2. SYNOPSIS

Name of Sponsor:
Amgen Inc., Thousand Oaks, CA

Name of Finished Product:
Denosumab (AMG 162)

Name of Active Ingredient:
Fully human monoclonal antibody to receptor activator for nuclear factor-κB ligand

Title of Study:
A Study to Evaluate Denosumab in the Treatment of Postmenopausal Osteoporosis.
FREEDOM (Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months)

Investigators and Study Centers:
The study was conducted at 214 centers: 83 in Western Europe (44.9% of subjects enrolled), 66 in Eastern Europe (34.7%), 48 in North America (7.4%), 10 in Latin America (11.9%), and 7 in Australia and New Zealand (1.2%). Centers and principal investigators are listed in Appendix 4.

Publications:
None as of the date of this report.

Study Period:
03 August 2004 (first subject enrolled) to 17 June 2008 (last subject's end-of-study visit)

Development Phase:
3

Introduction and Objectives:
Denosumab is a fully human monoclonal antibody with high affinity and specificity for the receptor activator of nuclear factor-κB ligand (RANKL). Denosumab binds to, and neutralizes the activity of, human RANKL. In a phase 2 study in postmenopausal women with low bone mineral density (BMD, assessed by dual energy x-ray absorptiometry [DXA]) (-4.0 ≤ T-score ≤ -1.8 for the spine or -3.5 ≤ T-score ≤ -1.8 for the total hip or femoral neck), denosumab administered for up to 4 years increased mean BMD at the lumbar spine, total hip, femoral neck, trochanter, distal 1/3 radius, and total body (without head).

The primary objective of the present study (20030216) was to determine whether denosumab treatment can reduce the number of postmenopausal osteoporotic women (BMD T-score < –2.5) with new vertebral fractures as compared with control (placebo plus vitamin D and calcium).

The primary safety objective was to characterize the safety and tolerability profile of denosumab in this population based on the adverse event incidence, changes in laboratory profiles, and immunogenicity to denosumab.

Secondary objectives were to assess the effect of denosumab on the time to first nonvertebral fracture and the time to first hip fracture. Tertiary and exploratory objectives are listed in Section 6.3 and Section 6.4, respectively.

Within the overall study, 7 substudies were conducted. Substudies assessed the effect of denosumab on BMD (DXA Substudy), trabecular and cortical bone at the lumbar spine and hip (quantitative computerized tomography [QCT] Spine/Hip Substudy), trabecular and cortical bone at the distal radius (QCT Distal Radius Substudy), bone turnover (Bone Marker Substudy), healing of distal radius fractures (Fracture Healing Substudy), and bone histology and histomorphometry (Bone Biopsy Substudy). In addition, sparse sampling of serum denosumab concentrations was obtained for population pharmacokinetic analyses (PK Substudy). Objectives of these 7 substudies are outlined in Section 6.5.

Methodology:
This international, multicenter, randomized, double-blind placebo-controlled study tested the clinical hypotheses that denosumab, as compared with placebo, is effective in reducing the risks of new vertebral, nonvertebral, and hip fractures 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). Subjects were randomized (1:1) in a double-blinded fashion to receive either denosumab (60 mg) or placebo every 6 months (Q6M) subcutaneously (SC) for 3 years (last dose at month 30; follow-up to month 36). Randomization was stratified by age at entry: 60 to 64 years, 65 to 69 years, 70 to 74 years, and ≥ 75 years. Subjects received daily calcium (≥ 1 g) and vitamin D (≥ 400 IU) supplementation. Subject safety was monitored on an ongoing basis throughout the trial by an external Data Monitoring Committee (DMC).

Number of Subjects Planned: 7200 (3600 in each treatment group)

Number of Subjects Enrolled: A total of 7868 subjects were enrolled at all sites and were randomized (1:1) to receive denosumab. Due to significant noncompliance at site [redacted], including irregularities in procedures for subject informed consent, data obtained from the 60 subjects enrolled at this site were excluded from all efficacy and safety analyses; the decision to exclude these data was made prior to unblinding. The number of subjects enrolled and randomized in this study is therefore reported as 7808 throughout this document (3902 randomized to denosumab, 3906 randomized to placebo).

Sex: 100% women

Mean (SD) Age: 72.3 (5.2) years

Ethnicity (Race): 92.7% White or Caucasian, 6.1% Hispanic or Latino, 0.7% Black or African American, 0.2% Asian, 0.1% Japanese, 0.1% other, and < 0.1% Native Hawaiian or Other Pacific Islander

Enrollment in Substudies:

	n	(% of study N)
DXA Substudy	441	(5.6%)
QCT of the Spine and Hip Substudy	209	(2.7%)
QCT of the Distal Radius Substudy	182	(2.3%)
Bone Marker Substudy	160	(2.0%)
PK Substudy	803	(10.3%)
Bone Biopsy Substudy	103	(1.3%)
Fracture Healing Substudy	25	(0.3%)

HT_Regulatory Writing. Source: Table 14-1.1.7

Diagnosis and Main Criteria for Eligibility:
Subjects were postmenopausal women with osteoporosis (BMD T-score < –2.5 at either the lumbar spine or the total hip, or at both locations, but ≥ –4.0 at both locations), ambulatory, in general good health, not receiving medications that affect bone metabolism, and free from any underlying conditions, other than osteoporosis, that may result in abnormal bone metabolism.

Duration of Treatment:
36 months (last scheduled dose of investigational product at month 30)

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number:
Denosumab was provided as a sterile, clear, colorless, preservative-free liquid in glass vials containing 60 mg denosumab per mL of [redacted] mM sodium acetate and [redacted]% sorbitol in Water for Injection, with a pH of [redacted]. One mL of blinded investigational product was administered SC at day 1 and at months 6, 12, 18, 24, and 30. Manufacturing batch numbers for denosumab used in this study were [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted].

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number:
Placebo was provided in containers identical to those provided for denosumab. The placebo formulation was identical to the denosumab formulation with the exception of the protein content. One mL of blinded investigational product was administered SC at day 1 and at months 6, 12, 18,

24, and 30. Manufacturing batch numbers for placebo used in this study were [redacted], [redacted], [redacted].

Study Endpoints

Primary Efficacy Endpoint:

- Subject incidence of new vertebral fractures during the entire 36-month treatment period

Secondary Efficacy Endpoints:

- Time to first nonvertebral fracture
- Time to first hip fracture

Safety Endpoints:

- Adverse events
- Reported values and changes in safety laboratory analytes
- Subject incidence of anti-denosumab antibodies
- Time to first positively adjudicated cardiovascular event (including any positively adjudicated cardiovascular event, death, acute coronary syndrome [ACS], stroke/transient ischemic attack [TIA], other vascular event, arrhythmia, and congestive heart failure [CHF])
- Change from baseline in total aortic calcification (AC) severity score at 12, 24, and 36 months
- Incidence of nonvertebral fractures with delayed healing

Tertiary, Exploratory, and Substudies Endpoints:

Tertiary and exploratory endpoints for the overall study, as well as endpoints for the substudies, are detailed in Section 7.10.3.

Statistical Methods:
For the primary efficacy endpoint (subject incidence of new vertebral fractures during the entire 36-month treatment period) and the secondary efficacy endpoints (time to first nonvertebral fracture and time to first hip fracture), a fixed sequence testing procedure was employed among these 3 endpoints in the order mentioned above for multiplicity adjustment to maintain the overall significance level at 0.05. Subjects were analyzed as randomized, and analyses followed intent-to-treat principles.

The significance of the treatment comparisons between denosumab and placebo for the primary efficacy endpoint (ie, new vertebral fracture [Yes/No]), as well as for other binary endpoints, were assessed using the score test from a logistic regression model with treatment as the main effect and age strata as a covariate. In addition to the estimate of the odds ratio from the logistic regression model, point estimates of absolute risk reduction (difference in proportions, placebo – denosumab) and risk ratio (ratio of proportions, denosumab over placebo) as well as the corresponding 95% confidence intervals were calculated using Mantel-Haenszel methodology adjusting for age strata. The significance of the treatment effect between denosumab and placebo on time-to-event endpoints was assessed using the score test from a stratified Cox proportional hazards model controlling for age strata with treatment as the independent variable. Time-to-event endpoints were summarized descriptively using the Kaplan-Meier estimates at time point(s) of interest.

Descriptive statistics were provided for selected baseline characteristics and demographic, efficacy, pharmacokinetic, and safety data. Continuous variables were summarized descriptively using mean, standard deviation (SD), minimum, maximum, and the number of non-missing observations, n. Median and other selected percentiles were substituted for mean and SD for some continuous parameters where parametric methods may not have been appropriate. Frequencies and percentages were presented for categorical variables.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 11.0 or higher and were tabulated by system organ class and preferred term. Relevant categories of adverse events (eg, serious adverse events, fatal adverse events, adverse events of interest), adverse events of infections, serious adverse events of infection, serious adverse events of opportunistic infection, adverse events potentially associated with hypersensitivity, and malignancies were tabulated similarly. Positively adjudicated events of osteonecrosis of the jaw (ONJ) were to be tabulated.

Time to first cardiovascular event that was positively adjudicated was analyzed using a Cox proportional hazards model with treatment group and baseline cardiovascular risk level as the independent variables. Treatment effect was measured using hazard ratios (relative risks) and 95% confidence intervals. No adjustments were made for multiple comparisons. Positively adjudicated cardiovascular event rates over time were graphically presented using Kaplan-Meier curves. [redacted]

Descriptive statistics of actual values and changes from baseline at each visit were provided for serum chemistry and hematology results and for vital signs. Shift tables for safety laboratory analytes were provided to compare baseline values with the most extreme postbaseline values, based on Common Terminology Criteria for Adverse Events v3.0 (CTCAE) categories.

Immunogenic response during the study was described by tabulating the numbers and percentages of subjects who tested positive for binding and neutralizing anti-denosumab antibodies.

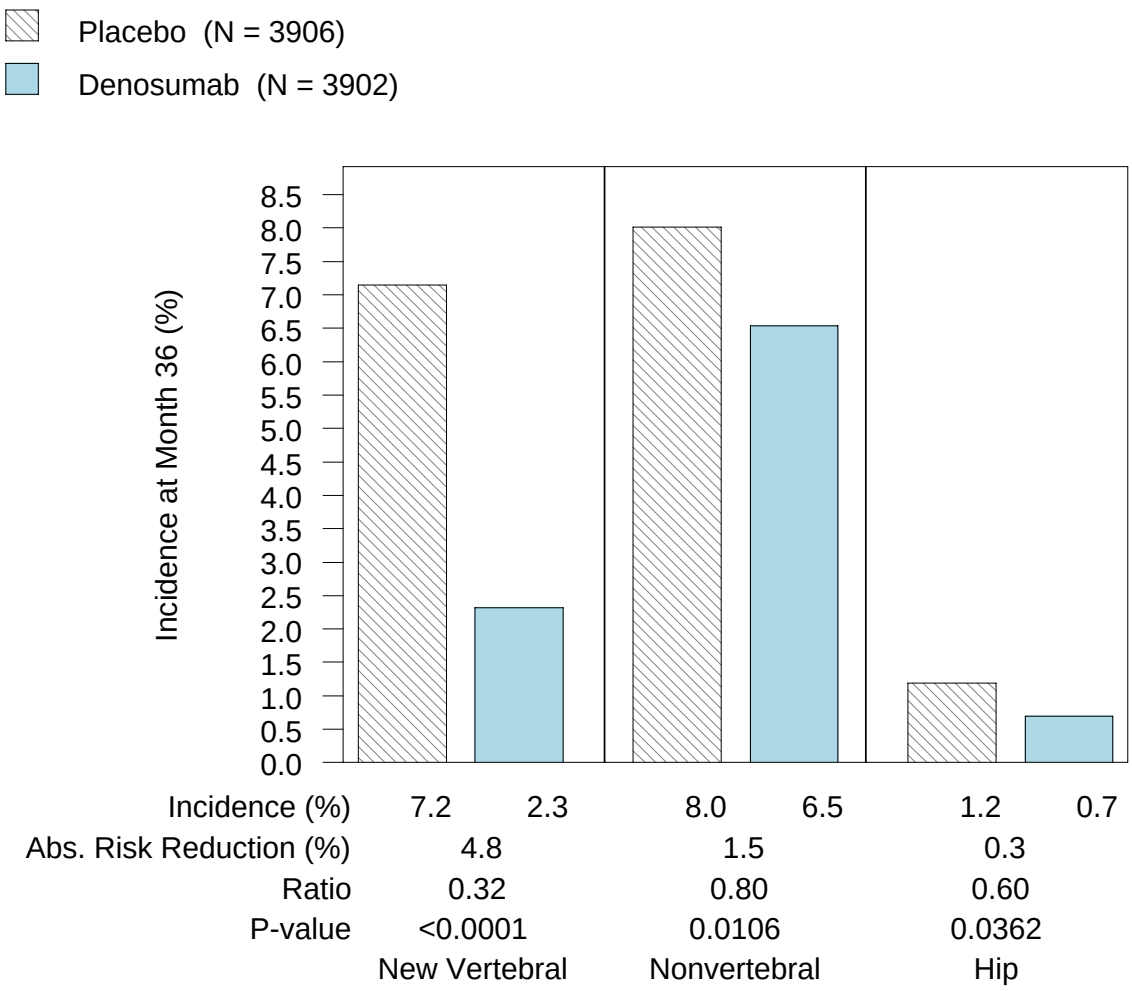
Summary of Results:

Subject Disposition:
A total of 7808 subjects were enrolled into the study, with 3902 subjects randomized to the denosumab group and 3906 subjects randomized to the placebo group. Randomization was stratified by age at entry: 60 to 64 years (5.4% of subjects enrolled), 65 to 69 years (21.2%), 70 to 74 years (41.9%); and ≥ 75 years (31.5%); randomization was well-balanced between treatment groups within the age strata. Eighty-three percent of subjects overall completed the study (denosumab 83.9%, placebo 82.1%), and 77.9% of subjects overall completed investigational product administration (80.2% denosumab, 75.5% placebo).

Baseline Characteristics:
All baseline characteristics were well-balanced for the overall study and for substudies. Baseline mean (SD) BMD T-scores at the lumbar spine and total hip were -2.83 (0.69) and -1.90 (0.81), respectively. Prevalent vertebral fractures were noted for 23.6% of subjects; 6.8% had more than 1 prevalent vertebral fracture. Based on the FRAX™ algorithm (Kanis et al, 2008), 10-year probabilities of major osteoporotic fractures and of hip fractures were 19% and 7%, respectively. Overall, the study population represented a wide range of fracture risk, including a large subset of subjects at significant risk for fracture.

Efficacy Results:
Denosumab significantly reduced the risk of new vertebral, nonvertebral, and hip fractures compared with placebo (Figure 2-1) based on the prespecified sequential testing procedure. The risk reduction for new vertebral fractures at month 36 (primary endpoint) was 68% (risk ratio: 0.32 [95% CI: 0.26, 0.41]; $p < 0.0001$). Risk reductions for nonvertebral fractures and hip fractures (secondary endpoints) were 20% (hazard ratio: 0.80 [0.67, 0.95]; $p = 0.0106$) and 40% (hazard ratio: 0.60 [0.37, 0.97]; $p = 0.0362$), respectively.

Figure 2-1. Summary of Primary and Secondary Efficacy Endpoints



Risk/Hazard ratio < 1 favors denosumab. Incidence is based on crude incidence for new vertebral fracture and Kaplan-Meier estimate for time to first nonvertebral fracture and hip fracture. Ratio represents risk ratio for new vertebral fracture and hazard ratio for time to first nonvertebral fracture and hip fracture. P-value is based on a logistic regression model adjusting for age stratification variable for new vertebral fracture and a Cox proportional hazards model stratified by age stratification variable for time to first nonvertebral fracture and hip fracture.
HT_Regulatory Writing. Source: Figure 14-1.1.1

When years 1, 2, and 3 were analyzed separately, the effect of denosumab was sustained, with significant risk reductions for new vertebral fractures of 61% (risk ratio: 0.39 [95% CI: 0.26, 0.58], $p < 0.0001$), 78% (0.22 [0.14, 0.34], $p < 0.0001$), and 65% (0.35 [0.24, 0.51], $p < 0.0001$), respectively. In addition, reductions in the incidences of nonvertebral and hip fractures were noted at 2 years.

In planned covariate analyses, denosumab reduced the incidence of fractures across subjects with a wide range of baseline 10-year fracture risk. The treatment effect of denosumab on fracture risk reduction remained significant after controlling for the 10-year probability of major osteoporotic fracture (for new vertebral and nonvertebral fracture endpoints) and for the 10-year probability of hip fracture (for hip fracture endpoint). In addition, the effects of denosumab were clinically relevant in subgroups of subjects with higher risk for subsequent fracture. When higher fracture risk was identified in a conventional manner (based on age, BMD, and prevalent

vertebral fracture), denosumab reduced the incidence of new vertebral and nonvertebral fractures in the high risk subgroup. Furthermore, in post-hoc analyses, denosumab showed consistent efficacy by reducing the risk of fracture in subgroups at higher fracture risk defined by other baseline characteristics: subjects with ≥ 2 prevalent vertebral fractures or having prevalent vertebral fractures with moderate or severe severity (for new vertebral fracture endpoint), subjects with femoral neck T score ≤ -2.5 (for nonvertebral and hip fracture endpoints), and subjects with age ≥ 75 years (for hip fracture endpoint).

Denosumab also reduced the risk of other prespecified categories of fractures (Table 2-1).

Table 2-1. Summary of Additional Fracture Endpoints

Fracture Category	Ratio Point Estimate [a]	95% CI	p-value
New and worsening vertebral [b]	0.33	(0.26, 0.42)	< 0.0001
Multiple new vertebral [b]	0.39	(0.24, 0.63)	< 0.0001
Major osteoporotic [c]	0.65	(0.55, 0.78)	< 0.0001
Major nonvertebral [c]	0.80	(0.66, 0.97)	0.0224
Clinical [c]	0.70	(0.59, 0.81)	< 0.0001
Clinical vertebral [c]	0.31	(0.20, 0.47)	< 0.0001
Any osteoporotic [b]	0.60	(0.53, 0.69)	< 0.0001

Fracture categories defined in Section 7.8.2.1.

[a] Risk or hazard ratio compared with placebo at month 36; ratio < 1 favors denosumab.

[b] Risk ratio based on the Mantel-Haenszel method stratified by age stratification variable; p-value based on a logistic regression model adjusting for age stratification variable

[c] Hazard ratio and p-value based on the Cox proportional hazards model stratified by age stratification variable

HT_ Regulatory Writing. Source: Tables 14-4.1.5, 14-4.10.1, 14-4.18.3, 14-4.18.1, 14-4.18.4, 14-4.18.5, and 14-4.18.6

For the overall study population (n = 7808), denosumab increased BMD (assessed by DXA) at the lumbar spine at month 36 ($p < 0.0001$; the only time point assessed for the overall population for lumbar spine) and at the total hip, femoral neck and trochanter at months 12, 24, and 36 ($p < 0.0001$). Mean differences in change from baseline to month 36 between the denosumab and placebo groups were 8.8% at the lumbar spine, 6.4% at the total hip, 5.2% at the femoral neck, and 8.3% at the trochanter. In subgroup analyses, denosumab significantly increased lumbar spine BMD at month 36 ($p < 0.0001$) in all subgroups of baseline characteristics examined (subgroups of age, geographic region; body weight, BMI, lumbar spine BMD T-score, total hip BMD T-score, and serum CTX1).

As demonstrated in the DXA Substudy (n = 441), denosumab increased BMD at all anatomic sites assessed at 36 months ($p < 0.0001$ for all). Increases in BMD were observed both in primarily trabecular bone sites and in primarily cortical bone sites, including the distal 1/3 radius (Table 2-2). Increases in BMD were noted at the 1 month time point for the lumbar spine ($p < 0.0001$), total hip ($p < 0.0001$), and trochanter ($p = 0.0002$).

Table 2-2. Summary of BMD Percent Change From Baseline and Difference Between Treatment Groups at Month 36 by Anatomic Site (DXA Substudy)

	Least Squares Mean (95% CI) for BMD Percent Change From Baseline to Month 36 [a]			
	Placebo	Denosumab	Difference	p-value [a]
Lumbar spine	0.2 (-0.5, 1.0)	9.4 (8.6, 10.1)	9.2 (8.2, 10.1)	<0.0001
Total hip	-1.1 (-1.7, -0.6)	4.8 (4.3, 5.3)	6.0 (5.2, 6.7)	<0.0001
Femoral neck	-0.9 (-1.6, -0.2)	3.9 (3.2, 4.6)	4.8 (3.9, 5.6)	<0.0001
Trochanter	-0.8 (-1.5, -0.1)	7.1 (6.5, 7.8)	7.9 (7.0, 8.9)	<0.0001
Distal 1/3 radius	-1.2 (-1.8, -0.7)	2.2 (1.7, 2.8)	3.5 (2.7, 4.2)	<0.0001

[a] Based on an ANCOVA model adjusting for treatment, baseline value, machine type, and baseline value-by-machine type interaction

HT_ Regulatory Writing Source: Tables 14-12.2.3, 14-12.3.3, 14-12.4.3, 14-12.5.3, and 14-12.6.3

Denosumab increased section modulus (a measure of resistance to bending loads) and decreased buckling ratio (a measure of susceptibility to axial compressive loads) at all 3 femur sites assessed by hip structural analysis (HSA) (femoral narrow neck, intertrochanter, and shaft). The effect of denosumab on these parameters was rapid, with increases observed starting at month 6 for the narrow neck and intertrochanter and starting at month 12 for the shaft.

QCT results were consistent with and supportive of HSA and DXA results. Denosumab, as compared with placebo at month 36, increased BMD (as assessed by QCT) of both trabecular and cortical bone at the trochanter, and of trabecular bone but not cortical bone at the femur. Denosumab increased total polar moment of inertia (a measure of resistance to torsion) at all 3 sites assessed by QCT (ultradistal, distal, and proximal radii). The effect of denosumab on this parameter was rapid, with increases observed starting at month 6 for the ultradistal radius and at month 12 for the distal and proximal radii.

Subjects who received denosumab had greater reductions from baseline in serum concentrations of bone resorption markers CTX1 and TRAP 5b at all time points assessed compared with subjects in the placebo group ($p < 0.0001$ for all, except day 1, hour 6 for TRAP 5b, $p = 0.0679$). As expected with an antiresorptive therapy, maximal decreases in BALP and P1NP, markers of bone formation, were observed later than those for the bone resorption markers in the denosumab group (month 6); reductions were sustained throughout the remainder of the treatment duration. iPTH was increased at month 1 in the denosumab group, likely as a compensatory response to modest, transient decreases in serum calcium, then returned to baseline levels. No differences were noted between treatment groups with respect to serum osteoprotegerin (OPG) levels.

Pharmacokinetics Results:
Mean and median serum denosumab concentrations at month 1 were similar to those observed at month 1 in previous denosumab studies in postmenopausal women. Mean and median trough serum denosumab concentrations and the proportion of subjects with quantifiable levels were similar from months 6 to 36. These results indicate that denosumab pharmacokinetics did not change with time.

Patient-reported Outcomes Results:
Overall, baseline health-related quality-of-life (HRQOL) values were similar to those of age-matched postmenopausal osteoporotic women, and no significant differences in the baseline HRQOL values were noted between treatment groups. Completion rates for HRQOL measures at month 36 were 83%, 82% and 83% for the Osteoporosis Assessment Questionnaire Short Version (OPAQ-SV), EuroQol-5 Dimensions (EQ-5D), and disability/back pain questionnaire, respectively. A statistically significant difference between treatment groups in HRQOL measures was not demonstrated, which is consistent with previously reported studies (Oglesby et al, 2003; Silverman et al, 2001). Incident fractures were shown to be associated with poor HRQOL. Compared to subjects without incident fractures, subjects with fractures reported significant declines in all OPAQ-SV dimensions and in EQ-5D health index scores and VAS scores, as well

as more days of back pain and of limited activity, hospitalization, and bed rest due to back pain. Analyses by fracture location showed that the greatest declines in OPAQ-SV dimensions of physical function and emotional status were observed in subjects with incident hip fractures, followed by subjects with vertebral fractures and subjects with non-vertebral non-hip fractures.

Safety Results:
A total of 7762 subjects (3886 who received denosumab, 3876 who received placebo only) received at least 1 dose of investigational product and were evaluable for safety. Adverse events were reported for 92.8% of subjects in the denosumab and 93.1% of subjects in the placebo group. The most frequent adverse events (> 10% in either group) were back pain (34.7% denosumab, 34.6% placebo), arthralgia (20.2%, 20.2%), hypertension (15.8%, 16.4%), nasopharyngitis (14.5%, 15.5%), pain in extremity (11.7%, 11.1%), and osteoarthritis (11.2%, 11.4%). Subject incidences of individual preferred terms were generally balanced between treatment groups. Adverse events considered by the investigator to be related to investigational product were reported for 12.0% of subjects in the denosumab group and 10.8% of subjects in the placebo group.

Serious adverse events were reported for 25.8% of subjects in the denosumab group and 25.1% of subjects in the placebo group; serious adverse events considered by the investigator to be related to treatment were reported for 1.1% and 0.7%, respectively. Seventy subjects (1.8%) in the denosumab group and 90 subjects (2.3%) in the placebo group died during the study. The most frequent cause of death was myocardial infarction (7 subjects [0.2%] denosumab, 6 subjects [0.2%] placebo). Fatal adverse events considered by the investigator to be related to investigational product were reported for 5 subjects (0.1%) in the denosumab group and 1 subject (< 0.1%) in the placebo group.

Subject incidences were similar between treatment groups for adverse events resulting in discontinuation of investigational product (4.9% denosumab, 5.2% placebo) and for adverse events resulting in withdrawal from study (2.4%, 2.1%).

Safety assessment categories prospectively identified to be ‘of interest’ for denosumab included hypocalcemia, cardiovascular adverse events, malignancies, infections, ONJ, hypersensitivity, and delayed fracture healing. Adverse events of hypocalcemia were reported for no subjects in the denosumab group and 3 subjects (0.1%) in the placebo group. Four subjects (0.1%) in each treatment group had albumin-adjusted calcium decreases of grade 2; no subjects in the denosumab group and 1 in the placebo group had a grade 3 decrease.

Subject incidences of positively adjudicated cardiovascular serious adverse events were similar overall between the treatment groups (4.8% denosumab, 4.6% placebo) and for predefined categories of these events. Changes from baseline in aortic calcification scores were similar between the treatment groups at all time points assessed.

Subject incidences of malignancies were balanced between the treatment groups (4.8% denosumab, 4.3% placebo); the most frequent malignancies were breast cancer (0.9%, 0.7%) and colon cancer (0.8%, 0.9%). Subject incidences of infections were balanced between treatment groups for overall adverse events of infection (52.9% denosumab, 54.4% placebo), serious adverse events of infection (4.1%, 3.4%), and serious adverse events of opportunistic infection (0.1% [3 subjects], 0.1% [4 subjects]). For individual preferred terms, certain infections reported as serious adverse events were numerically greater in the denosumab group; these events included erysipelas (0.2%, 0%) and cellulitis (0.2%, < 0.1%).

No subject in either treatment group had a positively adjudicated event of ONJ.

There was no evidence of an increased risk of hypersensitivity, drug hypersensitivity, or drug allergy reactions to denosumab. Furthermore, using a Standardized MedDRA Query (SMQ) narrow search, denosumab does not pose an increased risk for clinical consequences of hypersensitivity reactions.

The incidence of adverse events in the skin and subcutaneous tissues disorders system organ class was slightly higher in the denosumab group (14.8% vs 12%), which appeared to be due to more mild dermal events (eg, dermatitis and eczema).

Among subjects with nonvertebral fractures (303 in the denosumab group, 364 in the placebo group), 2 subjects in each treatment group experienced delayed healing, and 1 subject in the placebo group experienced nonunion of a fracture. In the fracture healing substudy, 1 subject in the denosumab group and 2 subjects in the placebo group had delayed radiographic healing of a distal radius fracture.

Consistent with previous studies (in which subjects received calcium and vitamin D supplementation, as in the present study), mild, transient decreases were observed at month 1 in the denosumab group for serum calcium (approximately 2%) and serum phosphorus (approximately 8%) that had no apparent clinical significance. Other than the expected decrease in alkaline phosphatase, no other consistent trends in serum chemistry or hematology parameters were noted. Denosumab did not have any clinically significant effect on vital signs monitored throughout the study.

In the Bone Biopsy Substudy, bone histologic parameters showed evidence of normal bone architecture, lamellar appearance, and mineralization. Evaluation of histomorphometric parameters showed changes consistent with decreased bone turnover. MicroCT analysis demonstrated a significant decrease in cortical porosity and an increase in cortical BMD in the denosumab group at 24 months. Denosumab did not impair matrix mineralization. Up to 35% of the bone biopsies showed either single tetracycline label or no label in cortical and/or trabecular bone surfaces; decreased bone turnover may have impeded uptake of tetracycline during the time of administration.

No subjects had neutralizing antibodies to denosumab. Twenty-four subjects (0.6%) in the denosumab group and 10 subjects (0.3%) in the placebo group developed anti-denosumab binding antibodies in postbaseline samples. There was no evidence of an effect of these antibodies on the subjects' safety or efficacy profiles.

Conclusions:

Denosumab, by selective inhibition of an essential mediator of bone resorption (RANKL), prevents vertebral, nonvertebral, and hip fractures in postmenopausal women with osteoporosis. Reductions in fracture risk due to denosumab were statistically significant, clinically meaningful, and consistent across subjects with a wide range of fracture risk and baseline characteristics. Denosumab's specific mechanism of action reduces bone turnover in a coupled and dynamic manner, results in clinically meaningful increases in BMD, and improves measures of bone strength. These skeletal benefits of denosumab were obtained with a safety profile similar to that of placebo. The results of this study demonstrate that denosumab, administered SC at a dose of 60 mg every 6 months, is effective and well tolerated for the treatment of postmenopausal osteoporosis.