analysis.

Table A33. Events for which Relative Risk was Associated with a P-value of Less Than 0.10 when All Severity Levels were Pooled in the Analysis: Broad SMQ Criteria.

Analysis	Events with Relative Risk Having p<0.10	Risk*	p-value
20030216	Gastrointestinal Haemorrhage	1.4	0.082
20040132	Haemorrhages	0.36	0.018
20040132	Haemorrhage Terms (excl lab)	0.36	0.018
20040132	Hypertension	0.4	0.044
20040141	Hypertension	0.61	0.103
20050234	Gastrointestinal Perforation, Ulceration, etc.	0.22	0.035
Pool large, pivotal studies	Disorders of Sinus Node Function	1.8	0.097
Pool any controlled PMO	Cardiomyopathy	0.88	0.056
Pool any controlled PMO	Embolic and Thrombotic Events, Venous	0.64	0.040
Pool any controlled PMO	Haemorrhages	0.86	0.073
Pool any controlled PMO	Haemorrhage Terms (excl lab)	0.87	0.089
Pool any controlled PMO	Hypertension	0.86	0.002
Pool any controlled PMO	Pulmonary Hypertension	0.81	0.086

*Relative Risk estimates are reported, unless otherwise noted.

Table A34 shows the events for which relative risk was associated with a p-value less than 0.10 when all severity levels were pooled in the narrow SMQ analysis.

Table A34. Events for which Relative Risk was Associated with a P-value of Less Than 0.10 when All Severity Levels were Pooled in the Analysis: Narrow SMQ Criteria. Note that in instances in which relative risk cannot be computed due to entries of zero, the number of subjects with the event are reported instead of RR.

Analysis	Events with Relative Risk Having p<0.10	Risk*	p-value
20040132	Haemorrhages	0.38	0.028
20040132	Haemorrhage Terms (excl lab)	0.38	0.028
20040132	Hypertension	0.4	0.044
20040138	Toxic-septic shock conditions**	0 DEN 4 PLA	0.061
20040141	Hypertension	0.61	0.103
Any controlled PMO	Embolic and Thrombotic Events, Venous	0.64	0.040
Any controlled PMO	Haemorrhages	0.87	0.100
Any controlled PMO	Haemorrhage Terms (excl lab)	0.87	0.100
Any controlled PMO	Hypertension	0.86	0.002

*Relative Risk estimates are reported, unless otherwise noted.
**Relative risk cannot be computed due to entries of zero, therefore, the number of subjects with the event are reported instead of RR.
DEN = Denosumab
PLA = Placebo

Table A35 shows the events for which relative risk was associated with a p-value less than 0.10 when all severity levels were pooled using the sponsor's preferred term grouping in the analysis.

Table A35. Events for which Relative Risk was Associated with a P-value Less Than 0.10 when All Severity Levels were Pooled in Analysis: Sponsor's Preferred Term Grouping. Note that in instances in which relative risk cannot be computed due to entries of zero, the number of subjects with the event are reported instead of RR.

Analysis	Events with Relative Risk Having p<0.10	Risk*	p-value
20030216	Acute Coronary Syndromes: Cardiac Disorder**	0 DEN 5 PLA	0.031
20030216	Arrhythmia: Sinus Tachycardia**	0 DEN 5 PLA	0.031
20030216	Arrhythmia: Tachycardia	1.6	0.076
20030216	Other Vascular Disorder: Aortic Stenosis	2.6	0.096
20040138	Acute Coronary Syndromes: Angina Pectoris	2.1	0.073
20040138	Congestive Heart Failure: Pulmonary Oedema**	0 DEN 4 PLA	0.0612
20050141	Acute Coronary Syndromes: All PTs	0.49	0.093
20050141	Acute Coronary Syndromes: Chest Pain	0.2	0.021
Pool Large, pivotal	Acute Coronary Syndromes: Cardiac Disorder	0.17	0.070
Pool Large, pivotal	Arrhythmia: Sick Sinus Syndrome	3.2	0.026
Pool Large, pivotal	Arrhythmia: Sinus Tachycardia**	0 DEN 5 PLA	0.031
Pool Large, pivotal	Congestive Heart Failure: Cardiac Failure	1.4	0.073
Pool Large, pivotal	Congestive Heart Failure: Cardiomegaly	0.25	0.0648
Pool Large, pivotal	Congestive Heart Failure: Oedema	0.46	0.106
Pool Large, pivotal	Congestive Heart Failure: Oedema Peripheral	1.2	0.063
Pooled placebo controlled PMO	Acute Coronary Syndromes: Cardiac Disorder**	0 DEN 5 PLA	0.031
Pooled placebo controlled PMO	Arrhythmia: Tachycardia	1.6	0.063
Pooled placebo controlled PMO	Congestive Heart Failure: Rales	4.0	0.109
Pooled placebo controlled PMO	Other Vascular Disorders: Aortic Stenosis	2.6	0.096
Pooled Controlled PMO	Acute Coronary Syndromes: Cardiac Disorder**	0 DEN 5 PLA	0.019
Pooled Controlled PMO	Arrhythmia: Extrasystoles	0.6	0.073
Pooled Controlled PMO	Arrhythmia: Sinus Tachycardia	0.17	0.098
Pooled Controlled PMO	Congestive Heart Failure: Cardiac Failure Congestive	0.58	0.088
Pooled Controlled PMO	Congestive Heart Failure: Dyspnoea	0.79	0.089
Pooled Controlled PMO	Other Vascular Disorders: Vascular Pseudo-Aneurysm**	0 DEN 3 PLA	0.094

*Relative Risk estimates are reported, unless otherwise noted.
**Relative risk cannot be computed due to entries of zero, therefore, the number of subjects with the event are reported instead of RR.
DEN = Denosumab
PLA = Placebo

Ta[redacted]36 shows the events for which relative risk was associated with a p-value less than 0.10 when Study 20030216 analyzed using a broad SMQ grouping of preferred terms.

Table A36. Events with Relative Risk Estimates Associated with a P-value Less Than 0.10: Analyzed Using a Broad SMQ Grouping of Preferred Terms. Note that only events reported in Study 20030216 are shown in this table.

Events with Relative Risk Having p<0.10	Severity	RR*	p-value
Arrhythmia related investigations	Mild	1.3	0.05
	Fatal	0.3	0.057
Bradyarrhythmias	Moderate	3.5	0.031
	Serious	1.9	0.095
Cardiac Arrhythmias	Fatal	0.3	0.057
Cardiac Failure	Moderate	1.3	0.069
Cardiomyopathy	Fatal	0.36	0.076
Disorders of Sinus Node Function	Moderate	3.7	0.057
Embolic and Thrombotic Events	Severe	1.5	0.018
Embolic and Thrombotic Events, Arterial	Severe	1.7	0.032
Embolic and Thrombotic Events, Unspecified	Severe	1.8	0.071
	≥Severe	1.6	0.071
Gastrointestinal Haemorrhage	All pooled	1.4	0.082
	Moderate	2.1	0.018
Gastrointestinal Perforation, Ulceration, etc.	Moderate	1.4	0.061
	Serious	1.4	0.103
Ischaemic Heart Disease	Severe	2.0	0.0007
	≥Severe	1.7	0.002
	Serious	1.4	0.021
Myocardial Infarction	Severe	2.5	0.011
	≥Severe	1.5	0.097
Pulmonary Hypertension	≥Severe	2.0	0.103
Thrombophlebitis	Severe	2.6	0.096
	≥Severe	2.6	0.096
	Serious	2.3	0.074
Torsade de Pointes/QT Prolongation	Fatal	0.3	0.057

*Relative Risk estimates are reported.

Table A37 shows the events for which relative risk was associated with a p-value less than 0.10 when studies analyzed separately analyzed using a broad SMQ grouping of preferred terms.

Table A37. Events with Relative Risk Estimates Associated with a P-value Less Than 0.10 when Studies Analyzed Separately: Each Study Analyzed Using a Broad SMQ Grouping of Preferred Terms. Note that in instances in which relative risk cannot be computed due to entries of zero, the number of subjects with the event are reported instead of RR. The events reported in Study 20030216 are reported in the previous table.

Study	Events with Relative Risk Having p<0.10	Severity	RR*	p-value
20040132	Haemorrhages	All pooled	0.36	0.018
		Mild	0.22	0.011
20040132	Haemorrhage Terms (excl lab)	All pooled	0.36	0.018
		Mild	0.22	0.011
20040132	Hypertension	All pooled	0.4	0.044
		Moderate	0.25	0.104
20040135	Hypertension	Moderate**	5 PLA 0 DEN	0.025
20040138	Cardiac Arrhythmias	Severe	2.0	0.056
20040138	Cardiac Failure	Mild	1.6	0.033
		Moderate	0.31	0.0003
		LT	0.17	0.069
20040138	Cardiomyopathy	Moderate	0.69	0.083
20040138	Gastrointestinal Perforation, ulceration, etc.	Mild	2.2	0.041
		Serious	0.47	0.054
20040138	Haemodynamic oedema, effusions, etc.	Mild	1.5	0.055
20040138	Pulmonary Hypertension	Serious	3.3	0.091
20040141	Gastrointestinal Haemorrhage	Mild**	4 ALE 0 DEN	0.061
20040141	Haemorrhages	Mild	1.9	0.085
20040141	Haemorrhage Terms (excl lab)	Mild	1.9	0.085
20040141	Hypertension	All pooled	0.61	0.103
20050234	Gastrointestinal Perforation, Ulceration, etc.	All pooled	0.22	0.035
		Moderate**	4 ALE 0 DEN	0.060
20050234	Haemorrhages	Moderate	0.16	0.067
20050234	Haemorrhage Terms (excl lab)	Moderate	0.16	0.067

*Relative Risk estimates are reported, unless otherwise noted.
**Relative risk cannot be computed due to entries of zero, therefore the number of subjects with the event are reported instead of RR.
ALE = Alendronate
DEN = Denosumab
LT = Life-threatening
PLA = Placebo

Table A38 shows the events for which relative risk was associated with a p-value less than 0.10 when the pooled large, pivotal trial dataset was analyzed using a broad SMQ grouping of preferred terms.

Table A38. Events with Relative Risk Estimates Associated with a P-value Less Than 0.10: Pooled Large, pivotal Trials Dataset Analyzed Using a Broad SMQ Grouping of Preferred Terms.

Events with Relative Risk Having p<0.10	Severity	RR*	p-value
Arrhythmia Related Investigations	Mild	1.25	0.090
Bradyarrhythmia	Moderate	2.3	0.061
	Severe	2.1	0.089
	≥Severe	2.1	0.073
	Serious	1.9	0.059
Cardiac Failure	LT	0.36	0.076
Conduction Defects	Severe	4.0	0.109
Disorders of Sinus Node Function	All	1.8	0.097
	Moderate	2.6	0.096
Embolic and Thrombotic Events	Severe	1.4	0.019
Embolic and Thrombotic Events, Arterial	Severe	1.7	0.017
	LT	0.5	0.054
Embolic and Thrombotic Events, Venous	Mild	0.5	0.100
Ischaemic Heart Disease	Severe	1.8	0.001
	≥Severe	1.4	0.030
Myocardial Infarction	Severe	2.5	0.003
Pulmonary Hypertension	≥Severe	1.7	0.106
	Serious	2.0	0.046
Thrombophlebitis	Serious	2.0	0.069

*Relative Risk estimates are reported.
All = All severity levels pooled
LT = Life Threatening

Table A39 shows the events for which relative risk was associated with a p-value less than 0.10 when the pooled placebo-controled trials dataset was analyzed using a broad SMQ grouping of preferred terms.

Table A39. Events with Relative Risk Estimates Associated with a P-value Less Than 0.10: Pooled Placebo-Controlled Trials Dataset Analyzed Using a Broad SMQ Grouping of Preferred Terms.

Events with Relative Risk Having p<0.10	Severity	RR*	p-value
Arrhythmia related investigations	Mild	1.3	0.033
	Fatal	0.3	0.057
Bradyarrhythmia	Moderate	3.5	0.031
	Serious	1.9	0.096
Cardiac arrhythmias	Fatal	0.3	0.057
Cardiomyopathy	Fatal	0.36	0.076
Disorders of Sinus Node Function	Moderate	3.7	0.057
Embolic and Thrombotic Events	Severe	1.5	0.024
Embolic and Thrombotic Events, Arterial	Severe	1.7	0.046
Embolic and Thrombotic Events, Unsp	Severe	1.8	0.071
	≥Severe	1.6	0.071
Gastrointestinal Haemorrhage	Moderate	1.9	0.024
Gastrointestinal Perforation, Ulceration, etc.	Moderate	1.4	0.033
	Serious	1.4	0.103
Ischaemic Heart Disease	Severe	1.8	0.002
	≥Severe	1.6	0.006
	Serious	1.4	0.027
Myocardial Infarction	Severe	2.3	0.020
Pulmonary Hypertension	≥Severe	2.0	0.103
Thrombophlebitis	Severe	2.6	0.096
	≥Severe	2.6	0.096
	Serious	2.3	0.074
Torsade de Pointes / QT Prolongation	Fatal	0.3	0.057

*Relative Risk estimates are reported.

Table A40 shows the events for which relative risk was associated with a p-value less than 0.10 when the pooled placebo- or active- controlled trials dataset was analyzed using a broad SMQ grouping of preferred terms.

Table A40. Events with Relative Risk Estimates Associated with a P-value Less Than 0.10: Pooled Placebo- or Active- Controlled PMO Trials Dataset Analyzed Using a Broad SMQ Grouping of Preferred Terms. Note that in instances in which relative risk cannot be computed due to entries of zero, the number of subjects with the event are reported instead of RR.

Events with Relative Risk Having p<0.10	Severity	Risk*	p-value
Arrhythmia related investigations	Fatal	0.33	0.061
Bradyarrhythmia	Moderate	2.9	0.058
Cardiac arrhythmias	Fatal	0.33	0.061
Cardiac arrhythmia terms	Mild	0.77	0.055
Cardiomyopathy	All	0.88	0.056
	Moderate	0.84	0.109
	Fatal	0.3	0.037
Disorders of Sinus Node Function	Moderate	3.1	0.105
Embolic and Thrombotic Events, Arterial	LT	0.33	0.061
Embolic and Thrombotic Events, Venous	All pooled	0.64	0.040
	Mild	0.42	0.050
	Moderate	0.53	0.058
Gastrointestinal Haemorrhage	Moderate	1.8	0.051
Haemorrhages	All pooled	0.86	0.073
	Mild	0.83	0.077
	Severe	0.62	0.077
Haemorrhage Terms (excl lab)	All pooled	0.87	0.089
	Mild	0.83	0.087
	Severe	0.62	0.077
Hypertension	All pooled	0.86	0.002
	Moderate	0.83	0.006
Ischaemic Heart Disease	Severe	1.6	0.029
	≥Severe	1.4	0.063
Myocardial Infarction	Mild**	0 DEN 3 PLA	0.094
	Severe	1.9	0.073
Pulmonary Hypertension	All pooled	0.81	0.086
	Moderate	0.68	0.033
Torsade de Pointes / QT Prolongation	Moderate	0.71	0.104
	Fatal	0.33	0.061

*Relative Risk estimates are reported, unless otherwise noted.
**Relative risk cannot be computed due to entries of zero, therefore the number of subjects with the event are reported instead of RR.
All = All severity levels pooled
DEN = Denosumab
LT = Life-threatening
PLA = Placebo

Table A41 shows the events for which relative risk was associated with a p-value less than 0.10 when the individual studies were analyzed using a narrow SMQ grouping of preferred terms.

Table A41. Events with Relative Risk Estimates Associated with a P-value Less Than 0.10 when Each Study Analyzed Separately: Analyzed Using a Narrow SMQ Grouping of Preferred Terms. Note that in instances in which relative risk cannot be computed due to entries of zero, the number of subjects with the event are reported instead of RR.

Dataset	Events with Relative Risk Having p<0.10	Severity	Risk*	p-value
20030216	Embolic and Thrombotic Events	Severe	1.5	0.071
20030216	Embolic and Thrombotic Events, Arterial	Severe	1.7	0.032
20030216	Ischaemic Heart Disease	Severe	2.0	0.0007
		≥Severe	1.7	0.002
		Serious	1.4	0.021
20030216	Myocardial Infarction	Severe	2.5	0.011
		≥Severe	1.5	0.097
20040132	Haemorrhages	All	0.38	0.028
		Mild	0.23	0.018
20040132	Haemorrhage Terms (excl lab)	All	0.38	0.028
		Mild	0.23	0.018
20040132	Hypertension	All	0.4	0.044
		Moderate	0.25	0.104
20040135	Hypertension	Moderate**	0 DEN 5 PLA	0.025
20040138	Cardiac Failure	Moderate	0.17	0.069
		LT	0.17	0.069
20040138	Embolic and thrombotic events	Moderate	2.1	0.059
20040138	Haemodynamic oedema, effusions, etc.	Mild	1.5	0.055
20040138	Toxic-septic shock conditions	All**	0 DEN 4 PLA	0.0612
		≥Severe**	0 DEN 4 PLA	0.0612
		Serious**	0 DEN 4 PLA	0.0612
20040141	Haemorrhages	Mild	1.9	0.085
20040141	Haemorrhage Terms (excl lab)	Mild	1.9	0.085
20040141	Hypertension	All	0.61	0.103
20050234	Haemorrhages	Moderate	0.16	0.067
20050234	Haemorrhage Terms (excl lab)	Moderate	0.16	0.067

*Relative Risk estimates are reported, unless otherwise noted.
**Relative risk cannot be computed due to entries of zero, therefore the number of subjects with the event are reported instead of RR.
All = All severity levels pooled
DEN = Denosumab
LT = Life-threatening
PLA = Placebo

Table A42 shows the events for which relative risk was associated with a p-value less than 0.10 when pooled trial datasets were analyzed using a narrow SMQ grouping of preferred terms.

Table A42. Events with Relative Risk Estimates Associated with a P-value Less Than 0.10: Pooled Datasets Analyzed Using a Narrow SMQ Grouping of Preferred Terms. Note that in instances in which relative risk cannot be computed due to entries of zero, the number of subjects with the event are reported instead of RR.

Pooled Data	Events with Relative Risk Having p<0.10	Severity	Risk*	p-value
Large PTs	Cardiac Failure	LT	0.36	0.076
Large PTs	Embolic and Thrombotic Events	Severe	1.4	0.045
Large PTs	Embolic and Thrombotic Events, Arterial	Severe	1.7	0.017
		LT	0.5	0.054
Large PTs	Embolic and Thrombotic Events, Venous	Mild	0.5	0.100
Large PTs	Ischaemic Heart Disease	Severe	1.8	0.001
		≥Severe	1.4	0.030
Large PTs	Myocardial Infarction	Severe	2.5	0.003
Large PTs	Thrombophlebitis	Moderate	0.33	0.092
PC	Embolic and Thrombotic Events	Severe	1.4	0.092
PC	Embolic and Thrombotic Events, Arterial	Severe	1.7	0.046
PC	Ischaemic Heart Disease	Severe	1.8	0.002
		≥Severe	1.6	0.006
		Serious	1.4	0.027
PC	Myocardial Infarction	Severe	2.3	0.020
Any control	Embolic and Thrombotic Events, Arterial	LT	0.33	0.061
Any control	Embolic and Thrombotic Events, Venous	All	0.64	0.040
		Mild	0.42	0.050
		Moderate	0.53	0.058
Any control	Haemorrhages	All pooled	0.87	0.100
		Mild	0.84	0.101
		Severe	0.62	0.077
Any control	Haemorrhage Terms (excl lab)	All	0.87	0.100
		Mild	0.84	0.101
		Severe	0.62	0.077
Any control	Hypertension	All	0.86	0.002
		Moderate	0.83	0.006
Any control	Ischaemic Heart Disease	Severe	1.6	0.029
		≥Severe	1.4	0.063
Any control	Myocardial Infarction	Severe	1.9	0.073
Any control	Shock-associated circulatory or cardiac conditions	Moderate**	0 DEN 3 PLA	0.094

*Relative Risk estimates are reported, unless otherwise noted.
**Relative risk cannot be computed due to entries of zero, therefore the number of subjects with the event are reported instead of RR.
All = All severity levels pooled; DEN = Denosumab; LT = Life-threatening; PLA = Placebo; PC = Placebo-controlled; PTs = Pivotal trials

~~U.S. Department of Health and Human Services~~
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION
Clinical Studies

BLA/Serial Number:	125320 and 125331 / 000
Drug Name:	Prolia (denosumab)
Indication(s):	Treatment (BLA 125320) and prevention (BLA 125331) of osteoporosis in postmenopausal women
Applicant:	Amgen, Inc.
Date(s):	Letter Date: December 19, 2008 PDUFA Date: October. 19, 2009
Review Priority:	1 Standard
Biometrics Division:	Division of Biometrics 3
Statistical Reviewer:	Sonia Castillo, Ph.D.
Biometrics Team Leader:	Mahboob Sobhan, Ph.D.
Medical Division:	Division of Reproductive and Urology Products
Clinical Team:	Vaishali Popat, M.D., Clinical Reviewer Adrienne Rothstein, Pharm.D., Clinical Analyst Theresa Kehoe, M.D., Clinical Team Leader
Project Manager:	Celia Peacock, M.P.H., R.D., Captain, U.S. Public Health Service

Key Words: Clinical studies, BLA review, Multinational Study

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The two submitted studies provide supportive evidence demonstrating the efficacy of Prolia (s.c. denosumab 60 mg twice yearly) Injection for the treatment and prevention of osteoporosis in postmenopausal women based on incidence of new vertebral fractures (treatment) and lumbar spine bone mineral density (prevention).

1.2 Background

This two study submission is a new biologic application for denosumab. These are multinational, randomized, multicenter, double-blind, parallel-group, placebo-controlled studies comparing the efficacy and safety of subcutaneous denosumab 60 mg twice yearly and placebo twice yearly for the treatment and prevention of osteoporosis in postmenopausal women. There is one study each for the treatment and prevention indications.

The Applicant's proposed indication is:

Prolia is indicated for the treatment and prevention of osteoporosis in postmenopausal women.

1.3 Statistical Issues and Findings

No statistical issues were identified 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.

From a statistical perspective, the two submitted studies (3-year treatment Study 20030216 and 2-year prevention Study 20040132) provide supportive evidence demonstrating the efficacy of Prolia (s.c. denosumab 60 mg twice yearly) Injection for the treatment and prevention of osteoporosis in postmenopausal women based on the endpoints of incidence of new vertebral fractures, incidence of non-vertebral fractures, incidence of hip fractures, lumbar spine bone mineral density, and total hip bone mineral density. Overall, there was a decrease in the incidence for new vertebral, non-vertebral, and hip fractures. Also, there was an increase in the bone mineral density of the lumbar spine and total hip with denosumab use compared to placebo.

However, when fracture data is tabulated by 1-year intervals, there were counterintuitive results given that the percentage of fractures should either decrease or remain the same when using an osteoporosis treatment. Specifically, within the denosumab group, for both new vertebral fractures and hip fractures, the percentage of fractures fluctuated by decreasing within year 2 compared to within year 1 and then increasing within year 3 compared to within year 2. That is, the percentage of new vertebral fractures and percentage of hip fractures within year 3 was nearly a threefold increase compared to within year 2. Also, the percentage of hip fractures within year 3 was greater in the denosumab group compared to the placebo group, suggesting that the percentage of hip fractures in the denosumab group had caught up with that in the placebo group.

2. INTRODUCTION

2.1 Overview

The Applicant has submitted two clinical studies (20030216 and 20040132) designed to demonstrate the safety and efficacy of s.c. denosumab 60 mg twice yearly injection for the treatment and prevention of osteoporosis in postmenopausal (PMO) women. Table 2.1 presents a brief summary of these studies.

Table 2.P
Brief Summary of Clinical Study for Denosumab

Study Number (No. of Sites / Country) Dates of Study Conduct	Subject Population	Treatment	Number Randomized (ITT[1])	Design[2]
20030216 (**Treatment**) (83 / W. Europe, 66 / E. Europe, 48 / N. America, 10 / Latin America, 7 / Australia and New Zealand) August 2004 to June 2008	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), 60 to 90 years old	s.c. denosumab 60 mg twice yearly s.c. placebo twice yearly **Total**	3933 (3902) 3935 (3906) **7868 (7808)**	DB, R, PC, PG, MC, 3 year
20040132 (**Prevention**) (16 / United States, 5 / Canada) August 2004 to Feb. 2007	Postmenopausal women with osteopenia (lumbar spine BMD T-score between -2.5 and -1.0), under 90 years old	s.c. denosumab 60 mg twice yearly s.c. placebo twice yearly **Total**	166 (163) 166 (163) **332 (326)**	DB, R, PC, PG, MC, 2 year

Source: Statistical Reviewer's listing.
[1] ITT = Intent to Treat
[2] DB = Double-blind, R = Randomized, PC = Placebo Control, PG = Parallel Group, MC = Multicenter

Denosumab is a bone mineral density (BMD) building therapy and according to the Applicant:

> Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. ... An estimated 10 million Americans have osteoporosis; an additional 34 million men and women have low bone mass and are at increased risk for osteoporosis and its potential complications.
>
> The morbidity and mortality associated with osteoporotic-related fractures result in significant clinical, human, and economic costs. About 40% to 50% of women and 13% to 22% of men are at risk of having an osteoporotic fracture in their lifetime. ...
>
> Spinal fracture is a common feature of osteoporosis and is a marker of disease progression and severity. ... Prevalent vertebral fractures, including asymptomatic vertebral fractures, are a predictor of subsequent vertebral fractures and are associated with long-term back pain, disabilities, and morbidity. Hip fractures are the most serious of osteoporotic fractures and have immediate clinical consequences as they almost always require surgical repair and often result in disability and loss of independence. ...
>
> The risk of fracture increases with decreasing bone mineral density (BMD) and increasing age. ... Overall, the lifetime risk of sustaining an osteoporotic fracture for a 50-year-old woman is about 40% to 50%.
>
> Reduction in estrogen levels at menopause prompts an increase in bone resorption. This increase in bone resorption is the result of a cytokine-driven increase in receptor activator of nuclear factor-κB ligand (RANKL), an essential mediator of osteoclast recruitment, activation, and activity. Increased bone resorption, relative to bone formation, leads to decreases in bone mass, decreases in bone density, and microarchitectural deterioration, all of which predispose a patient to fracture over time.
>
> ... RANKL, a member of the tumor necrosis factor (TNF) family of proteins, originally identified in dendritic cells, has been well documented as an essential factor in the formation, activation, and survival of osteoclasts, the cells responsible for bone resorption. Excessive RANKL has been implicated in bone diseases associated with increased bone resorption, such as osteoporosis. ... [P]reclinical models have demonstrated that inhibiting RANKL leads to significant improvements in cortical and trabecular bone density, volume, and strength.
>
> Denosumab is a fully human monoclonal antibody to RANKL with high affinity for RANKL. Denosumab binds RANKL, preventing the activation of RANK and inhibiting the formation, activation, and survival of osteoclasts. A reduction in bone resorption and an increase in cortical and trabecular bone mass, volume, and strength results. ... As a result of its unique and specific mechanism of action, denosumab is being investigated as a therapy for bone loss associated with osteoporosis and hormone ablation therapy. Denosumab binds RANKL and therefore blocks the differentiation, activation, and survival of osteoclasts. Denosumab has the potential to inhibit the deleterious effect of bone resorption on the skeleton, protecting against bone loss

and reducing the risk for fracture in the setting of osteoporosis. (Section 5.0, pages 130 to 132, Study 20030216 report, references removed for brevity)

2.2 Data Sources

The study report and additional information for these studies were submitted electronically. The submitted SAS data sets for each study were complete and well documented. These items are located in the Electronic Document Room at \\cbsap58\M\eCTD_Submissions\STN125320\0000 under submission dates 12-20-2008 and 3-13-2009.

3. STATISTICAL EVALUATION

3.1 Study Design

The Applicant has submitted two clinical studies (20030216 and 20040132) designed to demonstrate the efficacy and safety of denosumab compared to placebo in the treatment and prevention of osteoporosis in postmenopausal women. The review of treatment study 2003216 will focus on the primary and secondary objectives and the tertiary BMD endpoints of the lumbar spine and hip. The review of prevention study 20040132 will focus on the primary BMD endpoint at the lumbar spine and key secondary BMD endpoint at the total hip.

3.1.1 Treatment Study 20030216

Treatment study 20030216 was an international, multicenter, randomized, double-blind placebo-controlled, parallel group, 3-year study in postmenopausal women with osteoporosis (BMD T-score < –2.5 at either the lumbar spine or the total hip, or at both locations, but ≥–4.0 at both locations, as measured by dual energy x-ray absorptiometry (DXA)), 60 to 90 years old. Eligible subjects were equally randomized using an interactive voice recognition system to either denosumab 60 mg or placebo every 6 months subcutaneously for 3 years, with the last dose at month 30. Investigational product was administered during scheduled visits by a health care professional and all subjects received daily supplementation of calcium (at least 1 g) and vitamin D (at least 400 IU). Randomization was stratified by four age categories and restricted to the proportions as presented in Table 3.1. Subjects were followed for 36 months or until early termination.

Table 3.1
Study 20030216: Age Strata used for Randomization and Restrictions on Proportions of Subjects in Each Age Stratum

Age Strata	Proportion		
60 to 64 years	maximum of 5%		
65 to 69 years			
70 to 74 years			minimum of 70% of subjects ≥70 years of age
≥75 years	minimum of 35%	OR	

Source: Statistical Reviewer's listing.

A total of 7868 patients were randomized from 214 centers in 32 countries located worldwide as follows: 83 in Western Europe (44.9% of subjects enrolled), 66 in Eastern Europe, 48 in North America, 10 in Latin America, and 7 in Australia and New Zealand (see Table A.1 in the Appendix for a listing).

Lateral spine x-rays were acquired at screening and at months 12, 24, and 36. Also, 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 obtained a lateral spinal x-ray and submitted it to the central imaging vendor.

Non-vertebral fractures, including the hip, were those excluding those of the vertebrae, skull, facial, mandible, metacarpus, finger phalanges, and toe phalanges. Fractures associated with high trauma severity and pathologic fractures were excluded. New on-study fractures were radiographically confirmed by the central imaging vendor and included in the efficacy analysis.

For all subjects, dual x-ray absorptiometry (DXA) scans of the lumbar spine (required to include L1 through L4) were acquired at screening and months 24 and 36 and of the hip were acquired at screening and months 12, 24, and 36. The same DXA machine (GE Lunar or Hologic densitometers) was used for all study procedures for

individual subject. For assessment of lumbar spine BMD, eligible subjects were required to have at least two intact lumbar vertebrae in the L1-L4 region, as determined by the screening lumbar DXA assessed by the radiologist designated by the study center. In addition, eligible subjects were to have a BMD T-score < –2.5 at either the lumbar spine or the total hip, or at both locations, but ≥–4.0 at both locations. All images were sent to a central reader for final, blinded evaluation and BMD (g/cm^2) calculation.

The primary efficacy objective was to determine whether denosumab treatment reduces the number of postmenopausal osteoporotic women with new vertebral fractures compared to placebo. The primary efficacy endpoint was the subject incidence of new vertebral fractures after 3 years of treatment.

The two key secondary efficacy endpoints were the time to first non-vertebral fracture and the time to first hip fracture during the 3 year treatment period.

The two tertiary endpoints of clinical interest were the percent changes in BMD at the lumbar spine and total hip at Month 36 relative to baseline, that were based on the DXA derived BMD at baseline and after 36 months of treatment. A percent change from baseline endpoint was given by: *(Change from baseline value / Baseline value) * 100.*

The primary efficacy endpoint was the subject incidence of new vertebral fractures during the entire 36-month treatment period, and the secondary endpoints were time to first non-vertebral fracture and time to first hip fracture. A fixed sequence testing procedure was used among these 3 endpoints in the order mentioned above for multiplicity adjustment to maintain the overall significance level at 0.05. The significance level for each analysis of the tertiary efficacy endpoints was 0.05 without adjusting for multiplicity.

The primary efficacy analysis compared subject incidence of new vertebral fracture [Yes/No] between denosumab and placebo groups using a logistic regression model with treatment as the main effect (placebo as reference category) and age strata as a covariate. The adjusted odds ratio, 95% confidence interval, and p-value based on the score test were provided. This analysis included all randomized subjects with a baseline and ≥1 post-baseline evaluation during 36 months of treatment. Missing post-baseline vertebral fracture status due to missing spinal x-ray assessment was imputed using the status from the last non-missing post-baseline visit (i.e., last observation carried forward [LOCF]) because, according to the Applicant, "a vertebral fracture can only get worse or remain at the same severity over time."

The following primary efficacy sensitivity analyses were performed:

- 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 based on the Mantel-Haenszel method adjusting for age strata.
- A time-to-event analysis based on the full analysis subset (includes all randomized subjects) using a stratified Cox proportional hazards model stratifying for age strata with treatment as the independent variable. The treatment effect was assessed based on the hazard ratios, 95% confidence intervals, and the p-value from the score test. A subject who was lost to follow-up or withdrew before experiencing an event during the given period was considered censored at the last assessment or day 1, whichever was later.

  Time-to-event endpoints were summarized descriptively using Kaplan-Meier estimates at time point(s) of interest. In addition, a point estimate of the adjusted risk difference (difference in Kaplan-Meier estimates at time point of interest, placebo – denosumab) and 95% confidence intervals using the inverse variance-weighted method were calculated.

The two key secondary efficacy endpoints of time to first non-vertebral fracture and time to first hip fracture were analyzed in a similar manner to the primary efficacy endpoint time-to-event sensitivity analyses presented above.

The two tertiary endpoints of percent changes in BMD (lumbar spine and total hip) were analyzed using an ANCOVA model with main effects for treatment, baseline value of the endpoint, machine type and machine type-by-baseline value interaction to adjust for the effect of machine type on baseline value using LOCF imputation.

The least-squares mean of the treatment difference (denosumab – placebo) and 95% confidence interval were presented for each time point using a [illegible] model. Missing post-baseline BMD was imputed using the LOCF approach, by carrying forward the last non-missing post-baseline value prior to the missing value.

Sensitivity analyses of the lumbar spine and total hip BMD endpoints used a separate repeated measures model with treatment, age strata, visit, baseline value of the endpoint, and treatment-by-visit interaction, machine type (Hologic or Lunar), and machine type-by-baseline value interaction, to adjust for the effect of machine type on baseline value, as fixed effects using an unstructured variance-covariance structure. The least-squares mean of the treatment difference (denosumab – placebo) and 95% confidence interval were presented.
The overall study sample size was planned to provide adequate statistical power to detect the treatment effects at 36 months for all primary and secondary endpoints described below ($\alpha = 0.05$):

- At least a 45% reduction in the incidence of new vertebral fracture (> 99% power, chi-square test, placebo fracture rate of 4% per year, loss-to-follow-up vertebral radiograph rate of 5% per year)
- At least a 40% decrease in the risk of non-vertebral fracture (> 99% power, log-rank test, placebo fracture rate of 3.3% per year, rate of censoring for non-vertebral fracture assessment of 4% per year)
- At least a 40% decrease in the risk of hip fracture (91% power, log-rank test, placebo fracture rate of 1% per year, rate of censoring for hip fracture assessment of 4% per year)

The total sample size of 7200 subjects was based on the hip fracture endpoint because the expected rate of hip fractures was lower than the expected rates of new vertebral and non-vertebral fractures.

3.1.2 Prevention Study 20040132

Prevention study 20040132 was a two-phase, North American, multicenter, randomized, double blind, placebo-controlled, parallel group, 48 month study in postmenopausal women with osteopenia (lumbar spine BMD T-score between –1.0 and -2.5, as measured by dual energy x-ray absorptiometry) under 90 years old. The on-treatment period was through month 24 and the off-treatment extension was from month 25 through 48. Efficacy was assessed after all subjects had an opportunity to complete their Month 24 visits, with the remainder of study time used to assess the off-treatment effect of denosumab. Eligible subjects were equally randomized using an interactive voice recognition system to either 60 mg denosumab every 6 months subcutaneously for 2 years, with the last dose at month 18. Investigational product was administered during scheduled visits by a health care professional and all subjects received daily supplementation of calcium (at least 1 g) and vitamin D (at least 400 IU). Randomization was stratified by time since onset of menopause (≤5 years or > 5 years), with 75 subjects per treatment group within each stratum. A total of 332 patients were randomized from 16 centers in the United States and 5 centers in Canada. Subjects were followed for 48 months or until early termination.

Subject safety and efficacy was monitored on an ongoing basis by an external Data Monitoring Committee (DMC). The DMC members reviewed both safety and efficacy data at the DMC data review meetings convened approximately every 6 months. Unblinded yet masked data summaries from an Independent Contract Research Organization were provided to the voting DMC members who attended closed sessions. The DMC recommendation for early stopping due to efficacy was made difficult by applying the following strict guidelines:

- the treatment comparisons of denosumab versus placebo for the percent changes in lumbar spine BMD in both time-since-menopause strata (≤5 years and > 5 years) are statistically significant at the 0.0005 level, and
- the treatment comparisons of denosumab versus placebo for the incidences of new vertebral fracture in both time-since-menopause strata (≤5 years and > 5 years) are both statistically significant at the 0.0005 level.

According to the Applicant, "due to the conservative nature of the statistical criteria, no further adjustment to the type I error is warranted." The study was not stopped early due to either safety or efficacy.

All subjects underwent bone densitometry assessments of the lumbar spine (required to include L1 through L4) and hip acquired by dual x-ray absorptiometry (DXA) at screening and months 6, 12, and 24. The same DXA machine (GE Lunar or Hologic densitometers) was used for all study procedures for an individual subject. For assessment of lumbar spine BMD, eligible subjects were required to have at least two intact lumbar vertebrae in the L1-L4 region, as determined by the screening lumbar DXA assessed by the radiologist designated by the study center, and have a lumbar spine BMD T-score between –1.0 and -2.5. All images were sent to a central reader for final, blinded evaluation and BMD (g/cm^2) calculation.

T

The primary objective was to determine if denosumab treatment prevented lumbar spine bone mineral density (BMD) loss in both early and late postmenopausal women with osteopenia compared to placebo. The primary efficacy endpoint was the percent change from baseline in lumbar spine BMD after 24 months of treatment.

The key secondary objective of clinical interest was to determine whether denosumab prevented BMD loss at the total hip in both early and late postmenopausal women with osteopenia compared to placebo. The key secondary efficacy endpoint was the percent change from baseline in BMD of the total hip after 24 months of treatment. A percent change from baseline endpoint was given by: *(Change from baseline value / Baseline value) * 100.*

The overall two-sided significance level for testing the primary and secondary endpoints was controlled at 0.05. For testing within each stratum, a Bonferroni adjustment was used to equally distribute the type I error rate between early (0.025 for the stratum of ≤5 years since menopause) and late (0.025 for the stratum of > 5 years since menopause) postmenopausal osteopenic women. The approach for handling multiplicity for the primary and secondary endpoints within each time-since-menopause stratum included both hierarchical testing strategy and Hochberg procedure as follows:

- The treatment effect for the primary efficacy endpoint was tested at the two-sided significance level of 0.025.
- The treatment effect for the secondary efficacy endpoints were only made if the treatment effect for the primary efficacy endpoint was declared statistically significant. The Hochberg procedure was used for multiplicity adjustment of the secondary efficacy endpoints to maintain the overall two-sided significance level within each time-since-menopause stratum at 0.025.

The overall comparison was done in a similar manner except that the type 1 error rate was set to be 0.05.

The primary analysis to assess the treatment difference in the percent change from baseline in lumbar spine at Month 24 within each of the time-since-menopause strata (≤5 years and > 5 years) and overall used an ANCOVA model applied separately in each randomized stratum and overall. All these ANCOVA models included treatment as the main effect and covariates of baseline value of the endpoint, machine type (Hologic or Lunar), and machine type-by-baseline value interaction. The overall ANCOVA model also included time-since-menopause stratum (stratification factor). The efficacy population consisted of all randomized subjects who had a non-missing baseline measure and at least one post-baseline measure at or prior to the time point of interest because a both measurements were needed to calculate a percent change from baseline. The primary analysis used the last observation carried forward (LOCF) approach: missing post-baseline value was imputed using the last previous non-missing post-baseline value at or before the Month 24 visit. Missing baseline BMD values were not imputed.

The analysis of the key secondary BMD endpoint at the total hip was similarly conducted.

Sensitivity analyses for the primary and secondary endpoints were conducted separately within each time-since-menopause stratum and overall and include the following approaches for missing BMD values at the timepoint of interest:

- Repeated measures model using no imputation of missing post-baseline measurements analysis of BMD. All these repeated measures models 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. Visit is treated as a categorical variable. The overall repeated measures model also included time-since-menopause stratum [stratification factor].
- The mean of the other treatment group (MOTH) approach: missing post-baseline value was imputed using the other group information.

The sample size of 75 subjects per stratum per treatment group was based using a 2% treatment difference, standard deviation of 3.25%, type 1 error of 0.025, 90% power, and a 5% per year rate for lost to follow-up scans.

3.2 Evaluation of Efficacy

3.2.1 Treatment Study 20030216 Subject Disposition and Baseline Characteristics

For treatment study 20030216, Table 3.2 presents the number of randomized subjects and their disposition. A total of 7868 subjects were randomized, 3933 subjects to the denosumab group and 3935 to the placebo group. For the primary efficacy endpoint, 7762 of the 7868 randomized subjects were included in the ITT analysis. Sixty

subjects from Lithuanian Site 803 (31 in the denosumab group and 29 in the placebo group) were removed by the Applicant from the analyses prior to study unblinding due to Good Clinical Practice violations, including irregularities in procedures for subject informed consent and significant non-compliance. The Clinical Reviewer concurred with this decision. The study results were not affected by the removal of these 60 subjects because analyses including all subjects gave similar results. In addition, 23 randomized subjects from each treatment group did not take study drug.

Discontinuation rates were similar in both treatment groups (15.6% for denosumab and 17.4% for placebo). The primary reasons for study discontinuation were subject withdrawal of consent (8.5% for denosumab and 10.1% for placebo), adverse events (2.4% for denosumab and 2.1% for placebo), death (1.6% for denosumab and 2.0% for placebo), and lost to follow-up (1.5% for denosumab and 1.5% for placebo).

Table 3.2
Study 20030216: Randomization and Disposition of All Subjects

	Denosumab	Placebo
Number Randomized	3933	3935
Number Removed from Site 803 due to GCP Violations	31	29
Number Who Did not Take Study Product	23	23
Number Randomized and Took Study Product (ITT)	3879	3883
Completed n (%)*	3272 (84.4)	3206 (82.6)
Discontinued n (%)*	607 (15.6)	677 (17.4)
Primary Reason for Discontinuation n (%)*:		
Subject Withdrew Consent	331 (8.5)	392 (10.1)
Adverse Event	93 (2.4)	81 (2.1)
Death	62 (1.6)	78 (2.0)
Lost to Follow-up	57 (1.5)	57 (1.5)
Protocol Deviation	10 (0.3)	11 (0.3)
Noncompliance	13 (0.3)	16 (0.4)
Other	41 (1.2)	42 (1.3)

Source: Statistical Reviewer's listing based on SAS dataset ASLINFO.
* With respect to number of randomized subjects who took study product.

Both groups in the treatment study were similar in baseline and demographic characteristics based on the ITT population. The majority of subjects were Caucasian (92.7%) and greater than 65 years of age (94.7%), had a mean age of 72.3 years, had mean time since menopause of 24.2 years, and had a similar baseline mean BMD T-scores of -2.83 at the lumbar spine and -1.90 at the total hip. The percentages of subjects in each of the four randomization strata age groups, used as stratification variables in the analyses, were similar in both treatment groups: 60 to 64 years (5.3%), 65 to 69 years (21.1%), 70 to 74 years (42.0%), and 75 years or greater (31.6%). randomization was well-balanced between treatment groups within the age strata.

3.2.2 Treatment Study 20030216 Efficacy Results

The Applicant's results, which I have verified, for the primary vertebral fracture efficacy endpoint, two key secondary non-vertebral and hip efficacy endpoints, and the lumbar spine and total hip BMD endpoints are presented in Tables 3.3 to 3.7. Denosumab demonstrated improved efficacy compared to placebo in all primary and key secondary endpoints based on the pre-specified sequential testing procedure and in the two BMD endpoints as described below.

The analysis results for new vertebral fractures are presented in Tables 3.3 and 3.4 and are described below. These tables also provide 12- and 24-month incidence rates, absolute risk reduction, and relative risk reduction estimates.

- The incidence of new vertebral fractures at Month 36 was 2.2% for denosumab vs. 7.2% for placebo (Kaplan-Meier estimates in Table 3.4). Denosumab reduced the risk of new vertebral fractures by 68% at Month 36 (95% CI based on relative risk: 59% to 74%, p-value based on odds ratio analysis is <0.0001, both in Table 3.3). These results are consistent with those based on the crude incidences, odds ratio, and hazard ratio in Tables 3.3 and 3.4.

Table 3.3
[redacted]216: Subject Incidence, Absolute Risk Reduction, and Odds Ratio for New Vertebral Fracture Throug[redacted]
(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)	<0.0001
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.

Table 3.4
Study 20030216: Subject Incidence, Absolute Risk Reduction, and Hazard Ratio for New Vertebral Fracture Through Month 36
(Primary Efficacy 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
			12	24	36			
Denosumab (N=3879)	86	2.2	0.7	1.1	2.2	4.8 (3.8, 5.9)	0.32 (0.25, 0.40)	< 0.0001
Placebo (N=3883)	264	6.8	1.5	4.2	7.2			

Source: Table 14-4.1.2, page 454, 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 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.

The analysis results for non-vertebral fractures are presented in Table 3.5 and are described below. This table also provides 12- and 24-month incidence estimates. Note that the risk reduction percentage and its confidence interval described in the results below are calculated by subtracting the hazard ratio and the limits of its confidence interval from 1.0.

- The incidence of non-vertebral fractures at Month 36 was 6.5% for denosumab vs. 8.0% for placebo (Kaplan-Meier estimates in Table 3.5). Denosumab reduced the risk of non-vertebral fractures by 20% at Month 36 (95% CI: 5% to 33%, p-value is 0.0106, both based on hazard ratio analysis, Table 3.5). These results are consistent with those based on the crude incidences in Table 3.5.

Table 3.5
Study 20030216: Subject Incidence, Absolute Risk Reduction, and Hazard Ratio for Non-vertebral 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
			12	24	36			
Denosumab (N=3879)	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=3883)	293	7.5	3.1	5.8	8.0			

Source: Table 9-5, page 251, Study 20030216 report and Statistical Reviewer's calculation.
* The full analysis set includes all randomized subjects who took at least one dose of study drug.
[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.

The analysis results for hip fractures are presented in Table 3.6 and are described below. This table also provides 12- and 24-month incidence estimates. Note that the risk reduction percentage and its confidence interval described in the results below are calculated by subtracting the hazard ratio and the limits of its confidence interval from 1.0.

- The incidence of hip fractures at Month 36 was 0.7% for denosumab vs. 1.2% for placebo (Kaplan-Meier estimates in Table 3.6). Denosumab reduced the risk of hip fractures by 40% at Month 36 (95% CI: 3% to 63%, p-value is 0.0362, both based on hazard ratio analysis, Table 3.6. These results are consistent with those based on the crude incidences in Table 3.6.

Table 3.6
Study 20030216: Subject Incidence, Absolute Risk Reduction, and Hazard Ratio for 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
			12	24	36			
Denosumab (N=3879)	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=3883)	43	1.1	0.6	0.9	1.2			

Source: Table 9-6, page 254, Study 20030216 report and Statistical Reviewer's calculation.
* The full analysis set includes all randomized subjects who took at least one dose of study drug.
[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 was descriptively presented as the number and percentage of hip fractures within each 1-year time interval for year1, year 2, and year 3. Table 3.7 presents these results and this is what is observed:

- 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.
- Within the year 3 time interval, the percentage of hip fractures in the denosumab group is 0.34% and is greater than the percentage for the placebo group (0.26%).
- In the denosumab group, the percentage of hip fractures fluctuates by decreasing to 0.12% within year 2 compared to 0.26% within year 1 and then increasing to 0.34% within year 3 compared to 0.12% within year 2. 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. 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.

Table 3.7
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: Figure 9-7 on page 255 of Study 20030216 report and Statistical Reviewer's calculations.

For completeness, we decided to further investigate both new vertebral and non-vertebral fracture at yearly intervals as for hip fractures. Table 3.8 presents the results for new vertebral fractures. They are described below:

- The percentage of new vertebral fractures is greater in the placebo group compared to the denosumab group within all 1-year time intervals.

- In the denosumab group, the percentage of new vertebral fractures fluctuates by decreasing to 0.48% within year 2 compared to 0.59% within year 1 and then increasing to 1.38% within year 3 compared to 0.48% within year 2. The percentage of new vertebral fractures within year 3 is nearly a threefold increase compared to within year 2.

As with hip fractures, 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.

Table 3.8
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: Datasets ASLINFO and ASLEFF and Statistical Reviewer's calculations.

Table 3.9 presents the results for non-vertebral fractures and they are described below:

- The percentage of non-vertebral fractures is greater in the placebo group compared to the denosumab group within all 1-year time intervals.
- In the denosumab group, the percentage of non-vertebral fractures decreases to 2.03% within year 2 compared to 2.46% within year 1 and then stayed about the same at 2.07% within year 3 compared to 2.03% within year 2.

Table 3.9
Study 20030216: Number and Percentage of Non-Vertebral Fractures within Each 1-Year Time Interval

	Year 1		Year 2		Year 3	
	Number of subjects at beginning of interval	Number of fractures in interval (%)	Number of subjects at beginning of interval	Number of fractures in interval (%)	Number of subjects at beginning of interval	Number of fractures in interval (%)
Denosumab	3902	96 (2.46)	3594	73 (2.03)	3337	69 (2.07)
Placebo	3906	115 (2.94)	3578	97 (2.71)	3264	81 (2.48)

Source: Figure 9-6 on page 252 of Study 20030216 report and Statistical Reviewer's calculations.

The lumbar spine BMD and total hip BMD analysis results are presented in Table 3.10 and are described below.

- The mean percent change from baseline in lumbar spine BMD at Month 36 was 9.4% for denosumab vs. 0.6% for placebo. This gives a mean increase in lumbar spine BMD of 8.8% for denosumab compared to placebo (95% CI: 8.6% to 9.1%, $p < 0.0001$).
- The mean percent change from baseline in total hip BMD at Month 36 was 5.0% for denosumab vs. -1.4% for placebo. This gives a mean increase in total hip BMD of 6.4% for denosumab compared to placebo (95% CI: 6.2% to 6.6%, $p < 0.0001$).

Table 3.10
Study 20030216: Lumbar Spine and Total Hip BMD - Treatment Difference for Percent Change from Baseline at Month 36 (Modified ITT Population)

	n	LS Mean[1]	LS Mean Difference[1] (95% C.I.)	p-value
Lumbar Spine				
Denosumab	3203	9.4%	8.8% (8.6%, 9.1%)	< 0.0001
Placebo	3160	0.6%		
Total Hip				
Denosumab	3624	5.0%	6.4% (6.2%, 6.6%)	< 0.0001
Placebo	3608	-1.4%		

Source: Table 14-4.5.3 on page 320 and Table 9-2 on page 138 of Study 20040132 report.
[1] Least Squares mean estimates, confidence intervals, and p-values based on an ANCOVA model with treatment, age stratification variable, baseline value, machine type, and baseline value-by machine type interaction

3.2.3 *Prevention Study 20040132 Subject Disposition and Baseline Characteristics*

For prevention study 20040132, Table 3.11 presents the number of randomized subjects and their disposition. A total of 332 subjects were randomized, 166 subjects to the denosumab group and 166 to the placebo group. For the primary efficacy endpoint, 326 of the 332 randomized subjects were included for analysis. Two subjects in the denosumab group and one subject in the placebo group did not take any study drug; and one subject in the denosumab group and two subjects in the placebo group took one dose of study product but did not have post-baseline BMD data and they were excluded from the analysis.

Discontinuation rates were similar in both treatment groups (13.4% for denosumab and 12.7% for placebo). The primary reasons for study discontinuation were subject withdrawal of consent (6.1% for denosumab and 8.5 % for placebo) and lost to follow-up (4.3% for denosumab and 3.0% for placebo). The discontinuation rate due to adverse events was similar in both groups (0.6% for denosumab and 1.2% for placebo).

Both groups in the prevention study were similar in baseline and demographic characteristics based on the ITT population. The majority of subjects was Caucasian (83%), had a mean age of 59.4 years, and had a similar baseline mean lumbar spine BMD T-score of -1.6. The percentages of subjects in each of the two menopause groups, used as stratification variables in the analyses, were similar in both treatment groups: ≤5 years since menopause (50%) and > 5 years since menopause (50%).

Table 3.11
Study 20040132: Randomization and Disposition of All Subjects

	Denosumab	Placebo
Number Randomized and Took Study Drug (ITT)	164	165
Number Analyzed for Primary Efficacy of Lumbar Spine BMD n (%)*	163 (99.4)	163 (98.8)
Completed n (%)*	142 (86.6)	144 (87.3)
Discontinued n (%)*	22 (13.4)	21 (12.7)
Primary Reason for Discontinuation n (%)*:		
Subject Withdrew Consent	10 (6.1)	14 (8.5)
Lost to Follow-up	7 (4.3)	5 (3.0)
Adverse Event	1 (0.6)	2 (1.2)
Other	4 (2.4)	0 (0.0)

Source: Table 14-1.2.1, pages 219-220, Study 20040132 report and ASLINFO dataset.
* With respect to number of randomized subjects.

3.2.4 *Prevention Study 20040132 Efficacy Results*

The Applicant's results, which I have verified, for the primary efficacy endpoint of percent change from baseline in lumbar spine BMD at Month 24 and secondary efficacy endpoint of percent change from baseline in total hip BMD at Month 24 are presented in Tables 3.12 and 3.13 for each menopause subgroup and overall. Denosumab demonstrated improved efficacy compared to placebo as described below.

For lumbar spine BMD:

- In the ≤5 years since menopause subgroup, the mean percent change from baseline in lumbar spine BMD at Month 24 was 6.2% for denosumab vs. -1.2% for placebo. This gives a mean increase in lumbar spine BMD of 7.4% for denosumab compared to placebo (97.5% CI: 6.1% to 8.7%, $p < 0.0001$).
- In the > 5 years since menopause subgroup, the mean percent change from baseline in lumbar spine BMD at Month 24 was 6.8% for denosumab vs. 0.1% for placebo. This gives a mean increase in lumbar spine BMD of 6.7% for denosumab compared to placebo (97.5% CI: 5.4% to 8.0%, $p < 0.0001$).
- Overall, the mean percent change from baseline in lumbar spine BMD at Month 24 was 6.5% for denosumab vs. -0.6% for placebo. This gives a mean increase in lumbar spine BMD of 7.0% for denosumab compared to placebo (95% CI: 6.2% to 7.8%, $p < 0.0001$).

Table 3.12
[redacted] umbar Spine BMD - Treatment Difference for Percent Change from Baseline at Month 24
(Primary Efficacy Population, LOCF)

	n	LS Mean[1]	LS Mean Difference[1] (95% C.I.)	p-value
≤5 Years Since Menopause				
Denosumab	79	6.2%	7.4% (6.1%, 8.7%)	< 0.0001
Placebo	80	-1.2%		
> 5 Years Since Menopause				
Denosumab	84	6.8%	6.7% (5.4%, 8.0%)	< 0.0001
Placebo	83	0.1%		
	n	**LS Mean[1]**	**LS Mean Difference[1] (97.5% C.I.)**	**p-value**
Overall				
Denosumab	163	6.5%	7.0% (6.2%, 7.8%)	< 0.0001
Placebo	163	-0.6%		

Source: Table 9-1, page 133, Study 20040132 report.
[1] Least Squares mean estimates, confidence intervals, and p-values based on an ANOVA model (for each stratum) with treatment, baseline value, machine type, and baseline value-by-machine type interaction; the model for overall assessment also adjusts for strata.

For total hip BMD:

- In the ≤5 years since menopause subgroup, the mean percent change from baseline in total hip BMD at Month 24 was 3.5% for denosumab vs. -1.0% for placebo. This gives a mean increase in total hip BMD of 4.6% for denosumab compared to placebo (97.5% CI: 3.8% to 5.3%, p < 0.0001).
- In the > 5 years since menopause subgroup, the mean percent change from baseline in total hip BMD at Month 24 was 3.2% for denosumab vs. -1.2% for placebo. This gives a mean increase in total hip BMD of 4.5% for denosumab compared to placebo (97.5% CI: 3.7% to 5.3%, p < 0.0001).
- Overall, the mean percent change from baseline in total hip BMD at Month 24 was 3.4% for denosumab vs. -1.1% for placebo. This gives a mean increase in total hip BMD of 4.5% for denosumab compared to placebo (95% CI: 4.0% to 5.0%, p < 0.0001).

Table 3.13
Study 20040132: Total Hip BMD - Treatment Difference for Percent Change from Baseline at Month 24
(Primary Efficacy Population, LOCF)

	n	LS Mean[1]	LS Mean Difference[1] (95% C.I.)	p-value
≤5 Years Since Menopause				
Denosumab	79	3.5	4.6% (3.8%, 5.3%)	< 0.0001
Placebo	80	-1.0		
> 5 Years Since Menopause				
Denosumab	84	3.2	4.5% (3.7%, 5.3%)	< 0.0001
Placebo	83	-1.2		
	n	**LS Mean[1]**	**LS Mean Difference[1] (97.5% C.I.)**	**p-value**
Overall				
Denosumab	163	3.4%	4.5% (4.0%, 5.0%)	< 0.0001
Placebo	163	-1.1%		

Source: Table 9-2, page 138 of Study 20040132 report.
[1] Least Squares mean estimates, confidence intervals, and p-values based on an ANOVA model (for each stratum) with treatment, baseline value, machine type, and baseline value-by-machine type interaction; the model for overall assessment also adjusts for strata.

3.3 Evaluation of Safety

For information about the evaluation of safety, refer to the clinical evaluation of safety section.

4. FINDINGS IN SUBGROUP POPULATIONS

For treatment study 20030216, the clinical reviewer was interested in an analysis of new vertebral fractures by prevalent vertebral fracture at study entry. The results of this analysis, presented in Table 4.1, are similar to those for the overall population (see Table 3.3) at month 36.

Table 4.1
Study 20030216: Subject Incidence, Absolute Risk Reduction, and Odds Ratio for New Vertebral Fracture Through Month 36 by Prevalent Vertebral Fracture (Yes/No)
(Primary Efficacy Analysis Set*, LOCF Imputation)

		Number of Events	Crude Incidence %	Absolute Risk Reduction* % (95% C.I.)	Relative Risk Reduction[1] % (95% C.I.)	Odds Ratio[2] (95% C.I.)
Yes						
	Denosumab (N=883)	41	4.6	9.0 (6.3, 11.7)	66 (52, 76)	0.31 (0.21, 0.44)
	Placebo (N=853)	116	13.6			
No						
	Denosumab (N=2727)	45	1.7	3.6 (2.6, 4.6)	69 (56, 78)	0.30 (0.21, 0.42)
	Placebo (N=2727)	143	5.2			

Source: Table 14-4.3.8, page 476, Study 20030216 report.
* 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.

5. CONCLUSIONS

No statistical issues were identified 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.

From a statistical perspective, the two submitted studies (3-year treatment Study 20030216 and 2-year prevention Study 20040132) provide supportive evidence demonstrating the efficacy of Prolia (s.c. denosumab 60 mg twice yearly) Injection for the treatment and prevention of osteoporosis in postmenopausal women based on the endpoints of incidence of new vertebral fractures, incidence of non-vertebral fractures, incidence of hip fractures, lumbar spine bone mineral density, and total hip bone mineral density. Overall, there was a decrease in the incidence for new vertebral, non-vertebral, and hip fractures. Also, there was an increase in the bone mineral density of the lumbar spine and total hip with denosumab use compared to placebo.

However, when fracture data is tabulated by 1-year intervals, there were counterintuitive results given that the percentage of fractures should either decrease or remain the same when using an osteoporosis treatment. Specifically, within the denosumab group, for both new vertebral fractures and hip fractures, the percentage of fractures fluctuated by decreasing within year 2 compared to within year 1 and then increasing within year 3 compared to within year 2. That is, the percentage of new vertebral fractures and percentage of hip fractures within year 3 was nearly a threefold increase compared to within year 2. Also, the percentage of hip fractures within year 3 was greater in the denosumab group compared to the placebo group, suggesting that the percentage of hip fractures in the denosumab group had caught up with that in the placebo group.

6. APPENDIX

Table A.1
Study 20030216: Enrollment Summary by Country (Randomized Subjects)

Country	Total number of subjects enrolled n (%)
Denmark	1254 (15.9)
Poland	955 (12.1)
United Kingdom	790 (10.0)
Czech Republic	514 (6.5)
Argentina	477 (6.1)
Brazil	457 (5.8)
Estonia	429 (5.5)
United States	355 (4.5)
Hungary	234 (3.0)
Italy	220 (2.8)
Spain	209 (2.7)
Lithuania	192 (2.4)
Germany	183 (2.3)
Norway	161 (2.0)
Bulgaria	143 (1.8)
Sweden	135 (1.7)
Slovakia	122 (1.6)
France	120 (1.5)
Belgium	118 (1.5)
Mexico	114 (1.4)
Latvia	111 (1.4)
Canada	110 (1.4)
Austria	100 (1.3)
Netherlands	75 (1.0)
Switzerland	58 (0.7)
New Zealand	47 (0.6)
Australian	45 (0.6)
Greece	43 (0.5)
Finland	39 (0.5)
Malta	29 (0.4)
Serbia and Montenegro	17 (0.2)
Romania	12 (0.2)

Source: Table 14-1.1.9, pages 414 to 429, Study C20030216 report.

7. SIGNATURES

Sonia Castillo 8-17-09

Sonia Castillo, Ph. D.
Primary Statistical Reviewer

8-18-09

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA Number(s):	125-320, 125-331, 125-332, 125-333
Drug Name:	PROLIA (denosumab) 60mg/Q6M subcutaneous
Requested Indication(s):	(1) Treatment of postmenopausal osteoporosis (2) Prevention of postmenopausal osteoporosis (3) Treatment and prevention of bone loss associated with hormone ablation therapy with breast cancer (4) Treatment and prevention of bone loss associated with hormone ablation therapy with prostate cancer
Applicant:	Amgen, Inc.
Stamp Date:	12/19/08
PDUFA Date:	10/19/09
Review completed on:	8/10/09
Review Priority:	Standard
Biometrics Division:	Quantitative Safety and Pharmacopidemiology Group
Statistical Reviewer:	Anita Abraham, DrPH
Secondary Reviewers:	Paul Schuette, PhD; C. George Rochester, PhD, RAC
Medical Division(s):	Division of Reproductive and Urological Products (DRUP) and Division of Biologic Oncology Products (DBOP)
Clinical Team(s):	Suzanne Demko, PA-C (DBOP), Theresa Kehoe, MD (DRUP), Vaishali Popat, MD, MPH (DRUP) Adrienne Rothstein, PhD (DRUP)
Project Manager:	Melanie Pierce, BS (DBOP), Celia Peacock MPH, RD (DRUP)

Keywords: Osteoporosis, Bone Loss, Osteonecrosis of the Jaw, Delayed Fracture Healing, Malignancies

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1 EXECUTIVE SUMMARY

This document represents a statistical safety review of Amgen Inc.'s application for the approval of their fully monoclonal antibody, denosumab (PROLIA) (BLA#'s: 125-320, 125-331, 125-332, 125-333), for use in the prevention and treatment of osteoporosis in post-menopausal (PMO) women, and for use in the prevention and treatment of bone loss in patients undergoing hormone ablation therapy (HALT), administered at the proposed dose of 60mg injected subcutaneously every 6 months. This review is a safety review, evaluating denosumab's impact on three adverse events of interest: (1) Osteonecrosis of the Jaw (ONJ), (2) Delayed Fracture Healing, and (3) Incidence of New Primary Malignancies.

Denosumab is a fully monoclonal antibody that binds to and inhibits the action of receptor activator of nuclear factor κB (RANK) ligand. The RANK ligand is a type I membrane protein that is directly involved in the activation of osteoclasts upon ligand binding. This ligand has also been found on the surface of T cells and transcriptionally regulates the transcription necrosis factor (TNF). The inhibition of osteoclast function by this antibody is believed to reduce the level of bone loss experienced in patients with postmenopausal osteoporosis and those undergoing hormone ablation therapy. However, drugs used in similar indications, bisphosphonates, have also been associated with adverse events relating to this disruption in the bone creation/resorption cycle. Two of the adverse events of concern due to this disruption are osteonecrosis of the jaw and delayed fracture healing. Also, as this biologic is known to inhibit a regulator of TNF, adverse events relating to the immunogenic response are of concern. A specific adverse event of concern due to this mechanism is a potential increase in the incidence of malignancies. This review will consider the incidence of these three adverse events, primarily focusing on four pivotal Phase 3 clinical studies and additionally considering five other Phase 2 and Phase 3 studies where a control arm was present. The studies that focused on PMO women were pooled for further analysis.

1.1 Conclusions and Recommendations

There does not appear to be a difference in risk of osteonecrosis of the jaw or delayed fracture healing between denosumab and placebo groups. The results for new primary malignancies are not as consistent. However, as all three of these adverse events may take time to develop, continued monitoring is advised.

For ONJ, though there were concerns that the ONJ adjudication committee selected by the sponsor used a narrow criterion (using MedDRA v.11.0) when ascertaining ONJ cases and no cases were identified, a broadening of the criterion in this analysis resulted in no significant difference between the denosumab and placebo groups. There was a significant difference in the severity gradient between the alendronate subjects and the placebo subjects in trials employing active controls, with alendronate subjects experiencing more severe adverse events. However, the denosumab and placebo groups tended to have similar distributions of events in all the analyses.

For delayed fracture healing, the nonclinical overview showed that the sponsor found issues in bony callus formation among genetically modified mice that were monitored after being subjected to closed femoral fractures. The bony callus appeared to be larger and had a different consistency compared to those in the placebo group. This issue may affect the mobility of the bone, but is not expected to affect its strength. Only the four pivotal trials (Study #'s 20030216, 20040132, 20040135 and 20040138) contained data that specifically considered fracture healing outcomes. Moreover, as the outcome of delayed fracture healing is one that can take up to five years to be fully determined, further long-term follow-up of this adverse event would be worthwhile. From the data provided, there appears to be a balanced distribution between groups for fracture healing outcomes.

For new primary maligancies, there generally appears to be a balanced distribution of adverse events with one notable exception. The only study that had significantly more events in the denosumab group was Study 20040138 whose population consisted of men with non-metastatic prostate cancer undergoing androgen deprivation therapy. The high level group term that drives the difference between groups in this study is "Metastases" and further investigation of this term shows that the increased number of adverse events in the denosumab group is mainly due to the preferred term "Metastases to bone". In all the other populations studied by the sponsor, this metastases issue does not arise and the difference between treatment and control groups is minimal. Again, as the appearance of new primary malignancies tends to be a long-term outcome, continued monitoring of this adverse event would be of use.

1.2 Brief Overview of Clinical Studies

This review evaluates data provided by nine (9) studies. The studies that were chosen for the review included all blinded studies that contained a control arm (either alendronate and/or placebo). Four of these studies are considered to be pivotal by the sponsor (20030216, 20040132, 20040135 and 20040138). Of these nine trials, three were Phase 2 trials and six were Phase 3 trials. Seven of these studies (20010223, 20030216, 20040132, 20050141, 20050179, 20050234) evaluated the biologic in PMO women. Study 20040135 evaluated the biologic in a Phase 3 trial in women with breast cancer (HALT), and Study 20040138 evaluated the biologic in men with prostate cancer (HALT).

1.3 Statistical Issues and Findings

To quantitatively evaluate the three specific adverse events of interest in this review, categorical data analysis methods were used. First, after identifying subjects in the safety analysis set experiencing the adverse events of interest, differences between arms were quantified by risk differences and relative risks to determine if there was a significant difference between groups. If there were more than two groups in a study, Fisher's exact test was performed to determine if there was an overall difference between treatment arms, and this difference was then quantified using pairwise comparisons between the control arm and the arm of interest. A pooled analysis was performed, in which all subjects of the PMO studies of interest were pooled. In this analysis, for the denosumab arm, only subjects who received the 60mg Q6M dose of the investigational product were evaluated, as this is the dosage that is being evaluated for approval. In evaluating the pooled analyses, a Cochran-Mantel-Haenszel (CMH) chi-square was used to evaluate the difference between groups for severity gradients. Exact methods were employed when warranted by the number of events (fewer than 5 events in a category).

When evaluating ONJ related adverse events, there did not appear to be a significant difference between denosumab and the comparison arm in any of the studies. For the fracture healing outcome, fracture healing was evaluated only in the pivotal trials, so these four studies were evaluated separately. Only study 20030216 contained more than one subject per arm with a fracture healing complication, and while this may be due to a lack of events, the increased number in 20030216 may also be due to extra diligence as a radius healing substudy was a part of the protocol. For the evaluation of new primary malignancies, the only study that contained a statistically significant safety signal was study 20040138, as discussed previously. In all other studies evaluated, no major signals were observed.

2 INTRODUCTION

2.1 Overview

Denosumab is a fully monoclonal antibody that binds to and inhibits the action of receptor activator of nuclear factor κB (RANK) ligand. The RANK ligand is a type I membrane protein that is directly involved in the activation of osteoclasts upon ligand binding. This ligand has also been found on the surface of T cells and transcriptionally regulates the transcription necrosis factor (TNF). The inhibition of osteoclast function by this antibody is believed to reduce the level of bone loss experienced in patients with postmenopausal osteoporosis and those undergoing hormone ablation therapy. However, drugs used in similar indications, bisphosphonates, have also been associated with adverse events relating to this disruption in the bone creation/resorption cycle. Two of the adverse events of concern due to this disruption are osteonecrosis of the jaw and delayed fracture healing. Also, as this biologic is known to inhibit a regulator of TNF, adverse events relating to the immunogenic response are of concern. A specific adverse event of concern due to this mechanism is a potential increase in the incidence of malignancies. This review will consider the incidence of these three adverse events, primarily focusing on nine Phase 2 and Phase 3 studies and on a pooled analysis of the PMO trials.

2.2 Data Sources

Data from nine studies were used in the review. These studies were selected because they were double-blinded and had randomized treatment arms. In addition to these nine studies, other materials reviewed

included the nonclinical study report and the summary review of Phase 1 and Phase 2 studies provided by the sponosor. Clinical study reports for each of the studies reviewed were also considered. For assessment of the "Delayed Fracture Healing" adverse event, fracture healing outcomes included in the fracture healing analysis dataset (AAEFX) were considered, when provided. (Note: While study 20010223 did include an AAEFX dataset, this dataset did not include any fracture healing outcome data).

Table 1 lists the studies included in this review and provides a brief description of the study population and length of study in each trial:

Table 1: List of all studies included in analysis

Study	Phase	Treatment Period	Follow-up Period	Approximate # of Subjects per Arm	Study Population
20010223	Phase 2	24 months	24 months	40	PMO Women
20030216*	Phase 3	36 months	——	3900	PMO Women
20040132*	Phase 3	24 months	24 months	165	PMO Women
20040135*	Phase 3	24 months	24 months	130	Women with Breast Cancer (HALT)
20040138*	Phase 3	36 months	24 months	730	Men with Prostate Cancer (HALT)
20050141	Phase 3	12 months	——	600	PMO Women
20050172	Phase 2	12 months	——	50	Japanese PMO Women
20050179	Phase 2	12 months	——	80	PMO Women
20050234	Phase 3	12 months	——	250	PMO Women

* trials considered pivotal by sponsor

As can be observed in Table 1, seven of the studies focused on PMO women and two studies considered subjects on hormone ablation therapy. Two of the Phase 2 studies included, 20010223 and 20050172, were dose-ranging studies that considered the osteoporosis indication. The third Phase 2 study, 20050179, compared denosumab to placebo and alendronate, where the primary objective was to assess the effect of denosumab on the cortical thickness of the distal radius at 12 months. Including study 20050179, three trials included an alendronate comparison arm: Studies 20010223, 20050179 and 20050234. Table 29, in the Appendix, summarizes the datasets considered in this analysis and where they are found in the CDER Electronic Document Room (EDR)

3 OSTEONECROSIS OF THE JAW (ONJ)

3.1 Background

Osteonecrosis of the jaw (ONJ) is a rare condition that is usually identified by its unique clinical presentation of exposed bone in the oral cavity. Signs and symptoms of ONJ include localized pain, soft-tissue swelling and inflammation, loosening of previously stable teeth, drainage and exposed bone. The pathogenesis of this condition is not well understood, and it is likely that ONJ is a clinical entity with many possible etiologies. Recently, a link has been drawn between bisphosphonates and ONJ (Ruggiero et al. 2004). As both denosumab and bisphosphonates inhibit the action of osteoclasts, ONJ is an adverse event of interest for this biologic. Amgen assembled an external panel of independent experts to ensure that all potential cases of ONJ were reviewed and adjudicated based on standard definition criteria and events meeting these criteria were submitted for review by the independent ONJ Adjudication Committee, which was blinded to treatment assignments. There were no positively adjudicated cases of ONJ in any the studies under consideration, so this analysis will focus on possible symptoms of ONJ.

3.2 Analysis

To analyze the adverse event of ONJ, all the MedDRA version 11.0 preferred terms listed in the adverse events (AAE) dataset of the integrated summary of safety (ISS) were considered. The preferred terms that were determined to be possible signs, symptoms or precursors to ONJ were included in a list. After making this list, it was compared to the list of preferred terms used by the adjudication committee in selecting subjects to evaluate for this adverse event. The adjudication committee used 33 MedDRA preferred terms to select their subjects. An additional 35 preferred terms, which were considered to be related to ONJ, were included in the current evaluation. All of these terms and their occurence rates in the treatment groups compared to the control groups of the safety analysis datasets were tabulated and large differences in incidence.were considered; risk ratios, risk differences and related confidence intervals were calculated. If there were more than two groups in a study, Fisher's exact test was performed to determine if there was an overall difference between treatment arms, and this difference was then quantified using pairwise comparisons between the control arm and the arm of interest. Additional investigations include comparing serious vs. non-serious events and comparing the severity gradient for treatment in this class of events. A pooled analysis was performed, in which all subjects of the PMO studies analyzed were pooled. In this analysis, for the denosumab arm, only subjects who received the 60mg Q6M dose of the investigational product were evaluated, as this is the dosage that is being evaluated for approval. In evaluating the pooled analyses, a Cochran-Mantel-Haenszel chi-square was used to evaluate the difference between groups for severity gradients. Exact methods were employed when warranted by the number of events (fewer than 5 events in a category). Table 2 lists the terms used by the sponsor's ONJ adjudication committee and the additional terms used in this review:

Table 2: MedDRA v.11.0 Terms used to identify ONJ-related Adverse Events

Terms used by ONJ Adjudication Committee:		Additional terms used in search:	
Abscess jaw	Oral cavity fistula	Gingival bleeding	Oral discomfort
Abscess oral	Oral surgery	Gingival cyst	Oral disorder
Alveolar osteitis	Oroantral fistula	Gingival disorder	Oral infection
Bone debridement	Osteitis	Gingival erythema	Oral pain
Bone erosion	Osteomyelitis	Gingival hypertrophy	Periodontal disease
Bone fistula	Osteomyelitis chronic	Gingival infection	Periodontitis
Bone infarction	Osteomyelitis drainage	Gingival operation	Tooth abscess
Dental fistula	Osteonecrosis	Gingival pain	Tooth avulsion
Dental necrosis	Pain in jaw	Gingival recession	Tooth deposit
Gingival abscess	Periodontal destruction	Gingival swelling	Tooth disorder
Gingival erosion	Periodontal infection	Gingivitis	Tooth extraction
Gingival ulceration	Periodontal operation	Jaw cyst	Tooth fracture
Jaw lesion excision	Primary sequestrum	Jaw disorder	Tooth infection
Jaw operation	Secondary sequestrum	Jaw fracture	Tooth injury
Loose tooth	Sequestrectomy	Mouth cyst	Tooth loss
Maxillofacial operation	Tertiary sequestrum	Mouth ulceration	Tooth repair
Necrosis		Oral bacterial infection	Toothache

3.2.1 Pre-clinical Findings

No pre-clinical studies were conducted to specifically consider this adverse event.

3.2.2 Phase 1 and 2 Trials

One case of periodontal infection was found in the phase 1 study 20030164. Additionally, one case of ONJ was reported in the Phase 2 study 20050134, which was not included in the nine studies under review, since it did not contain a control arm. Tabulations of relevant adverse events from trials where data was analyzed can be found in the Appendix, Section 8.1.1, Tables 30-33. A listing of all adverse events found in the Phase 2 studies and a quantification of relative risks and risk differences are provided below. Additionally, if the study contained more than 2 arms, a Fisher exact test was conducted to determine if there was a difference between any of the groups, and relative risks and risk differences were calculated using the placebo group as the reference.

Table 3 lists the number of subjects with adverse events and total subjects in the studies by arm, and Table 4 lists the results from the data analysis.

Table 3: Summary Table of Adverse Events for Phase 1 and 2 Trials for ONJ

Study	Subjects with Adverse Event			Total Subjects		
Number	Denosumab	Placebo	Alendronate	Denosumab	Placebo	Alendronate
20010223	34	6	6	314	46	46
20050172	14	2	—	158	54	—
20050179	3	10	2	83	83	81

Table 4: Summary Table of Statistics for Phase 1 and 2 Trials for ONJ

Study		Fisher statistic	p-value
20010223	Difference between arms	0.5985	0.7414
20050179	Difference between arms	6.882	0.0314

Study	Placebo comparison group	Risk Diff.	95% CI	Rel. Risk	95% CI	p-value
20010223	Denosumab	-0.0222	(-0.152, 0.058)	0.8301	(0.391, 1.88)	0.6552
	Alendronate	0	(-0.146, 0.146)	1	(0.361, 2.77)	1
20050172*	Denosumab	0.0516	(-0.043, 0.115)	2.392	(0.626, 13.04)	0.2308
20050179*	Denosumab	-0.0843	(-0.180, -0.002)	0.3	(0.0651. 0.973)	0.0443
	Alendronate	-0.0958	(-0.190, -0.0177)	0.205	(0.0380, 0.808)	0.0191

*exact methods used

As can be observed from Table 4, there were no statistically significant differences in the number of adverse events in the treatment groups compared to placebo in any of trials. However, in Study 20050179, the placebo group had a significantly higher number of adverse events compared to the denosumab and alendronate groups.

3.2.3 Phase 3 Trials

All of the ONJ relevant adverse events in Phase 3 trials are tabulated below and differences between groups are quantified using relative risks and risk differences. A tabulation of all preferred terms used in the analysis are listed in the Appendix, Section 8.1.1, Tables 34-40.

Table 5 lists the number of subjects with adverse events and total subjects in the studies by arm, and Table 6 lists the risk differences and relative risks with their associated confidence intervals and p-values.

Table 5: Summary Table of Adverse Events for Phase 3 Trials for ONJ

Study	Subjects with Adverse Event			Total Subjects		
Number	Denosumab	Placebo	Alendronate	Denosumab	Placebo	Alendronate
20030216	158	155	—	3886	3876	—
20040132	20	16	—	164	165	—
20040135	3	1	—	129	120	—
20040138	19	24	—	731	725	—
20050141	30	—	25	593	—	586
20050234	6	—	11	253	—	249

Table 6: Summary Table of Statistics for Phase 3 Trials for ONJ

Study	Risk Diff.	95% CI	Rel. Risk	95% CI	p-value
20030216	0.00067	(-0.0081, 0.0095)	1.017	(0.8187, 1.263)	0.8809
20040132	0.025	(-0.438, 0.095)	1.258	(0.6825, 2.323)	0.468
20040135*	0.0149	(-0.0266, 0.0605)	2.791	(0.4092, 35.48)	0.5297
20040138	-0.0071	(-0.0254, 0.0107)	0.785	(0.4374, 1.409)	0.4229
20050141	0.0079	(-0.0166, 0.0328)	1.186	(0.7102, 1.981)	0.5187
20050234	-0.0205	(-0.0565, 0.0123)	0.537	(0.2084, 1.378)	0.2051

* exact methods used

Table 6 indicates that there were no significant differences between groups for the number of adverse events in any of the trials.

3.2.4 Serious Adverse Events

Only five of the studies have any serious ONJ-related adverse events. Only studies 20030216 and 20040138 had any serious adverse events in the denosumab group. There did not appear to be a difference between groups in the number of serious adverse events in any of the studies. Tabulations of serious adverse events in all studies where there were SAEs are provided in the Appendix, Section 8.1.2, Tables 41-46.

3.2.5 Severity Gradient

There does not appear to be a difference between groups for the severity gradient of ONJ-related adverse events in any of the trials. Full tabulations of the severity gradient in all studies are provided in the Appendix, Section 8.1.3, Tables 47-56.

3.2.6 PMO Pooled Analysis

For the pooled analysis, all studies targeting post-menopausal women who were randomized to denosumab were pooled. This led to the pooling of 7 trials: 20010223, 20030216, 20040132 (36-month), 20050141, 20050172, 20050179, 20050234. For this analysis differences between treatments (alendronate, Denosumab 60mg Q6M and Placebo) in terms of PTs, HLGTs, Serious Events, Severity Gradient and Discontinuation of Drug for subjects experiencing ONJ-related adverse events.

Tables 7 and 8 list the number of subjects with ONJ-related preferred terms in order of most common occurrence for all subjects in the pooled studies.

Table 7: PMO Pooled Analysis - ONJ Preferred Terms (Part 1)

Dictionary-Derived Term	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW
Subjects in Arm	5073 (100.00%)	4231 (100.00%)	963 (100.00%)
Tooth infection	34 (0.67%)	44 (1.04%)	7 (0.73%)
Toothache	34 (0.67%)	35 (0.83%)	8 (0.83%)
Periodontitis	27 (0.53%)	19 (0.45%)	5 (0.52%)
Gingivitis	18 (0.35%)	11 (0.26%)	3 (0.31%)
Tooth fracture	15 (0.30%)	9 (0.21%)	7 (0.73%)
Pain in jaw	11 (0.22%)	6 (0.14%)	5 (0.52%)
Gingival infection	8 (0.16%)	11 (0.26%)	2 (0.21%)
Tooth disorder	8 (0.16%)	7 (0.17%)	3 (0.31%)
Mouth ulceration	9 (0.18%)	6 (0.14%)	2 (0.21%)
Gingival pain	7 (0.14%)	1 (0.02%)	3 (0.31%)
Tooth extraction	6 (0.12%)	5 (0.12%)	0 (0.00%)
Osteitis	5 (0.10%)	6 (0.14%)	0 (0.00%)
Gingival abscess	4 (0.08%)	4 (0.09%)	1 (0.10%)
Periodontal disease	4 (0.08%)	3 (0.07%)	0 (0.00%)
Oral pain	3 (0.06%)	3 (0.07%)	0 (0.00%)
Osteonecrosis	5 (0.10%)	1 (0.02%)	0 (0.00%)
Tooth injury	5 (0.10%)	1 (0.02%)	0 (0.00%)
Oral infection	3 (0.06%)	2 (0.05%)	0 (0.00%)
Gingival bleeding	4 (0.08%)	1 (0.02%)	0 (0.00%)
Loose tooth	0 (0.00%)	3 (0.07%)	2 (0.21%)

continuing

Table 8: PMO Pooled Analysis - ONJ Preferred Terms (Part 2)

Dictionary-Derived Term	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW
Subjects in Arm	5073 (100.00%)	4231 (100.00%)	963 (100.00%)
Gingival swelling	0 (0.00%)	4 (0.09%)	0 (0.00%)
Abscess oral	1 (0.02%)	2 (0.05%)	0 (0.00%)
Gingival ulceration	0 (0.00%)	2 (0.05%)	0 (0.00%)
Osteomyelitis	2 (0.04%)	1 (0.02%)	0 (0.00%)
Periodontal infection	2 (0.04%)	0 (0.00%)	1 (0.10%)
Dental necrosis	1 (0.02%)	1 (0.02%)	0 (0.00%)
Gingival cyst	1 (0.02%)	1 (0.02%)	0 (0.00%)
Gingival disorder	1 (0.02%)	0 (0.00%)	1 (0.10%)
Oral bacterial infection	1 (0.02%)	1 (0.02%)	0 (0.00%)
Tooth loss	1 (0.02%)	0 (0.00%)	1 (0.10%)
Alveolar osteitis	0 (0.00%)	1 (0.02%)	0 (0.00%)
Bone erosion	0 (0.00%)	1 (0.02%)	0 (0.00%)
Bone fistula	0 (0.00%)	1 (0.02%)	0 (0.00%)
Bone infarction	0 (0.00%)	1 (0.02%)	0 (0.00%)
Gingival hypertrophy	1 (0.02%)	0 (0.00%)	0 (0.00%)
Gingival operation	0 (0.00%)	1 (0.02%)	0 (0.00%)
Jaw cyst	1 (0.02%)	0 (0.00%)	0 (0.00%)
Jaw disorder	1 (0.02%)	0 (0.00%)	0 (0.00%)
Mouth cyst	1 (0.02%)	0 (0.00%)	0 (0.00%)
Oral cavity fistula	1 (0.02%)	0 (0.00%)	0 (0.00%)
Oral disorder	0 (0.00%)	1 (0.02%)	0 (0.00%)
Tooth avulsion	0 (0.00%)	1 (0.02%)	0 (0.00%)
Tooth deposit	0 (0.00%)	1 (0.02%)	0 (0.00%)
Subjects with AE	206 (4.06%)	172 (4.06%)	41 (4.25%)

Table 9 lists the number of subjects with ONJ-related adverse events listed by high level group term.

Table 9: PMO Pooled Analysis - ONJ High Level Group Terms

High Level Group Term	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW
Subjects in Arm	5073 (100.00%)	4231 (100.00%)	963 (100.00%)
Dental and gingival conditions	100 (1.97%)	81 (1.91%)	24 (2.49%)
Infections - pathogen unspecified	51 (1.01%)	63 (1.49%)	8 (0.83%)
Bone disorder (excl. congenital and fractures)	23 (0.45%)	16 (0.38%)	5 (0.52%)
Injuries NEC	20 (0.39%)	11 (0.26%)	7 (0.73%)
Oral soft tissue conditions	12 (0.24%)	14 (0.33%)	2 (0.21%)
Head and neck therapeutic procedures	6 (0.12%)	6 (0.14%)	0 (0.00%)
Infections - pathogen class unspecified	3 (0.06%)	1 (0.02%)	3 (0.31%)
Bacterial infectious disorders	1 (0.02%)	1 (0.02%)	0 (0.00%)
Benign neoplasms gastrointestinal	1 (0.02%)	0 (0.00%)	0 (0.00%)
Gastrointestinal conditions NEC	1 (0.02%)	0 (0.00%)	0 (0.00%)
Subjects with AE	206 (4.06%)	172 (4.06%)	41 (4.25%)

Table 10 lists the risk difference, relative risk and associated confidence intervals and statistics for the pooled analysis to evaluate a difference between groups.

Table 10: PMO Pooled Analysis - Overall ONJ Relative Risk and Risk Difference

Reference Group= Placebo	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW	Fisher statistic value	p-value
Risk difference	0.000045	—	0.00192	0.1211	0.9444
RD 95% CI	(-0.0082, 0.0080)		(-0.01089, 0.0176)		
Relative Risk	0.9989	—	1.047		
RR 95% CI	(0.8195, 1.218)		(0.7505, 1.457)		

Table 11 lists the occurence of SAEs in the pooled analysis, and Table 12 evaluates the difference between treatment groups based on the frequency of SAEs by means of relative risk, risk difference and the Fisher exact test statistic.

Table 11: PMO Pooled Analysis - ONJ Serious Adverse Events

Serious Adverse Event	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW
Subjects in Arm	5073 (100.00%)	4231 (100.00%)	963 (100.00%)
No SAE	204 (4.02%)	170 (4.02%)	39 (4.05%)
SAE present	3 (0.06%)	2 (0.05%)	3 (0.31%)
Subjects with AE	206 (4.06%)	172 (4.06%)	41 (4.25%)

Table 12: PMO Pooled Analysis - ONJ SAE Relative Risk and Risk Difference

Reference Group= Placebo	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW	Fisher statistic value	p-value
Risk difference	0.00012	—	0.0026	5.45	0.0648
RD 95% CI	(-0.0012, 0.0013)		(.000353, 0.00867)		
Relative Risk	1.251	—	6.59		
RR 95% CI	(0.2502, 6.255)		(1.318, 32.92)		

Table 13 lists the ONJ associated adverse events in the pooled analysis by severity and evaluates the difference between groups using a Cochran-Mantel-Haenszel chi-square statistic.

Table 13: PMO Pooled Analysis - ONJ Severity Gradient

Adverse Event Severity Grade	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW	CMH Chi-square
Subjects in Arm	5073 (100.00%)	4231 (100.00%)	963 (100.00%)	3.178
Mild	121 (2.38%)	94 (2.22%)	22 (2.28%)	
Moderate	91 (1.79%)	77 (1.82%)	18 (1.87%)	
Severe	4 (0.08%)	11 (0.26%)	4 (0.42%)	p-value
Subjects with AE	206 (4.06%)	172 (4.06%)	41 (4.25%)	0.2042

Table 14 lists the subjects where the drug was discontinued among the pooled studies.

Table 14: PMO Pooled Analysis - ONJ Discontinuation of Drug

Drug Discontinued	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW
Subjects in Arm	5073 (100.00%)	4231 (100.00%)	963 (100.00%)
Drug discontinued	0 (0.00%)	0 (0.00%)	1 (0.10%)
Subjects with AE	206 (4.06%)	172 (4.06%)	41 (4.25%)

While there is no difference between any of the groups for ONJ-related adverse events (Table 10), there is a significant difference between the alendronate and placebo groups for serious adverse events (Table 12). There are significantly more serious adverse events for ONJ-related AEs in the alendronate group compared to the placebo group. This difference is not significant in the severity gradient or in the drug discontination tabulations (Tables 13 and 14). There are no differences in the number of events in any of the tables between the denosumab group and the placebo group.

3.3 Conclusions

From this analysis, there does not appear to be an increased risk of ONJ-related events in the denosumab group. There were some issues found with the sponsor's ONJ adjudication process, namely that the criterion provided by the sponsor for this adverse event may have been too narrow. However, using a larger number of ONJ-related dictionary-derived terms (or preferred terms, PTs) does not result in an imbalance between the denosumab and placebo groups in any of the trials. It could be argued that the larger list of adverse events used in this analysis may be too broad, but even considering events at the PT level, there does not appear to be a large difference between groups, and therefore it appears that denosumab does not increase the risk of ONJ-related adverse events.

4 DELAYED FRACTURE HEALING

4.1 Background

Denosumab's inhibition of the function of osteoclasts in bone resorption leads to the issue of whether fracture healing would occur normally. Drugs that inhibit osteoclasts, bisphosphonates, were shown to inhibit fracture healing, and to cause a delay in the formation of a bony callus, which in turn delayed the healing of the fracture. The only human studies that took account of fracture healing outcomes were the four "pivotal" trials. All four of these trials included a separate dataset that accounted for patients with non-vertebral fractures. None of the other studies have any accounting of these outcomes.

4.2 Analysis

4.2.1 Methodology

Since fracture healing was only evaluated in the four pivotal trials, the other trials could not be evaluated for this outcome. All fracture occurences in the other trials were tabulated and are present in the appendix. In the pivotal Phase 3 trials, the fracture healing outcomes were tabulated. Because only Study 20030216 had more than one fracture healing event per group, it was the only study where risk ratios, risk differences and related confidence intervals were calculated for all fracture healing complications. Also, for all tabulations of fractures, only non-vertebral fractures were considered, as they are the adverse events of primary concern when dealing with delayed fracture healing issues. Only non-vertebral fractures were evaluated by the sponsor in the fracture healing datasets of the pivotal trials.

4.2.2 Pre-clinical Findings

In Study R2006458, performed by the sponsor, the effects of denosumab on fracture repair were assessed with cohorts of huRANKL knock-in mice that were treated for up to 6 weeks with either denosumab or alendronate beginning 2 days after being subjected to a closed femoral fracture. Fractures were evaluated 21 and 42 days post-fracture. Fractured bones from both denosumab and alendronate-treated mice had greater torsional stiffness and/or maximum torque relative to fractured bones from vehicle controls at both time points. Micro-computerized tomography (microCT) analysis on days 21 and 42 indicated that fracture calluses from denosumab-treated mice had significantly greater bone mineral content, bone area and bone volume. Overall callus size on day 42 was significantly greater in denosumab-treated mice versus control, this may be related to a greater level of unabsorbed cartilage, which was also observed with alendronate treatment.

Figure 1 shows the comparative microCT views of the fracture callus. (Amgen Nonclinical Overview p.11)

Figure 1. Representative MicroCT Images of the Fracture Site in huRANKL Knock-In Mice Treated with Either Denosumab (AMG) or Alendronate (ALN)

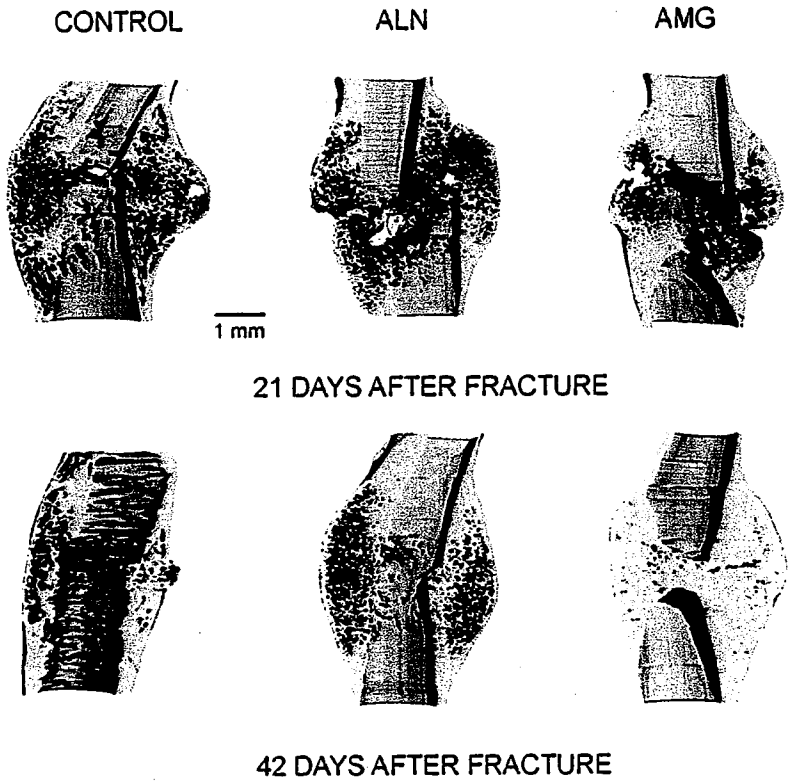

Figure 1: Amgen pre-clinical MicroCT findings comparing fracture healing outcomes in Control, Alendronate and Denosumab treated knock-in mice

Bone strength did not appear to be affected by the increased size of the callus, and the mechanical integrity of the fracture site was not decreased, however this large callus may pose an issue in patients that have fractures.

4.2.3 Phase 1 and 2 Trials

There were no Phase 1 or 2 studies that reported any abnormalities for fracture healing. However, since it does not appear that any evaluation of fracture healing outcomes were performed in the phase 1 and 2 trials, it may be that this is due to a lack of information. Considering the incidence rates of fractures in the Phase 2 studies evaluated, it appears that a maximum of 3% of all subjects experienced fractures during these studies, with foot and hand fractures being the most common. Tabulations of all fractures that occurred in the Phase 2 trials studied are listed in the Appendix, Section 8.2.1, Tables 57-60.

4.2.4 Phase 3 Trials

Tabulations of all fractures that occurred in the Phase 3 trials are listed in the Appendix, Section 8.2.1, Tables 61-66. The only Phase 3 studies that evaluated fracture healing outcomes were the pivotal trials. Of the four pivotal trials, the only study with significant data on fracture healing outcomes (more than 1 subject with a complication per group) was Study 20030216 which had a substudy that was focused on the

healing of distal radius fractures. The tables of all fracture healing outcomes in the four pivotal trials are listed in the Appendix, Section 8.2.2, Tables 67-70.

Table 15 displays the relative risks and risk differences evaluated from Study 20030216.

Table 15: Study 20030216- Relative Risks and Risk Differences for Fracture Healing Complications

Complication	RR	95% RR CI	RD	95% RD CI
Any Complication	0.9924	(0.5548, 1.772)	-0.00048	(-0.0378, 0.0387)
Delayed Heal	1.201	(0.2127, 6.782)	0.0011	(-0.014, 0.0188)
Malunion	1.201	(0.2787, 5.176)	0.00166	(-0.015, 0.0213)
Chronic Pain	0.7645	(0.3089, 1.886)	-0.0071	(-0.033, 0.020)
Other	1.716	(0.6832, 4.315)	0.0138	(-0.011, 0.0425)

As can be observed from this table, none of the fracture healing complications are significantly different between groups in this study. However it should be noted that this study followed the subjects for only 36 months and fracture healing outcomes can take up to 5 years to develop.

4.3 Conclusions

None of the data provided by the studies with human subjects appears to show a difference between groups for fracture healing outcomes. However, the nonclinical findings of callus formation issues in mice do suggest that there may be some cause of concern. While the data in Study 20030216 shows an equal distribution between groups for fracture healing complications, longer-term studies conducted by the sponsor will be of interest.

5 NEW PRIMARY MALIGNANCIES

5.1 Background

Tumor necrosis factor (TNF) plays an important role in host defense and tumor growth control. It is believed that anti-TNF antibody therapies may increase the risk of serious infections and malignancies. A meta-analysis in JAMA (Bongartz et al 2007) showed a statisticially significant increase in odds for malignancies in anti-TNF treated patients vs. placebo. Malignancies were significantly more common in patients treated with high-doses of anti-TNF antibodies.

5.2 Analysis

5.2.1 Methodology

To evaluate the occurence of new primary malignancies, the neoplasms system organ class (SOC) was the primary consideration. All adverse events in the neoplasm SOC that did not include the term "Benign" at the preferred term level or the high level group term level were tabulated, by high-level group term. The list of all preferred terms that appeared in the data using this criteria are tabulated in the appendix. All of these terms and their occurence rates in the treatment groups compared to the control groups of the safety analysis datasets were tabulated and large differences in incidence.were considered; risk ratios, risk differences and related confidence intervals were calculated. If there were more than two groups in a study, Fisher's exact test was performed to determine if there was an overall difference between treatment arms, and this difference was then quantified using pairwise comparisons between the control arm and the arm of interest. Additional investigations include comparing serious vs. non-serious events and comparing the severity gradient for treatment in this class of events. A pooled analysis was performed, in which all subjects of the PMO studies of interest were pooled. In this analysis, for the denosumab arm, only subjects who received the 60mg Q6M dose of the investigational product were evaluated, as this is the dosage that is being evaluated for approval. In evaluating the pooled analyses, a Cochran-Mantel-Haenszel chi-square was used to evaluate the difference between groups for severity gradients. Exact methods were employed when warranted by the number of events (fewer than 5 events in a category).

5.2.2 Pre-clinical Findings

No preclinical studies were conducted that considered this adverse event.

5.2.3 Phase 1 and 2 Studies

No Phase 1 and 2 malignancies were listed in the synopses of individual studies provided by the sponsor. The following tables outline the total number of events that occurred in the studies that were evaluated and evaluates the overall difference between groups in the studies with more than 2 arms (20010223 and 20050179) and quantifies the difference between groups using risk difference and relative risk. Tabulations of all events are provided in the Appendix, Section 8.3.1, Tables 71-74.

Table 16 lists the number of subjects with new primary malignancies and total subjects in the studies by arm, and Table 17 lists the results from the data analysis.

Table 16: Summary Table of Adverse Events for Phase 1 and 2 Trials for New Primary Malignancies

Study	Subjects with Adverse Event			Total Subjects		
Number	Denosumab	Placebo	Alendronate	Denosumab	Placebo	Alendronate
20010223	20	3	5	314	46	46
20050172	1	0	—	158	54	—
20050179	0	0	3	83	83	81

Table 17: Summary Table of Statistics for Phase 1 and 2 Trials for New Primary Malignancies

Study		Fisher statistic	p-value
20010223	Difference between arms	1.5	0.5729
20050179	Difference between arms	4.188	0.0344

Study	Placebo comparison group	Risk Diff.	95% CI	Rel. Risk	95% CI	p-value
20010223*	Denosumab	-0.0015	(-0.113, 0.053)	0.9766	(0.330, 3.20)	0.9878
	Alendronate	0.0435	(-0.086, 0.185)	1.667	(0.4584, 7.58)	0.5309
20050172*	Denosumab	0.0063	(-0.063, 0.035)	undefined		0.7277
20050179*	Denosumab	0		1		1
	Alendronate	0.037	(-0.0878, 0.105)	undefined		0.0803

*exact methods used

Table 17 indicates that there is no significant difference for new primary malignancies between the denosumab group and the placebo group in any of the studies. In study 20050179, there is a significant difference between the alendronate group and the two other arms due to 3 subjects who experienced new primary malignancies in this group compared to none in the other two arms.

5.2.4 Phase 3 Trials

All of the Phase 3 trials with relevant events are tabulated below and differences between groups are quantified using relative risk and risk difference measures. A tabulation of all relevant adverse events are provided in the Appendix, Section 8.3.1, Tables 75-81.

Table 18: Summary Table of Adverse Events for Phase 3 Trials for New Primary Malignancies

Study	Subjects with Adverse Event			Total Subjects		
Number	Denosumab	Placebo	Alendronate	Denosumab	Placebo	Alendronate
20030216	187	167	—	3886	3876	—
20040132	7	4	—	164	165	—
20040135	9	8	—	129	120	—
20040138	105	79	—	731	725	—
20050141	7	—	8	593	—	586
20050234	3	—	3	253	—	249

Table 19: Summary Table of Statistics for Phase 3 Trials for New Primary Malignancies

Study	Risk Diff.	95% CI	Rel. Risk	95% CI	p-value
20030216	0.005	(-0.0043, 0.0144)	1.117	(0.9112, 1.369)	0.2877
20040132*	0.018	(-0.0243, 0.0655)	1.761	(0.5523, 7.392)	0.5294
20040135	0.0031	(-0.065, 0.0697)	1.047	(0.4295, 2.556)	0.9228
20040138	0.0347	(0.00054, 0.069)	1.318	(1.004, 1.732)	0.0465
20050141	-0.0018	(-0.0163, 0.0122)	0.8647	(0.3278, 2.28)	0.7772
20050234*	-0.00019	(-0.0248, 0.0242)	0.9842	(0.1841, 5.263)	1

*exact methods used

From Tables 18 and 19, it is observed that the only study with a significantly higher risk difference and relative risk of new malignancies in the denosumab arm is in Study 20040138. Upon further examination of

this study, (Table 78 in the Appendix) the largest difference between groups is amongst those with the High Level Group Term (HLGT) "Metastases". To explore this issue further, we consider the Preferred Terms for subjects with this HLGT in Table 20:

Table 20: Study 20040138 - New Primary Malignancies - Preferred Terms where HLGT = "Metastases"

HLGT= Metastases Dictionary-Derived Term	Denosumab 60mg Q6M	Placebo
Subjects in Arm	731 (100.00%)	725 (100.00%)
Metastases to bone	34 (4.65%)	25 (3.53%)
Metastases to liver	4 (0.55%)	3 (0.41%)
Metastases to spine	4 (0.55%)	1 (0.14%)
Metastases to lymph nodes	1 (0.14%)	2 (0.27%)
Metastasis	3 (0.47%)	0 (0.00%)
Metastases to pleura	1 (0.14%)	1 (0.14%)
Metastases to lung	1 (0.14%)	0 (0.00%)
Metastases to abdominal cavity	1 (0.14%)	0 (0.00%)
Subjects with HLGT Metastases	48 (6.57%)	31 (4.28%)

The difference in subjects with this HLGT appears to be driven by a difference in patients experiencing bone metastasis when undergoing treatment with denosumab. However, this difference is not statistically significant ($p = 0.2445$).

5.2.5 Serious Adverse Events

Tabulations of serious adverse events for each study appear in the Appendix, Section 8.3.2, Tables 81-90. There does not appear to be a significant difference between groups with regards to serious adverse events in any of the studies, except for Study 20010223 (Tables 81, 82). In this study, the 4 subjects in the high dose denosumab group (100mg Q6M) who experienced an incidence of a new primary malignancy, all experienced serious adverse events Further investigation finds that 3 of these 4 subjects died due to cancer. When comparing this group to the placebo group, the risk difference is not statistically significant at the 0.05 level (p-value=0.0633), as shown in Table 104 in Appendix 5, Section 8.5. While the incidence of fatal events in this groups appears to be higher than in the alendronate and placebo groups (which had 2 SAEs in each group), it is not possible to determine if this is due to chance. Since the higher dose denosumab group in this same study (210mg Q6M) had fewer subjects with SAEs, 2, and did not have fatalities due to malignancies, it does not appear to be a dose-response relationship. The sponsor has stated that the three subjects that experienced fatalities all had issues that predisposed the patients to cancer (family history, previous neoplasm, smoking status) Differences in the number of SAEs between this group and the placebo, and between all denosumab groups and the placebo are not statistically significant.

5.2.6 Severity Gradient

Other than the fatal events described in the previous section that occured in Study 20010223, there does not appear to be a difference between groups with respect to a severity gradient. All studies appeared to have an equal distribution in terms of severity for the different treatment arms. All tabulations of the severity gradient are provided in the Appendix, Section 8.3.3, Tables 91-100.

5.2.7 PMO Pooled Analysis

For the pooled analysis, all studies targeting post-menopausal women that were randomized on denosumab were pooled. This lead to the pooling of 7 trials: 20010223, 20030216, 20040132 (36-month), 20050141, 20050172, 20050179, 20050234. For this analysis, the reviewer evaluated the differences between treatments

(alendronate, denosumab 60mg Q6M, and placebo) in terms of HLGTs, SOC, Serious Events, Severity Gradient and Discontinuation of Drug for subjects experiencing new primary malignancies.

Table 21 lists the occurrence of new primary malignancies by HLGT for each arm in descending order of total subject frequency.

Table 21: PMO Pooled Analysis - New Primary Malignancies - High Level Group Term

High Level Group Term	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW
Subjects	5073 (100.00%)	4231 (100.00%)	963 (100.00%)
Skin neoplasms	51 (1.00%)	49 (1.16%)	5 (0.52%)
Breast neoplasms	38 (0.75%)	30 (0.71%)	5 (0.52%)
GI neoplasms	37 (0.73%)	25 (0.59%)	1 (0.10%)
Respiratory and mediastinal neoplasms	15 (0.30%)	25 (0.59%)	2 (0.21%)
Reproductive neoplasms female	21 (0.41%)	9 (0.21%)	3 (0.32%)
Metastases	10 (0.20%)	9 (0.21%)	0 (0.00%)
Miscellaneious and site unspecified neoplasms	9 (0.18%)	5 (0.12%)	1 (0.10%)
Renal and urinary tract neoplasms	6 (0.12%)	8 (0.19%)	0 (0.00%)
Nervous system neoplasms	6 (0.12%)	7 (0.16%)	0 (0.00%)
Plasma cell neoplasms	6 (0.12%)	4 (0.09%)	0 (0.00%)
Endocrine neoplasms	7 (0.14%)	2 (0.05%)	0 (0.00%)
Lymphomas non-Hodgkin's B-cell	2 (0.04%)	4 (0.09%)	0 (0.00%)
Hepatobiliary neoplasms	1 (0.02%)	3 (0.07%)	0 (0.00%)
Leukaemias	2 (0.04%)	2 (0.05%)	0 (0.00%)
Lymphomas NEC	2 (0.04%)	2 (0.05%)	0 (0.00%)
Haematopoietic neoplasms	3 (0.06%)	0 (0.00%)	0 (0.00%)
Lymphomas non-Hodgkin's unspecified histology	1 (0.02%)	1 (0.02%)	1 (0.10%)
Cancer-related morbidities	2 (0.04%)	0 (0.00%)	0 (0.00%)
Lymphomas non-Hodgkin's T-cell	2 (0.04%)	0 (0.00%)	0 (0.00%)
Skeletal neoplasms malignant and unspecified	1 (0.02%)	1 (0.02%)	0 (0.00%)
Mesotheliomas	1 (0.02%)	0 (0.00%)	0 (0.00%)
Ocular neoplasms	0 (0.00%)	1 (0.02%)	0 (0.00%)
Soft tissue sarcomas	0 (0.00%)	1 (0.02%)	0 (0.00%)
Subjects with AE	206 (4.06%)	175 (4.14%)	18 (1.87%)

Table 22 lists the occurrence of adverse events by system organ class for the pooled analysis.

Table 22: PMO Pooled Analysis - New Primary Malignancies - System Organ Class

System Organ Class (SOC)	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW
Neoplasms	206 (4.06%)	175 (4.14%)	18 (1.87%)
Subjects	5073 (100.00%)	4231 (100.00%)	963 (100.00%)

Table 23 lists the risk difference, relative risk, and associated p-value for the difference between groups by SOC in the pooled analysis.

Table 23: PMO Pooled Analysis - New Primary Malignancies - Relative Risks and Risk Differences of SOC compared to Placebo

Reference Group= Placebo	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW	Fisher statistic value	p-value
Risk difference	-0.00075	—	-0.0227	13.41	0.001
RD 95% CI	(-0.0090, 0.0073)		(-0.0322, -0.0108)		
Relative risk	0.9818	—	0.4519		
RR 95% CI	(0.8063, 1.196)		(0.2805, 0.7256)		

Table 24 lists the number of subjects with serious adverse events in the pooled analysis.

Table 24: PMO Pooled Analysis - New Primary Malignancies - Serious Adverse Events

Serious Adverse Event	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW
Subjects	5073 (100.00%)	4231 (100.00%)	963 (100.00%)
No SAE	54 (1.06%)	50 (1.18%)	6 (0.62%)
SAE present	160 (3.15%)	129 (3.05%)	12 (1.25%)
Subjects with AE	206 (4.06%)	175 (4.14%)	18 (1.87%)

Table 25 lists the risk difference, relative risk, and associated p-value for the difference between groups by SAE occurrence in the pooled analysis.

Table 25: PMO Pooled Analysis - New Primary Malignancies - Relative Risks and Risk Differences of SAE compared to Placebo

Reference Group= Placebo	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW	Fisher statistic value	p-value
Risk difference	0.001	—	-0.018	12.56	0.002
RD 95% CI	(-0.006, 0.008)		(-0.026, -0.0078)		
Relative Risk	1.034	—	0.4087		
RR 95% CI	(0.8238, 1.299)		(0.2287, 0.7279)		

Table 26 lists the number of subjects by severity grade and the associated p-value in the pooled analysis.

Table 26: PMO Pooled Analysis - New Primary Malignancies - Severity Gradeient

Adverse Event Severity Grade	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW	CMH Chi-square
Subjects	5073 (100.00%)	4231 (100.00%)	963 (100.00%)	2.526
Mild	36 (0.71%)	27 (0.64%)	6 (0.62%)	
Moderate	58 (1.14%)	55 (1.30%)	3 (0.31%)	p-value
Severe	92 (1.81%)	64 (1.51%)	7 (0.62%)	0.2827
Life Threatening	14 (0.26%)	17 (0.40%)	2 (0.21%)	
Fatal	20 (0.39%)	26 (0.61%)	1 (0.10%)	
Subjects with AE	206 (4.06%)	175 (4.14%)	18 (1.87%)	

Table 27 lists the number of subjects that discontinued their treatment in the pooled analysis.

Table 27: PMO Pooled Analysis - New Primary Malignancies - Discontinuation of Drug

Drug Discontinued	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW
Subjects	5073 (100.00%)	4231 (100.00%)	963 (100.00%)
No	150 (2.96%)	137 (3.24%)	13 (1.65%)
Yes	63 (1.24%)	42 (0.99%)	5 (0.52%)
Subjects with AE	206 (4.06%)	175 (4.14%)	18 (1.87%)

Table 28 lists the risk difference, relative risk, and associated p-value for the difference between groups by drug discontinuation in the pooled analysis.

Table 28: PMO Pooled Analysis - New Primary Malignancies - Relative Risks and Risk Differences of drug discontinuation compared to Placebo

Reference Group= Placebo	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW	Fisher statistic value	p-value
Risk difference	0.012	—	-0.0047	4.387	0.1111
RD asy 95% CI	(-0.0019, 0.0068)		(-0.0094, 0.0025)		
Relative Risk	1.251	—	0.523		
RR asy 95% CI	(0.8506, 1.84)		(0.2136, 1.277)		

As can be observed from Tables 23, 25 and 28, there is no significant difference between denosumab and placebo in any of the analyses. There is a significant difference between placebo and alendronate in terms of the incidence of primary malignancies and serious events, but this difference may be due to the fact that malignancies are more likely to be captured in studies of longer duration, and the alendronate groups in the studies that are pooled have shorter follow up times compared to some of the denosumab and placebo groups. In Table 21, we observe that there is little difference between groups in the distribution of neoplasms by type, and in Table 22, we observe that the incidence of new malignancies by system organ class is nearly identical between denosumab and placebo.

5.3 Conclusions

In most of the studies, the incidence of new malignancies were balanced between the treatment and placebo groups, however, there were two populations for which a potential safety signal exists. First, in the population of men with prostate cancer undergoing HALT therapy (study 20040138), there did appear to be a higher rate of new malignancies in the denosumab arm, and this difference was driven primarily by metastases. Further investigation showed that this was primarily due to metastasis to the bone.

Another area of concern was in the patients in Study 20010223 that were in the high dose group (100mg Q6M). Of the four deaths in this study, three of the subjects belonged to this arm and experienced death due to a new primary malignancy. This issue was not observed in the higher dose arm of this study, and was not repeated in any of the other studies, but it is still notable.

Since malignancies develop over a longer term, this is still a potential area of concern which may need to be monitored for a longer duration.

6 DISCUSSION AND CONCLUSIONS

Subjects treated with denosumab had similar risk for osteonecrosis of the jaw and delayed fracture healing compared to placebo subjects. The results for new primary malignancies are not as consistent. However, as all three of these adverse events of interest can develop over long-term use of the drug, they still need to be monitored.

For ONJ, though there were concerns that the ONJ adjudication committee selected by the sponsor used a narrow criterion (using MedDRA v.11.0) when ascertaining ONJ cases and no cases were identified, a broadening of the criterion in this analysis resulted in no significant difference between the denosumab and placebo groups. There was a significant difference in the severity gradient between the alendronate subjects and the placebo subjects, in trials employing active controls, with alendronate subjects experiencing more severe adverse events. However, the denosumab and placebo groups tended to have similar distributions of events in all the analyses.

For delayed fracture healing, the nonclinical overview showed that the sponsor found issues in bony callus formation among genetically modified mice that were monitored after being subjected to closed femoral fractures. The bony callus appeared to be larger and had a different consistency compared to those in the placebo group. This issue may affect the mobility of the bone, but is not expected to affect its strength. Only the four pivotal trials (Study #'s 20030216, 20040132, 20040135 and 20040138) contained data that specifically considered fracture healing outcomes. Moreover, as the outcome of delayed fracture healing is one that can take up to five years to be fully determined, further long-term follow-up of this adverse event would be worthwhile. From the data provided, there appears to be a balanced distribution between groups for fracture healing outcomes.

For new primary maligancies, there generally appears to be a balanced distribution of adverse events with one notable exception. The only study that had significantly more events in the denosumab group was Study 20040138 whose population consisted of men with non-metastatic prostate cancer undergoing androgen deprivation therapy. The high level group term that drives the difference between groups in this study is "Metastases" and further investigation of this term shows that the increased number of adverse events in the denosumab group is mainly due to the preferred term "Metastases to bone". In all the other populations studied by the sponsor, this metastases issue does not arise and the difference between treatment and control groups is minimal. Again, as the appearance of new primary malignancies tends to be a long-term outcome, continued monitoring of this adverse event may be of use.

7 REFERENCES

References

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Ruggiero SL, Rosenberg TJ, Engroff SL.(2004) "Osteonecrosis of the Jaws Associated with the Use of Bisphosphonates: A review of 63 cases." JOMS 62: 527-534

8 APPENDICES

Table 29: Listing and location of all datasets used in review

Study	Phase	Location	Datasets
20010223	Phase 2	\\cbsap58\M\eCTD_Submissions\STN125320\0000\m5\datasets\20010223\analysis	AAE, ASLINFO, AEX
20030216	Phase 3	\\cbsap58\M\eCTD_Submissions\STN125320\0000\m5\datasets\20030216\analysis	AAE, ASLINFO, AEX, AAEFX
20040132	Phase 3	\\cbsap58\M\eCTD_Submissions\STN125320\0000\m5\datasets\20040132-36-Month\analysis	AAE, ASLINFO, AEX, AAEFX
20040135	Phase 3	\\cbsap58\M\eCTD_Submissions\STN125320\0000\m5\datasets\20040135\analysis	AAE, ASLINFO, AEX, AAEFX
20040138	Phase 3	\\cbsap58\M\eCTD_Submissions\STN125320\0000\m5\datasets\20040138\analysis	AAE, ASLINFO, AEX, AAEFX
20050141	Phase 3	\\cbsap58\M\eCTD_Submissions\STN125320\0000\m5\datasets\20050141\analysis	AAE, ASLINFO, AEX
20050172	Phase 2	\\cbsap58\M\eCTD_Submissions\STN125320\0000\m5\datasets\20050172\analysis	AAE, ASLINFO, AEX
20050179	Phase 2	\\cbsap58\M\eCTD_Submissions\STN125320\0000\m5\datasets\20050179\analysis	AAE, ASLINFO, AEX
20050234	Phase 3	\\cbsap58\M\eCTD_Submissions\STN125320\0000\m5\datasets\20050234\analysis	AAE, ASLINFO, AEX

8.1 Osteonecrosis of the Jaw (ONJ) Analysis Tables

8.1.1 Tables of Preferred Term by Treatment Group for ONJ Risk Factors

Table 30: Study 20010223 - ONJ Preferred Terms (Part 1)

Dictionary-Derived Term	Denosumab 6mg Q3M	14mg Q6M	14mg Q3M	30mg Q3M	60mg Q6M
Subjects in Arm	43	53	44	40	47
Toothache	3	1	0	1	2
Tooth infection	3	3	0	1	2
Tooth fracture	1	0	1	2	0
Gingival infection	0	0	0	0	1
Pain in jaw	0	0	0	1	0
Oral infection	0	0	0	1	0
Mouth ulceration	0	0	0	0	1
Gingivitis	1	0	0	0	0
Gingival pain	1	0	0	0	0
Gingival ulceration	0	1	0	0	0
Periodontal disease	0	0	0	0	0
Oral discomfort	0	0	0	0	0
Gingival disorder	0	0	0	0	0
Tooth disorder	0	1	0	0	0
Subjects with AE	5	5	1	6	5

Table 31: Study 20010223 - ONJ Preferred Terms (Part 2)

Dictionary-Derived Term	Denosumab 100mg Q6M	Denosumab 210mg Q6M	Alendronate	Placebo
Subjects in Arm	41	46	46	46
Toothache	0	3	2	1
Tooth infection	0	0	2	0
Tooth fracture	1	1	1	0
Gingival infection	0	1	1	1
Pain in jaw	0	0	1	1
Oral infection	1	1	0	0
Mouth ulceration	2	0	0	0
Gingivitis	1	1	0	0
Gingival pain	0	1	0	0
Gingival ulceration	0	0	0	1
Periodontal disease	0	0	0	2
Oral discomfort	0	0	0	1
Gingival disorder	0	0	1	0
Tooth disorder	0	0	0	0
Subjects with AE	5	7	6	6

Table 32: Study 20050172 - ONJ Preferred Terms

Dictionary-Derived Term	Denosumab 14mg Q6M	Denosumab 60mg Q6M	Denosumab 100mg Q6M	Placebo
Subjects in Arm	53	54	51	54
Gingivitis	1	3	1	1
Periodontitis	0	2	3	1
Tooth fracture	0	0	1	0
Toothache	0	0	1	0
Tooth extraction	1	0	0	0
Gingival bleeding	0	1	0	0
Gingival swelling	0	0	1	0
Subjects with AE	2	6	6	2

Table 33: Study 20050179 - ONJ Preferred Terms

Dictionary-Derived Term	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW
Subjects in Arm	83	83	81
Periodontitis	2	1	1
Tooth infection	1	1	0
Tooth abscess	0	1	1
Abscess jaw	0	1	0
Gingival infection	0	1	0
Loose tooth	0	1	0
Mouth ulceration	0	1	0
Oral discomfort	0	1	0
Oral infection	0	1	0
Pain in jaw	0	1	0
Toothache	0	1	0
Subjects with AE	3	10	2

Table 34: Study 20030216 - ONJ Preferred Terms (Part 1)

Dictionary-Derived Term	Denosumab 60mg Q6M	Placebo
Subjects in Arm	3886	3876
Tooth infection	26	41
Toothache	22	31
Periodontitis	20	17
Tooth abscess	19	12
Gingivitis	12	10
Tooth fracture	6	7
Tooth disorder	6	7
Gingival infection	7	6
Osteitis	5	6
Mouth ulceration	7	4
Pain in jaw	5	3
Tooth extraction	5	3
Tooth injury	5	1
Gingival abscess	2	4
Oral pain	2	3
Osteonecrosis	4	1
Gingival pain	3	1
Oral infection	3	1
Gingival bleeding	3	1
Periodontal disease	3	1

Table 35: Study 20030216 - ONJ Preferred Terms (Part 2)

Dictionary-Derived Term	Denosumab 60mg Q6M	Placebo
Subjects in Arm	3886	3876
Abscess oral	1	2
Gingival swelling	0	3
Periodontal infection	2	0
Osteomyelitis	1	1
Loose tooth	0	2
Oral bacterial infection	1	1
Mouth cyst	1	0
Jaw cyst	1	0
Gingival hypertrophy	1	0
Gingival disorder	1	0
Oral cavity fistula	1	0
Bone erosion	0	1
Bone fistula	0	1
Bone infarction	0	1
Gingival operation	0	1
Dental necrosis	1	0
Gingival ulceration	0	1
Gingival cyst	1	0
Oral disorder	0	1
Tooth avulsion	0	1
Tooth disorder	0	1
Subjects with AE	158	155

Table 36: Study 20040132 - 36 months - ONJ Preferred Terms

Dictionary-Derived Term	Denosumab 60mg Q6M	Placebo
Subjects in Arm	164	165
Toothache	4	2
Tooth abscess	4	2
Tooth infection	3	2
Pain in jaw	3	1
Tooth fracture	2	2
Tooth extraction	1	2
Gingival infection	0	3
Oral discomfort	1	0
Gingival abscess	1	0
Gingivitis	1	0
Gingival pain	1	0
Alveolar osteitis	0	1
Dental necrosis	0	1
Gingival cyst	0	1
Periodontal disease	1	0
Gingival swelling	0	1
Mouth ulceration	0	1
Subjects with AE	20	16

Table 37: Study 20040135 - ONJ Preferred Terms

Dictionary-Derived Term	Denosumab 60mg Q6M	Placebo
Subjects in Arm	129	120
Tooth infection	1	1
Tooth abscess	1	0
Pain in jaw	1	1
Subjects with AE	3	1

Table 38: Study 20040138 - ONJ Preferred Terms

Dictionary-Derived Term	Denosumab 60mg Q6M	Placebo
Subjects in Arm	731	725
Tooth infection	7	3
Toothache	1	6
Tooth abscess	2	3
Gingivitis	3	0
Bone erosion	0	3
Pain in jaw	1	1
Osteomyelitis	1	1
Oral pain	1	1
Tooth fracture	1	1
Tooth disorder	0	2
Gingival infection	1	0
Periodontal disease	1	0
Mouth ulceration	1	0
Gingival pain	1	0
Gingival recession	0	1
Jaw cyst	0	1
Oral disorder	0	1
Osteonecrosis	0	1
Tooth extraction	1	0
Tooth repair	0	1
Subjects with AE	19	24

Table 39: Study 20050141 - ONJ Preferred Terms

Dictionary-Derived Term	Denosumab 60mg Q6M	Alendronate 70mg QW
Subjects in Arm	593	586
Toothache	6	5
Tooth fracture	6	2
Tooth abscess	7	1
Tooth infection	2	4
Tooth disorder	2	3
Gingivitis	2	3
Gingival pain	2	3
Periodontitis	2	2
Mouth ulceration	1	2
Pain in jaw	2	1
Gingival abscess	1	1
Osteomyelitis	1	0
Oral pain	1	0
Loose tooth	0	1
Oral discomfort	0	1
Tooth loss	0	1
Osteonecrosis	1	0
Subjects with AE	30	25

Table 40: Study 20050234 - ONJ Preferred Terms

Dictionary-Derived Term	Denosumab 60mg Q6M	Alendronate 70mg QW
Subjects in Arm	253	249
Tooth fracture	1	4
Pain in jaw	1	3
Periodontitis	1	2
Periodontal infection	0	1
Loose tooth	0	1
Tooth abscess	0	1
Gingival infection	0	1
Tooth infection	0	1
Toothache	0	1
Gingival pain	1	0
Jaw disorder	1	0
Tooth loss	1	0
Subjects with AE	6	11

8.1.2 Tables of Serious Adverse Events (SAEs) by Treatment Group for ONJ Risk Factors

Table 41: Study 20010223 - ONJ Serious Adverse Events (Part 1)

Serious Adverse Event	Denosumab 6mg Q3M	14mg Q6M	14mg Q3M	30mg Q3M	60mg Q6M
Subjects in Arm	43	53	44	40	47
No SAE	5	5	1	6	5
SAE present	0	0	0	0	0
Subjects with AE	5	5	1	6	5

Table 42: Study 20010223 - ONJ Serious Adverse Events (Part 2)

Serious Adverse Event	Denosumab 100mg Q6M	210mg Q6M	Alendronate	Placebo
Subjects in Arm	41	46	46	46
No SAE	5	7	6	5
SAE present	0	0	0	1
Subjects with AE	5	7	6	6

Table 43: Study 20050141 - ONJ Serious Adverse Events

Serious Adverse Event	Denosumab 60mg Q6M	Alendronate 70mg QW
Subjects in Arm	593	586
No SAE	30	25
SAE present	0	1
Subjects with AE	30	25

Table 44: Study 20050234 - ONJ Serious Adverse Events

Serious Adverse Event	Denosumab 60mg Q6M	Alendronate 70mg QW
Subjects in Arm	253	249
No SAE	6	9
SAE present	0	2
Subjects with AE	6	11

Table 45: Study 20030216 - ONJ Serious Adverse Events

Serious Adverse Event	Denosumab 60mg Q6M	Placebo
Subjects in Arm	3886	3876
No SAE	156	154
SAE present	3	1
Subjects with AE	158	155

Table 46: Study 20040138 - ONJ Serious Adverse Events

Serious Adverse Event	Denosumab 60mg Q6M	Placebo
Subjects in Arm	731	725
No SAE	18	23
SAE present	1	1
Subjects with AE	19	24

8.1.3 Tables of Severity Gradient by Treatment Group for ONJ Risk Factors

Table 47: Study 20010223 - ONJ Severity Gradient (part 1)

Adverse Event	Denosumab				
Severity Grade	6mg Q3M	14mg Q6M	14mg Q3M	30mg Q3M	60mg Q6M
Subjects in Arm	43	53	44	40	47
Mild	1	3	0	3	3
Moderate	4	3	1	2	2
Severe	1	0	0	0	0
Subjects with AE	5	5	1	6	5

Table 48: Study 20010223 - ONJ Severity Gradient (part 2)

Adverse Event	Denosumab		Alendronate	Placebo
Severity Grade	100mg Q6M	210mg Q6M		
Subjects in Arm	41	46	46	46
Mild	0	3	2	4
Moderate	4	4	4	1
Severe	1	0	0	2
Subjects with AE	5	7	6	6

Table 49: Study 20050172 - ONJ Severity Gradient

Adverse Event		Denosumab		Placebo
Severity Grade	14mg Q6M	60mg Q6M	100mg Q6M	
Subjects in Arm	53	54	51	54
Mild	2	6	6	2
Moderate	0	0	0	0
Severe	0	0	0	0
Subjects with AE	2	6	6	2

Table 50: Study 20050179 - ONJ Severity Gradient

Adverse Event	Denosumab	Placebo	Alendronate
Severity Grade	60mg Q6M		70mg QW
Subjects in Arm	83	83	81
Mild	2	10	1
Moderate	1	0	1
Severe	0	0	0
Subjects with AE	3	10	2

Table 51: Study 20030216 - ONJ Severity Gradient

Adverse Event	Denosumab	Placebo
Severity Grade	60mg Q6M	
Subjects in Arm	3886	3876
Mild	82	78
Moderate	83	78
Severe	2	8
Subjects with AE	158	155

Table 52: Study 20040132 - 36 months - ONJ Severity Gradient

Adverse Event	Denosumab	Placebo
Severity Grade	60mg Q6M	
Subjects in Arm	164	165
Mild	10	6
Moderate	11	10
Severe	0	1
Subjects with AE	20	16

Table 53: Study 20040135 - ONJ Severity Gradient

Adverse Event Severity Grade	Denosumab 60mg Q6M	Placebo
Subjects in Arm	129	120
Mild	1	1
Moderate	2	0
Severe	0	0
Subjects with AE	3	1

Table 54: Study 20040138 - ONJ Severity Gradient

Adverse Event Severity Grade	Denosumab 60mg Q6M	Placebo
Subjects in Arm	731	725
Mild	11	14
Moderate	8	10
Severe	1	2
Subjects with AE	19	24

Table 55: Study 20050141 - ONJ Severity Gradient

Adverse Event Severity Grade	Denosumab 60mg Q6M	Alendronate 70mg QW
Subjects in Arm	593	586
Mild	24	17
Moderate	7	10
Severe	2	1
Subjects with AE	30	25

Table 56: Study 20050234 - ONJ Severity Gradient

Adverse Event Severity Grade	Denosumab 60mg Q6M	Alendronate 70mg QW
Subjects	253	249
Mild	6	3
Moderate	1	5
Severe	0	3
Subjects with AE	6	11

8.2 Delayed Fracture Healing Analysis Tables

8.2.1 Tables of All Non-vertebral Fractures by Treatment Group

Table 57: Study 20010223 - Fracture Preferred Terms (part 1)

Dictionary-Derived Term	Denosumab 6mg Q3M	14mg Q6M	14mg Q3M	30mg Q3M	60mg Q6M
Subjects in Arm	43	53	44	40	47
Foot fracture	0	2	2	2	4
Rib fracture	0	0	3	0	1
Fibula fracture	0	0	1	1	0
Humerus fracture	0	1	1	0	1
Hand fracture	0	1	0	0	1
Tibia fracture	0	0	1	1	0
Radius fracture	0	1	1	0	0
Sternal fracture	1	0	0	0	0
Ulna fracture	0	1	0	0	0
Fractured sacrum	0	0	0	0	1
Lumbar vertebral fracture	0	0	0	0	0
Femur fracture	0	0	0	0	0
Ilium fracture	0	0	0	0	0
Facial bones fracture	0	0	0	0	1
Subjects with AE	1	4	7	3	7

Table 58: Study 20010223 - Fracture Preferred Terms (part 2)

Dictionary-Derived Term	Denosumab 100mg Q6M	210mg Q6M	Alendronate	Placebo
Subjects in Arm	41	46	46	46
Foot fracture	1	4	1	3
Rib fracture	1	1	0	0
Fibula fracture	1	1	0	1
Humerus fracture	1	0	0	1
Hand fracture	0	1	1	0
Tibia fracture	1	0	0	0
Radius fracture	1	0	0	0
Sternal fracture	1	0	0	0
Ulna fracture	1	0	0	0
Fractured sacrum	0	1	0	0
Lumbar vertebral fracture	1	0	0	0
Femur fracture	0	0	1	0
Ilium fracture	0	1	0	0
Facial bones fracture	0	0	0	0
Subjects with AE	4	7	3	5

Table 59: Study 20050172 - Fracture Preferred Terms

Dictionary-Derived Term	Denosumab 14mg Q6M	Denosumab 60mg Q6M	Denosumab 100mg Q6M	Placebo
Subjects in Arm	53	54	51	54
Fibula fracture	0	0	0	1
Foot fracture	0	1	0	0
Radius fracture	0	0	0	1
Subjects with AE	0	1	0	2

Table 60: Study 20050179 - Fracture Preferred Terms

Dictionary-Derived Term	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW
Subjects in Arm	83	83	81
Hand fracture	0	0	1
Subjects with AE	0	0	1

Table 61: Study 20030216 - Non- Vertebral Fracture Preferred Terms

Dictionary-Derived Term	Denosumab	Placebo
Subjects in Arm	3886	3876
Radius fracture	104	116
Humerus fracture	42	50
Ulna fracture	37	39
Foot fracture	34	40
Rib fracture	40	33
Hand fracture	21	31
Fibula fracture	19	32
Femur fracture	15	28
Femoral neck fracture	16	20
Tibia fracture	9	15
Wrist fracture	8	10
Pelvic fracture	8	10
Clavicle fracture	8	6
Patella fracture	9	5
Facial bones fracture	3	8
Fractured ischium	2	3
Sternal fracture	2	3
Fractured sacrum	1	3
Scapula fracture	1	2
Fracture	1	2
Acetabulum fracture	2	0
Upper limb fracture	1	1
Skull fracture	1	1
Lower limb fracture	1	0
Fractured coccyx	1	0
Ilium fracture	0	1
Pubic rami fracture	0	1
Subjects with AE	306	367

Table 62: Study 20040132 - 36 months - Non- Vertebral Fracture Preferred Terms

Dictionary-Derived Term	Denosumab 60mg Q6M	Placebo
Subjects in Arm	160	161
Ankle fracture	0	2
Clavicle fracture	1	0
Fibula fracture	2	2
Foot fracture	6	7
Hand fracture	0	1
Humerus fracture	1	3
Patella fracture	2	1
Radius fracture	1	1
Tibia fracture	0	2
Subjects with AE	13	15

Table 63: Study 20040135 - Non- Vertebral Fracture Preferred Terms

Dictionary-Derived Term	Denosumab 60mg Q6M	Placebo
Sutbjects in Arm	117	108
Femoral neck fracture	1	1
Fibula fracture	2	0
Foot fracture	3	2
Fracture	1	0
Patella fracture	0	1
Radius fracture	1	2
Rib fracture	2	1
Tibia fracture	1	1
Wrist fracture	0	1
Subjects with AE	10	9

Table 64: Study 20040138 - Non- Vertebral Fracture Preferred Terms

Dictionary-Derived Term	Denosumab 60mg Q6M	Placebo
Subjects in Arm	731	725
Acetabulum fracture	2	0
Clavicle fracture	1	3
Facial bones fracture	1	1
Femoral neck fracture	3	2
Femur fracture	4	3
Fibula fracture	0	4
Foot fracture	6	0
Forearm fracture	1	0
Fracture	0	1
Fractured ischium	1	0
Fractured sacrum	0	1
Hand fracture	2	3
Humerus fracture	3	6
Ilium fracture	0	1
Patella fracture	1	0
Pelvic fracture	1	0
Radius fracture	2	12
Rib fracture	16	14
Scapula fracture	3	0
Skull fracture	1	0
Tibia fracture	1	4
Ulna fracture	2	6
Subjects with AE	45	44

Table 65: Study 20050141 - Fracture Preferred Terms

Dictionary-Derived Term	Denosumab 60mg Q6M	Alendronate 70mg QW
Subjects in Arm	593	586
Foot fracture	3	5
Radius fracture	2	5
Rib fracture	1	5
Humerus fracture	4	1
Hand fracture	3	1
Ulna fracture	1	3
Tibia fracture	2	1
Fibula fracture	1	2
Lumbar vertebral fracture	2	0
Thoracic vertebral fracture	1	1
Clavicle fracture	0	2
Facial bones fracture	1	1
Wrist fracture	1	0
Patella fracture	1	0
Femur fracture	0	1
Pelvic fracture	1	0
Subjects with AE	19	24

Table 66: Study 20050234 - Fracture Preferred Terms

Dictionary-Derived Term	Denosumab 60mg Q6M	Alendronate 70mg QW
Subjects in Arm	249	253
Wrist fracture	2	1
Foot fracture	2	1
Radius fracture	1	1
Fractured sacrum	0	1
Fibula fracture	1	0
Humerus fracture	1	0
Pelvic fracture	1	0
Rib fracture	1	0
Subjects with AE	8	4

8.2.2 Tables of Fracture Healing Outcomes from Four Pivotal Trials

Table 67: Study 20030216 - Fracture Healing Outcomes

Fracture Healing Complications	Denosumab 60mg Q6M	Placebo
Subjects in Arm	3886	3876
Any Complication	19	23
Delayed Heal	2	2
Malunion	3	3
Nonunion	0	1
Chronic Pain	7	11
Other	10	7
Subjects with non-vertebral fracture	303	364

Table 68: Study 20040132 - 36 months - Fracture Healing Outcomes

Fracture Healing Complications	Denosumab 60mg Q6M	Placebo
Subjects in Arm	164	165
Any Complication	1	0
Delayed Heal	1	0
Subjects with non-vertebral fracture	13	15

Table 69: Study 20040135 - Fracture Healing Outcomes

Fracture Healing Complications	Denosumab 60mg Q6M	Placebo
Sutbjects in Arm	129	120
Any Complication	0	1
Delayed Heal	0	1
Subjects with non-vertebral fracture	10	9

Table 70: Study 20040138 - Fracture Healing Outcomes

Fracture Healing Complications	Denosumab 60mg Q6M	Placebo
Subjects in Arm	731	725
Any Complication	1	1
Chronic Pain	1	0
Other	0	1
Subjects with non-vertebral fracture	44	44

8.3 New Primary Malignancies

8.3.1 Tables of High Level Group Terms by Treatment Group for Primary Malignancies

Table 71: Study 20010223 - New Primary Malignancies High Level Group Terms (Part 1)

High Level Group Term	Denosumab 6mg Q3M	14mg Q6M	14mg Q3M	30mg Q3M	60mg Q6M
Total Subjects	43	53	44	40	47
GI neoplasms	1	0	1	1	0
Breast neoplasms	0	0	2	1	0
Skin neoplasms	0	0	0	0	1
Miscellaneouse and site unspecified neoplasms	0	2	0	0	0
Lymphomas non-Hodgkin's B-cell	1	0	0	0	0
Respiratory and mediastinal neoplasms	0	2	0	0	0
Nervous system neoplasms	0	0	1	0	0
Reproductive neoplasms female	0	0	1	0	0
Skeletal neoplasms	0	0	0	0	0
Lymphomas non-Hodgkin's unspecified histology	0	0	0	0	0
Subjects with AE	2	4	5	2	1

Table 72: Study 20010223 - New Primary Malignancies High Level Group Terms (Part 2)

High Level Group Term	Denosumab 100mg Q6M	210mg Q6M	Placebo	Alendronate
Subjects in Arm	41	46	46	46
GI neoplasms	2	1	1	1
Breast neoplasms	0	1	0	0
Skin neoplasms	0	0	0	3
Miscellaneouse and site unspecified neoplasms	1	0	0	0
Lymphomas non-Hodgkin's B-cell	0	0	1	0
Respiratory and mediastinal neoplasms	0	0	0	0
Nervous system neoplasms	1	0	0	0
Reproductive neoplasms female	0	0	0	0
Skeletal neoplasms	0	0	1	0
Lymphomas non-Hodgkin's unspecified histology	0	0	0	1
Subjects with AE	4	2	3	5

Table 73: Study 20050172 - New Primary Malignancies High Level Group Terms

High Level Group Term	Denosumab 14mg Q6M	60mg Q6M	100mg Q6M	Placebo
Subjects in Arm	53	54	51	54
Breast neoplasms	0	1	0	0
Subjects with AE	0	1	0	0

Table 74: Study 20050179 - New Primary Malignancies High Level Group Terms

High Level Group Term	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW
Subjects in Arm	83	83	81
Breast neoplasms	0	0	2
Reproductive neoplasms female	0	0	1
Subjects with AE	0	0	3

Table 75: Study 20030216 - New Primary Malignancies High Level Group Terms

Adverse Event High Level Group Term	Denosumab 60mg Q6M	Placebo
Subjects in Arm	3886	3876
Skin neoplasms	46	49
Breast neoplasms	34	30
GI neoplasms	35	24
Respiratory and mediastinal neoplasms	15	25
Reproductive neoplasms female	19	9
Metstases	9	9
Renal and urinary tract neoplasms	5	8
Nervous system neoplasms	5	7
Plasma cell neoplasms	6	4
Miscellaneous and site unspecified neoplasms	7	3
Endocrine neoplasms	7	2
Leukaemias	2	2
Lymphomas non-Hodgkin's B-cell	2	2
Lymphomas NEC	2	2
Hepatobiliary neoplasms	1	3
Haematopoietic neoplasms	3	0
Ocular neoplasms	1	1
Lymphomas non-Hodgkin's unspecified histology	1	1
Cancer-related morbidities	2	0
Mesotheliomas	1	0
Soft tissue sarcomas	0	1
Skeletal neoplasms	1	0
Subjects with AE	187	167

Table 76: Study 20040132 - 36 months - New Primary Malignancies High Level Group Terms

Adverse Event High Level Group Term	Denosumab 60mg Q6M	Placebo
Total Subjects	164	165
Miscellaneous and site unspecified	1	2
Reproductive neoplasms female	2	0
Breast neoplasms	1	1
Nervous system neoplasms	1	0
Skin neoplasms	1	0
Lymphomas non-Hodgkin's B-cell	0	1
Lymphomas non-Hodgkin's T-cell	1	0
Subjects	7	4

Table 77: Study 20040135 - New Primary Malignancies High Level Group Terms

Adverse Event High Level Group Term	Denosumab 60mg Q6M	Placebo
Subjects in Arm	129	120
Metastases	3	3
Skin neoplasms	2	3
Breast neoplasms	3	1
Miscellaneous and site unspecified neoplasms	1	1
Endocrine neoplasms	1	0
Respiratory and mediastinal neoplasms	1	0
Cancer-related morbidities	1	0
Gastrointestinal neoplasms	0	1
Hepatobiliary neoplasms	1	0
Subjects with AE	9	8

Table 78: Study 20040138 - New Primary Malignancies High Level Group Terms

Adverse Event High Level Group Term	Denosumab 60mg Q6M	Placebo
Subjects in Arm	731	725
Metastases	48	31
Skin neoplasms	19	15
Gastrointestinal neoplasms	12	10
Reproductive neoplasms male	12	8
Renal and urinary tract neoplasms	7	6
Respiratory and mediastinal neoplasms	7	3
Miscellaneous and site unspecified neoplasms	6	1
Nervous system neoplasms	1	2
Leukaemias	1	1
Lymphomas non-Hodgkin's B-cell	1	1
Cancer related morbidities	1	0
Lymphomas NEC	1	0
Breast neoplasms	0	1
Endocrine neoplasms	0	1
Hepatobiliary neoplasms	0	1
Lymphomas non-Hodgkin's unspecified histology	0	1
Skeletal neoplasms	0	1
Subjects with AE	105	79

Table 79: Study 20050141 - New Primary Malignancies High Level Group Terms

High Level Group Term	Denosumab 60mg Q6M	Alendronate 70mg QW
Subjects in Arm	593	586
Breast neoplasms	1	2
Skin neoplasms	1	2
Respiratory and mediastinal neoplasms	2	0
Miscellaneous and site unspecified neoplasms	1	1
Reproductive neoplasms female	2	0
Lymphomas non-Hodgkin's T-cell	0	1
Metastases	0	1
Renal and urinary tract neoplasms	0	1
Gastrointestinal neoplasms	0	1
Subjects with AE	7	8

Table 80: Study 20050234 - New Primary Malignancies High Level Group Terms

High Level Group Term	Denosumab 60mg Q6M	Alendronate 70mg QW
Subjects in Arm	253	249
Skin neoplasms	1	1
Breast neoplasms	0	2
Respiratory and mediastinal neoplasms	1	0
Gastrointestinal neoplasms	1	0
Subjects with AE	3	3

8.3.2 Tables of Serious Adverse Events by Treatment Group for Primary Malignancies

Table 81: Study 20010223 - New Primary Malignancies - Serious Adverse Events (part 1)

Serious Adverse Event	Denosumab 6mg Q3M	14mg Q6M	14mg Q3M	30mg Q3M	60mg Q6M
Subjects	43	53	44	40	47
No SAE	0	4	1	1	1
SAE present	2	0	4	1	1
Subjects with AE	2	4	5	2	1

Table 82: Study 20010223 - New Primary Malignancies - Serious Adverse Events (part 2)

Serious Adverse Event	Denosumab 100mg Q6M	210mg Q6M	Placebo	Alendronate
Subjects in Arm	41	46	46	46
No SAE	0	0	1	3
SAE present	4	2	2	2
Subjects with AE	4	2	3	5

Table 83: Study 20050172 - New Primary Malignancies - Serious Adverse Events

Serious Adverse Event	Denosumab 100mg Q6M	14mg Q6M	60mg Q6M	Placebo
Subjects	53	54	51	54
No SAE	0	0	0	0
SAE present	0	0	1	0
Subjects with AE	0	0	1	0

Table 84: Study 20050179 - New Primary Malignancies - Serious Adverse Events

Serious Adverse Event	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW
Subjects in Arm	83	83	81
No SAE	0	0	0
SAE present	0	0	3
Subjects with AE	0	0	3

Table 85: Study 20030216 - New Primary Malignancies - Serious Adverse Events

Serious Adverse Event	Denosumab 60mg Q6M	Placebo
Subjects in Arm	3886	3876
No SAE	50	46
SAE present	144	125
Subjects with AE	187	167

Table 86: Study 20040132 - 36 months - New Primary Malignancies - Serious Adverse Events

Serious Adverse Event	Denosumab 60mg Q6M	Placebo
Subjects in Arm	164	165
No SAE	1	2
SAE present	6	2
Subjects with AE	7	4

Table 87: Study 20040135 - New Primary Malignancies - Serious Adverse Events

Serious Adverse Event	Denosumab 60mg Q6M	Placebo
Subjects in Arm	129	120
No SAE	7	7
SAE present	2	1
Subjects with AE	9	8

Table 88: Study 20040138 - New Primary Malignancies - Serious Adverse Events

Serious Adverse Event	Denosumab 60mg Q6M	Placebo
Subjects	731	725
No SAE	73	43
SAE present	36	41
Subjects with AE	105	79

Table 89: Study 20050141 - New Primary Malignancies - Serious Adverse Events

Serious Adverse Event	Denosumab 60mg Q6M	Alendronate 70mg QW
Subjects in Arm	593	586
No SAE	2	2
SAE present	6	5
Subjects with AE	7	8

Table 90: Study 20050234 - New Primary Malignancies - Serious Adverse Events

Serious Adverse Event	Denosumab 60mg Q6M	Alendronate 70mg QW
Subjects in Arm	253	249
No SAE	1	1
SAE present	2	2
Subjects with AE	3	3

8.3.3 Tables of Severity Gradient by Treatment Group for Primary Malignancies

Table 91: Study 20010223 - New Primary Malignancies - Severity Gradient (part 1)

Adverse Event			Denosumab		
Severity Grade	6mg Q3M	14mg Q6M	14mg Q3M	30mg Q3M	60mg Q6M
Subjects in Arm	43	53	44	40	47
Mild	1	3	0	0	1
Moderate	0	1	1	1	1
Severe	0	0	4	1	0
Life Threatening	1	0	0	0	0
Fatal	0	0	0	0	0
Subjects with AE	2	4	5	2	1

Table 92: Study 20010223 - New Primary Malignancies - Severity Gradient (part 2)

Adverse Event	Denosumab		Placebo	Alendronate
Severity Grade	100mg Q6M	210mg Q6M		
Subjects in Arm	41	46	46	46
Mild	0	0	0	3
Moderate	0	1	1	1
Severe	1	1	2	0
Life Threatening	0	0	0	1
Fatal	3	0	0	0
Subjects with AE	4	2	3	5

Table 93: Study 20050172 - New Primary Malignancies - Severity Gradient

Adverse Event		Denosumab		Placebo
Severity Grade	14mg Q6M	60mg Q6M	100mg Q6M	
Subjects in Arm	53	54	51	54
Mild	0	0	0	0
Moderate	0	0	0	0
Severe	0	1	0	0
Subjects with AE	0	1	0	0

Table 94: Study 20050179 - New Primary Malignancies - Severity Gradient

Adverse Event	Denosumab	Placebo	Alendronate
Severity Grade	60mg Q6M		70mg QW
Subjects in Arm	83	83	81
Mild	0	0	0
Moderate	0	0	0
Severe	0	0	3
Subjects with AE	0	0	3

Table 95: Study 20030216 - New Primary Malignancies - Severity Gradient

Adverse Event Severity Grade	Denosumab 60mg Q6M	Placebo
Subjects	3886	3876
Mild	31	26
Moderate	52	51
Severe	83	61
Life Threatening	14	17
Fatal	20	26
Subjects with AE	187	167

Table 96: Study 20040132 - 36 months - New Primary Malignancies - Severity Gradient

Adverse Event Severity Grade	Denosumab 60mg Q6M	Placebo
Subjects in Arm	164	165
Mild	2	1
Moderate	1	2
Severe	4	1
Subjects with AE	7	4

Table 97: Study 20040135 - New Primary Malignancies - Severity Gradient

Adverse Event Severity Grade	Denosumab 60mg Q6M	Placebo
Subjects in Arm	129	120
Mild	2	2
Moderate	5	1
Severe	4	4
Life Threatening	0	1
Fatal	1	1
Subjects with AE	9	8

Table 98: Study 20040138 - New Primary Malignancies - Severity Gradient

Adverse Event Severity Grade	Denosumab 60mg Q6M	Placebo
Subjects in Arm	731	725
Mild	13	13
Moderate	46	23
Severe	42	34
Life Threatening	7	7
Fatal	6	9
Subjects with AE	105	79

Table 99: Study 20050141 - New Primary Malignancies - Severity Gradient

Adverse Event Severity Grade	Denosumab 60mg Q6M	Alendronate 70mg QW
Subjects in Arm	593	586
Mild	1	1
Moderate	4	2
Severe	3	2
Life Threatening	0	1
Fatal	0	1
Subjects with AE	8	7

Table 100: Study 20050234 - New Primary Malignancies - Severity Gradient

Adverse Event Severity Grade	Denosumab 60mg Q6M	Alendronate 70mg QW
Subjects in Arm	253	249
Mild	1	2
Moderate	1	0
Severe	1	1
Subjects with AE	3	3

8.4 Preferred Terms found in Malignancies Search Using Specified Criteria

Table 101: MedDRA 11.0 Preferred Terms used in Malignancies Search (Part 1)

Abdominal neoplasm	Colon cancer	Lung neoplasm malignant
Acral lentiginous melanoma stage unspecified	Colon cancer metastatic	Lung squamous cell carcinoma stage unspecified
Acute myeloid leukaemia	Colon neoplasm	Lymph node cancer metastatic
Adenocarcinoma	Colorectal cancer	Lymphoma
Adenocarcinoma of the cervix	Diffuse large B-cell lymphoma	Lymphoproliferative disorder
Adenocarcinoma pancreas	Diffuse large B-cell lymphoma recurrent	Malignant ascites
Adrenal neoplasm	Dysplastic naevus syndrome	Malignant glioma
Basal cell carcinoma	Endometrial cancer	Malignant lymphoid neoplasm
B-cell lymphoma	Essential thrombocythaemia	Malignant melanoma
Bladder cancer	Follicle centre lymphoma, follicular grade I, II, III stage III	Malignant melanoma in situ
Bladder transitional cell carcinoma	Gallbladder cancer	Malignant neoplasm progression
Bone neoplasm malignant	Gallbladder cancer metastatic	Malignant pleural effusion
Bowen's disease	Gammopathy	Mantle cell lymphoma
Brain cancer metastatic	Gastric cancer	Maxillofacial sinus neoplasm
Brain neoplasm	Gastrointestinal carcinoma	Meningeal neoplasm
Brain neoplasm malignant	Giant cell tumour of tendon sheath	Meningioma
Breast cancer	Glioblastoma	Mesothelioma malignant
Breast cancer in situ	Glioblastoma multiforme	Metastases to abdominal cavity
Breast cancer metastatic	Head and neck cancer	Metastases to adrenals
Breast neoplasm	Hepatic neoplasm	Metastases to bone
Bronchial carcinoma	Hepatic neoplasm malignant	Metastases to bone marrow
Cancer pain	Infected neoplasm	Metastases to central nervous system
Carcinoid tumour of the stomach	Intestinal adenocarcinoma	Metastases to chest wall
Cerebellar tumour	Lentigo maligna stage unspecified	Metastases to fallopian tube
Cervix carcinoma	Lip and/or oral cavity cancer	Metastases to large intestine
Cervix carcinoma stage 0	Lung adenocarcinoma	Metastases to liver
Chondrosarcoma	Lung adenocarcinoma metastatic	Metastases to lung
Choroidal naevus	Lung cancer metastatic	Metastases to lymph nodes
Chronic lymphocytic leukaemia	Lung neoplasm	Metastases to meninges

Table 102: MedDRA 11.0 Preferred Terms used in Malignancies Search (Part 2)

Metastases to pleura	Oesophageal squamous cell carcinoma	Recurrent cancer
Metastases to skin	Ovarian cancer	Renal cancer
Metastases to spine	Ovarian cancer metastatic	Salivary gland cancer
Metastasis	Ovarian cancer recurrent	Skin cancer
Metastatic bronchial carcinoma	Ovarian epithelial cancer	Small cell lung cancer metastatic
Metastatic malignant melanoma	Ovarian neoplasm	Small cell lung cancer stage unspecified
Metastatic neoplasm	Pancreatic carcinoma	Small intestine carcinoma
Metastatic renal cell carcinoma	Pancreatic carcinoma metastatic	Squamous cell carcinoma
Multiple myeloma	Papillary thyroid cancer	Squamous cell carcinoma of skin
Mycosis fungoides	Paranasal sinus neoplasm	Teratoma
Myelodysplastic syndrome	Paraproteinaemia	Throat cancer
Nasal cavity cancer	Pharyngeal cancer stage unspecified	Thyroid cancer
Neoplasm	Plasmacytoma	Thyroid neoplasm
Neoplasm malignant	Prostate cancer	Tongue neoplasm malignant stage unspecified
Neoplasm prostate	Prostate cancer metastatic	Urethral cancer recurrent
Neurilemmoma	Prostate cancer recurrent	Uterine cancer
Neuroendocrine carcinoma of the skin	Pseudolymphoma	Uterine leiomyosarcoma
Non-Hodgkin's lymphoma	Rectal cancer	Vaginal cancer
Non-small cell lung cancer	Rectal cancer metastatic	Vaginal cancer metastatic
Non-small cell lung cancer metastatic	Rectal cancer stage III	Vulval cancer
Oesophageal carcinoma	Rectal neoplasm	Waldenstrom's macroglobulinaemia

8.5 Analysis of Malignancy Fatalities in Study 20010223

Table 103: Analysis of Malignancy Fatalities in Study 20010223

Comparison	Risk Difference	95% Exact CI	p-value
# of Deaths in 100mg Q6M Denosumab group compared to Placebo	0.0732	(-0.00784, 0.208)	0.0633
# of Deaths in all Denosumab groups compared to Placebo	.00096	(-0.0683, 0.0278)	0.682
# of SAEs in 100mg Q6M Denosumab group compared to Placebo	0.0541	(-0.0647, 0.193)	0.364
# of SAEs in all Denosumab groups compared to Placebo	-0.00526	(-0.111, 0.0372)	0.946

9 SIGNATURES

Primary Statistical Reviewer:
Date: August 10, 2009

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Secondary Reviewer(s):

August 10, 2009

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

BLA Number	125331, 125320, 125332, and 125333
Drug Name:	denosumab (PROLIA)
Indication(s):	- Prevention of osteoporosis in postmenopausal women - Treatment of osteoporosis in postmenopausal women - Treatment and prevention of bone loss associated with hormone ablation therapy with breast cancer - Treatment and prevention of bone loss associated with hormone ablation therapy in patients with prostate cancer
Applicant:	Amgen Inc.
Date submitted:	January 5, 2009
PDUFA Date:	October 19, 2009
Date review completed	July 8, 2009
Review Priority:	Standard
Biometrics Division:	Quantitative Safety and Pharmacoepidemiology Division
Statistical Reviewer:	Mandi Yu, Ph.D., Mathematical Statistician
Secondary Reviewers:	Paul Schuette, Ph.D., Mathematical Statistician George Rochester, Ph.D., Acting Director
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Keywords: serum calcium low, hypocalcemia, renal function, vitamin D, osteoporosis, bone loss, breast cancer, prostate cancer

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1. Executive Summary

Denosumab is a fully human monoclonal antibody that binds to RANKL with high affinity and specificity. Denosumab is intended to prevent and treat postmenopausal osteoporosis (PMO), and to prevent and treat bone loss associated with hormone-ablative therapy (HALT) with breast cancer or with prostate cancer. The proposed dose for denosumab is 60 mg of subcutaneous administration once every six months.

Hypocalcemia was one of the pre-identified composite adverse events during clinical drug development phase for safety surveillance. This review evaluated the effect of denosumab on the incidence and severity of hypocalcemia using data on adverse events (AE) and laboratory serum calcium. The evaluations were also conducted within subgroups of subjects by their baseline vitamin D levels, baseline creatinine clearance levels, and proton pump inhibitors (PPI) medication exposure status. Based on serum calcium data, evaluations on the maximum difference across the entire study period and the time to the first hypocalcemia event were conducted. The incidence of hypocalcemia during the extended off-treatment phases was also evaluated.

1.1. Conclusions and Recommendations

Based on AE data, denosumab was not associated with hypocalcemia in terms of incidence and severity for all subjects or subgroups of subjects with different baseline vitamin D levels, creatinine clearance levels, and proton pump inhibitors medication exposure status.

However, based on serum calcium data, a higher risk of mild hypocalcemia (i.e. Grade 1 hypocalcemia) was observed among denosumab subjects than placebo subjects for the pooled PMO pivotal studies (20040132 and 20030216) and HALT study 20040138. The relative risks of hypocalcemia for subjects treated with denosumab compared to subjects treated with placebo were 3.59 (95% CI 2.19-5.88) in the pooled PMO pivotal studies and 5.36 (95% CI 2.15-13.41) in study 20040138. If denosumab is approved, it is recommended that the sponsor consider labeling mild hypocalcemia as a potential adverse drug effect.

1.2. Statistical Issues and Findings

Because hypocalcemia adverse events are rare, trials were pooled where appropriate to assess the effect of denosumab on hypocalcemia. A wide range of pooling schemes was considered in this review. Among the four indications for which the sponsor was seeking approval, the first two concerns with the population of postmenopausal women (PMO), therefore, the phase-III pivotal trials (20040132 and 20030216) designed for these two indications were pooled together as well as analyzed separately. The pivotal trials for the two HALT indications were analyzed separately because each study focused on a single gender, men in 20040138 and women in 20040135. In addition, five phase-II or phase-III, non-pivotal, randomized, controlled trials with at least one denosumab arm were evaluated: 20010223, 20050141, 20050172, 20050179 and 20050234.

Based on AE data, the reported incidence of hypocalcemia is low, and denosumab was not associated with hypocalcemia, in terms of either incidence or severity, in all subjects and subgroups with differential baseline renal functions, baseline vitamin D levels, and concomitant PPI exposure status. However, it was observed that subjects exposed to PPI were associated with a higher rate of hypocalcemia than those with no PPI exposure regardless of their treatment assignments. For the pooled PMO studies, the rate of hypocalcemia is approximately 2.7% for both treatment groups. For HALT study 20040135, the rates are 6.2% for the denosumab group and 3.3% for the placebo group. For HALT study 20040138, the rates are 3.0% for the denosumab group and 2.2% for the placebo group. Most hypocalcemia events were symptomatic and mild to modest in severity.

Analysis of laboratory serum calcium data focused on subjects enrolled in pivotal studies. A lower normal cutoff value of 8.5mg/dl was used to identify hypocalcemia events. Denosumab subjects were 3.59 times (95% C.I.: 2.19-5.88) as likely to develop hypocalcemia than subjects in the placebo group in the pooled PMO studies. No difference was observed on HALT study 20040135. In HALT study 20040138, the risk ratio of hypocalcemia was 5.36 (95% C.I.: 2.15-13.41) for denosumab subjects compared to placebo subjects. However, when a cutoff value of 7.5md/gl was used, as suggested in [redacted] (b) (4), denosumab is not associated with hypocalcemia in any of the studies. The maximum differences in serum calcium values across all visits were small and comparable between treatment groups.

Approximately 58% of denosumab treated subjects had their first hypocalcemia event at their month-1 visit compared with only 18.5% of placebo treated subjects. The incidence of hypocalcemia was comparable between treatment groups for the remaining eight visits. A Kaplan-Meier survival analysis shows a statistically significant difference (p-value <0.0001) between the survival curves for the denosumab and the placebo groups. Denosumab subjects showed a higher risk of hypocalcemia than placebo subjects during the early stages of the study. At later stages, the survival curves were similar between the two treatment groups.

Finally, no statistically significant difference was observed for the incidence of hypocalcemia in the off-treatment AE data. Laboratory serum calcium data were not available for off-treatment assessments.

2. Introduction

Hypocalcemia is a condition in which there is a lower than normal level of calcium in the circulating blood. The concentration of calcium in the serum is regulated by the action of parathyroid hormone and vitamin D on the kidneys, bones, and gastrointestinal tract. Because denosumab may reduce the blood calcium levels, as do most antiresorpatives agents, hypocalcemia has been identified as a potential safety concern in patients who are administered denosumab.

The objectives for this safety analysis are to: 1) ascertain the frequency of hypocalcemia; 2) evaluate the risk of hypocalcemia for the denosumab treated group relative to the

placebo group; 3) ascertain the severity of the hypocalcemia adverse events; 4) evaluate the impact of denosumab on the time to hypocalcemia adverse events; 5) compare the incidences of hypocalcemia between the denosumab group and the placebo group within subgroups defined by baseline vitamin D level and baseline renal function status, and 6) evaluate the possible impact of proton pump inhibitors (PPI) on hypocalcemia.

3. Data Resources

This review focused on the safety population in all randomized, controlled clinical trials. The safety population, as defined by the sponsor, was comprised of all randomized subjects who received at least one dose of investigational drug. The primary focus was four phase-III, placebo-controlled, multi-national pivotal studies: PMO study 20030216, PMO study 20040132, HALT study 20040135 and HALT study 20040138.

Additional analyses on non-pivotal studies, which were also controlled, randomized trials with at least one denosumab treatment group, were also conducted. These selected non-pivotal studies are study 20010223, study 20050141, study 20050172, study 20050179, and study 20050234.

For the off-treatment evaluation of the risk of hypocalcemia, the following clinical trials were included: PMO study 20040132 24-48month, HALT study 20040135 and HALT study 20040138, the open-label PMO study 20060289 (extension study for study 20030216).

4. Methodology

4.1. Definition of hypocalcemia based on MedDRA (v11.0) terms

A hypocalcemia adverse event is defined as any MedDRA Preferred Term, which is potentially indicative of serum calcium level decreases, as listed in Table 1. A subject is classified as having hypocalcemia if the subject was associated with at least one hypocalcemia adverse event.

Table 1 lists the preferred terms used to define a hypocalcemia event in this review as well as those listed in the Sponsor's safety report. The first nine preferred terms used for this review are identical to those identified by the sponsor. Medical officers from the Division of Reproductive and Urologic Products provided the following terms to be added to the search: "Hypoparathyroidism," "Blood parathyroid hormone decreased," "Hypomagnesemia," "Magnesium deficiency," "Blood magnesium decreased," "Hyperphosphatemia," "Calcium phosphate product increased," "Blood phosphorus increased," "Vitamin D decreased," and "Vitamin D deficiency."

Only treatment-emergent adverse events, defined as events occurring after the first dose of the investigational drug, were considered for this analysis. To evaluate the sensitivity of our analyses to the selection of cutoff date for including an adverse event in the analysis dataset, two sets of analyses were conducted on adverse events that 1) occurred

up to 30 days after the last dose of investigational drug, and 2) occurred prior to the last visit regardless it was scheduled or unscheduled.

Table 1: Preferred terms for defining a possible hypocalcemia event (MedDRA v11.0)

Index	Preferred Terms	This review	The sponsor
1	Hypocalcaemia	√	√
2	Blood calcium decreased	√	√
3	Calcium ionised decreased	√	√
4	Calcium deficiency	√	√
5	Paraesthesia	√	√
6	Paraesthesia oral	√	√
7	Hypoaesthesia	√	√
8	Hypoaesthesia oral	√	√
9	Tetany	√	√
10	Hypoparathyroidism	√	
11	Blood parathyroid hormone decreased	√	
12	Hypomagnesemia	√	
13	Magnesium deficiency	√	
14	Blood magnesium decreased	√	
15	Hyperphosphatemia	√	
16	Calcium phosphate product increased	√	
17	Blood phosphorus increased	√	
18	Vitamin D decreased	√	
19	Vitamin D deficiency	√	

4.2. Definition of hypocalcemia based on laboratory calcium data

To fully capture hypocalcemia events, laboratory data on serum calcium were used as supplemental sources. Although the most definitive method to identify clinically relevant alterations in serum calcium is based on ionized calcium values, the sponsor did not provide the data due to data collection issues. The sponsor provided three serum calcium measures: calcium values, calcium values corrected for albumin if albumin is less than 4g/dL, and calcium values corrected for albumin regardless of albumin values. According to the NCI/CTCAE v3.0 guidance, hypocalcemia is confirmed if the calcium value corrected for albumin when serum albumin is less than 4.0g/dl, computed as total calcium (mg/dl)-0.8[albumin(g/dl)-4], is below an institution's lower limit of normal (LLN) range. Following this guidance, the measurements of albumin-adjusted calcium were used in this review to evaluate hypocalcemia.

According to the sponsor, all laboratory serum calcium values were assessed at a central laboratory and a uniform LLN value of 8.5mg/dl applied to the albumin-adjusted calcium measurements collected in the two pivotal PMO studies (20040132 and 20030216) and a uniform LLN value of 8.4mg/dl applied to the calcium measurements in the two pivotal HALT studies (20040135 and 20040138). These two LLN values were used as the criteria for confirming potential hypocalcemia adverse events in the corresponding pivotal studies in this review.

4.3. Stratification factors

4.3.1. 25-hydroxy vitamin D levels

Vitamin D is important in the absorption, metabolism, and function of calcium. Vitamin D deficiency can lead to low blood calcium. Although all study subjects should have a baseline serum 25-hydorxy vitamin D value greater than 20 ng/ml to be eligible (subjects with vitamin D values less than 20 ng/ml but greater than 12ng/ml at baseline were supplemented with 800-1000 IU vitamin D daily before being re-screened for eligibility), and were instructed to take at least 400 IU vitamin D daily during the treatment phase, subjects may still be at risk of low vitamin D for some study periods. Therefore, the impact of denosumab on hypocalcemia for subjects with various degrees of vitamin D levels was considered. 25-hydroxy vitamin D is considered the most accurate measure of the amount of vitamin D in a human body. The baseline values of this measure were used to classify subjects into four groups based on vitamin D levels. The normal 25-hydroxy vitamin D ranges provided by the sponsor varied by studies as shown in Table 2. Since the variations were relatively small, uniform cutoff values were used to obtain the vitamin D groups. According to guidance from the medical officer from FDA, the vitamin D subgroups were defined to be: less than 12ng/ml, no less than 12ng/ml to 20ng/ml, no less than 20ng/ml to 32ng/ml and greater than 32ng/ml.

Table 2: Normal ranges of 25-hydroxy vitamin D (ng/ml)

Study ID	Lower Limit of Normal Range (LLN)	Upper Limit of Normal Range (ULN)
20030216	9.5	52
20040132	9.5	52
20040135	10 or 15	68 or 80
20040138	9	37.6

4.3.2. Renal function

Low serum calcium levels are often seen in patients with kidney diseases. The impact of denosumab on hypocalcemia may vary by renal function. Because creatinine clearance provides more definitive information about the status of renal function than does creatinine, this measure was used in this review to evaluate a subject's baseline renal function.

The sponsor estimated the baseline values of creatinine clearance for all subjects in the four pivotal studies. The estimation equation adopted by the sponsor was Cockcroft and Gault equation as below:

$$\text{Creatinine Clearance}=\frac{(104-\text{age in years})\times\text{weight in kg}\times(0.85\text{ if female})}{72\times\text{serum creatinine in mg/dL}}.$$ However, the sponsor did not provide the corresponding normal reference ranges for the estimated creatinine clearance values. After consulting a medical officer, uniform cutoffs were used to classify subjects into four renal function groups based on the estimated baseline creatinine clearance values. The creatinine clearance ranges of each group were less than

30 ml/min, no less than 30 ml/min to 60 ml/min, no less than 60 ml/min to 90ml/min, and greater than or equal to 90ml/min.

4.4. Proton pump inhibitor (PPI) exposure

Hypocalcemia events can be influenced by concomitant use of PPI medications. In this review, PPI exposure was defined as whether one subject had received any PPI medications according to the World Health Organization ATC classification system and DDD assignment 2009 (http://www.whocc.no/atcddd/) across the entire study period. Table 3 shows the list of generic names for approved PPI medications by ATC/DDD index 2009.

Table 3: ATC codes and names of approved PPI (ATC code: A02BC) medications

ATC code	Name	DDD (mg)	Administration Route: Oral	Parenteral
A02BC01	omeprazole	20	√	√
A02BC02	pantoprazole	40	√	√
A02BC03	lansoprazole	30	√	
A02BC04	rabeprazole	20	√	
A02BC05	esomeprazole	30	√	√

4.5. Safety endpoints

Fifteen variables were derived and used to capture the frequency and the severity of hypocalcemia as summarized in Table 4. The first 14 variables are binary while the last is continuous. As noted earlier, the primary variable of interest, indicator variable 1, captured whether a subject had at least one hypocalcemia adverse event. This variable allows one to evaluate the incidence of hypocalcemia. Indicator variables 2-9 were derived based on the severity levels and toxicity grades of hypocalcemia adverse events assigned by the investigators, and were created to aid examine the severity of hypocalcemia.

Indicator variable 10 was used to determine whether one subject had any laboratory calcium value across the entire study period that fell below the pre-specified lower limit of normal range. In other words, this variable captured whether there was any confirmed hypocalcemia adverse event based on laboratory calcium measurements. Variables 11-14 are subject level variables based on laboratory calcium values. They show whether the lowest calcium value for one subject met the criterion for one of the non-death four toxicity grades according to NCI/CTCAE v3.0.

Table 4: Variables of interest for the evaluation of hypocalcemia

	Variable Name	Description
1	Hypocalcemia AE (Primary)	Any adverse event with any of the MedDRA preferred terms as listed in Table 1.
2	Hypocalcemia Serious AE	Any adverse event classified as Serious.
3	Severe hypocalcemia AE	Any most severe adverse event categorized as Severe.
4	Modest hypocalcemia AE	Any most severe adverse event categorized as Modest.
5	Mild hypocalcemia AE	Any most severe adverse event categorized as Mild.
6	Grade 1 toxicity hypocalcemia AE	Any most toxic adverse event classified as Grade 1.
7	Grade 2 toxicity hypocalcemia AE	Any most toxic adverse event classified as Grade 2.
8	Grade 3 toxicity hypocalcemia AE	Any most toxic adverse event classified as Grade 3.
9	Grade 4 Toxicity hypocalcemia AE	Any most toxic adverse event classified as Grade 4.
10	Calcium corrected<8.5mg/dl	Any study period Corrected Calcium value that falls below 8.5mg/dl.
11	Grade 1 toxicity calcium value	Any lowest Corrected Calcium value across all study period <8.5mg/dl and ≥8.0mg/dl.
12	Grade 2 toxicity calcium value	Any lowest Corrected Calcium value across all study period <8.0mg/dl and ≥7.0mg/dl.
13	Grade 3 toxicity calcium value	Any lowest Corrected Calcium value across all study period <7.0mg/dl and ≥6.0mg/dl.
14	Grade 4 toxicity calcium value	Any lowest Corrected Calcium value across all study period <6.0mg/dl.
15	Max calcium difference	Maximum changes in Corrected Calcium values during any study period and calculated as: Min. Calcium value-Max. Calcium value.

According to the sponsor's protocols, abnormal lab findings without clinical significance were not recorded as AE, but lab values changes requiring therapy or adjustment in prior therapy were considered as AE. Therefore, the proportion of hypocalcemia adverse event determined based on albumin-adjusted calcium laboratory data is expected to be higher than those obtained based on adverse event data.

The last variable of interest is a continuous variable, which captures the maximum changes in albumin-adjusted calcium values. Large negative values mean serum calcium declines, which may suggest the occurrences of hypocalcemia.

4.6. Analysis methods

This analysis focuses on the safety population in all randomized, controlled clinical trials. The safety population, as defined by the sponsor, was comprised of all randomized subjects who received at least one dose of study treatment. The initial analysis was conducted on the four pivotal studies that were phase III, placebo-controlled clinical trials. The study IDs for the pivotal studies are 20030216, 20040132, 20040135 and 20040138. Additional analyses on non-pivotal studies which were also controlled, randomized trials with at least one denosumab arm were also conducted. The study IDs for these selected non-pivotal studies are 20010223, 20050141, 20050172, 20050179 and

20050234. Denosumab dosing regimens tested in these studies include 100mg every 6 months (Q6M), 14mg every 3 months (Q3M), 14mg Q6M, 210mg Q6M, 30mg Q3M, 6mg Q3M, and 60mg Q6M. The route of administration for denosumab and placebo is subcutaneous (SC). An active control treatment, alendronate, was self-administered 70mg oral tablets weekly (QW). Table 5 and Table 6 show the intent to treat population sizes and the safety population sizes by treatment groups for all clinical studies involved in this analysis respectively.

Table 5: Sample sizes for the intent to treat population by studies and by treatments

Treatment Groups	Pivotal Studies (last 3 digits)				Non-pivotal Studies (last 3 digits)				
	216	132	135	138	223	141	179	234	172
alendronate 70mg QW	-	-	-	-	47	595	81	251	-
denosumab 100mg Q6M	-	-	-	-	42	-	-	-	57
denosumab 14mg Q3M	-	-	-	-	44	-	-	-	-
denosumab 14mg Q6M	-	-	-	-	54	-	-	-	57
denosumab 210mg Q6M	-	-	-	-	47	-	-	-	-
denosumab 30mg Q3M	-	-	-	-	41	-	-	-	-
denosumab 6mg Q3M	-	-	-	-	44	-	-	-	-
denosumab 60mg Q6M	3940	166	131	739	47	594	83	253	56
placebo	3928	166	121	729	46	-	83	-	56
Total subjects	7868	332	252	1468	412	1189	247	504	226

Table 6: Sample sizes for the safety population by studies and by treatments

Treatment Groups	Pivotal Studies (last 3 digits)				Non-pivotal Studies (last 3 digits)				
	216	132	135	138	223	141	179	234	172
alendronate 70mg QW	-	-	-	-	46	586	81	249	-
denosumab 100mg Q6M	-	-	-	-	41	-	-	-	51
denosumab 14mg Q3M	-	-	-	-	44	-	-	-	-
denosumab 14mg Q6M	-	-	-	-	53	-	-	-	53
denosumab 210mg Q6M	-	-	-	-	46	-	-	-	-
denosumab 30mg Q3M	-	-	-	-	40	-	-	-	-
denosumab 6mg Q3M	-	-	-	-	43	-	-	-	-
denosumab 60mg Q6M	3886	164	129	731	47	593	83	253	54
placebo	3876	165	120	725	46	-	83	-	54
Total subjects	7762	329	249	1456	406	1179	247	502	212

Data from off-treatment studies were used to determine the risk of hypocalcemia for subjects who no longer received denosumab for extended periods. The clinical trials for which the off-treatment assessments were conducted include PMO study 20040132 24-48month, HALT study 20040135, and HALT study 20040138. An open label PMO study 20060289 (extension study for study 20030216) was also evaluated. Separate analyses on the incidences of hypocalcemia based on adverse event data sets were carried out for each of the four trials separately. Additionally, the incidence of hypocalcemia on the laboratory calcium data was also evaluated for study 20040132. Laboratory data for the remaining three studies were not evaluated because they were not available. The sample sizes for the extension phase population are shown in Table 7.

Table 7: Sample Sizes for the off-treatment studies

	Study ID			
	20060289	20040132	20040135	20040138
Safety Population	7762*	329	249	1456
denosumab 60mg Q6M	3886*	164	129	731
placebo	3876*	165	120	725
Extension Phase Population	4549	256	185	778
denosumab 60mg Q6M†	2346	128	96	406
placebo†	2203	128	89	372

Notes: *: Sample sizes are based on the safety population of study 20030216
†: For the open-label, single-arm extension study 20060289, the treatment groups are the original assignments in study 20030216.

To evaluate the effect of denosumab on the incidence of hypocalcemia, both parametric and nonparametric tests were performed. The statistical tests include Pearson Chi-Square Test, Fisher's Exact Test, Risk Difference with 95% asymptotic confidence intervals and 95% exact confidence intervals, and Risk Ratio with 95% asymptotic confidence intervals and 95% exact confidence intervals.

5. Findings

5.1. On-treatment evaluations

5.1.1. Hypocalcemia based on adverse events data

5.1.1.1. Distribution of hypocalcemia adverse events

Among a total of 12342 safety subjects across all nine trials, 11184 had at least one adverse event of any kind and 352 had at least one hypocalcemia adverse event as defined in Table 1. The number and proportion of subjects with various number of hypocalcemia adverse events across all four pivotal studies and the selected non-pivotal studies are shown in Table 8 and Table 9 respectively. 142 (2.89%) subjects in the denosumab 60mg Q6M group and 130 (2.66%) subjects in the placebo group across all pivotal studies had at least one hypocalcemia adverse event. For both groups, most subjects had only one occurrence of hypocalcemia.

Table 8: Number of hypocalcemia adverse events per subject across all pivotal studies

Treatment Group	Number of hypocalcemia adverse events n (%)					
	0	1	2	3	4	6
denosumab 60mg Q6M (N=4910)	4768 (97.11)	119 (2.42)	18 (0.37)	4 (0.08)	1 (0.02)	0 (0.00)
placebo (N=4886)	4756 (97.34)	113 (2.31)	15 (0.31)	0 (0.00)	1 (0.02)	1 (0.02)

406 subjects in Study 20010223 had missing values for the variable TRTA (actual treatment received). For these subjects, the values on variable ARM (planned treatment) were used instead. Most subjects with hypocalcemia adverse event had only one event.

It is worth noting that one subject who received denosumab 60mg Q6M experienced four hypocalcemia episodes.

Table 9: Number of subjects with various number of hypocalcemia adverse events across all non-pivotal studies

Treatment Group	Number of hypocalcemia adverse events n (%)			
	0	1	2	4
alendronate 70mg QW (N=962)	943 (98.02)	18 (1.87)	1 (0.10)	0 (0.00)
denosumab 100mg Q6M (N=92)	84 (91.3)	7 (7.61)	1 (1.09)	0 (0.00)
denosumab 14mg Q3M (N=44)	37 (84.09)	4 (9.09)	3 (6.82)	0 (0.00)
denosumab 14mg Q6M (N=106)	102 (96.23)	3 (2.83)	1 (0.94)	0 (0.00)
denosumab 210mg Q6M (N=46)	44 (95.65)	2 (4.35)	0 (0.00)	0 (0.00)
denosumab 30mg Q3M (N=40)	38 (95.00)	2 (5.00)	0 (0.00)	0 (0.00)
denosumab 6mg Q3M (N=43)	42 (97.67)	0 (0.00)	1 (2.33)	0 (0.00)
denosumab 60mg Q6M (N=1030)	1003(97.38)	24 (2.33)	2 (0.19)	1 (0.10)
placebo (N=183)	173 (94.54)	10 (5.46)	0 (0.00)	0 (0.00)

5.1.1.2. Incidence of serious hypocalcemia adverse events

There were no deaths that can be attributed to hypocalcemia. Among the subjects in all four pivotal studies, four subjects had five serious hypocalcemia adverse events.

One subject (Unique Subject Id: 20030216-747091) reported to have a serious hypocalcemia adverse event was an 80-year old, white woman from the United Kingdom. She was enrolled in the PMO study 20030216, received placebo drug, and completed the study. She experienced an event reported as "Hypocalcemia" and was hospitalized after this event. The event end date was not provided, so the duration of this adverse event is not known.

The remaining three subjects were all enrolled in HALT study 20040138. Subject 20040138-235002 was a 75-year old white man from the United States who received denosumab 60mg Q6M treatment. He had two episodes of serious hypocalcemia events. Both events occurred on the same day and lasted for three days. One episode was reported to be "numbness in left arm" and the other was reported to be "numbness in right hand." Both events were coded at the MedDRA Preferred Term level as "Hypoaesthesia." He was also hospitalized after these events.

The third subject who had a serious hypocalcemia adverse event was subject 20040138-322003. He was an 83-year old white man recruited from Canada who received the placebo treatment. This adverse event was reported as "numbness right and left hands." After this event, this patient was hospitalized and removed from this study.

The fourth subject with serious hypocalcemia adverse event was assigned to the denosumab 60mg Q6M treatment group in the HALT study 20040138. This patient was an 83-year old white man from the United States. His unique subject id was 20040138-337032. The serious event was reported as "Hypocalcemia" and it occurred 12 days after the patient received the most recent dose of denosumab and lasted for 9 days. After this

event, this patient received medication, no longer received denosumab, was hospitalized and removed from this study.

5.1.1.3. Incidence of hypocalcemia

The primary objective is to compare the incidence of hypocalcemia between denosumab and placebo groups. The secondary focus is to evaluate whether subjects who received denosumab of proposed marketing dose were at higher risks of hypocalcemia compared with subjects who received the active comparator drug (i.e. alendronate 70mg QW).

The outline of this section is as follows. Section 5.1.1.3.1 presents the results of the pooled analysis based on four pivotal studies and five non-pivotal randomized controlled studies. Section 5.1.1.3.2 and Section 5.1.1.3.3 show the results on pivotal studies for PMO indications and HALT indications respectively.

5.1.1.3.1. Pooled analysis on pivotal and selected non-pivotal studies

Because of the low incidence of hypocalcemia, individual studies were pooled together, when appropriate, to support analysis. As defined earlier, an adverse event was defined as hypocalcemia if it was related to any pre-identified potential MedDRA preferred terms listed in Table 1. Table 10 presents the incidence of hypocalcemia by treatment groups based on all pivotal and all five non-pivotal randomized, controlled studies with at least one denosumab arm. Table 11 compares the incidences of hypocalcemia between proposed denosumab marketing dose group and placebo group on all pivotal studies and three selected placebo-controlled non-pivotal studies. Table 12 compares the incidences between the denosumab and the placebo groups on pivotal studies. Finally, Table 13 compares the incidences between the treatment groups on all non-pivotal studies. In all of the above tables, the placebo group was used as the reference in computing the inferential statistics for all denosumab groups. For alendronate group, the reference group was the proposed denosumab marketing dose treatment group. Because these analyses are exploratory, multiplicity correction issues are not considered.

The incidence of hypocalcemia was comparable between the denosumab group and the placebo group except for two non-marketing dose groups (denosumab 14mg Q3M and denosumab 100mg Q6M) on pooled pivotal and non-pivotal studies. Consistent results were observed across other sets of analysis.

Table 10: Incidence of hypocalcemia of any potential Preferred Term on pivotal (20040132, 20030216, 20040135, and 20040318) and selected non-pivotal studies (20010223, 20050141, 20050172, 20050179, and 20050234)

Treatment Group	Incidence n (%)	P-values		Estimates (asymptotic 95% CI)	
		Chisq	Fisher	RD (%)	RR
denosumab Any Dose (N=6311)	193 (3.06)	0.3513	0.3708	0.30 (-0.32, 0.92)	1.11 (0.89, 1.37)
denosumab 6mg Q3M (N=43)	1 (2.33)	0.8619	1.0000	-0.44 (-4.96, 4.96)	0.84 (0.12, 5.88)
denosumab 14mg Q6M (N=106)	4 (3.77)	0.5308	0.5406	1.01 (-2.64, 4.67)	1.37 (0.52, 3.62)
denosumab 14mg Q3M (N=44)	7 (15.91)	<0.0001	<0.0001	13.15 (2.33, 23.96)	5.76 (2.86, 11.58)
denosumab 30mg Q3M (N=40)	2 (5.00)	0.7357	0.3060	2.24 (-4.53, 9.01)	1.81 (0.46, 7.06)
denosumab 60mg Q6M (N=5940)	169 (2.85)	0.7921	0.8170	0.08 (-0.54, 0.70)	1.03 (0.83, 1.28)
denosumab 100mg Q6M (N=92)	8 (8.70)	*0.0007*	*0.0046*	5.93 (0.16, 11.71)	3.15 (1.59, 6.23)
denosumab 210mg Q6M (N=46)	2 (4.35)	0.5145	0.3668	1.59 (-4.32, 7.50)	1.57 (0.40, 6.17)
alendronate 70mg QW * (N=962)	19 (1.98)	0.1241	0.1352	-0.87 (-1.85, 0.11)	0.69 (0.43, 1.11)
placebo (N=5069)	140 (2.76)	NA	NA	NA	NA

Note: * denosumab 60mg Q6M was treated as the reference group

Table 11: Incidence of hypocalcemia of any potential Preferred Term on pivotal PMO studies (20040132 and 20030216) and selected non-pivotal PMO studies with placebo arm (20010223, 20050172, and 20050179)

Treatment Group	Incidence n (%)	P-values		Estimates (asymptotic 95% CI)	
		Chisq	Fisher	RD (%)	RR
denosumab 60mg Q6M (N=4234)	121 (2.86)	0.9627	1.0000	0.02 (-0.69, 0.73)	1.01 (0.78, 1.29)
placebo (N=4224)	120 (2.84)	NA	NA	NA	NA

Table 12: Incidence of hypocalcemia of any potential Preferred Term on pivotal studies only (20040132, 20030216, 20040135, and 20040318)

Treatment Group	Incidence n (%)	P-values		Estimates (asymptotic 95% CI)	
		Chisq	Fisher	RD (%)	RR
denosumab 60mg Q6M (N=4910)	142 (2.89)	0.4858	0.4992	0.23 (-0.42, 0.88)	1.09 (0.86, 1.37)
placebo (N=4886)	130 (2.66)	NA	NA	NA	NA

Table 13: Incidence of hypocalcemia of any potential Preferred Term on non-pivotal studies only (20010223, 20050141, 20050172, 20050179, and 20050234)

Treatment Group	Incidence n (%)	P-values		Estimates (asymptotic 95% CI)	
		Chisq	Fisher	RD (%)	RR
denosumab 6mg Q3M (N=43)	1 (2.33)	0.3894	0.6948	-3.14 (-8.72, 2.44)	0.43 (0.06, 3.24)
denosumab 14mg Q6M (N=106)	4 (3.77)	0.5188	0.5842	-1.69 (-6.59, 3.21)	0.69 (0.22, 2.15)
denosumab 14mg Q3M (N=44)	7 (15.91)	0.0181	0.0268	10.44 (-0.85, 21.74)	2.91 (1.17, 7.22)
denosumab 30mg Q3M (N=40)	2 (5.00)	0.9061	1.0000	-0.46 (-7.98, 7.05)	0.92 (0.21, 4.02)
denosumab 60mg Q6M (N=1030)	27 (2.62)	0.0393	0.0575	-2.84 (-6.28, 0.59)	0.48 (0.24, 0.97)
denosumab 100mg Q6M (N=92)	8 (8.70)	0.3067	0.3118	3.23 (-3.40, 9.86)	1.59 (0.65, 3.90)
denosumab 210mg Q6M (N=46)	2 (4.35)	0.7613	1.0000	-1.12 (-7.87, 5.63)	0.80 (0.18, 3.51)
alendronate 70mg QW * (N=962)	19 (1.98)	0.3372	0.3725	-0.65 (-1.96, 0.67)	0.75 (0.42, 1.35)
placebo (N=183)	10 (5.46)	NA	NA	NA	NA

Note: * denosumab 60mg Q6M was treated as the reference group

5.1.1.3.2. PMO indications

Table 14 shows the frequencies and incidences of potential hypocalcemia on the pooled PMO pivotal studies (i.e. 20040132 and 20030216). In total, 4050 subjects received denosumab 60mg Q6M and 4041 subjects received placebo.

No subject in the denosumab group was recorded to have an adverse effect that could be specifically named as "Hypocalcemia." Two subjects in the placebo groups were reported to have at least one specific hypocalcemia adverse event.

The counts and proportions of subjects who experienced any potential hypocalcemia event were similar for both treatment groups (112 (2.77%) for denosumab 60mg Q6M group and 110 (2.72%) for the placebo group). Statistical tests, e.g. Chi-square test, Fisher's exact test, as well as risk differences and risk ratios, for comparing the incidences of events between the two treatment groups were not statistically significant. Comparisons of incidences of hypocalcemia between the two treatment groups were also conducted at the MedDRA grouping levels of System Organ Class, High Level Group Term, High Level Term and Preferred Term respectively. The majority of hypocalcemic events were captured via the preferred terms of *Paresthesia* and *Hypoesthesia*. Both terms fell under *Nervous system disorders* System Organ Class, *Neurological disorders NEC* High Level Group Term. In terms of High Level Term, *Paresthesia* fell under *Paraesthesias and dysaesthesias* and *Hypoesthesia* fell under *Sensory abnormalities NEC*. At all of the above MedDRA levels, the difference of incidences between the denosumab and the placebo groups were not statistically significant.

Table 14: Frequency and incidence of hypocalcemia on the pooled PMO safety population by MedDRA (v11.0) Preferred Term, System Organ Class, High Level Group Term and High Level Term

MedDRA Grouping Level	MedDRA Terms	Treatment Group		P-values		Estimates (asymptotic 95% CI)	
		denosumab 60mg Q6M N=4050 n (%)	placebo N=4041 n (%)	Chisq	Fisher	RD (%)	RR
Any PT	Any Preferred Term related to hypocalcemia	112 (2.77)	110 (2.72)	0.9050	0.9458	0.04 (-0.67, 0.76)	1.02 (0.78, 1.32)
System Organ Class	Endocrine disorders	1 (0.02)	0 (0.00)	0.3178	1.0000	0.02 (-0.07, 0.14)	NA
	Gastrointestinal disorders	2 (0.05)	3 (0.07)	0.6528	0.6871	-0.02 (-0.17, 0.11)	0.67 (0.13, 3.33)
	Investigations	1 (0.02)	0 (0.00)	0.3178	1.0000	0.02 (-0.07, 0.14)	NA
	Metabolism and nutrition disorders	1 (0.02)	3 (0.07)	0.3161	0.3744	-0.05 (-0.20, 0.07)	0.33 (0.05, 2.32)
	Nervous system disorders	104 (2.57)	100 (2.47)	0.7890	0.8316	0.09 (-0.59, 0.78)	1.04 (0.79, 1.36)
High Level Group Term	Bone, calcium, magnesium and phosphorus metabolism disorders	0 (0.00)	2 (0.05)	0.1568	0.2494	-0.05 (-0.18, 0.05)	0.00 (0.00, 1.92)
	Neurological disorders NEC	104 (2.57)	100 (2.47)	0.7890	0.8316	0.09 (-0.59, 0.78)	1.04 (0.79, 1.36)
	Oral soft tissue conditions	2 (0.05)	3 (0.07)	0.6528	0.6871	-0.02 (-0.17, 0.11)	0.67 (0.13, 3.33)
	Parathyroid gland disorders	1 (0.02)	0 (0.00)	0.3178	1.0000	0.02 (-0.07, 0.14)	NA
	Vitamin related disorders	1 (0.02)	1 (0.02)	0.9987	1.0000	0.00 (-0.12, 0.12)	1.00 (0.10, 9.56)
	Water, electrolyte and mineral investigations	1 (0.02)	0 (0.00)	0.3178	1.0000	0.02 (-0.07, 0.14)	NA
High Level Term	Calcium metabolism disorders	0 (0.00)	2 (0.05)	0.1568	0.2494	-0.05 (-0.18, 0.05)	0.00 (0.00, 1.92)
	Fat soluble vitamin deficiencies and disorders	1 (0.02)	1 (0.02)	0.9987	1.0000	0.00 (-0.12, 0.12)	1.00 (0.10, 9.56)
	Hypoparathyroid disorders	1 (0.02)	0 (0.00)	0.3178	1.0000	0.02 (-0.07, 0.14)	NA
	Mineral and electrolyte analyses	1 (0.02)	0 (0.00)	0.3178	1.0000	0.02 (-0.07, 0.14)	NA
	Oral soft tissue pain and paraesthesia	1 (0.02)	2 (0.05)	0.5623	0.6245	-0.02 (-0.16, 0.09)	0.50 (0.07, 3.81)
	Oral soft tissue signs and symptoms	1 (0.02)	1 (0.02)	0.9987	1.0000	0.00 (-0.12, 0.12)	1.00 (0.10, 9.56)
	Paraesthesias and dysaesthesias	65 (1.60)	60 (1.48)	0.6613	0.7186	0.12 (-0.42, 0.67)	1.08 (0.76, 1.53)
	Sensory abnormalities NEC	42 (1.04)	42 (1.04)	0.9918	1.0000	0.00 (-0.45, 0.45)	1.00 (0.65, 1.52)
Preferred Term	Hypocalcaemia	0 (0.00)	2 (0.05)	0.1568	0.2494	-0.05 (-0.18, 0.05)	0.00 (0.00, 1.92)
	Paraesthesia	65 (1.60)	60 (1.48)	0.6613	0.7186	0.12 (-0.42, 0.67)	1.08 (0.76, 1.53)

Paraesthesia oral	1 (0.02)	2 (0.05)	0.5623	0.6245	-0.02 (-0.16, 0.09)	0.50 (0.07, 3.81)
Hypoaesthesia	42 (1.04)	42 (1.04)	0.9918	1.0000	0.00 (-0.45, 0.45)	1.00 (0.65, 1.52)
Hypoaesthesia oral	1 (0.02)	1 (0.02)	0.9987	1.0000	0.00 (-0.12, 0.12)	1.00 (0.10, 9.56)
Hypoparathyroidism	1 (0.02)	0 (0.00)	0.3178	1.0000	0.02 (-0.07, 0.14)	NA
Blood magnesium decreased	1 (0.02)	0 (0.00)	0.3178	1.0000	0.02 (-0.07, 0.14)	NA
Vitamin D deficiency	1 (0.02)	1 (0.02)	0.9987	1.0000	0.00 (-0.12, 0.12)	1.00 (0.61, 5.71)

5.1.1.3.3. HALT indications

Table 15 and Table 16 present the frequencies and incidences of hypocalcemia for study 20040135 and study 20040138 respectively. For 20040135, no subject was identified to have specific Hypocalcemia adverse event in either treatment groups. The incidences of hypocalcemia at all MedDRA grouping levels were comparable between the two treatment groups.

Table 15: Frequency and incidence of hypocalcemia on the safety population of 20040135 by MedDRA (v9.0) Preferred Term, System Organ Class, High Level Group Term and High Level Term

MedDRA Grouping Level	MedDRA Terms	Treatment Group		P-values		Estimates (Exact 95% CI)	
		denosumab 60mg G6M N=129 n (%)	placebo N=120 n (%)	Chisq	Fisher	RD (%)	RR
Any PT	Any Preferred Term related to hypocalcemia	8 (6.20)	4 (3.33)	0.2910	0.3797	2.87 (-3.28, 8.98)	1.86 (0.61, 7.15)
SOC	Gastrointestinal disorders	1 (0.78)	0 (0.00)	0.3338	1.0000	0.78 (-2.60, 4.68)	NA
	Nervous system disorders	7 (5.43)	4 (3.33)	0.4219	0.5426	2.09 (-3.87, 8.25)	1.63 (0.51, 6.89)
HLGT	Neurological disorders NEC	7 (5.43)	4 (3.33)	0.4219	0.5426	2.09 (-3.87, 8.25)	1.63 (0.51, 6.89)
	Oral soft tissue conditions	1 (0.78)	0 (0.00)	0.3338	1.0000	0.78 (-2.60, 4.68)	NA
HLT	Oral soft tissue pain and paraesthesia	1 (0.78)	0 (0.00)	0.3338	1.0000	0.78 (-2.60, 4.68)	NA
	Paraesthesias and dysaesthesias	2 (1.55)	2 (1.67)	0.9419	1.0000	-0.12 (-4.58, 4.19)	0.93 (0.12, 7.19)
	Sensory abnormalities NEC	6 (4.65)	4 (3.33)	0.5966	0.7505	1.32 (-4.48, 7.09)	1.40 (0.43, 6.41)
PT	Paraesthesia	2 (1.55)	2 (1.67)	0.9419	1.0000	-0.12 (-4.58, 4.19)	0.93 (0.12, 7.19)
	Paraesthesia oral	1 (0.78)	0 (0.00)	0.3338	1.0000	0.78 (-2.60, 4.68)	NA
	Hypoaesthesia	6 (4.65)	4 (3.33)	0.5966	0.7505	1.32 (-4.48, 7.09)	1.40 (0.43, 6.41)

For 20040138, one subject who received denosumab was identified to have specific hypocalcemia events and no subject in the placebo group had any specific hypocalcemia events. The incidences of hypocalcemia were comparable between the treatment groups at all MedDRA grouping levels. This finding is consistent with the those from the pooled PMO analysis and 20040135 analysis.

Table 16: Frequency and incidence of hypocalcemia on the safety population of 20040138 by MedDRA (v9.0) Preferred Term, System Organ Class, High Level Group Term and High Level Term

MedDRA Grouping Level	MedDRA Terms	Treatment Group		P-values		Estimates (Exact 95% CI)	
		Denosumab 60mg Q6M N=731 n (%)	placebo N=725 n (%)	Chisq	Fisher	RD (%)	RR
Any PT	Any Preferred Term related to hypocalcemia	22 (3.01)	16 (2.21)	0.3368	0.4116	0.80 (-0.93, 2.55)	1.36 (0.72, 2.56)
SOC	Metabolism and nutrition disorders	1 (0.14)	0 (0.00)	0.9953	1.0000	0.00 (-0.72, 0.72)	0.99 (0.06, 16.65)
	Nervous system disorders	21 (2.87)	15 (2.07)	0.3234	0.3993	0.80 (-0.87, 2.52)	1.39 (0.72, 2.65)
HLGT	Bone, calcium, magnesium and phosphorus metabolism disorders	1 (0.14)	0 (0.00)	0.3191	1.0000	0.14 (-0.42, 0.82)	NA
	Neurological disorders NEC	21 (2.87)	15 (2.07)	0.3234	0.3993	0.80 (-0.87, 2.52)	1.39 (0.72, 2.65)
	Vitamin related disorders	0 (0.00)	1 (0.14)	0.3152	0.4979	-0.14 (-0.83, 0.41)	0.00 (0.00, 7.94)
HLT	Calcium metabolism disorders	1 (0.14)	0 (0.00)	0.3191	1.0000	0.14 (-0.42, 0.82)	NA
	Fat soluble vitamin deficiencies and disorders	0 (0.00)	1 (0.14)	0.3152	0.4979	-0.14 (-0.83, 0.41)	0.00 (0.00, 7.94)
	Paraesthesias and dysaesthesias	6 (0.82)	6 (0.83)	0.9886	1.0000	-0.01 (-1.11, 1.08)	0.99 (0.34, 2.90)
	Sensory abnormalities NEC	16 (2.19)	9 (1.24)	0.1641	0.2256	0.95 (-0.43, 2.44)	1.76 (0.80, 3.94)
PT	Hypocalcaemia	1 (0.14)	0 (0.00)	0.3191	1.0000	0.14 (-0.42, 0.82)	NA
	Paraesthesia	6 (0.82)	6 (0.83)	0.9886	1.0000	-0.01 (-1.11, 1.08)	0.99 (0.34, 2.90)
	Hypoaesthesia	16 (2.19)	9 (1.24)	0.1641	0.2256	0.95 (-0.43, 2.44)	1.76 (0.80, 3.94)
	Vitamin D deficiency	0 (0.00)	1 (0.14)	0.3152	0.4979	-0.14 (-0.83, 0.41)	0.00 (0.00, 7.94)

5.1.1.4. Subgroup analysis on the incidence of hypocalcemia

5.1.1.4.1. Incidence of hypocalcemia by baseline vitamin D levels

Baseline vitamin D values were missing for two subjects in each of the four pivotal studies. The unique subject identification numbers were 2030216-434092, 20030216-631071, 20040132-108001, 20040132-123042, 20040135-102003, 20040135-102005, 20040138-149008 and 20040138-306002. Six of them were from North America, one from Western Europe and one from Latin America. Five were assigned to the placebo treatment and the rest were assigned to the Denosumab 60mg Q6M treatment. Six of them completed the study, one failed to comply due to a vacation occurred before month-18-visit, and the other subject did not complete because of "disease progression due to bone loss." None of them were identified as hypocalcemia patients based on adverse events data.

Table 17, Table 18 and Table 19 summarize the incidences of hypocalcemia of any potential preferred term and of each preferred term by baseline vitamin D values on the pooled pivotal PMO studies, the pivotal study 20040135 and the pivotal study 20040138 respectively. For the pooled PMO studies, the incidences of hypocalcemia with any potential PT and with each PT were comparable between the treatment groups. For study 20040135, among subjects whose baseline vitamin D were between 12ng/ml and 20ng/ml, the incidence of hypocalcemia with any potential PT was 6 (9.68%) for the denosumab group and zero for the placebo group. For study 20040138, the incidences of hypocalcemia were similar across the two treatment groups in all vitamin D groups.

5.1.1.4.2. Incidence of hypocalcemia by baseline renal function

A total of seven subjects had missing values on baseline creatinine clearance. Subject 20030216-759057 also had a missing value on creatinine. This subject was a white woman from Czech Republic who was 70-year old at the time of assignment to denosumab treatment. Her other baseline lab test results were within normal ranges. It appears that the other six subjects had missing values for creatinine clearance because their baseline weights were missing. These subjects were excluded from this stratified analysis.

Table 20, Table 21 and Table 22 present the subgroup analysis on the incidences of hypocalcemia by baseline creatinine clearance levels for the pooled pivotal PMO studies, the pivotal study 20040135 and the pivotal study 20040138 respectively. In an analysis similar to the subgroup analysis by baseline vitamin D levels, incidences of hypocalcemia was evaluated for adverse events defined by any potential PT and adverse events defined by each PT. For all three sets of analyses, the incidences of hypocalcemia were similar between the denosumab group and the placebo group.

Table 17: Incidence of hypocalcemia by baseline vitamin D levels for the pooled safety population of PMO studies (study 20040132-24 month and study 20030216)

MedDRA Preferred Terms	Vitamin D <12 (ng/ml) Treatment Group		12≤Vitamin D<20 (ng/ml) Treatment Group		20≤Vitamin D<32 (ng/ml) Treatment Group		Vitamin D≥32 (ng/ml) Treatment Group	
	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)
Number of subjects	10	9	2028	2016	1380	1410	630	604
Any potential Preferred Term	0	0	58 (2.86)	52 (2.58)	36 (2.61)	37 (2.62)	18 (2.86)	21 (3.48)
Paraesthesia	0	0	30 (1.48)	27 (1.34)	25 (1.81)	20 (1.42)	10 (1.59)	13 (2.15)
Hypoaesthesia	0	0	26 (1.28)	18 (0.89)	9 (0.65)	14 (0.99)	7 (1.11)	10 (1.66)
Hypoparathyroidism	0	0	1 (0.05)	0	0	0	0	0
Blood magnesium decreased	0	0	1 (0.05)	0	0	0	0	0
Vitamin D deficiency	0	0	1 (0.05)	0	0	0	0	0

Table 18: Incidence of hypocalcemia by baseline vitamin D levels for the safety population of study 20040135

MedDRA Preferred Terms	Vitamin D <12 (ng/ml) Treatment Group		12≤Vitamin D<20 (ng/ml) Treatment Group		20≤Vitamin D<32 (ng/ml) Treatment Group		Vitamin D≥32 (ng/ml) Treatment Group	
	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)
Number of subjects	16	26	62	47	50	46	0	0
Any potential Preferred Term	0	1 (3.85)	6 (9.68) **	0	2 (4.00)	3 (6.52)	0	0
Paraesthesia	0	1 (3.85)	1 (1.61)	0	1 (2.00)	1 (2.17)	0	0
Paraesthesia oral	0	0	1 (1.61)	0	0	0	0	0
Hypoaesthesia	0	1 (3.85)	4 (6.45)	0	2 (4.00)	3 (6.52)	0	0

Note: ** Fisher's exact test P-value=0.03565

Table 19: Incidence of hypocalcemia by baseline vitamin D levels for the safety population of 20040138 study

MedDRA Preferred Terms	Vitamin D <12 (ng/ml) Treatment Group		12≤Vitamin D<20 (ng/ml) Treatment Group		20≤Vitamin D<32 (ng/ml) Treatment Group		Vitamin D≥32 (ng/ml) Treatment Group	
	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)
Number of subjects	4	4	194	191	381	377	152	151
Any potential Preferred Term	0	0	3 (1.55)	4 (2.09)	15 (3.94)	9 (2.39)	4 (2.63)	3 (1.99)
Hypocalcaemia	0	0	0	0	0	0	1 (0.66)	0
Paraesthesia	0	0	0	1 (0.52)	6 (1.57)	5 (1.33)	0	0
Hypoaesthesia	0	0	3 (1.55)	3 (1.57)	10 (2.62)*	3 (0.80)	3 (1.97)	3 (1.99)
Vitamin D deficiency	0	0	0	0	0	1 (0.27)	0	0

Note: * Fisher's exact test P-value=0.0896

Table 20: Incidence of hypocalcemia by baseline creatinine clearance levels for the pooled safety population of PMO studies (study 20040132-24 month and study 20030216)

MedDRA Preferred Terms	Cr.Clearance<30 (ml/min) Treatment Group		30≤Cr.Clearance<60 (ml/min) Treatment Group		60≤Cr.Clearance<90 (ml/min) Treatment Group		Cr.Clearance≥90 (ml/min) Treatment Group	
	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)
Number of subjects	36	37	1425	1408	2089	2124	498	469
Any potential Preferred Term	0	1 (2.70)	36 (2.53)	37 (2.63)	66 (3.16)	62 (2.92)	10 (2.01)	9 (1.92)
Hypocalcaemia	0	1 (2.70)	0	0	0	1 (0.05)	0	0
Paraesthesia	0	0	18 (1.26)	23 (1.63)	45 (2.15)	32 (1.51)	2 (0.40)	5 (1.07)
Paraesthesia oral	0	0	1 (0.07)	0	0	2 (0.09)	0	0
Hypoaesthesia	0	0	17 (1.19)	12 (0.85)	18 (0.86)	24 (1.13)	7 (1.41)	5 (1.07)
Hypoaesthesia oral	0	0	1 (0.07)	0	0	0	0	1 (0.21)
Hypoparathyroidism	0	0	0	0	1 (0.05)	0	0	0
Blood magnesium decreased	0	0	0	0	1 (0.05)	0	0	0
Vitamin D deficiency	0	0	0	1 (0.07)	1 (0.05)	0	0	0

Table 21: Incidence of hypocalcemia by baseline creatinine clearance levels for the safety population of study 20040135

MedDRA Preferred Terms	Cr.Clearance<30 (ml/min) Treatment Group		30≤Cr.Clearance<60 (ml/min) Treatment Group		60≤Cr.Clearance<90 (ml/min) Treatment Group		Cr.Clearance≥90 (ml/min) Treatment Group	
	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)
Number of subjects	12	11	58	57	59	51	0	0
Any potential Preferred Term	0	0	3 (5.17)	1 (1.75)	5 (8.47)	3 (5.88)	0	0
Paraesthesia	0	0	0	0	2 (3.39)	2 (3.92)	0	0
Paraesthesia oral	0	0	0	0	1 (1.69)	0	0	0
Hypoaesthesia	0	0	3 (5.17)	1 (1.75)	3 (5.08)	3 (5.88)	0	0

Table 22: Incidence of hypocalcemia by baseline creatinine clearance levels for the safety population of study 20040138

MedDRA Preferred Terms	Cr.Clearance<30 (ml/min) Treatment Group		30≤Cr.Clearance<60 (ml/min) Treatment Group		60≤Cr.Clearance<90 (ml/min) Treatment Group		Cr.Clearance≥90 (ml/min) Treatment Group	
	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)
Number of subjects	4	2	173	183	350	341	203	199
Any potential Preferred Term	1 (25.00)	0	2 (1.16)	2 (1.09)	13 (3.71)	9 (2.64)	6 (2.96)	5 (2.51)
Hypocalcaemia	1 (25.00)	0	0	0	0	0	0	0
Paraesthesia	0	0	1 (0.58)	1 (0.55)	3 (0.86)	1 (0.29)	2 (0.99)	4 (2.01)
Hypoaesthesia	0	0	1 (0.58)	1 (0.55)	11 (3.14)	7 (2.05)	4 (1.97)	1 (0.50)
Vitamin D deficiency	0	0	0	0	0	1 (0.29)	0	0

5.1.1.5. PPI exposure on hypocalcemia

Table 23 shows the frequency and percentage of subjects with different number of PPI medications. Approximately 15% to 18% subjects had at least one PPI medication across all four pivotal studies. The majority of PPI exposed subjects had only one PPI medication. The maximum number of PPI medications per subject was around 3 to 4 for study 20040132, study 20040135, and study 20040138. For study 20030216, the maximum number of PPI medication one received is 10 and this occurred on only one subject.

Table 23: Frequency and percentage of subjects with different number of PPI medications by study

Study ID	No. of PPI Medications	No. of subjects	Percentage
20030216	0	6463	82.2
	1	997	12.7
	2	267	3.4
	3	94	1.2
	4	27	0.3
	5	9	0.1
	6	4	0.1
	10	1	0.0
20040132	0	285	85.8
	1	34	10.2
	2	10	3.0
	3	3	0.9
20040135	0	209	82.9
	1	31	12.3
	2	11	4.4
	4	1	0.4
20040138	0	1248	85.0
	1	180	12.3
	2	29	2.0
	3	7	0.5
	4	4	0.3

Table 24 presents the incidence of hypocalcemia for both treatment groups by PPI exposure status and by study. Within both PPI exposure groups, the incidence of hypocalcemia is similar between the two treatment groups for the pooled PMO studies (20040132 and 20030216), study 20040135, and study 20040138. For example, for the pooled PMO studies, the incidence of hypocalcemia is approximately 3.2% for both treatment groups among subjects with PPI exposure, and the incidence is around 2.6% for both treatment groups among subject without PPI exposure. However, based on additional logistic regression analysis of PPI exposure and treatments on the incidence of hypocalcemia (results not shown in the review), PPI exposure is associated with hypocalcemia for study 20040135 and study 20040138 regardless of treatment groups. In other words, subjects with PPI exposure were more likely to experience hypocalcemia than those with no PPI exposure for study 20040135 and study 20040138.

Table 24: Incidence of hypocalcemia within PPI exposed group and PPI not-exposed group by study

Study		PPI Exposed		PPI Not-exposed	
		denosumab 60mg Q6M	placebo	denosumab 60mg Q6M	placebo
Pooled PMO	No. of subjects	726	716	3324	3325
	No. (%) of cases	23 (3.2)	23 (3.2)	89 (2.7)	87 (2.6)
20040135	No. of subjects	16	27	615	621
	No. (%) of cases	2 (18.8)	2 (7.4)	5 (4.4)	2 (2.2)
20040138	No. of subjects	116	104	615	621
	No. (%) of cases	8 (6.9)	4 (3.8)	14 (2.3)	12 (1.9)

5.1.1.6. Severity/toxicity of hypocalcemia

5.1.1.6.1. Severity of hypocalcemia for PMO indications

The incidence of hypocalcemia of any potential PT and by each PT by severity levels on the pooled pivotal PMO studies (i.e. 20040132 and 20030216) are shown in Table 25. Most events were mild or moderate. Two denosumab treated subjects had at least one severe event. Both subjects were identified via potential symptoms of hypocalcemia. One subject was identified as having severe Paraesthesia and the other subject was identified as having severe Hypoaesthesia. In comparison, a total of six subjects who received the placebo drug had severe events. One subject experienced a severe Hypocalcemia episode, one subject had severe Paraesthesia and four subjects had severe Hypoaesthesia. To summarize the results, the incidences of hypocalcemia at each severity level were similar between the denosumab group and the placebo group.

Table 25: Incidence of hypocalcemia of any potential Preferred Term and by Preferred Term with differential severity levels on pooled PMO studies (20040132 and 20030216)

MedDRA Preferred Terms	Severity Level	Treatment Group	
		denosumab 60mg G6M n (%)	Placebo n (%)
Number of subjects		N=4050	N=4041
Any potential Preferred Term	Mild	79 (1.95)	77 (1.91)
	Moderate	29 (0.72)	26 (0.64)
	Severe	2 (0.05)	6 (0.15)
Hypocalcaemia	Moderate	0 (0.00)	1 (0.02)
	Severe	0 (0.00)	1 (0.02)
Paraesthesia	Mild	51 (1.26)	42 (104)
	Moderate	13 (0.32)	17 (0.42)
	Severe	1 (0.02)	1 (0.02)
Paraesthesia oral	Mild	0 (0.00)	1 (0.02)
	Moderate	1 (0.02)	1 (0.02)
Hypoaesthesia	Mild	27 (0.67)	30 (0.74)
	Moderate	14 (0.35)	8 (0.20)
	Severe	1 (0.02)	4 (0.10)
Hypoaesthesia oral	Mild	1 (0.02)	1 (0.02)
Hypoparathyroidism	Moderate	1 (0.02)	0 (0.00)
Blood magnesium decreased	Moderate	1 (0.02)	0 (0.00)
Vitamin D deficiency	Mild	0 (0.00)	1 (0.02)
	Moderate	1 (0.02)	0 (0.00)

5.1.1.6.2. Toxicity of hypocalcemia for HALT indications

Table 26 shows the incidences of hypocalcemia of any potential PT and by each PT at different toxicity grades by treatment groups. Most events were graded at toxicity level 1 or 2. For study 20040138, two subjects in denosumab group had toxicity grade 3 adverse events. One of the two subjects had toxicity grade 3 Hypocalcaemia and the other subject had toxicity grade 3 Hypoaesthesia. Except for this observation, the incidences were comparable across the two treatment groups at all toxicity grades.

Table 26: Incidence of hypocalcemia of any potential Preferred Term and by Preferred Term with differential toxicity grades on study 20040135 and study 20040138 separately

Study ID	MedDRA Preferred Term	Toxicity Grade	Treatment Group	
			denosumab 60mg G6M n (%)	placebo n (%)
Study 20040135	Number of subjects		N=129	N=120
	Any potential Preferred Term	Grade 1	7 (5.43)	3 (2.50)
		Grade 2	1 (0.78)	1 (0.83)
	Paraesthesia	Grade 1	1 (0.78)	2 (1.67)
		Grade 2	1 (0.78)	0 (0.00)
	Paraesthesia oral	Grade 1	1 (0.78)	0 (0.00)
	Hypoaesthesia	Grade 1	7 (5.43)	3 (2.50)
		Grade 2	0 (0.00)	1 (0.83)
Study 20040138	Number of subjects		N=731	N=725
	Any potential Preferred Term	Grade 1	14 (1.92)	10 (1.38)
		Grade 2	6 (0.82)	5 (0.69)
		Grade 3	2 (0.27)	0 (0.00)
	Hypocalcaemia	Grade 3	1 (0.14)	0 (0.00)
	Paraesthesia	Grade 1	4 (0.55)	5 (0.69)
		Grade 2	2 (0.27)	1 (0.14)
	Hypoaesthesia	Grade 1	11 (1.50)	5 (0.69)
		Grade 2	4 (0.55)	4 (0.55)
		Grade 3	1 (0.14)	0 (0.00)
	Vitamin D deficiency	Grade 1	0 (0.00)	1 (0.14)

5.1.2. Hypocalcemia based on laboratory data

5.1.2.1. Incidence and toxicity of hypocalcemia

A hypocalcemia event based on laboratory findings was confirmed if the lowest albumin-adjusted calcium value across the entire study fell below 8.5mg/dl. The toxicity level for such a hypocalcemia adverse event was also determined following NCI/CTCAT v3.0 guidance. Table 27 shows the incidences of hypocalcemia based on the laboratory data for the pooled PMO studies, Study 20040135 and Study 20040138 separately.

Table 27: Incidence of hypocalcemia defined as albumin-adjusted calcium<8.5mg/dl*

Study ID	denosumab 60mg Q6M		placebo		P-values		Estimates (asymptotic 95% CI)	
	n (%)	No. of subj.	n (%)	No. of subj.	Chisq	Fisher	RD (%)	RR
Pooled PMO	72 (1.78)	4050	20 (0.49)	4041	<.0001	<.0001	1.28 (0.82, 1.74)	3.59 (2.19, 5.88)
20040135	2 (1.55)	129	2 (1.67)	120	0.9419	1.000	-0.12 (-3.25, 3.01)	0.93 (0.13, 6.50)
20040138	27 (3.69)	731	5 (0.69)	725	<.0001	<.0001	3.00 (1.51, 4.50)	5.36 (2.07, 13.8341)

Note: * A LLN value of 8.4mg/dl is used for Study 20040135 and Study 20040138.

For the pooled PMO analysis (study 20040132 and study 20030216), 72 (1.78%) subjects who received denosumab had at least one albumin-adjusted calcium value less than 8.5mg/dl, and in comparison, 20 (0.49%) placebo treated subjects had at least one calcium value that falls below 8.5mg/dl. The relative risk of experiencing hypocalcemia was 3.59 for denosumab relative to placebo, and the Fisher's exact test for this incidence discrepancy was significant at .0001 level. For study 20040135, the incidences were comparable between the two treatment groups. For study 20040138, the relative risk of having hypocalcemia was 5.36 for denosumab treated subjects compared to placebo treated subjects, which was also statistically significant. The sensitivity of this analysis to the use of different calcium measures was evaluated. The findings on the total serum calcium values and the albumin-adjusted calcium values regardless of subjects' albumin levels are consistent with the results presented in Table 27.

Table 28 shows that most laboratory-confirmed hypocalcemia adverse events were toxicity-grade-1 events. Denosumab was found to be associated with higher risks of toxicity grade 1 hypocalcemia events for the pooled PMO studies (study 20040132 and study 20030216) and the HALT study 20040138. The incidence of toxicity grade 2 hypocalcemia was comparable between the denosumab and the placebo groups for all pivotal studies.

Table 28: Toxicity grades of hypocalcemia on laboratory albumin-adjusted calcium levels

Study ID	Toxicity Grade	denosumab 60mg Q6M		placebo		P-values		Estimates (asymptotic 95% CI)	
		n (%)	No.of subj.	n (%)	No.of subj.	Chisq	Fisher	RD (%)	RR
Pooled PMO	1	65 (1.60)	4050	15 (0.37)	4041	<.0001	<.0001	1.22 (0.80, 1.65)	4.32 (2.47, 7.57)
Pooled PMO	2	7 (0.17)	4050	4 (0.10)	4041	0.3675	0.5486	0.07 (-0.09, 0.23)	1.75 (0.51, 5.96)
Pooled PMO	3	0 (0.00)	4050	1 (0.02)	4041	0.3167	0.4994	-0.02 (-0.07, 0.02)	0.33 (0.01, 8.16)
20040135	1	2 (1.55)	129	2(1.67)	120	0.9419	1.000	-0.12 (-3.25, 3.01)	0.93 (0.13, 6.50)
20040138	1	24 (3.28)	731	4 (0.55)	725	0.0001	0.0002	2.73 (1.33, 4.13)	5.95 (2.08, 17.06)
20040138	2	3 (0.41)	731	1 (0.14)	725	0.3206	0.6245	0.27 (-0.26, 0.81)	2.98 (0.31, 28.54)

(b) (4), a cutoff value of 7.5mg/dl was adopted to evaluate the incidences of laboratory serum calcium declines. A sensitivity analysis based on this labeling criterion was carried out and the results for the incidence of hypocalcemia are shown in Table 29. Based on the cutoff value of 7.5mg/dl, the incidence of hypocalcemia was comparable between the denosumab treated subjects and placebo treated subjects on the pooled PMO studies. For the two HALT studies, no subject was identified to have hypocalcemia based on the cutoff value of 7.5mg/dl.

Table 29: Incidence of hypocalcemia defined as albumin-adjusted calcium<7.5mg/dl

Study ID	denosumab 60mg Q6M		placebo		P-values		Estimates (asymptotic 95% CI)	
	n (%)	No.of subj.	n (%)	No.of subj.	Chisq	Fisher	RD (%)	RR
Pooled PMO	2 (0.05)	4050	2 (0.05)	4041	0.9982	1.0000	-0.00 (-0.10, 0.10)	1.00 (0.14, 7.08)
20040135	0	129	0	120	NA	NA	NA	NA
20040138	0	731	0	725	NA	NA	NA	NA

5.1.2.2. Declines in albumin-adjusted calcium levels

Table 30 shows the means of the maximum differences in albumin-adjusted calcium values across the entire study for the pooled PMO studies, 20040135 and 20040138 respectively. The mean maximum difference was approximately 1 mg/dl in all studies. The maximum difference in calcium values was slightly greater for the denosumab group compared with the placebo groups. Although the differences between treatment groups were statistically significant, given the width of normal calcium range, of approximately 2.7mg/dl, these results alone do not provide authoritative evidence that denosumab is potentially associated with higher risks of serum calcium reduction.

Table 30: Mean maximum differences in albumin-adjusted calcium levels

Study ID	Treatment Group		Mean Diff. (denosumab-placebo) (mg/dl)	S.E (Mean Diff.)
	denosumab 60mg Q6M (mg/dl)	placebo (mg/dl)		
Pooled PMO	-0.97	-0.91	-0.06	0.01***
20040135	-0.96	-0.78	-0.18	0.04***
20040138	-1.01	-0.81	-0.20	0.02***

Note: *** denotes the mean difference is statistically significant at 0.001 level based on the two-sample t-test.

Because using the mean to summarize a distribution can be misleading when outliers are present, an alternative approach was used. Table 31 presents the minimum, 5th percentile, 25th percentile, 50th percentile, 75th percentile and maximum to further describe the distributions of the maximum calcium reduction within each treatment groups. For the pooled PMO analysis, the largest calcium differences were 3.2mg/dl and 3.9mg/dl for the denosumab and the placebo groups respectively. Although the magnitudes of the maximum difference for both groups were large, the differences were comparable. The remaining statistics were also comparable across the two treatment groups.
Similar patterns were observed for study 20040135 and study 20040138. Boxplots for comparing the distributions of maximum calcium changes between denosumab and

placebo groups are displayed in Figure 1. From this figure, the maximum calcium changes across the entire study period were distributed similarly in the denosumab group and the placebo groups for all pivotal studies (pooled studies for PMO indications), although the magnitude of the difference is slightly larger for denosumab than placebo.

Table 31: Percentiles of the maximum declines in albumin-adjusted calcium levels

Study ID	Statistics	Treatment Group		Percentile Difference (denosumab-placebo)
		denosumab 60mg Q6M (mg/dl)	placebo (mg/dl)	
Pooled PMO	Number of subjects	4050	4041	
	Minimum	-3.2	-3.9	0.7
	5th Percentile	-1.6	-1.5	-0.1
	25th Percentile	-1.2	-1.1	-0.1
	50th Percentile	-0.9	-0.9	0
	75th Percentile	-0.8	-0.7	-0.1
	Maximum	0	0	0
Study 20040135	Number of subjects	129	120	
	Minimum	-2.5	-2.1	-0.4
	5th Percentile	-1.5	-1.35	-0.15
	25th Percentile	-1.2	-0.9	-0.3
	50th Percentile	-0.9	-0.8	-0.1
	75th Percentile	-0.7	-0.6	-0.1
	Maximum	-0.1	-0.3	0.2
Study 20040138	Number of subjects	731	725	
	Minimum	-2.4	-2	-0.4
	5th Percentile	-1.7	-1.4	-0.3
	25th Percentile	-1.2	-1	-0.2
	50th Percentile	-1	-0.8	-0.2
	75th Percentile	-0.8	-0.6	-0.2
	Maximum	-0.1	0	-0.1

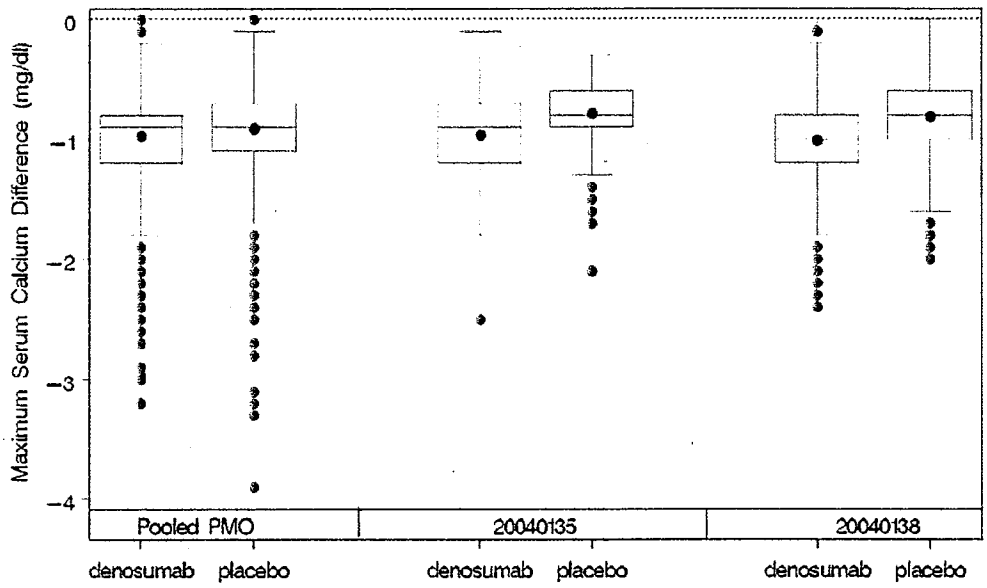

Figure 1: Boxplots for maximum serum calcium differences in denosumab and placebo groups for the pooled PMO studies (20040132 and 20030216), study 20040135, and study 20040138.

5.1.2.3. Time to hypocalcemia event

Consistent with the definition in Section 4.1.2.1, a hypocalcemia adverse event is confirmed if an albumin-adjusted calcium value fell below 8.5mg/dl. Because hypocalcemia events are rare, evaluations of the time to hypocalcemia were based on the pooled data from all four pivotal studies (20040132, 20030216, 20040135, and 20040138).

A total of 128 subjects across all pivotal studies had abnormal lab calcium values throughout the entire study period. Among these subjects, three had two abnormal calcium tests and the rest of 125 subjects had only once abnormal test results. The unique subject identification numbers for these three subjects are 20030216-412042, 20030216-654019 and 20040138-618009. Table 32 lists the abnormally low albumin-adjusted calcium laboratory values and the time to these abnormal values for subjects with more than once abnormal tests throughout the entire study period. For these subjects, the time to hypocalcemia was defined as the time to the first abnormal calcium test. For the remaining 125 subjects with only one abnormal test, the time to hypocalcemia was the time to their abnormal calcium test.

Table 32: Days to abnormal albumin-adjusted calcium tests for subjects with more than one abnormal calcium values

Subject ID	Visit	Days to Abnormal Lab Tests	Lab Results	Normal Low Limit
20030216-412042	Month 1	34	8.4	8.5
	Month 36	1079	8.4	8.5
20030216-654019	Month 24	734	8.4	8.5
	Month 36	1098	8.4	8.5
20040138-618009	Day 1	1	8.2	8.4
	Month 30	911	8.2	8.4

Figure 2 shows the histogram of time to hypocalcemia for the 128 subjects with at least one hypocalcemia adverse events on laboratory calcium values in all pivotal studies by study visits and by treatment assignments. From this figure, most laboratory hypocalcemia adverse events occurred at the beginning of the study, i.e. day-1 visit or month-1 visit. A modest proportion of hypocalcemia adverse events occurred at month-12 visit when subjects received the second dose of the investigational drug. More hypocalcemia events were observed to occur at month 1 for subjects who received denosumab than those who received placebo. Table 33 presents the frequency and percentage of subjects who had their first hypocalcemia event at each visit by treatment groups across all pivotal studies. Approximately 58% of denosumab treated subjects had their first hypocalcemia event at month-1 visit compared with only 18.5% of placebo treated subjects did. The incidence of hypocalcemia is comparable between the two treatment groups at the remaining eight visits.

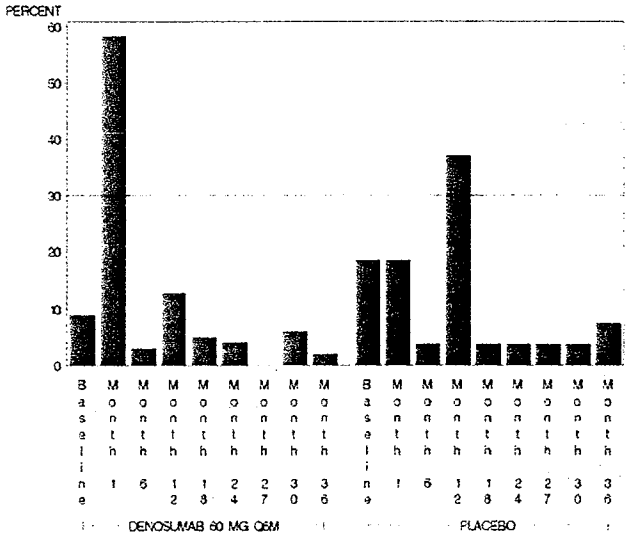

Figure 2: Histogram of the time to hypocalcemia for subjects with at least one hypocalcemia adverse events on laboratory calcium values in all pivotal studies by visit names and by treatment assignments.

Table 33: Frequency and percentage of subjects who had their first hypocalcemia event at each visit by treatment groups across all pivotal studies

Visit	denosumab 60mg Q6M (No. of subjects: 4910)		placebo (No. of subjects: 4886)	
	Frequency	Percentage	Frequency	Percentage
Baseline	9	8.9	5	18.5
Month 1	59	58.4	5	18.5
Month 6	3	3.0	1	3.7
Month 12	13	12.9	10	37.0
Month 18	5	5.0	1	3.7
Month 24	4	4.0	1	3.7
Month 27	0	0.0	1	3.7
Month 30	6	5.9	1	3.7
Month 36	2	2.0	2	7.4
Total	101	100.0	27	100.0

To further explore the effect of denosumab on the time to hypocalcemia, Kaplan-Meier survival analysis was performed to estimate the rate of hypocalcemia. Figure 3 shows the Kaplan-Meier curves for the two treatment groups.

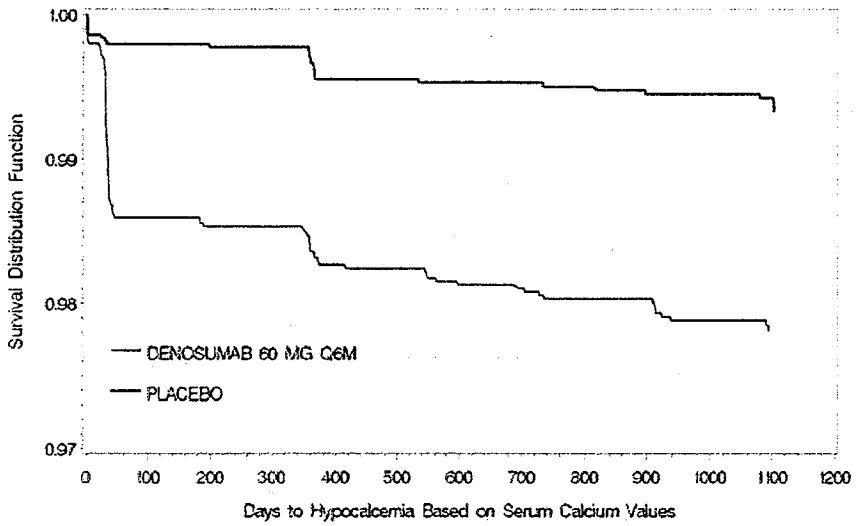

Figure 3: Kaplan-Meier survival curve of days to hypocalcemia event on serum calcium values for all pivotal studies

The difference between the survival curves for the denosumab group and the placebo group was statistically significant according to the logrank test (chi-square=42.453; p <.0001.) The denosumab subjects appear to be associated with a higher risk of hypocalcemia than the placebo subjects are during earlier stage of the study. At later stages of study, the survival curves are similar between the two treatment groups.

This survival analysis is based on hypocalcemia data derived from the laboratory calcium values collected at each scheduled clinical visit. Note that these nine scheduled visits are not equally spaced. Month-1 visit is the only visit scheduled at one month after a subject

receives a dose of treatment. From Figure 3, the main contributor for the difference in survival curves between the two treatments seems to be the rapid decline in the survival function occurred after about 30 days for the denosumab group. Because laboratory calcium data are not available for one month after each dose administration, whether a decline in survival curve will occur for denosumab subjects one month after each successive dose administration cannot be determined.

5.2. Off-treatment evaluations

As shown in Table 34, the incidence of hypocalcemia is small for the 2-year off-treatment phase of study 20040132. There is zero incidence of hypocalcemia during the off-treatment phase for both study 20040135 and 20040138. For the open-label, single arm study 20060289, the incidence of hypocalcemia is small and comparable between the original treatment groups as in study 20030216.

Table 34: The number of hypocalcemia adverse events

Study ID	Treatment Group	Number of adverse events n (%)		
		0	1	2
20060289	denosumab 60mg Q6M (N=2346)	2295 (97.83)	45 (1.92)	6 (0.26)
	placebo (N=2203)	2156 (97.87)	43 (1.95)	4 (0.18)
20040132	denosumab 60mg Q6M (N=128)	125 (97.66)	3 (2.34)	-
	placebo (N=128)	126 (98.44)	2 (1.56)	-
20040135	denosumab 60mg Q6M (N=96)	96 (100.0)	-	-
	placebo (N=89)	89 (100.0)	-	-
20040138	denosumab 60mg Q6M (N=406)	406 (100.0)	-	-
	placebo (N=372)	372 (100.0)	-	-

6. Discussion

Based on adverse event data, there were no statistically significant differences in terms of incidence and severity of hypocalcemia between denosumab 60mg Q6M and placebo for all pivotal studies. The hypocalcemia events identified in the adverse event data were mainly associated with the symptoms of hypocalcemia. Two MedDRA Preferred Terms were responsible for around 90% of all hypocalcemia events, and they were: Hypoaesthesia and Paraesthesia.

However, based on the laboratory data, statistically significant higher risk of hypocalcemia was observed among subjects who received denosumab 60mg Q6M than subjects who received placebo drug for the pooled PMO pivotal studies (study 20040132 and study 20030216) and study 20040138. The relative risk for hypocalcemia can be as high as 5.36, which was observed for study 20040138. These analyses were conducted based on the lower limit of the reference range of albumin-adjusted calcium (i.e. 8.5mg/dl) provided by the sponsor. Although the analyses presented in this report are exploratory, the magnitudes of these two relative risks suggest a potential safety signal.

Larger incidences of hypocalcemia based on laboratory data were observed (denosumab 60mg Q6M: 129 (2.63%) vs. placebo: 30 (0.61%)) than the incidence of hypocalcemia based on adverse events data (denosumab 60mg Q6M: 1 (0.02%) vs. placebo: 2 (0.04%)). These observed discrepancies may be due to the way the adverse events data were collected as described in the sponsor's protocols: "abnormal lab findings without clinical significance should not be recorded as AE, however, lab values changes requiring therapy or adjustment in prior therapy are considered AE". It is worth noting that in the (b) (4) a cutoff value of 7.5mg/dl was used to evaluate laboratory serum calcium declines. Under this criterion, no difference in terms of hypocalcemia incidence was observed for any of the pivotal studies.

The average of the maximum differences in calcium across all visits was no more than 1 mg/dl. Slightly larger differences were observed in the denosumab group than the placebo group. Given the width of calcium normal range, 2.7mg/dl, it was difficult to determine whether this difference was clinically meaningful. There were no statistically significant differences in the incidences of hypocalcemia between the denosumab 60mg Q6M group and placebo group by baseline renal function, by baseline vitamin D levels, or by PPI exposure status.

Among subjects who had at least one hypocalcemia event based on serum calcium values, a higher proportion of denosumab treated subjects, 59 (58.4%), had their first hypocalcemia event at month-1 visit than did the placebo treated subjects, 5 (18.5%). For the remaining visits, the proportion of subjects with hypocalcemia was comparable between the denosumab and the placebo groups. In addition, the Kaplan-Meier survival analysis on the time to hypocalcemia suggests that denosumab subjects were associated with a higher risk of hypocalcemia than the placebo subjects during earlier stage of the study. According to the logrank test, the difference between the survival curves for the denosumab group and the placebo group was statistically significant.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

BLA Numbers	125331, 125320, 125332 and 125333
Drug Name	Denosumab (PROLIA)
Indications	(1) Treatment of osteoporosis in postmenopausal women (2) Prevention of osteoporosis in postmenopausal women (3) Treatment and prevention of bone loss associated with hormone-ablative therapy for breast cancer (4) Treatment and prevention of bone loss associated with hormone-ablative therapy for prostate cancer
Applicant	Amgen, Inc.
PDUFA Date	October 19, 2009
Date Submitted	July 10, 2009
Review Priority	Standard
Biometrics Division	Quantitative Safety and Pharmacoepidemiology Division
Statistical Reviewer	John Stephen Yap, PhD, Mathematical Statistician
Secondary Reviewers	Paul Schuette, PhD, Mathematical Statistician
Secondary Reviewers	C. George Rochester, PhD, RAC, Acting Director
Medical Divisions	Division of Reproductive and Urologic Products (DRUP) Division of Biologic Oncology Products (DBOP)
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Keywords: Hypersensitivity, Immunogenicity, Osteoporosis

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1 Executive Summary

This is a statistical safety review of the hypersensitivity and immunogenicity of denosumab as submitted by Amgen. The main objective of this safety review is to provide a quantitative assessment of the hypersensitivity and immunogenicity of denosumab using data from phase 2 and 3 clinical trial studies as part of BLA package 125-320. The sponsor requested approval for four indications: (1) treatment for postmenopausal osteoporosis (PMO) in women (2) prevention of PMO in women (3) treatment and prevention of bone loss in patients undergoing aromatase inhibitor therapy (AIT) for non-metastatic breast cancer (BC) and (4) treatment and prevention of bone loss in patients undergoing androgen deprivation therapy (ADT) for prostate cancer (PC). Data used in this review were from phase 3 pivotal trials (20030216, 20040132, 20040135 and 20040138) and other phase 2 and 3 trials (20010223, 20040245, 20050141, 20050172, 20050179, 20050141, 20050233, 20050234 and 20050237).

The pre-specified safety outcomes were incidence of hypersensitivity and immunogenicity. Exploratory analyses of outcomes for hypersensitivity were also done at all levels of the MedDRA hierarchy, by demographics and baseline characteristics, and severity or NCI toxicity grade, where applicable.

Hypersensitivity was defined in this review using a narrow list of preferred terms (see Appendix A) that were considered by the sponsor in their analysis and other preferred terms that were determined by the reviewer to be directly related to hypersensitivity. Additional terms that were determined by the medical officer in the Quantitative Safety and Pharmacoepidemiology Group were also included (see Appendix B) to allow for a broader analysis.

The pivotal PMO studies 20030216 and 20040132 (pooled or not pooled) yielded statistically significant findings. Study 200301216 was the largest among the four pivotal studies with almost 80% of the total subjects in the safety population. The MedDRA high level

terms (HLTs) Dermatitis and eczema (Eczema, Dermatitis, Dermatitis allergic, Dermatitis atopic and Dermatitis contact) and Rashes, eruptions and exanthems NEC (Rash, Rash generalised, Rash macular, Rash maculo-papular and Rash vesicular) were significantly different between treatment arms. The number of events (incidence) for denosumab vs placebo were 124 (3.1%) vs 69 (1.7%) for the Dermatitis and eczema HLT, and 117 (2.9%) vs 83 (2.1%) for the Rashes, eruptions and exanthems NEC HLT. Eczema was significantly different between treatment arms (relative risk 1.959 [95% CI: (1.235,3.107)] and risk difference of 0.006 [95% CI: (0.002,0.011)]) with crude incidences of 1.3% (denosumab) vs 0.7% (placebo). Rash was the most common event in the Rashes, eruptions and exanthems NEC HLT and was also significantly different between treatment arms (p-value = 0.026, relative risk 1.387 [95% CI (1.038,1.852)] and risk difference of 0.007 [95% CI (0.001,0.014)]) with crude incidences of 2.6% (denosumab) vs 1.9% (placebo).

Eczema and Rash were each reported as the first adverse event most of the time within the Skin and subcutaneous tissue disorders SOC (Skin SOC) in the adverse event database prior to reports of subsequent Skin SOC events. In terms of severity of Eczema, there were many more moderate cases in the denosumab arm compared to placebo. The onset times of Eczema were generally early for denosumab and late for placebo. It was difficult to assess duration because of many continuing cases in both arms. At least 94% of all subjects in both arms either continued treatment or completed the study. Nine Eczema subjects in denosumab and one in placebo had Eczema reported prior to the study. Excluding these subjects from the analysis did not affect the results. For the onset times of Rash, there were more events early on for denosumab than placebo but the two arms were similar thereafter.

No significant findings were found in HALT studies 20040135 and 20040138, pooled or not pooled.

Events for SMQs, baseline and demographic characteristics, and events considered serious were largely balanced between treatment arms for all four pivotal studies. However, the following events were reported only in the denosumab arm and not in placebo: one life-threatening and one fatal case of Shock, one case of Circulatory collapse, four cases of Dermatitis atopic, and four cases of Toxic skin eruption (one of which was considered serious).

The hypersensitivity events found in the adverse event database for the four pivotal studies were very similar to those reported in other phase 2 and 3 studies. They were also approximately similar in terms of crude incidence rates. There were no indications of hypersensitivity associated with varying doses and the adverse events for denosumab were not different from active-control.

For immunogenicity, positive tests for binding antibodies were found in 6 of 12 studies but the subject incidence was only at most 1.6% in any of the studies. There was no evidence of any correlation between subjects with positive binding antibody tests and their respective adverse event profiles. No neutralizing antibodies were found in any of the studies with antibody tests.

In conclusion, denosumab does not appear to be immunogenic. However, hypersensitivity seems to be a concern particularly in the Dermatitis and eczema and Rashes, eruptions and exanthems NEC HLTs within the Skin SOC. This review provided exploratory statistical results that show higher incidences and significant differences of denosumab over placebo of potential hypersensitivity events within these MedDRA grouping levels. Eczema (specially moderate to severe cases) and Rash, in particular, were found to be of major concern. Cautions regarding these two events, including other events within the Dermatitis and eczema and Rashes, eruptions and exanthems NEC HLTs, may warrant inclusion in the label and that post-market monitoring could also be considered.

2 Introduction

As a monoclonal antibody, denosumab has the potential of immunogenicity or eliciting an immune response. The main concerns are (1) drug allergenicity or hypersensitivity and (2) the alteration of the pharmacokinetics, pharmacodynamics or toxicities ([4],[6]-[8]). Hypersensitivity is a condition where a stimulus causes symptoms that are said to be objectively reproducible and that occur at a dose that is within tolerance levels of normal subjects ([1]). It may be allergic (immune-mediated) or non-allergic (not immune-mediated).

The objectives of this statistical safety review are the following:

- Review the immunogenicity of denosumab based on antibody tests (both pre-existing and developing).
- For patients with positive antibody test results, characterize antibody responses and investigate potential correlation with any adverse events or hypersensitivity reactions.
- Evaluate the risks of hypersensitivity of denosumab relative to placebo at various Medical Dictionary for Regulatory Activities (MedDRA) version 11.0 grouping levels: Preferred Term (PT), High Level Term (HLT), High Level Group Term (HLGT) and primary System Organ Class (SOC).
- Summarize the baseline and demographic characteristics of subjects with hypersensitivity and determine which groups are potentially at risk.
- Determine the incidence, timing and accounting for severity/toxicity grade of hypersensitivity outcomes.
- Compare denosumab with the active-control in terms of hypersensitivity outcomes.

3 Statistical Methods

3.1 Endpoints

The following list of MedDRA preferred terms was used to define hypersensitivity:

I. Hypersensitivity and Drug hypersensitivity

II. Application site hypersensitivity, Documented hypersensitivity to administered drug, Human seminal plasma hypersensitivity, Implant site hypersensitivity, Infusion site hypersensitivity, Injection site hypersensitivity, Type I hypersensitivity, Type II hypersensitivity and Type IV hypersensitivity

III. PTs based on the following Standardised MedDRA Queries (SMQs) : (a) Angioedema (b) Anaphylactic reaction (b) Severe cutaneous adverse reaction

IV. Dermatitis, Dermatitis allergic, Dermatitis atopic, Dermatitis contact and Eczema

This list is called the primary set (or set P). A subject with at least one adverse event in set P is said to have a hypersensitivity reaction. Items I, III and IV were considered by the sponsor in their analysis. Events in II are in the same MedDRA high level term (HLT) as the Hypersensitivity PT. A complete listing of events for the SMQs is given in Appendix A.

A sensitivity analysis was also carried out by analyzing a broader set consisting of PTs from set P plus additional PTs given in Appendix B. The PTs in Appendix B were reviewed by the medical officer in the Quantitative Safety and Pharmacoepidemiology Group (QSPG) and were classified as possible causes of allergic reactions. This broader set of PTs is called the sensitivity set (or set S). Note that set S has more sensitivity but may have less specificity than set P when comparing treatment arms at various MedDRA levels. However, it is of interest to evaluate the analysis based on set S and compare it with the analysis of set P.

The following primary SOCs were also reviewed for potential hypersensitivity PTs: (1) Skin and subcutaneous tissue disorders (2) Immune system disorders (3) General disorders and administration site conditions.

3.2 Statistical Tools

In order to detect and assess associations between treatment arms (denosumab vs placebo), p-values obtained from the Pearson Chi-square and Fisher's Exact tests were reported. The Chi-square test is appropriate when expected counts in a cross-table are relatively large (≥ 5) whereas the Fisher's Exact test is appropriate when the expected counts are low (< 5). To estimate the magnitude of associations that are found to be significant, the odds ratios, relative risk and risk difference, with corresponding 95% confidence intervals, were also reported. The confidence interval for the odds ratio is exact whereas those for relative risk and risk difference are asymptotic. All calculations were done in SAS 9.1.

3.3 Data

The main analysis for hypersensitivity was carried out on the pivotal studies which included phase 3 randomized, multi-center, double-blind and placebo-controlled studies for postmenopausal osteoporosis (PMO; studies 20030216 and 20040132) and hormone-ablative therapy (HALT; studies 20040135 and 20040138). See Table 1 for a short summary of these studies. Other phase 2 (20010223, 20050172, and 20050179) and phase 3 (20050141 and 20050234) studies were also reviewed for crude incidence rates and potentially dose-related hypersensitivity events. These five studies all involved PMO subjects.

For immunogenicity, the following studies with available data for antibody tests were reviewed: 20010223, 20030216, 20030245, 20040132, 20040135, 20040138, 20050141, 20050172,

Table 1: Summary of Pivotal Studies.

	Study	Treatment Arm Size Denosumab	Placebo	Total	Population	Study Duration
PMO	20030216	3886	3876	7762	women with low BMD	36 months
	20040132	164	165	329	women with low BMD; $\leq$ 90 yr non-mBC with AIT	24 months plus 24 months safety follow-up
HALT	20040135	129	120	249	women with low BMD; $\geq$ 18 yr; non-mBC with AIT	24 months plus 24 months safety follow-up
	20040138	731	725	1456	men with low BMD; non-mPC with ADT	36 months plus 24 months safety follow-up

BMD = bone mineral density; AIT = aromatase inhibitor therapy; ADT = androgen deprivation therapy; mBC = metastatic breast cancer; mPC = metastatic prostate cancer

20050179, 20050233, 20050234 and 20050237.

The primary data sources for this review were the following analysis data model (ADaM) files:

- Subject Level Information Analysis Data (ASLINFO)
- Adverse Events Analysis Data (AAE)
- Antibody Analysis Data (AAB)
- Investigational Product Administration Analysis Data (AEX; Exposure Data)
- General Medical and Surgical History Analysis Data (AMHGENL)

Only events that occurred during the treatment period for all subjects in the safety population were considered in the analysis. Unless stated otherwise, the treatment period was

defined as the time from the first dose date up to 213 days over the last dose date (approximately 6 months plus 30 days). Six months was the window between dose administration of the pivotal studies.

4 Hypersensitivity

4.1 Pivotal Studies

In this section, the four pivotal studies [20030216 and 20040132 (PMO); 20040135 and 20040138 (HALT)] were reviewed. For brevity, PMO in this section refers to studies 20030216 and 20040132 and HALT refers to studies 20040135 and 20040138.

4.1.1 Various MedDRA Levels Analyses

Table 2: Number of Groups Per MedDRA Level

	Set P		Set S	
MedDRA Level	PMO	HALT	PMO	HALT
PT	28	14	38	19
HLT	19	11	24	14
HLGT	10	7	12	8
SOC	7	5	8	6

Table 2 provides a summary of the number of PTs, HLTs, HLGTs, and SOCs, within the treatment periods, that were found in the adverse event database using sets P and S. For example, there 28 PTs found in the adverse event dataset for the PMO studies using set P. These PTs were mapped to 19 HLTs, 10 HLGTs and 7 primary SOCs. Only primary SOC mappings were considered in the analysis.

To assess possible associations between a MedDRA grouping level and treatment arms, all identified groups from each level were analyzed using a SAS macro that calculates p-values from the Pearson Chi-square and Fisher's Exact tests, and also odds ratios, relative risks and risk differences, with corresponding confidence intervals. P-values at the 0.05 level where considered significant. As an example, when all 38 set S PTs from the PMO studies were run using the SAS macro, the Eczema was found to be significant. Tables 3 and 4 show the results for the PMO studies including other MedDRA levels.

Table 3: MedDRA Level Analysis (Set P, Denosumab vs Placebo, PMO)

MedDRA Level	Name	No. of PTs		Pearson's Chi-square p-value	Fisher's Exact p-value	Odds Ratio (95% CI)	Relative Risk (95% CI)	Risk Difference (95% CI)
		Denosumab	Placebo					
PT	Eczema	53	27	0.004	0.005	1.971 (1.215,3.266)	1.959 (1.235,3.107)	0.006 (0.002,0.011)
HLT	Dermatitis and eczema	124	69	< 0.001	< 0.001	1.817 (1.338,2.484)	1.792 (1.340,2.398)	0.014 (0.007,0.020)
HLGT	Epidermal and dermal conditions	132	74	< 0.001	< 0.001	1.805 (1.343,2.441)	1.779 (1.342,2.356)	0.0143 (0.007,0.0211)
SOC	Skin and subcutaneous tissue disorders	161	106	0.001	0.001	1.536 (1.190,1.990)	1.515 (1.190,1.928)	0.0135 (0.006,0.021)

Table 3 shows that, aside from the Eczema PT, the Dermatitis and eczema HLT, Epidermal and dermal conditions HLGT and Skin and subcutaneous tissue disorders SOC were all significantly different between treatment arms when considering set P. The relative risk for denosumab over placebo ranged from 1.5 to almost 2 from the top to bottom in the MedDRA hierarchy. When each study was analyzed separately, only 20030216 was found to be significant, with very similar results as the pooled analysis. This means that the pooled PMO results were being driven by 20030216 which has the largest number of subjects enrolled (see Table 1). Table 5 shows events in the Skin and subcutaneous tissue disorders SOC based on set S. Eczema has a higher crude incidence rate in the denosumab arm than placebo (1.3% vs 0.6%) for study 20030216. In general, events in set P under the Dermatitis and eczema HLT have higher crude incidences (3.1% vs 1.7%) in the denosumab arm over placebo.

Table 4: MedDRA Level Analysis (Set S, Denosumab vs Placebo, PMO)

MedDRA Level	Name	No. of PTs		Pearson's Chi-square p-value	Fisher's Exact p-value	Odds Ratio (95% CI)	Relative Risk (95% CI)	Risk Difference (95% CI)
		Denosumab	Placebo					
PT	Eczema	53	27	0.004	0.005	1.971 (1.215,3.266)	1.959 (1.235,3.107)	0.006 (0.002,0.011)
	Rash	107	77	0.026	0.030	1.397 (1.029,1.904)	1.387 (1.038,1.852)	0.007 (0.001,0.014)
HLT	Dermatitis and eczema	124	69	< 0.001	< 0.001	1.817 (1.338,2.484)	1.792 (1.340,2.398)	0.014 (0.007,0.020)
	Rashes, eruptions and exanthems NEC	117	83	0.016	0.018	1.418 (1.057,1.908)	1.405 (1.064,1.856)	0.008 (0.002,0.015)
HLGT	Epidermal and dermal conditions	253	161	< 0.001	< 0.001	1.602 (1.303,1.974)	1.564 (1.290,1.897)	0.022 (0.013,0.032)
SOC	Skin and subcutaneous tissue disorders	282	193	< 0.001	< 0.001	1.489 (1.228,1.807)	1.455 (1.218,1.738)	0.022 (0.011,0.032)

Table 4 shows the results when using the set S PTs for the pooled PMO studies. The Dermal and epidermal conditions HLGT and the Skin and subcutaneous tissue disorders SOC (Skin SOC) were both found to be significantly different between treatment arms. Within the Dermal and epidermal conditions HLGT, the Dermatitis and eczema and Rashes, eruptions and exanthems NEC HLTs were significantly different between treatment arms. Within the Dermatitis and eczema HLT, Eczema was significantly different between treatment arms and within the Rashes, eruptions and exanthems NEC HLT, Rash was significantly different between treatment arms. Thus, significant differences between arms were found in the following two mappings: (1) Eczema PT, Dermatitis and eczema HLT, Epidermal and dermal conditions HLGT, and Skin and subcutaneous tissue disorders SOC and (2) Rash PT, Rashes, eruptions and exanthems NEC HLT, Epidermal and dermal conditions HLGT, and Skin and subcutaneous tissue disorders SOC. For (1), similar results were obtained (i.e. all levels were significant) when 20030216 was analyzed alone instead of the pooled PMO. When 20040132 was analyzed alone, there were no significant results at any level. For (2), Rash was significant only in study 20040132 when the studies were analyzed individually. The Rashes, eruptions and exanthems NEC HLT was significant for the pooled PMO studies but not for either of the studies analyzed individually. For the Rashes, eruptions and exanthems NEC HLT, there were 117 (2.9%) vs 83 (2.1%) events in the denosumab vs placebo arms, most of which were Rash.

Table 5: Skin and subcutaneous tissue disorders SOC (Set S)

	PMO				HALT				TOTAL	
	20030216		20040132		20040135		20040138			
HLGT, HLT, and PT	D	P	D	P	D	P	D	P	D	P
Safety Population	3886 (%)	3876 (%)	164 (%)	165 (%)	129 (%)	120 (%)	731 (%)	725 (%)	4910 (%)	4886 (%)
Epidermal and dermal conditions	234 (6.0)	150 (3.9)	19 (11.6)	11 (6.7)	13 (10.1)	12 (10.0)	24 (3.3)	28 (3.9)	290 (5.9)	201 (4.1)
Dermatitis and eczema	119 (3.1)	65 (1.7)	5 (3.0)	4 (2.4)	2 (1.6)	5 (4.2)	8 (1.1)	8 (1.1)	134 (2.7)	82 (1.7)
Eczema*	50 (1.3)	25 (0.6)	3 (1.8)	2 (1.2)	1 (0.8)	1 (0.8)	2 (0.3)	3 (0.4)	56 (1.1)	31 (0.6)
Dermatitis allergic*	36 (0.9)	23 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.4)	36 (0.7)	27 (0.6)
Dermatitis*	21 (0.5)	14 (0.4)	1 (0.6)	1 (0.6)	1 (0.8)	2 (1.7)	4 (0.5)	1 (0.1)	27 (0.5)	18 (0.4)
Dermatitis contact*	8 (0.2)	3 (0.1)	1 (0.6)	0 (0.0)	0 (0.0)	2 (1.7)	2 (0.3)	1 (0.1)	11 (0.2)	6 (0.1)
Dermatitis atopic*	4 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)	0 (0.0)
Rashes, eruptions and exanthems NEC	103 (2.7)	77 (2.0)	14 (8.5)	6 (3.6)	10 (7.8)	7 (5.8)	16 (2.2)	17 (2.3)	143 (2.9)	107 (2.2)
Rash**	93 (2.4)	72 (1.9)	14 (8.5)	5 (3.0)	10 (7.8)	6 (5.0)	16 (2.2)	17 (2.3)	133 (2.7)	100 (2.0)
Rash generalised**	7 (0.2)	3 (0.1)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.1)	4 (0.1)
Rash macular**	3 (0.1)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)	1 (0.0)
Rash maculo-papular**	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Rash vesicular**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Other HLTs	12 (0.3)	8 (0.2)	0 (0.0)	1 (0.6)	1 (0.8)	0 (0.0)	0 (0.0)	3 (0.4)	13 (0.3)	12 (0.2)
Angiodema and urticaria	27 (0.7)	28 (0.7)	2 (1.2)	4 (2.4)	2 (1.6)	0 (0.0)	3 (0.4)	3 (0.4)	34 (0.7)	35 (0.7)
Total PTs	261 (6.7)	178 (4.6)	21 (12.8)	15 (9.1)	15 (11.6)	12 (13.3)	27 (3.7)	31 (4.3)	324 (6.6)	236 (4.8)

* in set P; ** not in set P; D = Denosumab, P = Placebo

For the HALT studies, there were no significant differences found when treatment arms were compared under various MedDRA levels. This was true when the studies were either analyzed individually or pooled together.

Additional exploratory MedDRA levels analysis was done by pooling all four pivotal studies (PMO and HALT). The results were similar to what was found in the PMO studies. That is, significant differences between treatment arms were found for all the MedDRA levels in column two of Table 3 when considering set P PTs and in column two of Table 4 when considering set S PTs. Because no significant differences between treatment arms were found in the HALT studies, the PMO studies were the main driver of these results.

In Table 5, the number of events under the Dermatitis and eczema and Rashes, eruptions and exanthems NEC HLTs generally have higher crude incidences in the denosumab arm over placebo (2.7% vs 1.7% and 2.9% vs 2.2%, respectively) when events from set S were pooled together using all four pivotal studies. For the Epidermal and dermal conditions HLGT, the crude incidence of events in denosumab over placebo was 5.9% vs 4.1%. Because the Angioedema and urticaria HLGT was balanced between arms, the large difference between arms in the Epidermal and dermal conditions HLGT was the main factor for the large differences between treatment arms when considering the Skin SOC level (6.6% vs 4.8%, for denosumab vs placebo, respectively).

In PMO study 20030216, there were 4 each of Dermatitis atopic and Toxic skin eruption events found under the denosumab arm but none in the placebo. None of these events were found in all other pivotal studies. One case of Toxic skin eruption was reported to be serious in Section 4.1.3. Furthermore, there were 9 vs 2 Bronchospasm events, in denosumab vs placebo, respectively. Of the denosumab cases, 7 were from study 20030216 and 1 each from studies 20040135 and 20040138. The two placebo cases were from study 20030216. The

Bronchospasm events were mostly mild and the rest were moderate. None of them were reported as serious.

All PTs in the entire adverse event database under the following primary SOCs were also reviewed: (1) Skin and subcutaneous tissue disorders (2) Immune system disorders (3) General disorders and administration site conditions. There were no significant findings found in these primary SOCs.

4.1.2 Frequency of Events, SMQs and Baseline and Demographic Characteristics

The frequencies of the hypersensitivity events within treatment periods are given in Table 6. Table 6 shows that most of the events occurred only once and only a few occurred more than once. Furthermore, the denosumab arm has many more events than placebo (195 vs 138) for study 20030216 only but not for the other pivotal studies.

Table 6: Frequencies of Adverse Events Per Subject.

	Set P						Set S							
	Denosumab			Placebo			Denosumab				Placebo			
Study	1	2	3	1	2	3	1	2	3	4	1	2	3	4
PMO	195	12	2	142	6	2	285	35	2	1	221	18	2	0
20030216	183	11	1	130	6	2	266	31	2	0	207	16	2	0
20040132	12	1	1	12	0	0	19	4	0	1	14	2	0	0
HALT	23	0	0	21	2	0	45	2	0	0	38	6	0	0
20040135	7	0	0	5	2	0	16	0	1	0	10	3	0	0
20040138	16	0	0	16	0	0	29	2	0	0	28	3	0	0

Table 7 summarizes the set P events according to SMQs. None of the event counts were large enough to show significant differences between treatment arms. Toxic skin reaction

occurred only in the denosumab arm and not in placebo as seen earlier, and constitutes an adverse skin reaction. One case was considered serious in the following section.

Table 7: Summary of SMQ Events (Set P)

	PMO				HALT				TOTAL	
	20030216		20040132		20040135		20040138			
SMQ and PT	D	P	D	P	D	P	D	P	D	P
Safety Population	3886 (%)	3876 (%)	164 (%)	165 (%)	129 (%)	120 (%)	731 (%)	725 (%)	4910 (%)	4886 (%)
Angioedema	38 (1.0)	41 (1.1)	6 (3.7)	6 (3.6)	2 (1.6)	1 (0.8)	4 (0.5)	6 (0.8)	50 (1.0)	52 (1.1)
Allergic oedema	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)	0 (0.0)
Angioedema	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	2 (0.0)
Conjunctival oedema	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)	0 (0.0)
Corneal oedema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.0)	0 (0.0)
Eye oedema	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Eye swelling	1 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	2 (1.1)	2 (0.0)	3 (0.1)
Eyelid oedema	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.0)
Face oedema	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.0)
Gingival swelling	0 (0.0)	3 (0.1)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)
Laryngeal oedema	1 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	2 (0.0)
Lip swelling	0 (0.0)	1 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)	2 (0.0)
Pharyngeal oedema	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Swelling face	2 (0.1)	2 (0.1)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)	3 (0.1)
Swollen tongue	1 (0.0)	1 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)	1 (0.0)
Tongue oedema	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Urticaria	27 (0.7)	26 (0.7)	2 (1.2)	4 (2.4)	1 (0.8)	0 (0.0)	3 (0.4)	3 (0.4)	33 (0.7)	33 (0.7)
Anaphylactic shock	5 (0.1)	4 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	5 (0.1)	5 (0.1)
Anaphylactic shock	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Circulatory collapse	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.0)	1 (0.0)
Shock	4 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)	2 (0.0)
Severe cutaneous adverse reaction	6 (0.2)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	6 (0.1)	4 (0.1)
Erythema multiforme	2 (0.1)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)	1 (0.0)
Exfoliative rash	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.0)
Skin necrosis	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.0)
Toxic skin reaction	4 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)	0 (0.0)
Total PTs	49 (1.3)	47 (1.2)	6 (3.7)	6 (3.6)	2 (1.6)	1 (0.8)	5 (0.7)	8 (1.1)	61 (1.2)	61 (1.2)

D = Denosumab, P = Placebo

The baseline and demographic characteristics of subjects who have events from set P are shown in Table 8. For study 20030216, there were many more events from set P in the denosumab arm than placebo as seen earlier (195 vs 138; see also Sex category) even though the arms were balanced in terms of the number of subjects in the safety population (3886 vs 3876). The subcategories where there were many more events from set P in the denosumab arm than in the placebo were the following:

- 70-74 age group: 76 denosumab vs 49 placebo (safety population: 1634 denosumab vs 1628 placebo)
- White or Caucasian race: 181 denosumab vs 129 placebo (safety population: 3594 denosumab vs 3600 placebo)
- Geographical region: 66 denosumab vs 38 placebo (safety population: 1337 denosumab vs 1317 placebo) for Eastern Europe and 38 denosumab vs 20 placebo (safety population: 467 denosumab vs 460 placebo) for Latin America

For study 20040132, the following subcategories were slightly imbalanced in terms of the number of events in set P:

- 50-54 age group: 7 denosumab vs 1 placebo (safety population: 1634 denosumab vs 1628 placebo)
- Menopause ($\leq$ 5 years): 10 denosumab vs 3 placebo (safety population: 77 denosumab vs 80 placebo)
- Menopause ($>$ 5 years): 4 denosumab vs 9 placebo (safety population: 87 denosumab vs 85 placebo)

Table 8: Baseline and Demographic Characteristics of Subjects With Set P Events

	PMO				HALT			
	20030216		20040132		20040135		20040138	
	D	P	D	P	D	P	D	P
Safety Population	3886	3876	164	165	129	120	731	725
Age (years)								
< 50	-	-	1	0	1	0	0	0
50 – 54	-	-	7	1	1	3	0	0
55 – 59	-	-	3	6	4	1	0	0
60 – 64	12	7	1	2	1	1	0	1
65 – 69	46	37	2	2	0	2	0	1
70 – 74	76	49	0	1	0	0	9	6
75 – 79	53	38	0	0	0	0	5	4
80 ≤	8	7	0	0	0	0	2	4
Sex								
Male	-	-	-	-	-	-	16	16
Female	195	138	14	12	7	7	-	-
Race								
American Indian or Alaska Native	0	0	0	0	0	0	0	0
Asian	1	0	1	2	0	0	0	0
Black or African American	1	0	0	0	0	1	1	1
Hispanic or Latino	11	7	0	0	0	0	2	2
Japanese	1	1	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	1	0	0
White or Caucasian	181	129	13	10	6	5	13	13
Other	0	1	0	0	1	0	0	0
Geographical Region								
Eastern Europe	66	38			0	0	0	0
Europe					0	0	3	1
Latin America	38	20			0	0	0	0
North America	15	9	14	12	7	7	13	15
Western Europe	76	71			0	0	0	0
Menopause								
≤ 5 years	-	-	10	3	-	-	-	-
> 5 years	-	-	4	9	-	-	-	-
AIT								
≤ 6 months	-	-	-	-	1	3	-	-
> 6 months	-	-	-	-	6	4	-	-
ADT (months)								
≤ 6 (age < 70 years)	-	-	-	-	-	-	0	0
≤ 6 (age ≥ 70 years)	-	-	-	-	-	-	1	5
> 6 (age < 70 years)	-	-	-	-	-	-	0	2
> 6 (age ≥ 70 years)	-	-	-	-	-	-	15	9

D = Denosumab; P = Placebo; AIT = aromatase inhibitor therapy;
ADT = androgen deprivation therapy

There were no remarkable differences in the categories or subcategories between treatment arms in studies 20040135 and 20040138.

4.1.3 Severity, Toxicity Grade and Seriousness

Severity data was available only for the PMO studies. Adverse events for the HALT studies were assessed by toxicity grade using the National Cancer Institute (NCI) grading scale.

This review analyzed severity at two levels: (1) all hypersensitivities irrespective of event and (2) hypersensitivity based on a given event. For (1), the most severe hypersensitivity event was chosen for each subject. The order from most to least severe is death, life threatening, severe, moderate and mild. For (2), the most severe of a given hypersensitivity event was chosen. For example, a subject may have two types of hypersensitivity events: eczema and rash. For this patient, the most severe eczema and rash episodes were chosen.

Table 9: Severity Irrespective of Hypersensitivity Event, Level (1).

	Set P						Set S					
	20030216		20040132		Total		20030216		20040132		Total	
Severity	D	P	D	P	D	P	D	P	D	P	D	P
Mild	106	87	6	5	112	92	174	150	14	6	188	156
Moderate	78	45	7	5	85	50	112	67	9	7	121	74
Severe	9	6	1	2	10	8	11	8	1	3	12	11
Life Threatening	1	0	0	0	1	0	1	0	0	0	1	0
Fatal	1	0	0	0	1	0	1	0	0	0	1	0
Total	195	138	14	12	209	150	299	225	102	108	323	241

D = Denosumab, P = Placebo

Table 9 shows the number of hypersensitivities irrespective of type [level (1)] classified by severity. There was one life threatening and one fatal case from study 20030216. The life threatening case was Shock (reported term: Circulatory failure; subject id: 6830247).

This event occurred about 17-18 months after the first dose was given, lead to patient hospitalization but not withdrawal from the study. The fatal case was also Shock (reported term: Mixed shock; subject id: 6430214).

Table 10: Severity for Epidermal and dermal conditions HLGT [Set S, PMO, Level (2)].

	Mild		Moderate		Severe		Total	
HLT and PT	D	P	D	P	D	P	D	P
Dermatitis and eczema HLT	67 (54.0)	49 (71.0)	54 (43.5)	20 (29.0)	3(2.4)	0 (0.0)	124	69
Eczema*	26 (49.1)	21 (77.8)	25 (47.2)	6 (22.2)	2 (3.8)	0 (0.0)	53	27
Dermatitis allergic*	18 (50.0)	14 (58.3)	18 (50.0)	10 (41.7)	0 (0.0)	0 (0.0)	36	24
Dermatitis*	15 (68.2)	11 (73.3)	7 (31.8)	4 (26.7)	0 (0.0)	0 (0.0)	22	15
Dermatitis contact*	6 (66.7)	3 (100.0)	2 (22.2)	0 (0.0)	1 (21.1)	0 (0.0)	9	3
Dermatitis atopic*	2 (50.0)	0 (0.0)	2 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	4	0
Rashes, eruptions and exanthems NEC HLT	77 (65.8)	55 (66.3)	39 (33.3)	25 (30.1)	1 (0.9)	3 (3.6)	117	83
Rash**	72 (67.3)	51 (66.2)	34 (31.8)	24 (31.2)	1 (0.9)	2 (2.6)	107	77
Rash generalised**	3 (42.9)	3 (0.8)	4 (57.1)	1 (0.2)	0 (0.0)	0 (0.0)	7	4
Rash macular**	2 (66.7)	1 (100.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	3	1
Rash maculo-papular**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0	1
Other HLTs	8 (66.7)	7 (77.8)	3 (0.3)	2 (22.2)	1 (8.0)	0 (0.0)	12	9
Total	152 (60.1)	111 (68.9)	96 (37.9)	47 (29.2)	5 (2.0)	3 (0.0)	253	161

* in set P; ** not in set P; D = Denosumab, P = Placebo

Table 10 gives the summary for Epidermal and dermal conditions HLGT broken down into counts at lower MedDRA levels when considering severity in hypersensitivity of a given event [level (2)]. For Eczema, there is a large difference in number (25 vs 6) between the denosumab and placebo arms at moderate severity. There were also 2 severe cases in the denosumab arm versus 0 from placebo. The two severe cases were from subjects 6613020 (reported term: Worsening eczema on both hands) and 6837187 [reported term: Eczema (Keratosis on the whole body - especially heels)]. Subject 6613020 completed the study whereas 6837187 discontinued treatment and withdrew from the study.

Toxicity grades were reported from 1-5 with 1 having the lowest toxicity grade and 5 the highest. For the HALT studies, there were no significant differences between arms across

Table 11: Serious Hypersensitivity Events (set S)

	PMO				HALT					
	20030216		20040132		20040135		20040138		TOTAL	
SOC and PT	D	P	D	P	D	P	D	P	D	P
Immune system disorders	1	1	0	0	0	0	1	0	2	1
Anaphylactic shock*	0	1	0	0	0	0	0	0	0	1
Drug hypersensitivity*	1	0	0	0	0	0	1	0	2	0
Respiratory, thoracic and mediastinal disorders	1	3	0	0	0	0	0	0	1	3
Bronchospasm**	1	0	0	0	0	0	0	0	1	0
Laryngeal oedema*	0	2	0	0	0	0	0	0	0	2
Pharyngeal oedema*	0	1	0	0	0	0	0	0	0	1
Skin and subcutaneous tissue disorders	3	4	0	0	0	0	0	1	3	5
Angioedema*	0	1	0	0	0	0	0	0	0	1
Dermatitis*	1	0	0	0	0	0	0	0	1	0
Dermatitis allergic*	1	0	0	0	0	0	0	0	1	0
Rash maculo-papular**	0	1	0	0	0	0	0	0	0	1
Skin necrosis*	0	0	0	0	0	0	0	1	0	1
Toxic skin eruption**	1	0	0	0	0	0	0	0	1	0
Urticaria**	0	2	0	0	0	0	0	0	0	2
Vascular disorders	2	0	0	0	0	0	3	0	5	0
Circulatory collapse*	0	0	0	0	0	0	3	0	3	0
Shock*	2	0	0	0	0	0	0	0	2	0
Total	6	7	0	0	0	0	4	1	10	9

* in set P; ** not in set P; D = Denosumab, P = Placebo

toxicity grades. There were also no reported toxicity grades higher than 3.

Table 11 summarizes the events that were classified as serious. The crude incidences were very low and do not appear to be imbalanced between treatment arms. One case each of Drug hypersensitivity in the denosumab arm was reported in 20030216 and 20040138. One of the four cases of Toxic skin reaction in the denosumab arm seen in the previous section is reported here as serious. Two cases of Shock in the denosumab arm, reported as life threatening and fatal in previous sections, is reported here as serious. Three cases of Circulatory collapse in the denosumab arm were reported as serious in 20040138 but occurred only on the same subject (subject id: 138644025). This subject was hospitalized but did not

withdraw from the study.

4.1.4 Eczema and Rash

Onset Time of Eczema and Rash

In this section, the analysis for onset time was limited to study 20030216 because the other pivotal studies only had a few of the events in each arm and had different lengths of completion. All start dates of adverse events were imputed by the sponsor to the first day of the month for events with missing days.

Figure 1 shows the onset time or time to the first occurrence (in months) of Eczema for study 20030216. For denosumab (50 subjects), there were two epochs that had high incidence: within a month of the first dose administration and immediately before the third dose administration or 8-12 months. The other cases were more or less uniformly spread throughout the entire study. The mean onset time was 15.40 months, standard deviation (SD) 10.48 months, median 12.16 months, range 33.84 months, minimum (min) 0.36 months and maximum (max) 34.20 months. For placebo (25 subjects), there were no marked spikes in incidence but there were three notable clusters at 2-12 months, 18-28 months and 29-36 months. More than half of all occurrences were towards the end of the study. The mean onset time was 21.05 months, SD 11.81 months, median 24.34 months, range 33.54 months, min 2.33 months, max 35.88 months.

Figure 2 shows the onset time (in months) of Rash in study 20030216. For denosumab (93 subjects), there was higher incidence within the first two months than placebo (72 subjects) but thereafter, incidence in both arms were very similar. The mean onset time under the denosumab arm was 11.33 months, SD 10.61 months, median 8.31 months, range 35.29 months, min of 0.00 months and max of 35.29 months. The mean onset time under placebo

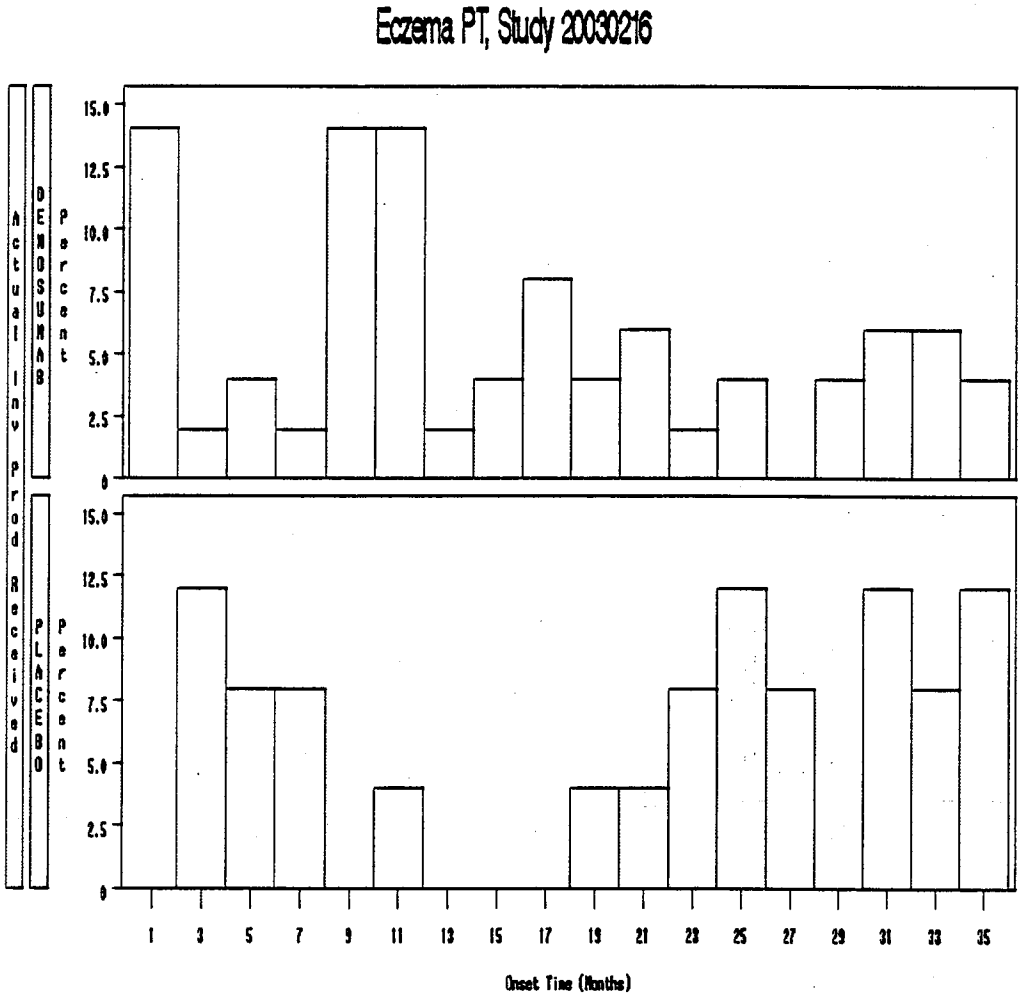

Figure 1: Onset Time of Eczema (Study 20030216)

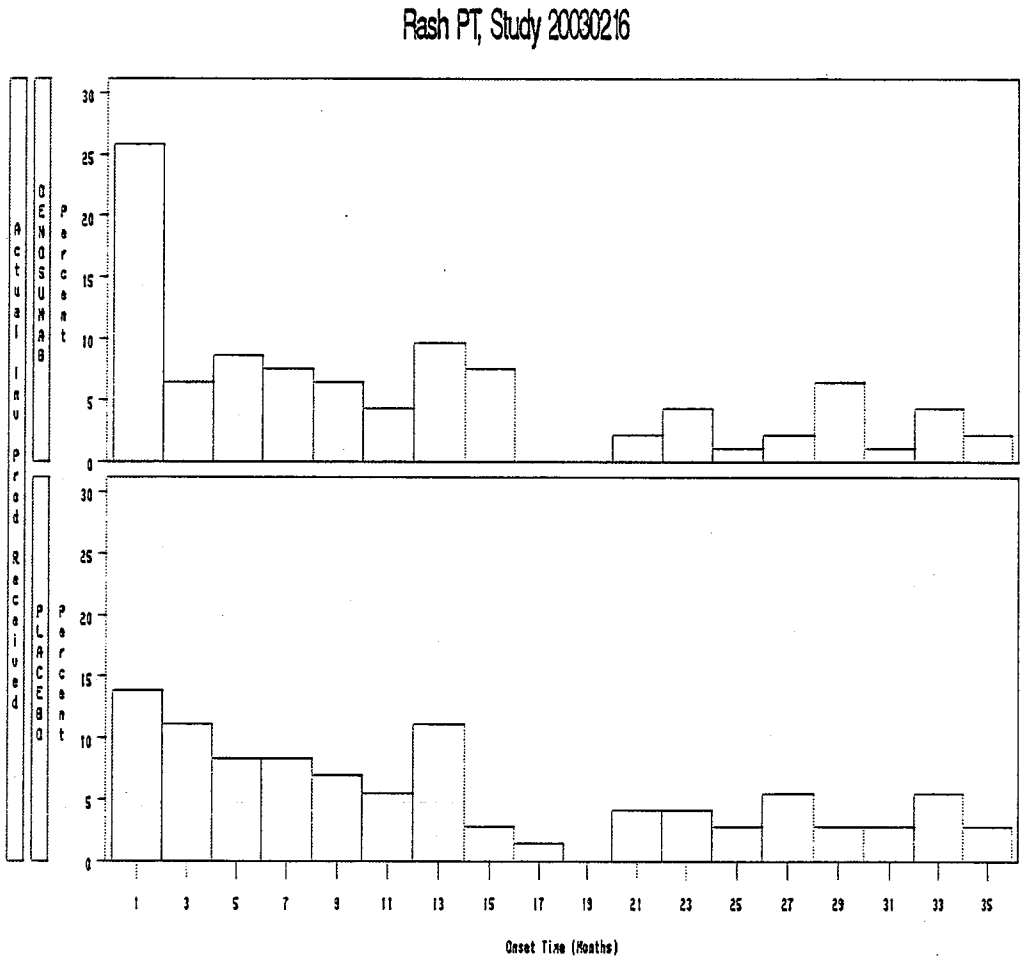

Figure 2: Onset Time of Rash (Study 20030216)

was 13.14 months, SD 10.95 months, median 10.89 months, range 35.81 months, min 0.00 months and max 35.81 months.

Duration of Eczema

Table 12: Duration Statistics (in Months) for Eczema (Study 20030216).

Eczema PT Status	Treatment Arm	n (%)	Mean	SE	Min	Median	Max	Range
Not continuing	Denosumab	29 (56.9)	4.06	5.41	0.20	2.35	26.17	25.97
	Placebo	15 (60.0)	4.74	5.65	0.26	2.04	22.26	22.00
Continuing	Denosumab	22 (43.1)	15.76	10.43	1.44	14.22	33.69	32.24
	Placebo	10 (40.0)	5.95	4.76	0.03	5.48	12.21	12.18
Combined	Denosumab	51 (100.0)	8.88	9.71	0.20	3.91	33.69	33.49
	Placebo	25 (100.0)	5.16	5.30	0.03	3.78	22.26	22.23

n = number of cases; SE = standard error; Min = minimum; Max = maximum

Some end dates for Eczema had the day of the month missing and no imputation was done by the sponsor. In order to compute duration, this review imputed these end dates to the first day of the month. Furthermore, the Eczema events were reviewed and the end dates were chosen, when necessary, to yield realistic durations. For example, cases that were recorded multiple times for one subject, with the same start date, but were different only in the location of the subject's body where the Eczema occurred was considered as one Eczema case only. For a complete description of how the end dates were chosen, see Appendix C.

Table 13: Characteristics of Subjects With Eczema (Study 20030216).

	Denosumab		Placebo	
Event	Yes	No	Yes	No
Medication Taken	36 (71%)	15 (29%)	17 (68%)	8 (32%)
Discontinuation of Treatment	2 (4%)	49 (96%)	1 (4%)	24 (96%)
Withdrawal from Study	1 (2%)	50 (98%)	1 (4%)	24 (96%)
Study Completer	48 (94%)	3 (6%)	24 (96%)	1 (4%)

Table 12 shows the summary statistics for the duration of Eczema. Both treatment arms

have approximately the same rate of continuing and not continuing cases (40% and 60%, respectively). For cases that were not continuing, denosumab had a slightly lower average time to resolution than placebo, although the median and maximum cases were slightly higher. The durations for continuing cases were taken to be the reference end dates minus the adverse event start dates. In this case, the mean, standard error and median for denosumab were significantly higher than placebo. When both continuing and not continuing cases were combined, the mean and standard error for denosumab were still higher than placebo and the median was only slightly higher. As observed previously, most of the cases for denosumab occurred early on compared to placebo which had many cases late in the study. It appears that most continuing cases for denosumab had earlier onset times than placebo. Because of continuing cases, a comparative assessment of duration between treatment arms is not feasible.

Table 13 gives a summary of the characteristics of Eczema cases. Approximately 70% of subjects in both treatment arms have taken medication for Eczema. Only at most two subjects discontinued treatment but only one subject withdrew from the study in each arm. No subjects had their dose altered nor were there any hospitalized. None of the cases were reported as serious.

Medical History of Subjects with Eczema

There were 9 subjects in the denosumab arm and 1 in the placebo who had histories of Eczema and also had Eczema during the study. Of the 9 denosumab subjects, 3 where classified as mild, 5 moderate and 1 severe. The placebo case was mild. All cases were reportedly continuing except for 2 in the denosumab arm. When all these cases were excluded in the MedDRA levels analysis, the results were still significant within the 0.05 level.

Other Reported Skin Adverse Events of Subjects With Eczema and Rash

All subjects with Eczema and Rash were reviewed for other adverse events reported in the Skin SOC. The results for study 20030216 are summarized in Tables 23 and 24 in Appendix D. In Table 23, the first row shows that there was one subject in the denosumab arm that had Eczema. This subject was previously reported to have Dermatitis contact and then Dermatitis prior to Eczema and later was reported to have Skin Lesion. In Table 23, at least 80% of all subjects with Eczema in both arms reported Eczema as the first adverse event in the Skin SOC. A few cases may have possibly been reported as early stages of Eczema, e.g Rash or Dry skin, before actually developing into Eczema or these cases may have been concomitant Skin SOC PTs to Eczema.

In Table 24, around 90% of all cases in both arms reported Rash as the first adverse event in the Skin SOC. Only 3 and 1 cases in the denosumab and placebo arms, respectively, reported Eczema cases later.

4.2 Other Phase 2 and 3 PMO Studies

This section summarizes adverse events crude incidence rates obtained from other phase 2 and phase 3 PMO studies. Some details about the specific studies are given in Tables 14 and 15.

Each study has a treatment arm with a dose of 60 mg of the investigational product and administered subcutaneously every 6 months (Table 15). This is the dose that was used in the pivotal studies and is the dose for which the sponsor is seeking approval. Age should not be a major issue in pooling studies (Table 14) because only study 20050141 had 11 subjects over 80 years. Except for subjects each 85, 88 and 91 years old, the rest of the subjects were at most 83 years old.

The major issues for pooling the studies are (1) the population for study 20050172 are

Table 14: Summary of Other Phase 2 and 3 Studies

Study	Phase	Population	Denosumab Doses	Study Duration
20010223	2	PMO women with low BMD; $\leq$ 80 yr	6, 14, 30 mg SC every 3 months and 14, 60, 100, 210 mg SC every 6 months; other	24 months; months 24-48
20050172	2	Japanese PMO women with low BMD; $\leq$ 80 yr	14, 60, 100 mg SC every 6 months	12 months
20050179	2	PMO women with low BMD; 50-70 yr; stratify by $\leq$ 60 yr or > 60 yr	60 mg SC every 6 months	12 months
20050141	3	PMO women with low BMD	60 mg SC every 6 months	12 months
20050234	3	PMO women with low BMD; prior AL therapy: 6-12, 12-24 or > 24 months	60 mg SC every 6 months	12 months

BMD = bone mineral density; AL = alendronate; SC = subcutaneous

Table 15: Safety Population Sizes of Other Phase 2 and 3 Studies

	Phase 2			Phase 3		
Arm	20010223	20050172	20050179	20050141	20050234	Total
Alendronate 70 MG QW	46	0	82	586	249	963
Denosumab 60 MG Q6M	47	54	83	593	253	1030
Placebo	46	55	82	0	0	183
Denosumab 210 MG Q6M	46	0	0	0	0	46
Denosumab 100 MG Q6M	41	50	0	0	0	91
Denosumab 30 MG Q3M	40	0	0	0	0	40
Denosumab 14 MG Q6M	53	53	0	0	0	106
Denosumab 14 MG Q3M	44	0	0	0	0	44
Denosumab 6 MG Q3M	43	0	0	0	0	43
Total	406	212	247	1179	502	2546

MG = milligrams; QW = weekly; Q6M = every 6 months; Q3M = every 3 months

Japanese women whereas all the other studies are mainly Caucasian (2) study 20010223 has 48 months duration whereas all the other studies have 12 months (3) the population for study 20050234 have a history of alendronate (a bisphosphonate) use whereas all the other studies do not. This may be an issue because alendronate could have hypersensitivity effects that may confound denosumab. Item (2) can be resolved by considering only the adverse events within 12 months from the start of the study. Therefore, crude incidence rates are shown separately for studies 20010223, 20050141 and 20050179 combined, 20050234 (have history of alendronate use) and 20050172 (Japanese women). The crude incidences of set S events are presented in Table 16.

It should be noted that the crude incidences in Table 16 are only for a 12 month duration and that the PMO pivotal studies are 24 (20040132) and 36 (20030216) months duration. Furthermore, the placebo is a pooling from studies 20010223, 20050172, and 20050179. Care should be taken in interpreting this column because 20050172 has a different population (Japanese women) as 20010223 and 20050179 (mostly Caucasian). This pooling nonetheless can give a sense of how the incidences compare with the other treatment arms. The Skin SOC in Table 16 reports very similar events as those in Table 5 for the PMO pivotal studies. Perhaps due to trial differences (e.g. sample sizes), the events in these two tables do not match exactly.

Table 17 summarizes the events by SOCs for studies 20010223 and 20050172 separately under different dose arms and treatment frequencies and the placebo. It is difficult to discern any definitive trends because of the low counts of events. However, in study 20010223, Rash occurred in all denosumab arms and none in the placebo. For the 6 month frequency, the largest count was 5 in the highest dose (210 mg) versus only 2 in all other doses. The counts in the 3 and 6 month frequencies were both nondecreasing by increasing dose.

Table 16: Hypersensitivity Events in Other Phase 2 and 3 Studies (Set S)

SOC and PT	Denosumab 20010223, 20050141 and 20050179	Denosumab 20050234	Denosumab 20050172	Placebo***
Safety Population	723 (%)	253 (%)	54 (%)	183 (%)
Blood and lymphatic system disorders				
Eosinophilia**	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)
Eye disorders				
Eye oedema*	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Eyelid oedema*	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Corneal oedema*	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Immune system disorders				
Hypersensitivity*	4 (0.6)	1 (0.4)	0 (0.0)	1 (0.5)
Drug hypersensitivity*	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders				
Rash**	19 (2.6)	2 (0.8)	0 (0.0)	2 (1.1)
Eczema*	1 (0.1)	1 (0.4)	4 (7.4)	5 (2.7)
Dermatitis contact*	3 (0.4)	1 (0.4)	0 (0.0)	2 (1.1)
Dermatitis*	3 (0.4)	1 (0.4)	0 (0.0)	1 (0.5)
Urticaria**	3 (0.4)	0 (0.0)	0 (0.0)	1 (0.5)
Dermatitis allergic*	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.5)
Dermatitis atopic*	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Exfoliative rash*	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Rash erythematous**	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Rash generalised**	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.5)
Skin exfoliation**	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders				
Peripheral circulatory failure**	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)

* in set P; ** not in set P; *** from 20010223, 20050172 and 20050179

Table 17: Hypersensitivity Events in Study 20010223/20050172 By Dose (Set S)

	Denosumab Doses							
	3 Months (Q3M)			6 Months (Q6M)				
SOC and PT	6	14	30	14	60	100	210	Placebo
Sample size	43	44	40	53/53	47/54	41/50	46	46/55
Eye disorders								
Corneal oedema*	0	0	1	0/0	0/0	0/0	0	0/0
Eyelid oedema*	0	0	0	0/0	0/0	0/1	0	0/0
Eye swelling*	0	0	0	0/1	0/0	0/0	0	1/1
Gastro-intestinal disorders								
Gingival swelling*	0	0	0	0/0	0/0	0/1	0	0/0
General disorders and administration site conditions								
Face oedema*	0	0	0	0/0	0/0	0/1	0	0/0
Immune system disorders								
Drug hypersensitivity*	0	0	0	0/0	0/0	1/1	0	0/0
Hypersensitivity*	2	0	0	0/0	3/0	0/1	0	1/0
Skin and subcutaneous tissue disorders								
Dermatitis*	0	0	1	0/0	0/0	0/1	0/0	0/1
Dermatitis allergic*	0	0	0	0/0	0/0	1/0	0	0/0
Dermatitis contact*	2	1	2	1/1	0/0	3/1	0/0	0/1
Eczema*	0	0	0	1/6	0/4	1/6	0	0/5
Rash**	1	1	3	2/0	2/0	2/0	5/0	0/1
Rash erythematous**	1	0	0	0/0	0/0	0/0	0/0	0/0
Rash generalised**	0	0	0	0/0	0/0	2/0	1/0	1/0
Skin exfoliation**	0	0	0	0/0	1/0	0/0	1/0	0/0
Urticaria**	0	0	2	2/0	0/0	0/0	0/0	0/0
Vascular disorders								
Peripheral Circulatory Failure**	0	0	0	0/0	0/1	0/0	0/0	0/0

* in set P; ** not in set P

4.3 Additional MedDRA Levels Analyses

4.3.1 Pooled PMO Studies

In this section, the denosumab (60 mg dose every 6 months subcutaneously) and placebo arms in the pivotal (20030216 and 20040132) and other phase 2 and 3 (20010223, 20050172, 20050179, 20050141 and 20050234) PMO studies were all pooled together ignoring (1) the duration of each study (2) race (mostly Caucasian in all studies except 20050172 who were all Japanese) and (3) no history of alendronate use in all studies except 20050234. Moreover, all the studies were placebo-controlled except for 20050141 and 20050234 which were both active-controlled. The resulting total population sizes were 5080 in the denosumab versus 4224 in the placebo arm. The results are shown in Tables 18 and 19.

Table 18: MedDRA Level Analysis (Set P, Denosumab vs Placebo, Pooled PMO)

MedDRA Level	Name	No. of PTs Denosumab	No. of PTs Placebo	Pearson's Chi-square p-value	Fisher's Exact p-value	Odds Ratio (95% CI)	Relative Risk (95% CI)	Risk Difference (95% CI)
PT	Eczema	59	32	0.049	0.056	1.539 (0.983,2.452)	1.533 (0.999,2.353)	0.004 (0.000,0.008)
HLT	Dermatitis and eczema	142	78	0.003	0.003	1.528 (1.147,2.047)	1.513 (1.151,1.989)	0.009 (0.003,0.016)
HLGT	Epidermal and dermal conditions	151	83	0.002	0.002	1.528 (1.157,2.028)	1.512 (1.160,1.970)	0.010 (0.004,0.016)
SOC	Skin and subcutaneous tissue disorders	183	116	0.020	0.021	1.323 (1.039,1.691)	1.311 (1.043,1.649)	0.009 (0.001,0.016)

Table 18 gives similar results as those for the pivotal PMO studies (Table 3) except that Eczema is no longer conclusively significant at 0.05 when comparing treatment arms at the PT level because the p-values and risk assessments are not in agreement. The results in Table 19 are also similar to those for the pivotal PMO studies (Table 4) except that Eczema is not conclusively significant and Rash is insignificant at 0.05 when comparing treatment arms at the PT level.

Table 19: MedDRA Level Analysis (Set S, Denosumab vs Placebo, Pooled PMO)

MedDRA Level	Name	No. of PTs Denosumab	No. of PTs Placebo	Pearson's Chi-square p-value	Fisher's Exact p-value	Odds Ratio (95% CI)	Relative Risk (95% CI)	Risk Difference (95% CI)
PT	Eczema	59	32	0.049	0.056	1.539 (0.983,2.452)	1.533 (0.999,2.353)	0.004 (0.000,0.008)
	Rash	128	79	0.034	0.040	1.356 (1.013,1.824)	1.347 (1.021,1.778)	0.006 (0.001,0.012)
HLT	Dermatitis and eczema	142	78	< 0.003	< 0.003	1.528 (1.147,2.047)	1.513 (1.151,1.989)	0.007 (0.003,0.016)
	Rashes, eruptions and exanthems NEC	139	86	0.029	0.030	1.353 (1.023,1.797)	1.343 (1.030,1.752)	0.007 (0.001,0.013)
HLGT	Epidermal and dermal conditions	296	173	< 0.001	< 0.001	1.447 (1.189,1.764)	1.421 (1.183,1.706)	0.017 (0.008,0.026)
SOC	Skin and subcutaneous tissue disorders	328	206	0.001	0.001	1.345 (1.120,1.617)	1.322 (1.116,1.567)	0.016 (0.006,0.025)

4.3.2 Denosumab Versus Active-Control

The hypersensitivity adverse events in the denosumab arm were also compared to those in the active-control arm (alendronate) for studies 20050141 and 20050234 (see Tables 14 and 15). There were no significant differences between treatment arms when analysis was done at various MedDRA levels. Table 20 shows the counts and crude incidence rates of the Skin SOC. The MedDRA level groups listed are the same as in Table 5. In general, denosumab has about the same incidence rate for Skin SOC events than alendronate when considering either both studies or each study separately.

Table 20: Skin and subcutaneous tissue disorders SOC (Set S, Active-control)

	20050141		20050234		Total	
HLGT, HLT, and PT	Denosumab	Alendronate	Denosumab	Alendronate	Denosumab	Alendronate
Safety Population	593 (%)	586 (%)	253 (%)	249 (%)	846 (%)	835 (%)
Epidermal and dermal conditions	19 (3.2)	14 (2.4)	7 (2.8)	7 (2.8)	26 (3.1)	21 (2.5)
Dermatitis and eczema	6 (1.0)	2 (0.3)	4 (1.6)	2 (0.8)	10 (1.2)	4 (0.5)
Dermatitis*	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.4)	2 (0.2)	2 (0.2)
Dermatitis allergic*	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Dermatitis atopic*	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Dermatitis contact*	3 (0.5)	0 (0.0)	1 (0.4)	0 (0.0)	4 (0.5)	0 (0.0)
Eczema*	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.4)	2 (0.2)	2 (0.2)
Rashes, eruptions and exanthems NEC	11 (1.9)	10 (1.7)	3 (1.2)	3 (1.2)	14 (1.7)	13 (1.6)
Rash**	11 (1.9)	8 (1.4)	2 (0.8)	3 (1.2)	13 (1.5)	11 (1.3)
Rash generalised**	0 (0.0)	2 (0.3)	1 (0.4)	0 (0.0)	1 (0.1)	2 (0.2)
Other HLTs	2 (0.3)	2 (0.3)	0 (0.0)	2 (0.8)	2 (0.2)	4 (0.5)
Angiodema and urticaria	3 (0.5)	4 (0.7)	0 (0.0)	1 (0.4)	3 (0.4)	5 (0.6)
Total PTs	22 (3.7)	18 (3.1)	7 (2.8)	8 (3.2)	29 (3.4)	26 (3.1)

* in set P; ** not in set P

4.4 Follow-up and Extension Phases of Pivotal Studies

Study 20030216 has a follow-up open-label and single-arm extension study, 20060289. All subjects enrolled in Study 20060289, regardless of treatment arm in Study 20030216, re-

ceived denosumab 60 mg subcutaneously every six months for two years. Studies 20040132, 20040135 and 20040138 each has a 24-month safety follow-up period where no investigational product was administered. The follow-up and extension phase studies were still ongoing at the time this report was written.

5 Immunogenicity

As a biologic product, denosumab has the potential of inducing countering antibodies or cell-based immune responses. Specific adverse events that may indicate an immunogenicity include reactions due to systemic infusion, local injection site and hypersensitivity. The sponsor conducted two types of tests: the presence or formation of (1) binding antibodies and (2) neutralizing antibodies. Two was only conducted when patients tested positive or found to be reactive for (1) at the same time point. Tests (1) and (2) used electrochemiluminescent (ECL) bridging immunoassay and cell-based chemiluminescent mRNA expression assay, respectively. The data for antibody testing was in a domain called AB (in Standard Data Tabulation Model or SDTM format) and AAB (ADaM format). Neither datasets contained antibody titers/concentration levels or measurements and only positive or negative test results for antibody formations.

A summary of the results for positive binding antibodies testing is given in Table 21. In study 20030216, the largest study, only 25 of 3886 or about 0.6% of all subjects developed binding antibodies. The largest incidence in any of the studies was about 1.6% (study 20040135). Table 22 shows the subject visits when the positive test results where collected for study 20030216. This table shows that there were $7+5+3+2+0+2=19$ subjects that tested positive for only one binding antibody test and most of them were on the first and

Table 21: Positive Binding Antibody Test Results.

Study	Size	Pre-existing	Developing	Frequency 1	2	3
20030216	3886	5	25	19	5	1
20010223	314	0	2	2	0	0
20040132	164	0	2	2	0	0
20040135	129	0	2	2	0	0
20040138	731	0	1	1	0	0
20050233*	200	0	1	1	0	0

* ongoing at the time of BLA submission

sixth months. There were 5 subjects that tested positive in two occasions during the study and most of the positive tests were on the sixth and twelfth months. Only one subject tested positive thrice (on months 1, 6 and 12). No pre-existing nor developing antibodies were found in any of the subjects in studies 20040245, 20050141, 20050172, 20050179, 20050234 and 20050237. Furthermore, there were no positive test results for neutralizing antibodies in any of the studies.

Table 22: Positive Binding Antibody Tests Per Visit (Study 20030216).

No. of positive tests	Analysis Visit Month 1	6	12	18	24	30
1	7	5	3	2	0	2
2	1	0	1	0	0	0
2	0	1	0	1	0	0
2	0	1	1	0	0	0
2	0	1	1	0	0	0
2	0	1	1	0	0	0
3	1	1	1	0	0	0
Total	9	10	8	3	0	2

The presence or formation of binding antibodies may result in adverse events or hypersensitivity reactions. Thus, the adverse event profiles of subjects who were positive for binding

antibodies were reviewed. The results are summarized in Table 25 of Appendix E for study 20030216. Table 25 categorizes the adverse events according to severity and occurrence since the last antibody testing that was positive. There were 5 severe adverse cases reported, two of which were from the same subject: Subject IDs 6104077 (Urinary incontinence), 6614001 (Arthralgia and Osteoarthritis), 6672059 (Gastric perforation) and 6749148 (Ligament rupture). The Osteoarthritis and Gastric perforation cases were considered serious and lead to hospitalization. None of the 5 cases were considered life-threatening, nor were there discontinuation or alteration of treatment and withdrawal. However, only subjects 6614001 and 6672059 completed the study. Most of the other cases were either mild or moderate in severity and there were more adverse events after 6 months of positive tests than within 6 months. Finally, of all adverse events reported in subjects with positive binding antibody tests, only Eczema PTs was a potential hypersensitivity case.

6 Summary and Conclusions

This safety review considered primary (P) and secondary (S) sets of preferred terms for hypersensitivity analysis. The events in set P were considered, reviewed and analyzed by the sponsor except for a few that were added by the statistical safety reviewer. Based on the analysis of the pooled pivotal PMO studies, the Skin SOC was found to be significantly different between treatment arms with p-value of ≤ 0.001 when considering either set P or S. The denosumab arm had higher relative risk [1.515 with 95% CI (1.190, 1.928) for set P and 1.455 with 95% CI (1.218,1.738) for set S] and risk difference [0.0135 with 95% CI (0.006, 0.021) for set P and 0.022 with 95% CI (0.011,0.032) for set S] when compared to placebo. When considering set S, the crude incidence rate of events in study 20030216 (the

largest of the 4 pivotal studies) was 6.7% (261/3886) for denosumab and 4.6% (178/3876) for placebo. Significant differences were also found in the following MedDRA levels within the Skin SOC: Epidermal and dermal conditions HLGT, Dermatitis and eczema HLT, Rashes, eruptions and exanthems NEC HLT, Eczema PT and Rash PT. The Epidermal and dermal conditions HLGT, Dermatitis and eczema HLT, and Eczema PT were significant whether set P or S was considered whereas the Rashes, eruptions and exanthems NEC HLT and Rash PT were significant only when set S was considered. Most results were mainly driven by study 20030216 but for the Rash, significance was only found in study 20030132. No significant results were found for the HALT studies.

For set P events, the three SMQs searched, baseline and demographic characteristics, and events considered serious were largely balanced between treatment arms for the four pivotal studies. Severity and toxicity grade were assessed at the level of a specific event and across events and differences between arms were found for Eczema. Mild cases were about the same in both arms but moderate to severe cases were significantly higher in denosumab (27) than placebo (6). The onset time patterns were very different in both arms. Most denosumab cases happened early on whereas those in placebo happened late in the study. As many subjects in both arms were continuing cases, it was difficult to assess duration. However, almost all subjects with Eczema in either arm completed the study and did not discontinue treatment. For Rash, the onset time was higher in the beginning for denosumab but was similar to placebo thereafter.

Two cases of Shock (an Anaphylactic Reaction SMQ) was reported as life-threatening and fatal in study 20030216. There were 3 cases of Circulatory collapse in study 20040138 that were reported as serious but occurred only on the same subject. The subject was hospitalized but did not withdraw from the study. There were 9 vs 2, mostly mild, Bronchospasm in

the denosumab and placebo arms, respectively across all four pivotal studies. Other less common events that were noted as occurring only in the denosumab arm and not in the placebo were 4 cases each of Dermatitis atopic and Toxic skin eruption. One case of Toxic skin eruption was considered serious.

The review of secondary studies did not suggest different events nor crude incidence rates when compared to the pivotal studies. Furthermore, no dose-varying adverse events were observed. In the analysis of denosumab versus the active-control alendronate, there were no significant differences found between treatment arms.

For immunogenicity, the sponsor conducted two antibody tests. The first was a test for binding antibodies and the second test was a follow-up on the first one to confirm if the binding antibodies were neutralizing or not. Based on the data submitted by the sponsor, 6 of 12 studies with antibody tests had positive results: 20030216 (25/3886 or 0.6%), 20010223 (2/314 or 0.6%), 20040132 (2/164 or 1.2%), 20040135 (2/129 or 1.6%), 20040138 (1/731 or 0.1%) and 20050233 (1/200 or 0.5%). In 20030216, 19 subjects tested positive once only, 5 were positive twice and 1 was positive thrice. There was no correlation observed between subjects with positive binding antibody tests and their adverse event profiles. None of the subjects that were positive for binding antibodies were positive for neutralizing antibodies.

In conclusion, denosumab does not appear to be immunogenic but there are some hypersensitivity concerns when it comes to particular types or groups of Skin SOC events. Specific cases that were found to be significant were Eczema and Rash. For Eczema, the main difference between treatment arms were those classified as moderate and severe. The Dermatitis and eczema and Rashes, eruptions and exanthems NEC HLTs, which contained the Eczema and Rash events, respectively, were also of concern because of higher incidences of other PTs in denosumab compared to placebo. Although most of the subjects with Eczema and Rash

completed the study, it is recommended that the labeling of denosumab should indicate the potential occurrence of these events while on treatment. Additionally, it is recommended that the label includes the potential occurrence of other PTs within the Dermatitis and eczema and Rashes, eruptions and exanthems NEC HLTs. Furthermore, it is recommended that safety monitoring in postmarketing should record and evaluate the occurrences of all these events.

7 APPENDICES

A. Standardised MedDRA Queries (SMQ) Searched for Set P

ANGIOEDEMA SMQ:

Allergic oedema	Angioedema	Circumoral oedema
Conjunctival oedema	Corneal oedema	Epiglottic oedema
Eye oedema	Eye swelling	Eyelid oedema
Face oedema	Gingival oedema	Gingival swelling
Gleich's syndrome	Hereditary angioedema	Idiopathic urticaria
Laryngeal oedema	Laryngotracheal oedema	Lip oedema
Lip swelling	Oculorespiratory syndrome	Oedema mouth
Oropharyngeal swelling	Palatal oedema	Periorbital oedema
Pharyngeal oedema	Scleral oedema	Small bowel angioedema
Swelling face	Swollen tongue	Tongue oedema
Tracheal oedema	Urticaria	Urticaria cholinergic
Urticaria chronic	Urticaria papular	

ANAPHYLACTIC REACTION SMQ:

Anaphylactic reaction	Anaphylactic shock	Anaphylactoid reaction
Anaphylactoid shock	Circulatory collapse	First use syndrome
Shock	Type I hypersensitivity	

SEVERE CUTANEOUS ADVERSE REACTION SMQ:

Acute generalised exanthematous pustulosis	Cutaneous vasculitis	Dermatitis bullous
Dermatitis exfoliative	Dermatitis exfoliative generalised	Epidermal necrosis
Erythema multiforme	Exfoliative rash	Skin necrosis
Stevens-Johnson syndrome	Toxic epidermal necrolysis	Toxic skin eruption

B. Additional Potential Hypersensitivity Preferred Terms Searched For Set S

Anaphylaxis treatment	Bronchospasm	Circulatory collapse
Drug eruption	Eosinophilia	Erythema multiforme
Exfoliative rash	Peripheral circulatory failure	Rash
Rash erythematous	Rash generalised	Rash macular
Rash maculo-papular	Rash morbilliform	Rash vesicular
Skin exfoliation	Toxic skin eruption	Urticaria

C. Computation of Duration for Eczema Preferred Terms (Study 20030216)

- Subjects 20030216-413206, 20030216-631011, 20030216-853011 had the same start dates for the same PT but were coded multiple times for different location of occurrence on the body. The multiple records were counted as one PT.

- Subject 20030216-613020 was coded with one eczema case (aeterm: "worsening eczema on both hands") with a start date of June 12, 2006 and an end date of Jan. 10, 2007. However, another eczema case (aeterm: "eczema both hands") was reported as having started on Jan. 11, 2007 and reported as continuing (aecont='Y'). Another eczema case (aeterm: "eczema in the face") was reported with start date of March 18, 2007 with an end date of April 15, 2007. For this subject, all three cases were considered as one eczema case with start date of June 12, 2006 and reported as continuing.

- Subject 20030216-631200 had two coded eczema events that were both continuing. For

this subject, only one case was included in the analysis using the earliest start date of August 22, 2005.

- Subject 20030216-631435 had eczema (aeterm: "eczema both palms") with start date of Nov. 1, 2005 and end date of Oct. 1, 2007. Three other cases (aeterms: "eczema left palm", "eczema on sole right foot", and "eczema right palm") were reported with the same start date of Dec. 28, 2007 and reported as continuing. For this subject, one case of eczema was reported with start date of November 1, 2005 and continuing.

- For subject 20030216-632021, eczema (aeterm: worsening eczema) was reported to have started on Feb. 1, 2007 and ended on March 1, 2007. However, another eczema case with the same aeterm was reported to have started on March 2, 2007 and continuing. For this subject, only one case of eczema was included in the analysis with start of Feb. 1, 2007 and continuing.

- Usubjid 20030216-684020 had two reported cases of eczema (aeterm: "eczema" for both) with start dates of March 12, 2007 and September 21, 2007. Both were treated as separate cases in the analysis. 20030216-726016 had two continuing cases. Only one case was considered using the earliest start date. 20030216-853011 had two continuing cases with same start date and only one was considered in analysis.

D. Other Reported Skin Adverse Events of Subjects With Eczema and Rash (Study 20030216)

Table 23: Other Reported Skin Primary SOC Adverse Events of Subjects With Eczema (Study 20030216)

Adverse events	No. of Subjects	
	Denosumab	Placebo
Dermatitis contact, Dermatitis, Eczema, Skin lesion	1	0
Skin inflammation, Pruritus, Eczema, Rash	1	0
Eczema, Hyperkeratosis, Lichen planus, Pruritus	1	0
Rash, Eczema, Pruritus	1	1
Urticaria, Eczema, Dermatitis allergic	0	1
Eczema, Dermal cyst	1	0
Eczema, Dry skin	1	0
Eczema, Pruritus	0	1
Eczema, Skin nodule	0	1
Eczema, Toxic skin eruption	1	0
Eczema, Urticaria	1	1
Alopecia areata, Eczema	1	0
Dry skin, Eczema	1	0
Pain of skin, Eczema	1	0
Pruritus, Eczema	2	1
Rash, Eczema	1	0
Skin ulcer, Eczema	1	0
Urticaria, Eczema	1	0
Eczema	34	19
Total	50	25

Table 24: Other Reported Skin Primary SOC Adverse Events of Subjects With Rash (Study 20030216)

Adverse events	No. of Subjects	
	Denosumab	Placebo
Rash, Onychoclasis, Psoriasis, Nail disorder, Nail dystrophy	1	0
Onychoclasis, Dry skin, Hyperhidrosis, Rash	0	1
Skin inflammation, Pruritus, Eczema, Rash	1	0
Rash, Blister, Pruritus	1	0
Rash, Eczema, Pruritus	1	1
Rash, Ingrowing nail, Alopecia	1	0
Rash macular, Rash, Rash pruritic	1	0
Dermatitis allergic, Rash, Pruritus	1	0
Dermatitis contact, Seborrhoeic Dermatitis	1	0
Dry skin, Rash, Rash pruritic	1	0
Skin discolouration, Rash, Skin lesion	1	0
Rash, Actinic keratosis	1	0
Rash, Alopecia	1	0
Rash, Dermal cyst	1	0
Rash, Dermatitis	1	0
Rash, Dermatitis allergic	0	2
Rash, Dermatitis contact	1	0
Rash, Dry skin	1	1
Rash, Eczema	1	0
Rash, Granuloma annulare	1	0
Rash, Pain of skin	1	0
Rash, Parapsoriasis	0	1
Rash, Pruritus	0	1
Rash, Purpura	0	1
Rash, Rash generalised	2	0
Rash, Rash macular	1	0
Rash, Rash pruritic	2	0
Rash, Rosacea	0	1
Rash, Skin nodule	0	1
Rash, Skin ulcer	1	1
Rash, Urticaria	2	1
Dermatitis, Rash	0	1
Dermatitis allergic, Rash	0	2
Dry skin, Rash	1	0
Erythema, Rash	1	0
Prurigo, Rash	1	0
Pruritus, Rash	2	1
Purpura, Rash	0	1
Swelling face, Rash	0	1
Rash	61	54
Total	93	72

E. Adverse Events For Subjects Who Were Positive For Binding Antibodies (Study 20030216)

System Organ Class	0-6 Months*			> 6 Months*		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Musculoskeletal and connective tissue disorders	4	5	0	4	8	2
Back pain	2	3	0	2	2	0
Arthralgia	0	0	0	2	2	1
Osteoarthritis	0	0	0	0	1	1
Pain in extremity	0	1	0	0	1	0
Intervertebral disc space narrowing	1	0	0	0	0	0
Muscle rigidity	0	0	0	0	1	0
Spinal osteoarthritis	1	0	0	0	0	0
Joint swelling	0	0	0	0	1	0
Musculoskeletal pain	0	1	0	0	0	0
Infections and infestations	5	5	0	4	4	0
Nasopharyngitis	3	0	0	2	1	0
Influenza	0	1	0	0	1	0
Viral infection	0	0	0	2	0	0
Gastroenteritis	1	0	0	0	0	0
Furuncle	1	0	0	0	0	0
Gingival infection	0	0	0	0	1	0
Lower respiratory tract infection	0	1	0	0	0	0
Tooth abscess	0	0	0	0	1	0
Herpes ophthalmic	0	1	0	0	0	0
Upper respiratory tract infection	0	1	0	0	0	0
Urinary tract infection	0	1	0	0	0	0
Gastrointestinal disorders	0	2	0	1	3	1
Abdominal pain upper	0	1	0	1	0	0
Constipation	0	0	0	0	2	0
Diarrhoea	0	1	0	0	0	0

Continued on next page

Table 25 – continued from previous page

System Organ Class	0-6 Months*			> 6 Months*		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Gastric perforation	0	0	0	0	0	1
Gastroduodenal ulcer	0	0	0	0	1	0
Injury, poisoning and procedural complications	2	3	1	0	1	0
Procedural pain	0	0	0	0	1	0
Limb injury	0	1	0	0	0	0
Contusion	1	0	0	0	0	0
Fall	0	1	0	0	0	0
Foot fracture	0	1	0	0	0	0
Ligament rupture	0	0	1	0	0	0
Rib fracture	1	0	0	0	0	0
Nervous system disorders	0	1	0	1	4	0
Headache	0	0	0	1	1	0
Dizziness	0	1	0	0	0	0
Hyperreflexia	0	0	0	0	1	0
Paraesthesia	0	0	0	0	1	0
Sciatica	0	0	0	0	1	0
Metabolism and nutrition disorders	2	0	0	2	0	0
Hypercholesterolaemia	1	0	0	1	0	0
Hyperlipidaemia	0	0	0	1	0	0
Type 2 diabetes mellitus	1	0	0	0	0	0
Psychiatric disorders	1	0	0	2	1	0
Anxiety	1	0	0	1	0	0
Depression	0	0	0	0	1	0
Insomnia	0	0	0	1	0	0
Skin and subcutaneous tissue disorders	2	1	0	0	0	0
Alopecia	1	0	0	0	0	0
Onychoclasis	1	0	0	0	0	0
Eczema	0	1	0	0	0	0
Reproductive system and breast disorders	0	0	0	3	0	0

Continued on next page

Table 25 – continued from previous page

System Organ Class	0-6 Months*			> 6 Months*		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Breast mass	0	0	0	1	0	0
Genital haemorrhage	0	0	0	1	0	0
Vaginal haemorrhage	0	0	0	1	0	0
General disorders and administration site conditions	0	0	0	1	2	0
Gait disturbance	0	0	0	0	1	0
Oedema peripheral	0	0	0	1	0	0
Non-cardiac chest pain	0	0	0	0	1	0
Renal and urinary disorders	0	1	0	0	0	1
Urinary incontinence	0	0	0	0	0	1
Dysuria	0	1	0	0	0	0
Eye disorders	0	0	0	2	0	0
Lacrimation increased	0	0	0	1	0	0
Cataract	0	0	0	1	0	0
Vascular disorders	1	0	0	0	0	0
Haematoma	1	0	0	0	0	0
Ear and labyrinth disorders	1	0	0	1	0	0
Tinnitus	0	0	0	1	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0	1	0
Bronchitis chronic	0	0	0	0	1	0
Total	18	18	1	21	24	4

* since last positive binding antibody test

8 References

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SIGNATURES/DISTRIBUTION LIST

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July 28, 2009

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STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

BLA /

NDA Number: 125320 Applicant: Amgen Stamp Date: 12/19/09

Drug Name: Prolia (Denosumab) NDA/BLA Type: Standard

On initial overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.				
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.				
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.				
Appropriate references for novel statistical methodology (if present) are included.				
Safety data organized to permit analyses across clinical trials in the NDA/BLA.				
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.				

File name: 5_Statistics Filing Checklist for a new NDA_BLA110207

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Paul H. Schuette — January 29, 2009
Reviewing Statistician — Date

[illegible] — 1/29/09
Supervisor/Team Leader — Date

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

STATISTICS FILING CHECKLIST FOR A NEW BLA

BLA Numbers: 125320 and 125331 / S-000 **Applicant:** Amgen, Inc. **Stamp Date:** 12-19-2008

Drug Name: PROLIA (Denosumab) **BLA Type:** Standard

Indication: Treatment (BLA 125320) and prevention (BLA 125331) of osteoporosis in postmenopausal women

On **initial** overview of the BLA applications for RTF:

	Content Parameter for RTF	Yes	No	NA	Comments
1A	Paper Submission			X	
1B	Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	X			All subjects are female
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

THE STATISTICAL SECTION OF THE TWO APPLICATIONS ARE FILEABLE **Yes**

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			For study 20030216, no justification given for changing the primary efficacy analysis from a Cochran-Mantel-Haentzel analysis to a logistic regression model analysis prior to data unblinding.
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.		X		For both studies, no formal interim analyses were done but the DSMB make a benefit/risk assessment with the possibility to stopping early for efficacy if the p-value was less than 0.0005 at any meeting time. This needs to be further assessed as no adjustments to the overall α-level were made.
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			For study 20030216, according to the sponsor, all subjects from Lithuanian site 803 (n=60) were excluded from all efficacy and safety analyses due to GCP noncompliance and the potential for confounding of safety and efficacy analyses (see page 223 of study report). This needs to be further investigated, as well other country primary efficacy results. This may result in potential DSI assessment of this site and other sites.

STATISTICS FILING CHECKLIST FOR A NEW BLA

[redacted] here.

1. For both Studies 20030216 and 20040132, Appendix 22: *Safety/Data Monitoring Committee Meeting Minutes and Correspondence* only includes the DSMB charter. The DSMB meeting minutes, correspondence, and list of meeting dates for each study should be submitted to each application.

2. For study 20030216, provide the following:
   - A justification for changing the primary efficacy analysis from a Cochran-Mantel-Haentzel analysis to a logistic regression model analysis prior to data unblinding.
   - The Amgen/Quintiles quality assurance audit documentation and the subsequent monitoring documentation for Lithuanian site 803 where you identified GCP noncompliance.

Sonia Castillo, Ph.D. Reviewing Statistician — 1-28-2009 Date

Mahboob Sobhan, Ph.D., Team Leader — 1-28-2009 Date