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 RANK ligand (RANKL)

Title of Study: A Multicenter, Randomized, Double-blind, Placebo-controlled Study to Compare the Efficacy and Safety of Denosumab versus Placebo in Males with Low Bone Mineral Density (BMD)

Investigator(s) and Study Center(s): This was a multicenter study conducted at 27 study centers in Denmark, the United States, Belgium, France, Poland, Canada, and Sweden. Centers and principal investigators are listed in Appendix 4.

Publication(s): None at issue.

Study Period: First subject screened on 10 September 2009; last 12-month visit on 21 June 2011; the open-label phase of the study is ongoing

Development Phase: 3

Objectives:

Primary:

To evaluate the effect of denosumab 60 mg once every 6 months (Q6M) compared with placebo on lumbar spine BMD at 12 months in men with low BMD.

Secondary:

To evaluate the effects of denosumab in men with low BMD compared to placebo on:

- BMD at proximal femur (total hip, hip trochanter, femoral neck) and distal radius at 12 months
- Type-1 collagen C-telopeptide (CTX1) at day 15

Exploratory:

To evaluate the effects of denosumab in men with low BMD on:

- CTX1 at 6 and 12 months compared to placebo
- CTX1 change from baseline at 18 and 24 months
- BMD for all skeletal sites at 6 months compared to placebo
- BMD change from baseline for all skeletal sites at 24 months
- Bone histology and histomorphometry in a subset of subjects at 12 months

Methodology: This multicenter, randomized, double-blind, placebo-controlled study in men with low bone mass comprised 2 treatment periods: a 12-month double-blind phase during which approximately 232 subjects were planned for randomization (1:1) to receive single 60-mg SC administrations of denosumab or matching placebo Q6M (ie, 1 dose on day 1 and the second dose at month 6), and a 12-month open-label phase during which all enrolled subjects (independent of randomization) received 60-mg SC denosumab Q6M (ie, single doses at month 12 and month 18). Final study assessments will be conducted at month 24 (end-of-study [EOS] visit).

All potential subjects attended a screening visit within the 35 days prior to dosing on day 1 to establish eligibility; subjects who satisfied the eligibility criteria returned to the research facility for baseline (predose) procedures on day 1. Subjects were randomized to receive either denosumab or placebo on day 1 and at month 6. The randomization schedule was stratified by the minimum BMD T-score ($\leq$ -2.5 vs. > -2.5) at either the lumbar spine or femoral neck. At least 116 subjects with a T-score $\leq$ -2.5 were enrolled.

On each dosing day of the double-blind (day 1 and month 6) and open-label (months 12 and 18) periods, SC injections of investigational product were administered after all other study visit

procedures were completed. All subjects were to receive daily supplements of calcium (≥ 1000 mg elemental calcium) and vitamin D (≥ 800 IU) through month 24.

At scheduled time points through the EOS visit, subjects returned to the research facility on an outpatient basis for clinical procedures, which included dual-energy x-ray absorptiometry (DXA) scans of the spine, hip, and distal radius (for densitometer-specific BMD values); lateral spine x-ray (for assessment of incident vertebral fracture); and collection of blood samples for laboratory analyses (including serum CTX1). Safety was assessed by antidenosumab antibody analysis, adverse events monitoring, and by changes in laboratory parameters and vital signs results.

Substudy: In order to evaluate the effect of denosumab on bone histology and histomorphometry, approximately 20 subjects were enrolled at selected study sites to undergo a transiliac bone biopsy within 30 days prior to the month 12 visit. All subjects scheduled for the biopsy followed a double tetracycline/demeclocycline labeling procedure prior to undergoing the biopsy.

This report summarizes data from the 12-month double-blind phase. Results from the open-label phase will be reported separately.

Number of Subjects Planned: 232

Number of Subjects Enrolled: 242

Diagnosis and Main Criteria for Eligibility: Eligible subjects were ambulatory men between 30 and 85 years of age (inclusive). To be eligible for participation, subjects were required to have BMD values (g/cm^2) at the local site that corresponded to T-score ≤ -2.0 and ≥ -3.5 at the lumbar spine or femoral neck OR a T-score ≤ -1.0 and ≥ -3.5 at the lumbar spine or femoral neck in subjects with a history of major osteoporotic fracture.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Denosumab (manufacturing lot numbers: [redacted] and [redacted]) was provided as a sterile, clear, colorless to slightly yellow, preservative-free liquid in a pre-filled syringe (PFS) containing 60 mg denosumab per mL of [redacted] mM sodium acetate at pH [redacted], containing [redacted]% sorbitol in water for injection. Denosumab was provided in individual-dose boxes, each containing one 1-mL PFS. A single syringe was used for each SC dose; no special preparation was required prior to denosumab administration.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Matching placebo (manufacturing lot number: [redacted]) was provided in containers identical to that used for denosumab; the formulation was identical to denosumab with the exception of the protein content.

Duration of Treatment: The study duration was 2 years. Each subject received single SC doses of denosumab or placebo twice during the 12-month double-blind phase; during the 12-month open-label phase, each subject will receive single SC doses of denosumab at months 12 and 18.

Study Endpoints:

Primary: The primary endpoint was the percent change from baseline in lumbar spine BMD at 12 months.

Secondary: Secondary endpoints were percent change from baseline in BMD of the total hip, femoral neck, hip trochanter, and distal radius at month 12, and the percent change from baseline in CTX1 at day 15.

Exploratory: The exploratory endpoints were the percent change in BMD for all sites at 6 and 24 months; the percent change in CTX1 at 6, 12, 18, and 24 months; and bone histology and histomorphometry in a subset of subjects at 12 months.

Safety: The safety endpoints included adverse event incidence by system organ class and preferred term at months 12 and 24; changes from baseline in safety laboratory analytes (serum chemistry, hematology) at each visit and shifts between baseline and the worst on-study value; and changes in vital signs at each visit.

Statistical Methods: All binary endpoints were summarized using the number and percentage of subjects having the response of interest by treatment group. All ordinal endpoints were summarized using the number and percent of subjects in each category by treatment group. All continuous endpoints were summarized using descriptive statistics including mean, standard deviation, minimum, 25th percentile, median (50th percentile), 75th percentile, maximum, and number of nonmissing observations (n).

The primary analyses of efficacy endpoints were completed on the Primary Analysis Set, comprising all randomized subjects who had a nonmissing baseline and ≥ 1 nonmissing postbaseline evaluation at (or prior to) the time point under consideration. The primary inference was to test for a treatment difference in the percent change in lumbar spine BMD after 12 months of treatment. If statistical significance was declared for the primary endpoint, then further formal inferential testing for secondary endpoints was performed. The secondary inferences included tests for treatment differences in BMD at the total hip, femoral neck, hip trochanter, and distal radius after 12 months of treatment and CTX1 after 15 days of treatment. The Hochberg step-up procedure (Hochberg, 1988) was used to adjust for multiple testing for secondary endpoints at the level of 0.05.

Analysis of covariance (ANCOVA) models were used for the primary analysis of the primary and secondary BMD efficacy endpoints (treatment as the main effect and the minimum baseline BMD T-score [stratification factor] as covariate) with a last observation carried forward (LOCF) imputation. Percent change in CTX1 was analyzed using the van Elteren stratified rank test.

All adverse events were summarized by the actual treatment received. Treatment-emergent, treatment-related, serious, serious treatment-related, and fatal adverse events, as well as adverse events leading to IP discontinuation and/or study withdrawal were grouped by preferred term and system organ class according to the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Laboratory data were summarized descriptively by visit for the actual values and changes from baseline. Laboratory data also were summarized using shifts in recorded values from baseline to worst on-study value during the 12-month double-blind phase. Vital signs were summarized descriptively by visit for the recorded values and changes from baseline. Antidenosumab antibody results were listed for each subject and summarized.

Summary – Results:

Subject Disposition:

In total, 242 subjects were enrolled and randomized to receive either denosumab (n = 121) or placebo (n = 121) during the 12-month double-blind phase of the study. Two subjects (1 subject in each treatment group) were withdrawn prior to receiving investigational product due to violations of eligibility criteria. Of the 240 subjects who received ≥ 1 dose of investigational product (120 subjects in each treatment group), 13 subjects (9 denosumab-treated subjects; 4 placebo-treated subjects) discontinued investigational product within the first 12 months of the study; the remaining 227 (94%) subjects completed the study (111 denosumab-treated subjects [92%]; 116 placebo-treated subjects [97%]).

Baseline Demographics:

Sex: 100% men

Age (mean [SD]): 65 (9.8) years of age, overall (denosumab: 65 [10.5] years; placebo: 65 [9.1] years)

Ethnicity/Race: Denosumab: 121 (100%) white/Caucasian subjects. Placebo: 107 (88.4%) white/Caucasian, 10 (8.3%) Hispanic/Latino; 2 (1.7%) Asian; 1 (0.8%) black/African-American; 1 (0.8%) Native Hawaiian or Other Pacific Islander.

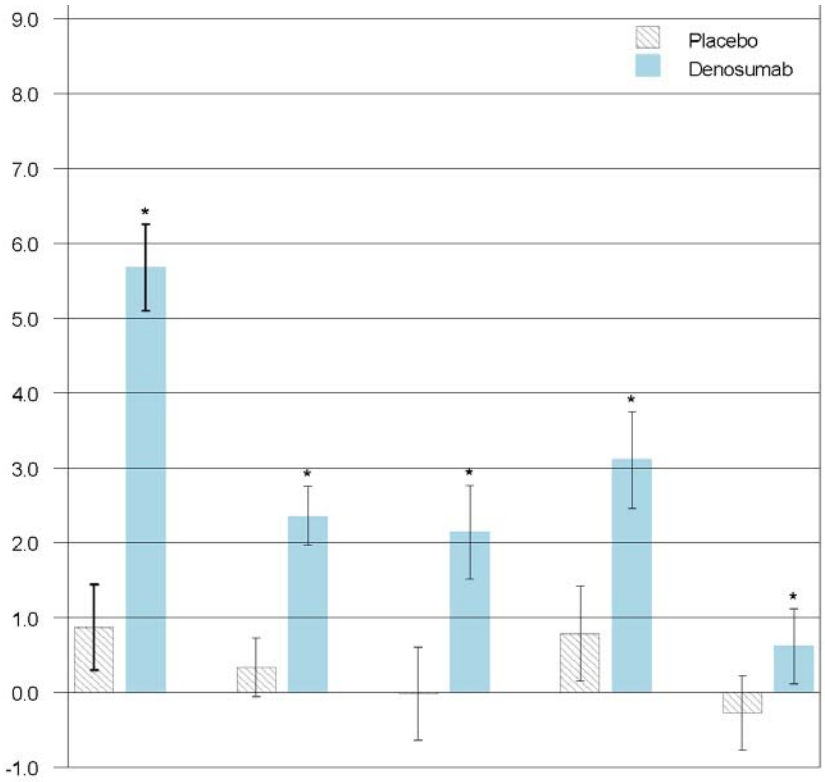
Efficacy Results:

Denosumab statistically significantly increased lumbar spine BMD at month 12. The mean difference in lumbar spine BMD between treatment groups was 4.8% ($p < 0.0001$; 95% CI: 4.0%, 5.6%).

Denosumab significantly increased BMD at all other skeletal sites measured, with mean differences compared with placebo of 2.0%, 2.2%, 2.3%, and 0.9% at total hip, femoral neck, trochanter, and distal radius, respectively.

Results of sensitivity analyses of the BMD efficacy endpoints were consistent with the primary analysis, demonstrating that the results of the primary analyses were robust. Results of subgroup analyses, including by age, geographic region, baseline serum CTX1, minimum baseline BMD T-score, baseline testosterone, and baseline 10-year major osteoporotic fracture risk (with BMD), demonstrated that denosumab increased lumbar spine BMD at the primary assessment time point compared with placebo in all subgroups.

Bone Mineral Density Percent Change From Baseline at Month 12 by Anatomical Site (Least Squares Means and 95% CIs From ANCOVA) (Primary Efficacy Analysis Set, LOCF) (20080098 First 12 Months Analysis)



Point estimates and nominal 95% confidence intervals are based on an ANCOVA model with treatment as main effect and level of baseline BMD T-score as covariate
* Adjusted p-value < 0.05.

Source: Figure 14-2.501

Denosumab also significantly decreased median serum CTX1 concentration, a marker of bone resorption, compared with placebo at day 15. Median percent changes from baseline in serum CTX1 concentration at day 15 were -45% in the denosumab group and -2% in the placebo group. The median decrease in CTX1 in the denosumab group of this study was smaller than those estimated in previous denosumab clinical studies. This is due to a higher lower limit of quantification (LLOQ) of 0.2 ng/mL defined by the central laboratory of this study ([redacted]; [redacted]) compared with a LLOQ of 0.05 ng/mL defined in previous denosumab studies (PKDM, Amgen; Thousand Oaks, CA). CTX1 values that were lower than the laboratory-defined LLOQ were imputed as the LLOQ in the analysis, and almost all denosumab-treated subjects had

CTX1 values below the LLOQ at day 15. The same serum CTX1 assay has been used in the denosumab clinical trial program (Serum Crosslaps ELISA [redacted]).

In order to make a comparable assessment to previous studies, raw data was obtained from [redacted] for subjects who had values below the LLOQ to recalculate median percent change. In a supplemental analysis using these raw data, median percent changes from baseline in serum CTX1 concentration at day 15 were -81% in the denosumab group and -7% in the placebo group, consistent with previous studies.

Bone Biopsy Substudy Results:

A total of 29 subjects (17 denosumab, 12 placebo) were enrolled in the bone biopsy substudy. Overall, bone biopsy results showed normal bone histology. After 12 months of denosumab treatment, there was evidence of normal lamellar bone, normal mineralization, and normal osteoid in both treatment groups. There was no evidence of osteomalacia, marrow fibrosis, woven bone, or abnormal osteoid. Denosumab did not impair matrix mineralization.

In accordance with denosumab's mechanism of action, evaluation of histomorphometric parameters showed changes consistent with decreased bone remodeling in subjects treated with denosumab compared with placebo. Decreased bone remodeling led to reductions in tetracycline uptake and therefore labeling. As a consequence, a reduction in single and double labels was observed in a number of biopsies in the denosumab group. Evaluation of dynamic bone histomorphometry in the subset of samples in which double or single labels was present showed changes consistent with decreased remodeling in subjects treated with denosumab.

Antibody Results:

All subjects treated with denosumab (n = 120) for up to 12 months were negative for antidenosumab binding antibodies at all tested time points.

Safety Results:

A total of 240 subjects received ≥ 1 dose of denosumab (n = 120) or placebo (n = 120), constituting the Safety Analysis Set.

Overall, the subject incidences of adverse events, serious adverse events, and fatal adverse events were similar between treatment groups. A total of 86 subjects (72%) in the denosumab group and 84 subjects (70%) in the placebo group experienced ≥ 1 adverse event during the first 12 months of the study. The most frequently experienced adverse events (≥ 5% in either treatment group [denosumab, placebo]) were back pain (8%, 7%), arthralgia (7%, 6%), nasopharyngitis (7%, 6%), and constipation (0, 6%). Most of the adverse events in both groups were categorized as being of mild-to-moderate severity. The incidence of treatment-related adverse events was 1.7% in the denosumab group and 5.0% in the placebo group.

Serious adverse events were reported for 9.2% of subjects in the denosumab group and 8.3% of subjects in the placebo group. The only serious adverse events reported in more than 1 subject per treatment group were prostate cancer, reported for 3 subjects (2.5%) in the denosumab group (with 2 of 3 cases being likely present at baseline based on medical history) and no subjects in the placebo group, and arterial thrombosis limb, reported for 2 subjects (1.7%) in the denosumab group and no subjects in the placebo group. All other serious adverse events were reported in a single subject per treatment group (< 1%).

Two deaths were reported: myocardial infarction in a subject receiving denosumab and basilar artery thrombosis in a subject receiving placebo.

In the denosumab and placebo groups, 3 subjects (2.5%) and 0 subjects, respectively, had adverse events leading to investigational product discontinuation. None of the adverse events leading to investigational product discontinuation were considered related to investigational product administration.

Hypocalcemia, ONJ, fracture healing complications, and atypical femur fractures were not reported during the first 12 months of the double-blind treatment phase, and no skin infections

were reported in the denosumab group. Rates of infections, acute pancreatitis, vascular disorders, and adverse events potentially associated with hypersensitivity were similar between treatment groups.

Malignancy adverse events were reported for 4 subjects (3.3%) in the denosumab group and no subjects in the placebo group. The events consisted of prostate cancer in 3 subjects (2.5%) and basal cell carcinoma in 1 subject (0.8%). None of the events was considered by the investigator to be related to the investigational product. In 2 of the 3 subjects with prostate cancer, the cancers were likely present at baseline, based on subject medical histories.

Adverse events in the MedDRA system organ class of cardiac disorders were reported for 8 subjects (6.7%) in the denosumab group and 3 subjects (2.5%) in the placebo group. Four subjects in the denosumab group reported adverse events coded to the preferred term angina pectoris. Upon further clinical review, 2 of the cases of angina pectoris were identified as angina tonsillitis that had been incorrectly coded to angina pectoris due to differences in verbatim reporting across geographic regions. The subjects who experienced the 2 remaining cases of angina pectoris had a history of [redacted]. The incidence of serious cardiac adverse events was similar between treatment groups. The incidence of vascular disorders adverse events and serious adverse events was also similar between treatment groups.

Eczema was reported for 2 subjects (1.7%) in the denosumab group and no subjects in the placebo group. The events were mild or moderate in severity and resolved within 7 weeks of onset; both subjects continued denosumab administration without evidence of recurrence.

Consistent with previous studies, denosumab administration was associated with transient decreases in serum calcium. At day 15, median change from baseline in albumin-adjusted serum calcium was -1.1% in the denosumab group and 0.0 % in the placebo group. No decrease in serum calcium was observed at months 6 and 12. No subjects had Common Terminology Criteria for Adverse Effects (CTCAE) grade 3 or 4 low serum calcium values during the 12-month double-blind treatment phase. Denosumab administration also was associated with decreases in serum phosphorus. Median change from baseline in phosphorus was (denosumab, placebo) -6.0%, 2.9% at day 15; -4.7%, 0.0% at month 6; and 0.0%, 0.0% at month 12. No subjects had CTCAE grade 3 or 4 low serum phosphorus values during the 12-month double-blind treatment phase. Denosumab administration was not associated with changes in other serum chemistry or hematology parameters or clinically significant changes in vital signs.

Conclusion:

Denosumab 60 mg Q6M effectively increased BMD in men with low BMD during the 12-month study period. The safety profile observed in this study was consistent with that observed in previous studies. No new safety risks associated with denosumab treatment were identified.

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 RANK ligand (RANKL)

Title of Study: A Multicenter, Randomized, Double-blind, Placebo Controlled Study to Compare the Efficacy and Safety of Denosumab versus Placebo in Males with Low Bone Mineral Density

Investigators and Study Centers: This was a multicenter study conducted at 27 study centers in Denmark, the United States, Belgium, France, Poland, Canada, and Sweden. Centers and principal investigators are listed in Appendix 4.

Publications: Orwoll E, Teglbjrg CS, Langdahl BL, et al. A randomized, placebo-controlled study of the effects of denosumab for the treatment of men with low bone mineral density. *J Clin Endocrinol Metab.* 2012;97:3161-3169.

Study Period:

First subject screened on 10 September 2009; first subject enrolled on 14 October 2009

Last subject completed month 12 on 21 June 2011; last subject completed month 24 on 23 May 2012

Development Phase: 3

Objectives:

Primary:

To evaluate the effect of denosumab 60 mg once every 6 months (Q6M) compared with placebo on lumbar spine bone mineral density (BMD) at month 12 in men with low BMD

Secondary:

To evaluate the effects of denosumab in men with low BMD compared with placebo on:

- BMD at proximal femur (total hip, hip trochanter, femoral neck) and distal radius at month 12
- Serum type-1 collagen C-telopeptide (CTX1) at day 15

Exploratory:

To evaluate the effects of denosumab in men with low BMD on:

- CTX1 at months 6 and 12 compared with placebo
- CTX1 change from baseline at months 18 and 24
- BMD for all skeletal sites at month 6 compared with placebo
- BMD change from baseline for all skeletal sites at month 24
- Bone histology and histomorphometry in a subset of subjects at month 12

Methodology:

This multicenter, randomized, double-blind, placebo-controlled study in men with low bone mass comprised 2 treatment periods: a 12-month double-blind phase during which approximately 232 subjects were planned for randomization (1:1) to receive single 60-mg subcutaneous (SC) administrations of denosumab or matching placebo Q6M (ie, 1 dose on day 1 and the second dose at month 6), and a 12-month open-label phase during which all enrolled subjects (independent of randomization) received 60-mg SC denosumab Q6M (ie, single doses at

month 12 and month 18). Final study assessments were conducted at month 24 (end-of-study [EOS] visit).

All potential subjects attended a screening visit within the 35 days prior to dosing on day 1 to establish eligibility; subjects who satisfied the eligibility criteria returned to the research facility for baseline (predose) procedures on day 1. Subjects were randomized to receive either denosumab or placebo on day 1 and at month 6. The randomization schedule was stratified by the minimum BMD T-score (≤ -2.5 or > -2.5) at either the lumbar spine or femoral neck, whichever was lower. At least 116 subjects with a minimum BMD T-score ≤ -2.5 were to be enrolled.

On each dosing day of the double-blind (day 1 and month 6) and open-label (months 12 and 18) periods, SC injections of investigational product were administered after all other study visit procedures were completed. All subjects received daily supplements of calcium (≥ 1000 mg elemental calcium) and vitamin D (≥ 800 IU) through month 24.

At scheduled time points through to the EOS visit, subjects returned to the research facility on an outpatient basis for clinical procedures, which included dual-energy x-ray absorptiometry (DXA) scans of the spine, hip, and distal radius (for densitometer-specific BMD values); lateral spine x-ray (for assessment of incident vertebral fracture); and collection of blood samples for laboratory analyses (including CTX1). A substudy in approximately 20 subjects evaluated the effect of denosumab on bone histology and histomorphometry at month 12. Safety was assessed by anti-denosumab antibody analysis, by adverse events monitoring, and by changes in laboratory parameters and vital signs results.

This clinical study report (CSR) reflects the final analysis performed for the 24-month study period and focuses on the 12-month open-label phase (months 12 to 24), summarized by the placebo/denosumab (crossover) group and the denosumab/denosumab (long-term) group. The analysis results of the 12-month double-blind treatment phase, including the bone histology and histomorphometry substudy results, have been previously presented in the Month 12 CSR (dated 01 November 2011) and are not re-presented in the present report. Briefly, the double-blind-phase results demonstrated that denosumab 60 mg Q6M effectively increased BMD in men with low BMD during the 12-month study period. The safety profile observed was consistent with that observed in previous studies. No new safety risks associated with denosumab treatment were identified.

Number of Subjects Planned: 232

Number of Subjects Enrolled: 242

Diagnosis and Main Criteria for Eligibility: Eligible subjects were ambulatory men between 30 and 85 years of age (inclusive). To be eligible for participation, subjects were required to have BMD values (g/cm^2) at the local facility that corresponded to T-score ≤ -2.0 and ≥ -3.5 at the lumbar spine or femoral neck OR a T-score ≤ -1.0 and ≥ -3.5 at the lumbar spine or femoral neck in subjects with a history of major osteoporotic fracture.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Denosumab (manufacturing batch numbers: [redacted], [redacted], and [redacted]) was provided as a sterile, clear, colorless to slightly yellow, preservative-free liquid in a pre-filled syringe (PFS) containing 60 mg denosumab per mL of [redacted] mM sodium acetate at pH [redacted], [redacted]% sorbitol in water for injection. Denosumab was provided in individual-dose boxes, each containing one 1-mL PFS. A single syringe was used for each SC dose; no special preparation was required prior to denosumab administration.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: No reference therapy was used in the open-label phase of the study.

Duration of Treatment: The study duration was 2 years. Each subject received single SC doses of denosumab or placebo twice during the 12-month double-blind phase; during the 12-month open-label phase, each subject received single SC doses of denosumab at months 12 and 18.

Study Endpoints:

Primary: The primary endpoint was percent change from baseline in lumbar spine BMD at month 12.

Secondary: Secondary endpoints were percent change from baseline in BMD of the total hip, femoral neck, hip trochanter, and distal radius at month 12, and percent change from baseline in CTX1 at day 15.

Exploratory: Exploratory endpoints were percent change in BMD of the lumbar spine, total hip, femoral neck, hip trochanter, and distal radius at months 6 and 24; percent change from baseline in CTX1 at months 6, 12, 18, and 24; and bone histology and histomorphometry in a subset of subjects at month 12.

Safety: The safety endpoints included adverse event incidence by system organ class and preferred term at months 12 and 24; changes from baseline in safety laboratory analytes (serum chemistry, hematology) at each visit, and shifts between baseline and the worst on-study value; and changes in vital signs at each visit.

(The analyses of the primary and secondary endpoints were reported in the Month 12 CSR dated 01 November 01 2011.)

Statistical Methods:

All continuous endpoints were summarized using descriptive statistics including mean, standard deviation (SD), minimum, 25th percentile, median (50th percentile), 75th percentile, maximum, and number of nonmissing observations. All binary endpoints were summarized by treatment group using the number and percentage of subjects having the response of interest. All ordinal endpoints were summarized using the number and percent of subjects in each category by treatment group.

The efficacy analysis set comprised all subjects who entered the open-label phase. Observed data were used for the efficacy analyses including subjects who had a nonmissing study baseline and a nonmissing evaluation at the time point under consideration. The means and 95% confidence intervals (CIs) of percent changes from baseline in BMD were estimated at months 18 and 24 by ANCOVA model with treatment as main effect and minimum baseline BMD T-score (stratification factor) as covariate. The percent changes from baseline in CTX1 concentrations at each visit were summarized by median and interquartile.

Adverse events in the open-label phase were summarized by treatment group (long-term, crossover). Treatment-emergent, treatment-related, serious, serious treatment-related, and fatal adverse events, as well as adverse events leading to investigational product discontinuation and/or study discontinuation were summarized by preferred term and system organ class according to the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Laboratory data were summarized descriptively by visit for the actual values and changes from baseline. Laboratory data also were summarized using shifts in recorded values from baseline to worst on-study value. Vital signs were summarized descriptively by visit for the recorded values and changes from baseline. Anti-denosumab antibody results were listed for each subject and summarized.

Summary – Results:

Subject Disposition:

In total, 242 subjects were initially enrolled and randomized to receive either placebo (N = 121) or denosumab (N = 121) during the 12-month double-blind phase of the study. Two-hundred twenty-eight subjects (228/242 = 94%) completed the double-blind phase and entered the open-label phase, 1 of whom (crossover) never received denosumab in this phase but remained on study and completed study.

Of the 228 subjects who entered the open-label phase, 96% (219/228) (105/111 [95%] long-term, 114/117 [97%] crossover) completed this phase. For the overall study, of the 242 initially

randomized subjects, 90.5% (219/242) (105/121 [87%] denosumab/long-term, 114/121 [94%] placebo/crossover) completed 24 months of study participation.

Baseline Demographics (for subjects who entered the open-label phase; N = 111 long-term, 117 crossover):

Sex: 100% men

Age (mean [SD]): 65.0 (9.7) years of age, overall (long-term, 65.0 [10.2] years; crossover, 65.1 [9.2] years)

Ethnicity/Race: Long-term – 111 (100%) white/Caucasian subjects
Crossover – 104 (88.9%) white/Caucasian, 9 (7.7%) Hispanic/Latino; 2 (1.7%) Asian; 1 (0.9%) black/African-American; 1 (0.9%) Native Hawaiian or Other Pacific Islander

Efficacy Results:

In the open-label phase, for the efficacy analysis set of subjects who entered the open-label phase [N = 111 long-term, 117 crossover]), BMD at the lumbar spine, total hip, femoral neck, hip trochanter, and distal radius continued to increase from month 12 to month 24 in the long-term group. In this group, mean percent increases from baseline were 8.0%, 3.4%, 3.4%, 4.6%, and 0.7% for lumbar spine, total hip, femoral neck, hip trochanter, and distal radius, respectively, at month 24 compared with 5.8%, 2.3%, 2.2%, 3.2%, and 0.6% at month 12.

In the crossover group, increases from month 12 to month 24 were similar to those observed in the long-term group from baseline to month 12 during the initial denosumab treatment. In this group, mean percent changes from baseline were 5.7%, 2.0%, 1.8%, 2.7%, and 0.6% for lumbar spine, total hip, femoral neck, hip trochanter, and distal radius, respectively, at month 24 compared with 0.8%, 0.3%, -0.1%, 0.8%, and -0.3% at month 12.

In the open-label phase, the decrease in median percent change from baseline in CTX1 observed through month 12 (-60%) in the denosumab/long-term group was maintained through months 18 and 24 (-57% and -50%, respectively). Similar decreases were observed at month 18 and month 24 (-68% and -59%, respectively) in the placebo/crossover group after the first administration of denosumab for this group at month 12.

Antibody Results: All subjects tested during the overall 24 months of the study (n = 239 [119 denosumab/long-term, 120 placeobo/crossover]) were negative for anti-denosumab binding antibodies at all time points at which testing was done.

Safety Results:

A total of 227 subjects received ≥ 1 dose of denosumab in the long-term group (N = 111) or in the crossover group (N = 116) during the open-label phase, constituting the safety analysis set for that phase.

During the open-label phase, subject incidences of overall adverse events were 63% in the long-term group and 52% in the crossover group. System organ classes with the highest subject incidences of adverse events were Musculoskeletal and Connective Tissue Disorders (22% long-term, 12% crossover) and Infections and Infestations (21%, 20%). By preferred term, the most frequent adverse events (subject incidence ≥ 5% in either treatment group) were back pain (5.4% long-term, 2.6% crossover), arthralgia (6.3%, 4.3%), and nasopharyngitis (4.5%, 6.0%). Most of the adverse events in both groups were reported as mild or moderate in severity.

Subject incidences of serious adverse events were 8.1% in the long-term group and 4.3% in the crossover group. By preferred term, no serious adverse events were reported for more than 1 subject; the system organ class with the highest subject incidences of serious adverse events was Infections and Infestations: 5/111 subjects (4.5%) in the long-term group and 1/116 subjects (0.9%) in the crossover group. One death was reported during the open-label phase as endocarditis (long-term group).

There were no reports of hypocalcemia, osteonecrosis of the jaw (ONJ), fracture healing complications, or atypical femoral fractures during the open-label phase. Rates of adverse

events potentially associated with hypersensitivity, infections, skin infections, cardiovascular disorders, eczema, and acute pancreatitis were low and did not appear to increase over time. Malignancy adverse events were reported for 1/111 subjects (0.9%) in the long-term group (gastric cancer plus metastases to the lung plus rectal neoplasm [benign]) and 2/116 subjects (1.7%) in the crossover group (bladder cancer; and malignant lung neoplasm plus metastases to central nervous system).

Median serum phosphorus decreased in the crossover group of subjects who transitioned from placebo to denosumab during the open-label phase. Median serum calcium at months 12 and 24 was similar to that at baseline for both the long-term group and the crossover group. Denosumab administration was not associated with changes in other serum chemistry or hematology parameters or clinically significant changes in vital signs.

Conclusion:

Denosumab 60 mg Q6M continued to increase BMD during the 12-month open-label phase in men with low BMD receiving long-term treatment. In addition, subjects who transitioned from placebo in the double-blind phase to denosumab 60 mg Q6M in the open-label phase experienced gains in BMD that were consistent with those experienced by subjects who received denosumab during the double-blind phase. Safety results in the open-label phase indicated that denosumab was well tolerated. No new safety risks associated with denosumab treatment were identified.