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Name of Sponsor: Amgen Inc.

Name of Finished Product: Denosumab (AMG 162)

Name of Active Ingredient: Fully human monoclonal antibody to RANKL

Title of Study: A Randomized Study to Evaluate Safety and Efficacy of Transitioning Therapy from Alendronate to Denosumab (AMG 162) in Postmenopausal Women with Low Bone Mineral Density (Study of Transitioning from AleNdronate to Denosumab – The STAND Trial)

Investigators and Study Centers: This was a multicenter study conducted at 42 centers including 23 centers in North America (19 in the United States and 4 in Canada) and 19 centers in Europe (7 in Poland, 5 in France, 4 in Italy, and 3 in Estonia).

Publications: No publications as of the date of this report.

Study Period: The first subject was enrolled on 02 October 2006 and the last patient completed the study on 27 March 2008.

Development Phase: 3b

Introduction and Objectives: Denosumab is a fully human monoclonal antibody with high affinity and specificity for RANKL. Denosumab binds to and neutralizes the activity of human RANKL.

The primary objective of this study was to evaluate the effect of denosumab 60 mg Q6M on total hip bone mineral density (BMD) at 12 months in postmenopausal women with low BMD previously treated with alendronate 70 mg QW or equivalent compared to that in subjects continuing on alendronate therapy.

The secondary objectives of the study were to evaluate the effects of transitioning to denosumab in comparison to treatment with continuing alendronate therapy on:

- Bone turnover markers (serum type 1 CTX [CTX1], intact N-terminal propeptide of type 1 procollagen [P1NP], bone-specific alkaline phosphatase [BSAP], and urinary N-telopeptide [uNTX]) at post-day 1 (one visit at 5, 10, or 15 days post dose); months 1, 3, 6; post month 6 (one visit at 5, 10, or 15 days post dose); and months 9 and 12
- BMD at the lumbar spine, femoral neck, hip trochanter, and distal 1/3 radius at 12 months
- BMD at the total hip, lumbar spine, femoral neck, hip trochanter, and distal 1/3 radius at 6 months

The safety objective was to evaluate the effects of transitioning to denosumab compared with continuing on alendronate therapy on the safety and tolerability measured by evaluating adverse events, laboratory parameters, serum calcium levels, bone histology and histomorphometry, and immunogenicity to denosumab over 12 months.

Methodology: This international, multicenter, randomized, double-blind, active-controlled, double-dummy, parallel-group study enrolled postmenopausal women with BMD T score ≤ -2.0 and ≥ -4.0 at the lumbar spine or total hip. Subjects were randomized (1:1) to receive either 60 mg denosumab every 6 months (Q6M) subcutaneously (SC) plus placebo for alendronate once weekly (QW) orally (PO) or 70 mg alendronate QW PO plus placebo for denosumab SC Q6M. The treatment period for each group was 12 months. Randomization was stratified by length of prior alendronate therapy (6 to < 12 months, 12 to 24 months, or > 24 months). All

subjects received daily supplementation with calcium (at least 1 g) and vitamin D (at least 400 IU) through month 12. Subject safety was monitored on an ongoing basis throughout the trial by a DMC.

Number of Subjects Planned: 500 total: 250 in each of 2 treatment groups

Number of Subjects Enrolled: A total of 504 subjects were enrolled in the study; 251 to the alendronate group and 253 to the denosumab group.

Sex: 100% were female

Age: Mean (SD) age was 67.6 (7.8) years.

Ethnicity (Race): White or Caucasian (93%); Hispanic or Latino (5%); Black or African American, Asian, Japanese, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and other each made up less than 1% of the population.

Diagnosis and Main Criteria for Eligibility: Eligible subjects were ambulatory, postmenopausal women with BMD T-score ≤ -2.0 and ≥-4.0 at the lumbar spine or total hip who received alendronate 70 mg QW or equivalent for at least 6 months prior to screening. Subjects were not receiving medication that affected bone metabolism (other than calcium and vitamin D) and were free from any underlying condition (other than low BMD) that might have resulted in abnormal bone metabolism.

Investigational Product, Dose and Mode of Administration: Denosumab was provided as a sterile, clear, colorless, preservative-free liquid in glass vials containing 60 mg denosumab per milliliter of 10 mM sodium acetate and 5% sorbitol in Water for Injection, with a pH of 5.2. One milliliter of blinded investigational product was administered SC every 6 months (Q6M, ie, on day 1 and month 6).

Reference Therapy, Dose and Mode of Administration:
Alendronate was provided as a tablet to be taken orally once weekly (QW). Alendronate (Fosamax®, Merck Sharp & Dohme) was provided as a white, crystalline, nonhygroscopic tablet containing 91.37 mg of alendronate monosodium salt trihydrate (molar equivalent to 70 mg of free acid) and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, and magnesium stearate. One tablet of blinded investigational product was taken orally QW.

Subjects randomized to the denosumab group received placebo for alendronate orally once per week. The placebo formulation was identical to the alendronate formulation with the exception of the active ingredient (alendronate monosodium salt trihydrate). One tablet of blinded investigational product was taken PO QW.

Subjects in the alendronate group received placebo for denosumab SC Q6M (ie, on day 1 and month 6). Placebo for denosumab 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.

Duration of Treatment: After a 1-month run-in period, the planned study treatment period was 12 months.

Study Endpoints

As defined in the statistical analysis plan (version 2.1), the key endpoints of the study were:

Primary Efficacy Endpoint: Percent change in total hip BMD from baseline to 12 months

Secondary Efficacy Endpoints:

- Percent change from baseline in serum CTX1 at month 3
- Percent change from baseline in lumbar spine BMD at month 12

Safety Endpoints:

- Adverse event incidence by system organ class and preferred term
- Minimum serum calcium on study
- Serum calcium and phosphorus at 5, 10, or 15 days post injection
- Changes in safety laboratory analytes (serum chemistry, hematology) at specific visits and to "worst" on-study value
- Subject incidence of anti-denosumab antibody appearance
- Changes in vital signs
- Histologic and histomorphometric assessments from transiliac bone biopsies

Other Endpoints:

- Percent change from baseline in total hip BMD at month 6
- Percent change from baseline in lumbar spine BMD at month 6
- Percent change from baseline in hip trochanter, femoral neck, and distal 1/3 radius BMD at months 6 and 12
- Bone markers (serum Type 1 CTX, P1NP, BSAP and uNTX) at post-day 1 (at 5, 10, or 15 days post dose), months 1, 3, 6, post-month 6 visit (at 5, 10, or 15 days post dose), and months 9 and 12.

Exploratory Endpoints:

- Patient reported preference
- Patient reported satisfaction

Statistical Methods:

Descriptive statistics were provided for selected baseline characteristics and demographic, efficacy, 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.

The primary, secondary, and other efficacy endpoints were tested using inferential analysis using a step-down multiple testing procedure to control the family-wise error rate. Any comparisons that were not in the step-down procedure were considered exploratory.

The primary analysis to assess the treatment difference in the percent change from baseline in BMD of the total hip at Month 12 employed a repeated measures model which included treatment, time of BMD assessment, treatment by time of BMD assessment interaction, baseline BMD value, length of prior alendronate therapy stratification variable (6 to < 12 months, 12 to 24 months, or > 24 months, machine type [Hologic or Lunar] and baseline BMD value, and machine type interaction as variables. The least-squares mean estimate for the treatment difference at Month 12 is presented with its corresponding confidence interval and p-value. If the lower bound of the 95% confidence interval was > -0.35 (non-inferiority margin), non-inferiority was confirmed.

Statistical inferences of the treatment effects on the secondary hypotheses were only to be made when denosumab was concluded non-inferior to alendronate with respect to mean percent change in total hip BMD at month 12 at the 1-sided significance level of 0.025. The secondary hypotheses were tested sequentially (including superiority hypothesis testing of serum CTX1, superiority testing of total hip BMD, and non-inferiority testing of lumbar spine BMD). The treatment comparisons for the percent change from baseline in bone turnover markers at each visit were analyzed using a van Elteren stratified rank test and the observed data subset. The secondary BMD endpoints were analyzed using the repeated measures model, similar to the primary endpoint.

Safety was characterized by tabulating adverse event incidence by system organ class and preferred term (coded using Medical Dictionary for Regulatory Authorities [MedDRA] version 10.0); changes in safety laboratory analytes (serum chemistry and hematology) at each visit and shifts between baseline and the worst on-study value; changes in vital signs; subject incidence of antidenosumab antibody appearance (negative/positive); and values for histologic and histomorphometric bone biopsy assessments. Adverse events and serious adverse events were also summarized for the period between informed consent and the first dose of double-blind investigational product (run-in period).

Summary of Results:

Subject Disposition:

A total of 504 subjects were enrolled into the study in 6 countries (United States, Canada, Poland, Estonia, France, and Italy) throughout North America and Europe. Two-hundred fifty-one subjects were randomized to the alendronate treatment group and 253 were randomized to the denosumab treatment group. Study completion rates were similar between the alendronate (95%) and denosumab (96%) treatment groups.

Randomization was stratified according to prior alendronate exposure and was well-balanced between treatment groups among individual strata. Overall, 89 (18%) subjects had received 6 to < 12 months of alendronate therapy prior to screening in the study, 119 (24%) subjects had received 12 to 24 months therapy prior to screening, and 296 (59%) subjects had received more than 24 months of alendronate therapy prior to screening.

Efficacy Results:

All primary and secondary efficacy endpoints in this study, including testing for both non-inferiority and superiority of transitioning from alendronate to denosumab, compared with continuing on alendronate therapy, were met with statistical significance. Using the repeated measures model, the mean percent change from baseline in total hip BMD at month 12 was 1.90% in the denosumab group and 1.05% in the alendronate group with a difference of 0.85% (95% CI: 0.44, 1.25; $p<0.0001$).

Results of superiority testing were statistically significantly in favor of the denosumab group for the difference in the mean percent change from baseline in BMD at month 12 at the total hip. Although the pre-specified sequential testing procedure did not include superiority testing at other anatomical sites, analyses of percent change from baseline in BMD at the lumbar spine, femoral neck, hip trochanter, and distal 1/3 radius at 12 months were also statistically significant in favor of denosumab (all $p \leq 0.01$ at the 2-sided, 5% level).

Exploratory analyses of the difference in the mean percent change from baseline in BMD by DXA at month 6 was also statistically greater at the total hip ($p= 0.027$), lumbar spine ($p= 0.0008$), femoral neck ($p= 0.0075$), and hip trochanter ($p= 0.0121$) for subjects transitioning to denosumab compared with those continuing on alendronate. The percent change from baseline in least square mean BMD at the 1/3 distal radius at month 6 was also greater in the denosumab group than in the alendronate group; however, the difference did not reach statistical significance.

Subjects who received denosumab also had significantly greater decreases (all $p<0.01$) in serum concentrations of CTX1 from baseline at months 1, 3, 6, 9 and 12 compared with subjects who continued on alendronate therapy. Median decreases in concentrations of P1NP and urine NTX/ creatinine were also greater for denosumab-treated subjects than those in the alendronate group.

A review of the PSQ showed that more subjects, regardless of treatment group, indicated a preference for a 6-month injection over a weekly oral tablet and were more satisfied with the frequency of 6-month administration over weekly administration.

Safety Results:

A total of 502 subjects (249 randomized to alendronate, 253 randomized to denosumab) received investigational product and were evaluated for safety.

The overall adverse event profiles were similar in the denosumab and alendronate groups. The incidences of adverse events, serious adverse events, withdrawals due to adverse events, and fatal adverse events were similar between treatment groups. A total of 197 (77.9%) subjects in the denosumab group and 196 (78.7%) subjects in the alendronate group experienced at least 1 adverse event during the study. The most frequent adverse events in the denosumab and alendronate groups were nasopharyngitis (13.4% and 10.8%, respectively), back pain (10.7% and 11.6%), bronchitis (6.3% and 5.6%), arthralgia (5.9% and 10.4%), constipation (5.1% and 4.8%), and pain in the extremity (4.7% and 8.4%). The incidence of treatment-related adverse events was 13.0% in each group.

Serious adverse events occurred in 15 (5.9%) subjects in the denosumab group and 16 (6.4%) subjects in the alendronate group. Only 1 serious adverse event in the study (atrial fibrillation in an alendronate-treated subject) was considered related to investigational product by the investigator. One death (cerebrovascular accident) occurred in the study in a subject in the denosumab group. This death was considered unrelated to investigational product by the investigator.

No adverse events of hypocalcemia were reported in either group during the treatment period. Adverse events and serious adverse events of infection were balanced between treatment groups; there were no serious adverse events of opportunistic infections reported during the study in either treatment group. Adverse events of hypersensitivity were reported for 1 (0.4%) denosumab and 4 (1.6%) alendronate subjects. Serious adverse events within the system organ class of neoplasms were well-balanced between treatment groups (3 subjects; 1.2% in each group). There were no adjudicated positive adverse events of osteonecrosis of the jaw.

The proportions of subjects who discontinued investigational product (denosumab 2.8%, alendronate 2.0%) or withdrew from the study (denosumab 1.2%, alendronate 0.8%) due to adverse events were also similar between the two treatment groups.

No 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.

Bone histology results were evaluable for 36 of the 39 subjects who participated in the bone biopsy substudy. In the 15 denosumab-treated subjects with evaluable biopsies, there was no evidence of pathological findings, osteomalacia, marrow dyscrasia, marrow fibrosis, woven bone, cortical trabecularization, abnormal osteoid, or other findings suggestive of deleterious effects on bone histology. One subject treated with alendronate showed evidence of marrow fibrosis, but did not have any clinical or biochemical abnormalities. Examination of transiliac crest bone biopsies from 36 of 39 subjects with available samples indicated that bone histology was not adversely affected after 12 months of treatment with denosumab. Evaluation of labeling status and histomorphometric parameters showed changes consistent with decreased bone turnover in subjects treated with denosumab compared with alendronate. Denosumab did not impair matrix mineralization.

No subjects in the denosumab group developed antibodies to denosumab.