2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: Denosumab (AMG 162)

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

Title of Study: A Randomized, Double-Blind, Placebo-controlled Study to Evaluate AMG 162 in the Treatment of Bone Loss in Subjects Undergoing Androgen-Deprivation Therapy for Nonmetastatic Prostate Cancer

Investigator(s) and Study Center(s): This study was conducted at 156 sites in the United States, Canada, Mexico, and, Europe. Study centers and principal investigators are listed in Appendix 4.

Publication(s): None as of the date of this report

Study Period: 02 August 2004 (first subject enrolled) to 16 May 2008 (last subject completed month-36 assessment)

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 human RANKL and neutralizes its activity resulting in an inhibition of osteoclast formation, function, and survival. Previous studies, including one in women with breast cancer treated with aromatase inhibitor therapy, have demonstrated that denosumab decreases markers of bone resorption and bone formation and increases bone mineral density (BMD).

The primary objective of this study was to determine the treatment effect of denosumab compared with placebo on lumbar spine BMD at month 24 in men with nonmetastatic prostate cancer undergoing androgen deprivation therapy (ADT).

The secondary objectives were to determine the treatment effect of denosumab compared with placebo on percentage change of femoral neck BMD and total hip BMD from baseline to month 24; percentage change of lumbar spine BMD, femoral neck BMD, and total hip BMD from baseline to month 36; subject incidence of any fracture (ie, osteoporotic fracture at any skeletal site including vertebral fractures, but excluding skull, facial, mandible, metacarpus, finger phalanges, and toe phalanges) and subject incidence of new vertebral fracture over the 36-month treatment period; time to first clinical fracture over the 36-month treatment period; and subject incidence of any fracture over the 24-month treatment period. Other secondary objectives included assessment of the safety and pharmacokinetics of denosumab over the 36-month treatment period.

Exploratory objectives are detailed in Section 6.3.

Methodology: This was an international, multicenter, randomized, double-blind, placebo-controlled study in subjects with nonmetastatic prostate cancer who were undergoing ADT. Subjects were randomized (1:1) to receive either placebo or denosumab 60 mg subcutaneously (SC) once every 6 months for a total of 6 doses over the 36-month treatment period. Randomization was stratified by age group (< 70 years vs. ≥ 70 years) and duration of ADT with gonadotropin-releasing hormone (GnRH) agonists or orchiectomy at study entry

(≤ 6 months vs. > 6 months). All subjects received daily supplemental calcium (≥ 1 g) and were instructed to take vitamin D (≥ 400 IU). Bone mineral density assessments by dual x-ray absorptiometry (DXA) for the lumbar spine, total hip, femoral neck, and trochanter were obtained in all subjects, and BMD of the total body and 1/3 distal radius performed in a subset of subjects (N = 309). Throughout the study, a blinded central image reader identified or confirmed all vertebral fractures, and confirmed all nonvertebral fractures. An external Data Monitoring Committee monitored subject safety on an ongoing basis for the duration of the 36-month treatment period.

Upon completion of the 36-month treatment period, subjects were continued on study for 24 months during which no investigational product was administered, or were offered enrollment in a 2-year extension study (20080537). Results from the 36-month treatment period are included in this report; results from the 24-month safety follow-up period and the extension study will be reported separately.

Number of Subjects Planned: 1226 subjects (613 subjects in each treatment group)

Number of Subjects Enrolled: A total of 1468 subjects were enrolled and randomized to receive denosumab (734 [50%]) or placebo (734 [50%]).

Sex: 100% men

Age: Mean (SD): 75.4 (7.1) years

Ethnicity (Race): 83.4% white, 10.8% Hispanic, 4.6% black, 0.5% Asian, 0.3% Japanese, 0.1% American Indian or Alaska Native, 0.2% other

Diagnosis and Main Criteria for Eligibility: Eligible subjects met the following criteria: men ≥ 70 years of age with histologically confirmed prostate cancer, or men < 70 years of age with histologically confirmed prostate cancer and a history of osteoporotic fracture or BMD T-score at the lumbar spine, total hip, or femoral neck < -1.0 (using the normative male database); BMD T-score at the lumbar spine, total hip or femoral neck not < -4.0; have undergone bilateral orchiectomy or initiated ADT with GnRH agonists and are expected to continue on with ADT for at least 12 months; Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; no distant metastases; no evidence of current unstable systemic disease, organic or psychiatric disorder, or inadequate organ function that could have interfered with completion of the study or interpretation of results; and no recent exposure to bisphosphonates or other medications known to influence bone metabolism.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Denosumab was administered subcutaneously every 6 months at a dose of 60 mg and was provided as a sterile, clear, colorless, preservative-free, 60 mg/mL liquid solution in glass vials. The manufacturing batch numbers used during this study were [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted].

Duration of Treatment: The 60-month study includes a 36-month treatment period (with last dose administered at month 30) and a 24-month safety follow-up period.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Placebo was administered subcutaneously every 6 months and was provided as a sterile, clear, colorless, preservative-free liquid solution in glass vials. The appearance and formulation of the placebo was identical to denosumab, with the exception of the active protein ingredient. The manufacturing batch numbers used during this study were [redacted], [redacted], and [redacted].

Study Endpoints

Endpoints are described per the Statistical Analysis Plan (SAP; Appendix 2), which also provides more detailed information on the safety endpoints.

Primary

The primary endpoint was the percentage change in lumbar spine BMD from baseline to month 24.

Secondary

Secondary efficacy endpoints were the following:

- percentage change in femoral neck BMD and total hip BMD from baseline to month 24
- percentage change in lumbar spine BMD, femoral neck BMD, and total hip BMD from baseline to month 36
- subject incidence of any fracture (ie, osteoporotic fracture at any skeletal site, including vertebral, but excluding skull, facial, mandible, metacarpus, finger phalanges, and toe phalanges), and subject incidence of new vertebral fracture over the 36-month treatment period
- time to first clinical fracture over the 36-month treatment period
- subject incidence of any fracture over the 24-month treatment period

Safety

- subject incidence of adverse events by system organ class and preferred term (including all adverse events; treatment-related adverse events; Common Terminology Criteria for Adverse Events (CTCAE) grade 3, 4, and 5 adverse events; CTCAE grade 3, 4, and 5 treatment-related adverse events; adverse events leading to investigational product discontinuation; adverse events leading to study discontinuation; treatment-related adverse events leading to investigational product discontinuation; treatment-related adverse events leading to study discontinuation; serious adverse events; treatment-related serious adverse events; fatal adverse events; events of interest; and time to first cardiovascular event endpoint based on adjudicated positive cardiovascular events)
- recorded values and changes from baseline for serum chemistry, hematology, and other laboratory (including iPTH, 25-hydroxyvitamin D, free testosterone, and total testosterone) values
- recorded values and changes from baseline in vital signs, height, weight, and BMI
- subject incidence of anti-denosumab antibodies

Pharmacokinetics

- serum denosumab levels at baseline and months 1, 3, 6, 12, 15, 18, 24, 30, and 36

Exploratory

Exploratory endpoints are described in Section 7.10.3.1.

Statistical Methods:

The primary and secondary analyses included data from the 36-month treatment period and were performed when all subjects had completed month 36 assessments. Results from the 24-month safety follow-up period, when available, will be analyzed and reported separately.

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 (denoted as "n"). Median and other selected percentiles were substituted for mean and SD for parameters exhibiting a lack of normality (continuous). Frequencies and percentages were presented for categorical variables.

Efficacy

The statistical inferences of the treatment effects on secondary efficacy endpoints were only made if the treatment effect on the primary efficacy endpoint was found to be statistically significant in favor of denosumab over placebo at the final analysis. If the primary null hypothesis was rejected, the null hypotheses for the secondary endpoints were tested in a stepwise fashion over 5 steps at a significance level of 0.05. No further testing was conducted if any 1 of hypotheses was not rejected at a previous step. The stepwise testing procedure is described in more detail in the SAP (Appendix 2). Adjusted p-values, corresponding to this multiplicity adjustment procedure, were provided for all primary and secondary endpoints.

Analysis of the continuous primary and secondary BMD endpoints employed an analysis of covariance (ANCOVA) model using last observation value carried forward (LOCF) imputation with treatment group, baseline BMD value, machine type (Lunar vs. Hologic), the interaction of baseline BMD value and machine type, age group (< 70 versus ≥ 70 year old), and duration of ADT (≤ 6 versus > 6 months) as covariates.

Efficacy conclusions based on the primary endpoint were made using the least-squares mean estimate for the treatment difference (denosumab – placebo) and its 2-sided 95% confidence interval (CI) at month 24. Efficacy conclusions on secondary BMD endpoints were made similarly.

The subject incidence of fracture endpoints, including any fracture and new vertebral fractures, were analyzed using a logistic regression model with stratification variables and treatment group as covariates. The treatment effect was measured using the estimate of the odds ratio of denosumab compared with placebo and its corresponding 2-sided 95% CI; the p-values were based on the score test. In addition, the point estimates of absolute risk difference (difference in proportion, placebo – denosumab) and risk ratio (ratio of proportions, denosumab/placebo) and their corresponding 95% CI were calculated using the Mantel-Haenszel method, adjusting for stratification variables. The endpoint of time to first clinical fracture was analyzed using a stratified Cox proportional hazards model that included treatment group as the independent variable and was stratified by the stratification variables. The hazard ratio and its corresponding confidence interval and p-value of the score test from the Cox proportional hazards model for denosumab compared with placebo were reported.

Percent changes in bone turnover markers were analyzed for all randomized subjects who had a value at the time point evaluated and employed a non-parametric methodology; treatment groups were compared using the van Elteren rank test stratified by the stratification variables.

Analysis of patient-reported outcomes employed a likelihood-based mixed effects model repeated measures approach, with treatment group, stratification variables, baseline patient-reported outcome value, visit, and visit-by-treatment interaction included as fixed effects in the model with an unstructured within-subject variance and covariance matrix.

Safety endpoints were analyzed for all randomized subjects who received ≥ 1 dose of investigational product; subjects were analyzed according to actual treatment received. The subject incidence of each adverse event was tabulated by system organ class and preferred term. Time to first adjudicated positive cardiovascular serious adverse event was analyzed for the following categories: all cardiovascular events, acute coronary syndrome, congestive heart failure, stroke/ transient ischemic attack, arrhythmia, other vascular disorder, and cardiovascular death. In addition, the subject incidence of adjudicated positive cases of osteonecrosis of the jaw (ONJ) was summarized. Clinical laboratory parameters were summarized using descriptive statistics and/or shift tables between baseline and the worst on-study value. Vital signs, weight, and height were summarized using descriptive statistics. The percentage of subjects developing anti-denosumab antibodies was tabulated.

Analysis of overall survival through 36 months employed a Cox proportional hazards model including treatment group, baseline cardiovascular risk level, baseline PSA level, and prostate cancer recurrence risk as the independent variables, and stratified by the stratification variables. Differences in the Kaplan-Meier event rate between the denosumab and placebo groups with corresponding 95% CI were calculated using the inverse variance-weighted method to adjust the stratification variables.

Summary of Results:

Subject Disposition:

A total of 1468 subjects were randomized in this study (734 randomized to denosumab, 734 randomized to placebo). Randomization was stratified by age group and duration of ADT at study entry; the majority of subjects (63%) (460 denosumab, 460 placebo) were in the stratum of subjects ≥ 70 years of age who had received > 6 months of ADT. Of the 1468 enrolled subjects, 1456 subjects (726 denosumab, 730 placebo) received at least 1 dose of investigational product. Sixty-four percent of subjects in the denosumab group and 61% of subjects in the placebo group completed the 36-month treatment period.

Efficacy Results:

The primary efficacy endpoint and all secondary BMD-associated efficacy endpoints were met with statistical significance. Treatment with denosumab statistically significantly increased BMD relative to placebo, as assessed by DXA, at the lumbar spine, total hip, and femoral neck at month 24 and month 36 (adjusted $p < 0.0001$) (Table 2-1). The least squares mean change in lumbar spine BMD at month 24 (the primary endpoint) was 5.6% in the denosumab group compared with -1.0% in the placebo group, a statistically and clinically significant difference of 6.7% (95% CI: 6.2, 7.1) (adjusted $p < 0.0001$). Results of sensitivity and subgroup analyses confirmed the robustness of the results from the primary analyses. [redacted].

Significant increases in BMD were observed both in predominantly trabecular (eg, lumbar spine) and predominantly cortical (eg, 1/3 distal radius) bone sites. The effect of treatment with denosumab was rapid (significant differences between treatment groups were seen as early as month 1) and sustained throughout the 36-month treatment period; mean percentage changes from baseline in BMD at all anatomic sites were greater in the denosumab group than in the placebo group at each postbaseline assessment.

Denosumab preserved lumbar spine BMD (ie, > 0% change from baseline) in 90%, 93% and 92% of subjects at months 12, 24 and 36, respectively. Moreover 63%, 75%, and 78% of subjects who received denosumab had increases of > 3% from baseline in BMD of the lumbar spine at months 12, 24 and 36 respectively. Similar results were observed at the other anatomic sites.

Denosumab significantly reduced the subject incidence of new vertebral fracture through month 36 by 62% (relative risk, 0.38; 95% CI, 0.19 to 0.78) (adjusted p = 0.0125). The subject incidence of new vertebral fracture through 36 months was 1.5% (10/679) in the denosumab group and 3.9% (26/673) in the placebo group. This difference was apparent in the first year, and was also observed in the second year. Consistent with the results for new vertebral fracture, denosumab also reduced the incidence of new and worsening vertebral fractures by 58% (relative risk, 0.42; 95% CI, 0.21 to 0.84) (p = 0.0114). The denosumab group also had a lower incidence of any fracture relative to placebo (5.2% denosumab, 7.2% placebo; 28% relative risk reduction) at 36 months, primarily driven by the difference in new vertebral fracture, although the difference between groups was not statistically significant (p = 0.1048).

Denosumab treatment resulted in marked, rapid, and sustained decreases in serum concentrations of type 1 C-telopeptide (CTX1), procollagen type I N-terminal peptide (P1NP) and tartrate-resistant alkaline phosphatase 5b (TRAP 5b) relative to placebo ($p < 0.0001$ at all time points).

Table 2-1. Summary of Treatment Comparisons for Primary and Secondary Efficacy Endpoints

	Placebo (N=734) n	Denosumab 60 mg Q6M (N=734) n	Estimate	95% CI	p-value	Adjusted p-value[d]
BMD Endpoints						
Lumbar spine BMD Percent change from baseline at Month 24[a]	716	714	6.7	(6.2, 7.1)	<.0001	<.0001
Femoral neck BMD Percent change from baseline at Month 24[a]	706	701	3.9	(3.5, 4.4)	<.0001	<.0001
Total hip BMD Percent change from baseline at Month 24[a]	706	701	4.8	(4.4, 5.1)	<.0001	<.0001
Lumbar spine BMD Percent change from baseline at Month 36[a]	716	714	7.9	(7.4, 8.4)	<.0001	<.0001
Femoral neck BMD Percent change from baseline at Month 36[a]	706	701	4.9	(4.4, 5.4)	<.0001	<.0001
Total hip BMD Percent change from baseline at Month 36[a]	706	701	5.7	(5.4, 6.1)	<.0001	<.0001
Fracture Endpoints						
Subject incidence of any fracture through Month 36[b]	734	734	0.70	(0.46, 1.08)	0.1048	0.1048
Subject incidence of new vertebral fracture through Month 36[b,e]	673	679	0.37	(0.18, 0.78)	0.0063	0.0125
Time to first clinical fracture through Month 36[c]	734	734	0.94	(0.57, 1.55)	0.7961	0.7961
Subject incidence of any fracture through Month 24[b]	734	734	0.70	(0.44, 1.11)	0.1282	0.7961

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N = Number of subjects randomized.
[a] Difference from placebo based on ANCOVA model adjusting for age group, ADT duration at study entry, baseline value, machine type, and baseline value-by -machine type interaction.
[b] Odds ratio relative to placebo based on logistic regression model adjusting for the stratification variables of age group and ADT duration at study entry.
[c] Hazard ratio relative to placebo based on Cox proportional hazards model stratified by the stratification variables of age group and ADT duration at study entry.
[d] P-values for all endpoints are adjusted for multiplicity according to the prespecified sequential testing strategy.
[e] Only subjects with a nonmissing baseline and ≥ 1 postbaseline assessment were included.
Transcribed from Table 14-4.1.5 and modified from Table 14-4.100.2

Safety Results:

Of the 1468 subjects randomized, 1456 subjects (99.2%) received at least 1 dose of investigational product (denosumab or placebo) and were included in the safety analysis set.

The overall adverse event profile was balanced between the denosumab and placebo groups. Adverse events were reported for a similar proportion of subjects in the denosumab group (87.3%) and placebo group (86.5%). Most adverse events were of mild or moderate severity; the proportion of subjects with grade 3 (severe) or higher adverse events was 36.8% in the denosumab group and 33.7% in the placebo group. The most common adverse events (≥ 10% of subjects in either treatment group were (denosumab, placebo) arthralgia (12.6%, 11.0%), back pain (11.1%, 10.2%), and constipation (10.0%, 10.3%) Subject incidences of individual adverse preferred terms were similar between treatment groups (≤ 2% difference) with the exception of

adverse events of cataracts. Over 3 years, the incidence of adverse events of cataracts (including new diagnoses, worsening of existing cataracts, and cataract extractions) was 4.7% in the denosumab group and 1.2% in the placebo group. Many of these events occurred in subjects with a reported history of cataracts (13 of the 34 subjects with the event in the denosumab group, and 2 of 9 subjects in the placebo group). The majority of subjects with adverse events of cataracts in the denosumab group (18 of 34 subjects [52.9%]) had events reported within the first year of study (2.5% denosumab, 0.4% placebo); the incidence of these events, decreased in the denosumab group during the second (1.9% denosumab, 0.5% placebo) and third years (1.0% denosumab, 0.7% placebo), suggesting that the risk did not increase with prolonged exposure.

Adverse events considered by the investigator to be related to investigational product were reported for 8.5% of subjects in the denosumab group and 9.0% of subjects in the placebo group.

Serious adverse events were reported for 34.6% of subjects in the denosumab group and 30.6% of subjects in the placebo group. Serious adverse events considered by the investigator to be related to treatment were reported for 3 subjects in the denosumab group (0.4%) and 4 subjects in the placebo group (0.6%). No treatment-related serious adverse event was reported for more than 1 subject in either treatment group. Six percent of subjects in each treatment group died on study. No individual fatal adverse event was reported for more than 1% of subjects in either treatment group. Fatal adverse events considered related to investigational product were reported for 1 subject in the placebo group (cardiovascular disorder) and no subjects in the denosumab group.

Subject incidences were similar between treatment groups for adverse events resulting in discontinuation of investigational product (6.7% denosumab, 6.5% placebo) and for adverse events resulting in withdrawal from study (7.0% denosumab, 6.1% placebo).

Subject incidences of positively-adjudicated cardiovascular serious adverse events were similar between treatment groups for all cardiovascular events (10.9% denosumab, 11.0% placebo), cardiovascular death, acute coronary syndrome, congestive heart failure, other vascular disease, stroke/transient ischemic attack, and arrhythmia. Subject incidences of new primary malignancies were also balanced between the treatment groups (5.1% denosumab, 4.6% placebo); the most frequent new primary malignancies were bladder cancer (0.7% denosumab, 0.6% placebo) and colon cancer (0.7% denosumab, 0.6% placebo). Within the infection and infestation system organ class, adverse events were reported for 35.2% of subjects in the denosumab group and 31.2% of subjects in the placebo group; no single adverse event term accounted for the higher incidence in the denosumab group. The incidence of infections reported as serious adverse events was 5.9% and 4.6% in the denosumab and placebo groups, respectively. No subject in either treatment group had a positively adjudicated event of ONJ. Two subjects in the denosumab group (0.3%) and no subjects in the placebo group reported adverse events of hypersensitivity, one subject in the denosumab group (0.1%) reported an adverse event of drug hypersensitivity; subject incidences of adverse events potentially resultant from hypersensitivity were similar (0.7% denosumab, 1.1% placebo). There were no reports of delayed fracture healing or nonunion of fractures for nonvertebral fractures in either treatment group; 3 subjects (2 denosumab, 1 placebo) had an unknown status for fracture healing at 6 months postfracture.

Mild, transient, clinically insignificant decreases in serum calcium were observed at the month 1 timepoint in the denosumab group. Adverse events of hypocalcemia were reported for one subject in the denosumab group (0.1%) and none of the subjects in the placebo group. Three subjects in the denosumab group (0.4%) and 1 subject in the placebo group (0.1%) had albumin-adjusted calcium decreases of grade $\geq$ 2; these reductions were not associated with clinical sequelae. Consistent with previous studies, reductions in serum phosphorus (approximately 10% at month 1) were observed in the denosumab group and 4 subjects in the denosumab group had grade $\geq$ 3 decreases in phosphorus. Serum prostate specific antigen and testosterone were balanced between treatment groups.

No subjects had neutralizing antibodies to denosumab. One subject in each treatment group (0.1%) developed transient anti-denosumab binding antibodies in postbaseline samples. There was no evidence of an effect of anti-denosumab antibodies on safety profiles or efficacy outcomes.

There was no difference in overall survival between denosumab and placebo. The proportion of subjects who were alive at 36 months, and the Kaplan-Meier estimates of survival were identical for each treatment group (94% and 93%, respectively).

Pharmacokinetic Results:

Mean and median serum denosumab concentrations at month 1 were similar to those observed at month 1 in previous denosumab studies using a dose of 60 mg Q6M. Mean and median trough serum denosumab concentrations were similar from months 6 to 36. In addition, mean and median concentrations at months 3 and 15 (approximately 3 months postdose) were similar. These results indicate that denosumab pharmacokinetics did not change with time.

Conclusions:

Denosumab is a fully human monoclonal antibody that binds to RANKL resulting in reduced bone resorption and increased bone mass. This study demonstrated that in subjects with prostate cancer undergoing ADT, denosumab was well tolerated and rapidly (as early as 1 month) increased BMD throughout the skeleton at both trabecular and cortical sites and that these increases were sustained over time. This study also demonstrated a long-term (3-year) fracture benefit in men with prostate cancer undergoing ADT: treatment with denosumab reduced vertebral fracture risk by 62%.

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2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: Denosumab (AMG 162)

Name of Active Ingredient: Fully human monoclonal antibody to RANK ligand (RANKL)

Title of Study: A Randomized, Double-blind, Placebo-controlled Study to Evaluate AMG 162 in the Treatment of Bone Loss in Subjects Undergoing Androgen-deprivation Therapy for Nonmetastatic Prostate Cancer

Investigators and Study Centers: This study was conducted at 156 sites in the United States, Canada, Mexico, and, Europe. For the safety follow-up period, subjects participated at 128 centers (52 in the United States, 35 in Canada, 33 in Europe, and 8 in Mexico). The study centers and principal investigators participating in the follow-up period are listed in Appendix 2.

Publications: A complete list of publications is provided in Appendix 5.

Study Period: The first subject was enrolled on 02 August 2004, the last subject completed the last 36-month visit of the treatment period on 16 May 2008, and the last subject completed the last 60-month visit of the safety follow-up period on 11 May 2010.

Development Phase: 3

Introduction and Objectives:

Denosumab is a fully human monoclonal antibody with high affinity and specificity for RANK ligand (RANKL). Denosumab binds to human RANKL and neutralizes its activity resulting in an inhibition of osteoclast formation, function, and survival. Previous studies, including one in women with breast cancer treated with aromatase inhibitor therapy, have demonstrated that denosumab decreases markers of bone resorption and bone formation and increases bone mineral density (BMD).

The primary objective of this study was to determine the treatment effect of denosumab compared with placebo on lumbar spine BMD at month 24 in men with nonmetastatic prostate cancer undergoing androgen deprivation therapy (ADT). The secondary objectives were to determine the treatment effect of denosumab compared with placebo on percentage change of femoral neck BMD and total hip BMD from baseline to month 24; percentage change of lumbar spine BMD, femoral neck BMD, and total hip BMD from baseline to month 36; subject incidence of any fracture (ie, osteoporotic fracture at any skeletal site including vertebral fractures, but excluding skull, facial, mandible, metacarpus, finger phalanges, and toe phalanges) and subject incidence of new vertebral fracture over the 36-month treatment period; time to first clinical fracture over the 36-month treatment period; and subject incidence of any fracture over the 24-month treatment period. Other secondary objectives included assessment of the safety and pharmacokinetics of denosumab over the 36-month treatment period. The evaluation of these objectives has been fully described in the 36-month report, dated 15 October 2008.

The study included a 24-month evaluation period after the discontinuation of investigational product to provide safety follow-up information. All subjects who completed the 36-month treatment period were asked to participate in the safety follow-up period of the current study. The objective of the follow-up period in the current study was to evaluate the safety profile of subjects that participated in the follow-up period. The results from the 24 months of follow-up in the current study, months 37 to 60, are reported in this 60-month document. Results from the 36-month treatment period are provided as appropriate to provide context for the results of the follow-up period. Subsequent to the initiation of the follow-up period, enrollment was also offered in a 2-year extension study (20080537) in which all subjects received denosumab. Subjects were permitted to transition from the follow-up period of this study to Study 20080537. Results from the extension study (20080537) will be reported separately.

Methodology:

This was an international, multicenter, randomized, double-blind, placebo-controlled study in subjects with nonmetastatic prostate cancer who were undergoing ADT. Subjects were randomized (1:1) to receive either placebo or denosumab 60 mg subcutaneously (SC) once every 6 months for a total of 6 doses over the 36-month treatment period. Randomization was stratified by age group (< 70 years vs ≥ 70 years) and duration of ADT with gonadotropin-releasing hormone (GnRH) agonists or orchiectomy at study entry (≤ 6 months vs > 6 months). All subjects received daily supplemental calcium (≥ 1 g) and were instructed to take vitamin D (≥ 400 IU). Bone mineral density assessments by dual x-ray absorptiometry (DXA) for the lumbar spine, total hip, femoral neck, and trochanter were obtained in all subjects, and BMD of the total body and 1/3 distal radius were performed in a subset of subjects (N = 309). Throughout the study, a blinded central image reader identified or confirmed all vertebral fractures, and confirmed all nonvertebral fractures. An external Data Monitoring Committee monitored subject safety on an ongoing basis for the duration of the 36-month treatment period. Results from the 36-month treatment period were reported previously (clinical study report dated 15 October 2008).

Upon completion of the 36-month treatment period, subjects continued on study for 24 months during which no investigational product was administered. Subjects who completed the 36-month treatment period and chose to participate in the follow-up period provided written informed consent. During the safety follow-up period (months 37 to 60), no investigational product was administered. Adverse events were collected by clinic visit or telephone contact approximately every 6 months for up to 2 years after month 36 (end of the on-treatment period). After the on-treatment period, study center personnel had access to the original treatment assignment that subjects had received in the on-treatment period; therefore, the study was no longer blinded.

Number of Subjects Planned: 1226 subjects (613 subjects in each treatment group)

Number of Subjects Enrolled: A total of 1468 subjects were enrolled and randomized to receive denosumab (734 [50%]) or placebo (734 [50%]) in the treatment period.

Of the 912 subjects that completed the 36-month treatment period, 802 (413 who received denosumab and 389 who received placebo during the treatment period) continued on study in the follow-up period (54.6% of those randomized in the study initially). Three hundred fifty-nine of these 802 subjects completed the follow-up period (181 [24.7%] subjects initially randomized to denosumab, 178 [24.3%] initially randomized to placebo). A total of 443 subjects withdrew from the safety follow-up period (232 [31.6%] initially randomized to denosumab, 211 [28.7%] initially randomized to placebo). The most common reason for discontinuation in the follow-up period was to enroll in the open-label study, 20080537 (168 [22.9%] initially randomized to denosumab, 143 [19.5%] initially randomized to placebo). Demographic data from baseline of the treatment period for subjects with a visit in the follow-up period are presented below.

Sex: 100% men

Age (Mean [range]):

Prior denosumab (n = 413): 74.4 (range: 48 to [redacted]) years
Prior placebo (n = 389): 74.1 (range: 52 to [redacted]) years

Ethnicity (Race):

Prior denosumab (n = 413): 347 (84.0%) White, 47 (11.4%) Hispanic/Latino, 18 (4.4%) Black/African American, and 1 (0.2%) Asian
Prior placebo (n = 389): 318 (81.7%) White, 51 (13.1%) Hispanic/Latino, 13 (3.3%) Black/African American, 7 (1.8%) Other

Diagnosis and Main Criteria for Eligibility: Eligible subjects for the study met the following criteria: men ≥ 70 years of age with histologically confirmed prostate cancer or men < 70 years of age with histologically-confirmed prostate cancer and a history of osteoporotic fracture or BMD T-score at the lumbar spine, total hip, or femoral neck < -1.0 (using the normative male database); BMD T-score at the lumbar spine, total hip, or femoral neck not < -4.0; have undergone bilateral orchiectomy or initiated ADT with GnRH agonists and are expected to continue on with ADT for at least 12 months; Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; no distant metastases; no evidence of current unstable systemic disease, organic or psychiatric disorder, or inadequate organ function that could have interfered with completion of the study or interpretation of results; and no recent exposure to bisphosphonates or other medications known to influence bone metabolism.

Subjects who completed the treatment period and provided informed consent were eligible to continue into the safety follow-up period of the study. During the follow-up period, there were no proscribed therapies; investigators could prescribe any concomitant medications or treatments deemed necessary to provide adequate care.

Investigational Product, Dose and Mode of Administration, Manufacturing Lot Number: During the on-treatment period, denosumab was administered subcutaneously every 6 months at a dose of 60 mg and was provided as a sterile, clear, colorless, preservative-free, 60 mg/mL liquid solution in glass vials. Denosumab was not administered during the follow-up period.

Duration of Treatment: The 60-month study includes a 36-month treatment period (with last dose administered at month 30) and a 24-month safety follow-up period.

Reference Therapy, Dose and Mode of Administration, Manufacturing Lot Number: During the treatment period, placebo was administered subcutaneously every 6 months and was provided as a sterile, clear, colorless, preservative-free liquid solution in glass vials. Placebo was not administered during the follow-up period.

Study Endpoints

This report summarizes adverse events during the safety follow-up period. Results for the final analyses of the 36-month treatment period were reported previously (clinical study report dated 15 October 2008).

Statistical Methods:

Descriptive statistics were provided for disposition characteristics and selected demographic and safety data. Continuous variables (eg, duration on study and subject age) were summarized descriptively using mean, standard deviation (SD), minimum, maximum, and the number of nonmissing observations (n). Median and other selected percentiles were substituted for mean and SD for parameters exhibiting a lack of normality (continuous or ordinal categorical). Frequencies and percentages were presented for nominal categorical variables.

The safety profile was described by summarizing the nature, frequency, severity, and relationship to investigational product for all adverse events. Adverse events were tabulated by system organ class and preferred term (coded using Medical Dictionary for Regulatory Authorities [MedDRA] version 13.0).

Data displays for the safety follow-up period were organized by treatment group in the treatment period (months 1 to 36).

Summary of Results:

Subject Disposition:

A total of 1468 subjects were enrolled into the study with 734 subjects randomized to receive denosumab and 734 randomized to receive placebo; 467 (64%) subjects in the denosumab group and 445 (61%) subjects in the placebo group completed the 36-month treatment period.

A total of 802 subjects (413 subjects who were randomized to receive denosumab and 389 who were randomized to receive placebo during the treatment period) continued on study in the follow-up period (54.6% of those randomized in the study initially). Three hundred fifty-nine of these 802 subjects completed the study (181 [24.7%] subjects initially randomized to denosumab, 178 [24.3%] initially randomized to placebo). Four hundred forty-three subjects withdrew from the follow-up period (232 [31.6%] initially randomized to denosumab, 211 [28.7%] initially randomized to placebo). The most common reason for discontinuation in the follow-up period was to enroll in the open-label extension study, 20080537 (168 [22.9%] initially randomized to denosumab, 143 [19.5%] initially randomized to placebo).

During the follow-up period, the median (Q1, Q3) duration of time on study was 21.0 (16.56, 23.85) months for subjects initially randomized to denosumab and 21.7 (17.12, 23.72) months for subjects initially randomized to placebo. For subjects that enrolled in the open-label study, the median (Q1, Q3) duration of time on study was 17.9 (15.41, 21.03) months for subjects initially randomized to denosumab and 17.9 (15.77, 20.60) months for subjects initially randomized to placebo.

Efficacy Results:

The primary, secondary, and exploratory efficacy endpoint results were reported in the month-36 report dated 15 October 2008. No additional efficacy data were collected during the 24-month safety follow-up period.

Safety Results:

All 802 subjects who entered the safety follow-up period were evaluated. The overall adverse event profiles were similar in the prior denosumab and prior placebo groups: 222 (53.2%) subjects in the prior denosumab group and 188 (48.8%) subjects in the prior placebo group had at least 1 adverse event. The most frequently reported adverse events (≥ 3% incidence in either group) were (prior denosumab, prior placebo) arthralgia (5.0%, 3.6%), urinary tract infection (3.8%, 3.4%), anemia (3.1%, 3.1%), hematuria (3.1%, 2.9%), constipation (2.9%, 2.3%), back pain (2.9%, 2.1%), diarrhea (2.9%, 1.6%), prostate cancer (2.6%, 1.3%), pneumonia (2.6%, 0.8%), and hypertension (1.4%, 3.4%). Four subjects (1.0%) in the prior denosumab group and 7 subjects (1.8%) in the prior placebo group reported an adverse event of cataract.

The system organ classes in which adverse events were most frequently reported (> 10% incidence in either group) were musculoskeletal and connective tissue disorders (17.3% denosumab, 13.2% placebo); infections and infestations (13.2%, 11.9%); gastrointestinal disorders (12.7%, 10.9%); renal and urinary disorders (11.5%, 13.0%); neoplasms benign, malignant and unspecified (including cysts and polyps) (10.3%, 7.3%); and nervous system disorders (7.9%, 9.9%).

The overall incidence of serious adverse events was 18.7% in the prior denosumab group and 18.2% in the prior placebo group. The most frequently reported serious adverse events (≥ 7 subjects overall) were (prior denosumab, prior placebo) death (1.4%, 0.5%), pneumonia (1.4%, 0.5%), hematuria (1.2%, 0.8%), prostate cancer (1.2%, 0.8%), and cerebrovascular accident (0.5%, 1.3%). No subjects withdrew due to serious adverse events. Subject incidence of adverse events of Common Terminology Criteria of Adverse Events (CTCAE) grade 3, 4, or 5 was 16.8% in the prior denosumab group and 18.2% in the prior placebo group. Twenty-six subjects in each treatment group (6.2% prior denosumab and 6.8% prior placebo) had a fatal adverse event, with no deaths considered by the investigator to be related to investigational product. Based on a clinical review of the 26 fatal events in the prior denosumab group, 9 were due to prostate cancer disease progression, 5 were due to new malignancies, and 12 were due to other causes. Based on a clinical review of the 26 fatal events in the prior placebo group, 7 were due to prostate cancer disease progression, 2 were due to new malignancies, and 17 were due to other causes.

Fractures were reported as adverse events during the follow-up period in 11 subjects (2.6%) in the prior denosumab group and 16 subjects (4.2%) in the placebo group. Nonvertebral fractures were reported for 10 subjects (2.4%) in the prior denosumab group and 12 subjects (3.1%) in the prior placebo group ([redacted] [denosumab-treated] reported both vertebral and nonvertebral fractures). Osteoporotic, nonvertebral fractures occurred in 7 subjects (1.7%) in the prior denosumab group and 11 subjects (2.9%) in the prior placebo group. Vertebral fractures were reported for 2 subjects in the prior denosumab group and 4 subjects in the prior placebo group. All 4 subjects in the prior placebo group had pathologic vertebral fractures. No subjects had investigator-reported or adjudicated positive adverse events of osteonecrosis of the jaw.

The number of subjects with adverse events within the neoplasms benign, malignant and unspecified SOC (including cysts and polyps) was 43 (10.3%) in the prior denosumab group and 28 (7.3%) in the prior placebo group. Of these events, an adverse event of progression of underlying prostate cancer was reported for 23 (5.5%) and 15 (3.9%) subjects in the prior denosumab and placebo groups, respectively. The number of subjects with an adverse event of new primary malignancy was 15 (3.6%) in the prior denosumab group and 8 (2.1%) in the prior placebo group. No trends in the incidence of new primary malignancy were observed over the entire study period: the yearly incidence ranged from 1.0% (year 4) to 2.5% (year 1) for subjects who received placebo and from 1.3% (year 5) to 2.4% (year 4) for subjects who received denosumab. Five subjects (1.2%) in the prior denosumab group and no subjects in the prior placebo group withdrew due to adverse events. Four of the subjects withdrew from the study due to adverse events related to progression of prostate cancer and 1 withdrew from the study due to a severe adverse event (worsening Alzheimer's disease) that was not considered related to investigational product.

Conclusions:

The overall safety profile of previously treated denosumab subjects during the safety follow-up period was generally similar to previously treated placebo subjects. There was no discernable pattern of differences between the prior treatment groups in the types of other events.