2. SYNOPSIS

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

Name of Finished Product: Denosumab

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

Title of Study: A Randomized Open Label Study to Evaluate the Safety and Efficacy of Denosumab and Monthly Actonel® Therapies in Postmenopausal Women Transitioned from Weekly or Daily Alendronate Therapy

Investigator(s) and Study Center(s): This study was conducted at 82 centers in Canada, the European Union, and Australia. Centers and principal investigators are listed in Appendix 4.

Publication(s): None to date

Study Period: 19 October 2009 (first subject randomized) through 17 January 2012 (last subject end-of-study date)

Development Phase: 3b

Objectives:

Primary:

The primary objective of the study was to evaluate the effect of denosumab 60 mg given subcutaneously (SC) once every 6 months (Q6M) compared with Actonel (risedronate) 150 mg given orally once monthly (QM) on total hip bone mineral density (BMD) at 12 months in postmenopausal women transitioning from previous alendronate therapy.

Secondary:

The secondary objective of the study was to evaluate the effects of denosumab 60 mg Q6M and risedronate 150 mg QM on:

- Type-1 serum C-telopeptide (CTX1) in a subset of subjects at 1 month
- BMD at the femoral neck at 12 months
- BMD at the lumbar spine at 12 months

Safety Objective:

To evaluate the effect of denosumab 60 mg Q6M compared with risedronate 150 mg QM on safety and tolerability measured by evaluating adverse events, antidenosumab antibodies, and laboratory parameters over 12 months.

Exploratory:

[redacted]

Methodology: This was an international, multicenter, randomized, open-label, parallel-group study in postmenopausal women with osteoporosis who had previously been treated with daily or weekly oral alendronate therapy, but demonstrated an insufficient adherence to treatment or had discontinued alendronate therapy. Approximately 800 subjects were randomized (1:1) to receive either SC administrations of denosumab 60 mg Q6M (total of 2 injections) or risedronate 150 mg orally (PO) QM (2× 75-mg tablets; each tablet taken on consecutive days). The treatment duration was 12 months. Subjects randomized to denosumab received their first SC dose on day 1 at the study site, and their second (final) denosumab dose at the month 6 visit. Oral doses

of risedronate were self-administered QM by the subject. Subsequent to the day 1 visit, all subjects returned to the study site for 2 additional visits, at month 6 and month 12 (end-of-study [EOS] visit). During the study, all subjects were required to take daily supplements of calcium (≥ 1000 mg elemental calcium) and vitamin D (≥ 800 IU). Safety was assessed by adverse events monitoring, antidenosumab antibody analysis, and by changes in laboratory parameters and vital signs results.

[redacted].

Number of Subjects Planned: 800

Number of Subjects Enrolled: 870

Diagnosis and Main Criteria for Eligibility: Ambulatory, postmenopausal women aged 55 years or older with osteoporosis who had received their first prescription of daily or weekly alendronate therapy ≥ 1 month prior to screening. In addition, eligible subjects had either discontinued alendronate treatment prior to the screening visit or were still receiving treatment but had demonstrated insufficient adherence to their prescribed medication (as measured by a score of < 6 on the OS-MMAS).

Investigational Product, Dose, and Mode of Administration, Manufacturing Batch Number:

Denosumab (manufacturing lot numbers are provided in Appendix 18) was manufactured and provided by Amgen Inc. as a sterile, clear, colorless, preservative-free liquid in prefilled syringe (PFS) containing 60 mg denosumab per mL of [redacted] mM sodium acetate at pH [redacted], containing [redacted]% sorbitol in water for injection. Each box of denosumab contained one PFS of denosumab. No special preparation was required before denosumab administration.

Reference Therapy, Dose, and Mode of Administration, Manufacturing Batch Number:

Actonel 75-mg tablets (commercially available oval pink tablets marked with “RSN” on one side and “75 mg” on the reverse; manufacturing lot numbers are provided in Appendix 18) were provided in packages of 6 or 12 tablets/pack. Risedronate does not require any special storage conditions. The inactive ingredients for risedronate tablets include microcrystalline cellulose, crospovidone, and magnesium stearate.

Duration of Treatment: 12 Months

Study Endpoints:

Primary: Percent change from baseline in total hip BMD at month 12

Secondary:

- Percent change from baseline in serum CTX1 at month 1 (in a subset of subjects)
- Percent change from baseline in femoral neck BMD at month 12
- Percent change from baseline in lumbar spine BMD at month 12

Exploratory:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Safety:

- Adverse event incidence
- Changes in safety laboratory analytes (serum chemistry, hematology)
- Changes in vital signs
- Subject incidence of antidenosumab antibodies

Statistical Methods:

All efficacy analyses were performed based on subjects' randomized treatment assignment, regardless of the treatment received, and were summarized by randomized treatment group. All safety data were summarized by actual treatment received, where subjects who received ≥ 1 dose of denosumab were analyzed in the denosumab treatment group regardless of the randomized treatment. Continuous variables were summarized descriptively using mean, median, standard deviation (SD), quartiles (Q1 and Q3), minimum, maximum, and number of nonmissing observations. Frequencies and percentages were presented for nominal and ordinal categorical variables. All statistical hypothesis testing was conducted at the 2-sided, 5% significance level. Based on the Full Analysis Set, the primary analysis used an analysis of covariance (ANCOVA) model adjusting for treatment, time of BMD assessment (study day [continuous]), treatment-by-time interaction, baseline BMD value, dual energy x-ray absorptiometry (DXA) machine type [Hologic or Lunar], and baseline BMD value by DXA machine type interaction. Analysis of variance results included least-squares means (LSM) point estimates of the percent change from baseline for each treatment group at month 12. The 95% two-sided confidence interval (CI) and associated p-value were provided for the treatment difference between the LSM for denosumab and risedronate.

The subject incidence of each adverse event was tabulated by system organ class, preferred term, seriousness, and relationship to treatment. Clinical laboratory parameters were summarized using descriptive statistics and/or shift tables. The proportion of subjects developing antidenosumab antibodies was calculated.

Summary – Results

Subject Disposition:

In total, 870 subjects were enrolled and randomized to receive either denosumab (n = 435) or risedronate (n = 435); of these, 858 (99%) received ≥ 1 dose of investigational product (429 subjects in each treatment group) and were included in the safety analysis set. (One subject [redacted] who received risedronate per randomized assignment during the first 6 months was incorrectly given denosumab at the month-6 visit; this subject was counted in both treatment groups for investigational product exposure and was analyzed in the denosumab treatment group for all safety analyses.) Forty-six subjects (13 denosumab; 33 risedronate) withdrew from the study; in both treatment groups (denosumab; risedronate), the most commonly cited reasons for study discontinuation were withdrawal of consent (7/435 [2%] subjects; 15/435 [3%] subjects) and adverse event occurrence (3/435 [1%] subjects; 13/435 [3%] subjects). Overall, 824 (95%) subjects completed the study (422 [97%] denosumab-treated subjects; 402 [92%] risedronate-treated subjects).

Baseline Demographics:

Sex: 100% women

Age (mean [SD]): 67.7 (6.9) years of age, overall (denosumab: 67.8 [7.0] years; risedronate: 67.7 [6.8] years)

Ethnicity/Race:
Denosumab: 424 (97.5%) white/Caucasian; 7 (1.6%) Hispanic/Latino; 3 (0.7%) Asian; 1 (0.2%) Japanese.

Risedronate: 425 (97.7%) white/Caucasian, 6 (1.4%) Hispanic/Latino; 4 (0.9%) Asian.

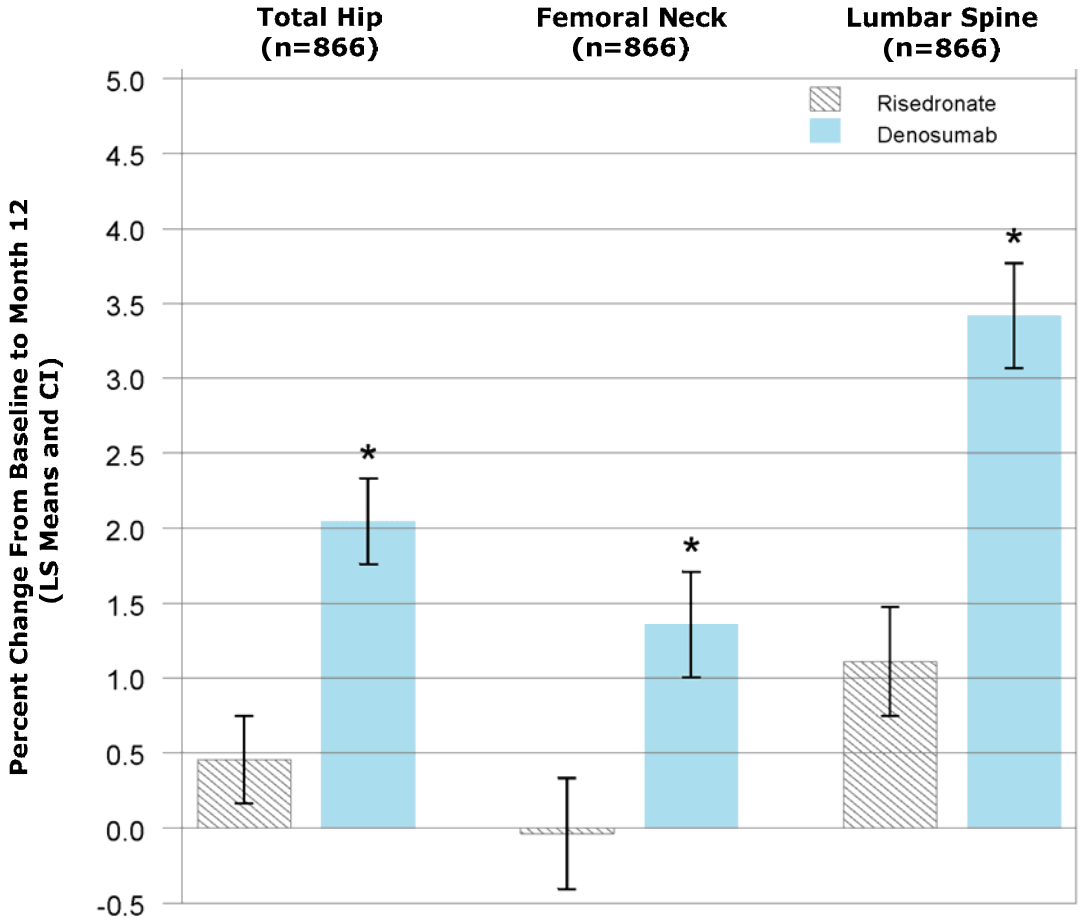
Efficacy Results:

Relative to risedronate (150 mg PO QM), denosumab (60 mg SC Q6M) significantly increased total hip BMD at month 12; the difference between treatment groups in mean percent change from baseline was 1.6% ($p < 0.0001$; 95% CI: 1.2%, 2.0%). Denosumab also significantly ($p < 0.0001$) increased BMD at all other skeletal sites measured, compared with risedronate, with mean differences between treatment groups of 1.4% and 2.3% at the femoral neck and lumbar spine, 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. After controlling for additional covariates (baseline age, prior alendronate treatment [duration, time since initiation, time since discontinuation, and branded or generic alendronate], previous osteoporotic fractures, and serum CTX1), individually and simultaneously in the primary ANCOVA model, the effect of denosumab treatment was consistent and significant ($p < 0.0001$ for the treatment effect in each analysis) at all three skeletal sites.

When primary and secondary endpoints were analyzed by subgroups—including by age, prior alendronate treatment (duration, time since initiation, time since discontinuation and branded or generic alendronate), previous osteoporotic fractures, and serum CTX1—the results demonstrated that increases in total hip, femoral neck, and lumbar spine BMD were numerically greater in the denosumab group than in the risedronate group at month 12 in all subgroups. While significant quantitative interactions were detected in subgroups determined by age group (< 75 and ≥ 75 years) for total hip and baseline serum CTX for all sites, no qualitative interactions were detected (Gail and Simon test). These results show that while BMD increases were consistently evident in all denosumab-treated subjects within these subgroups, the magnitude of increases at the total hip was greater among younger (< 75 years) subjects, and was greater at all skeletal sites among subjects in the middle and upper CTX1 tertiles.

Bone Mineral Density Percent Change From Baseline at Month 12 by Anatomical Site – Least Squares Means and 95% CIs From ANCOVA (Full Analysis Set, Regression Imputation for Missing Postbaseline)



* Indicates significance at the 1% level without multiplicity adjustments.
Source: Modified from Figure 14-4.5.1

[redacted]

Safety Results:

A total of 858 subjects received ≥ 1 dose of either denosumab (n = 429) or risedronate (n = 429), constituting the Safety Analysis Set.

Overall, the subject incidence of adverse events was 269 subjects (62.7%) in the denosumab group and 293 subjects (68.3%) in the risedronate group, with the most frequently experienced adverse events (≥ 4% in either treatment group [denosumab, risedronate]) being hypertension (4.2%, 2.6%), arthralgia (4.0%, 4.4%), nasopharyngitis (3.5%, 4.2%), and constipation (3.3%, 5.1%). Most of the adverse events in both groups were categorized as being either mild or moderate in severity. The incidence of adverse events considered by the investigator to be related to investigational product was 8.2% in the denosumab group and 11.2% in the risedronate group. The most common (> 1 subject) treatment-related adverse events among denosumab-treated subjects included flatulence in 3 subjects, as well as arthralgia, pruritus, and atrial fibrillation, occurring at a prevalence of 2 subjects for each event. In the risedronate group, the most common (> 1 subject) treatment-related adverse events were gastroesophageal reflux disease (8 subjects), upper abdominal pain (7 subjects), nausea (6 subjects), constipation (5 subjects), dyspepsia (5 subjects), influenza-like illness (3 subjects), and—in 2 subjects each—diarrhea, gastritis, vomiting, fatigue, and pyrexia.

In the denosumab and risedronate groups, 3 subjects (0.7%) and 13 subjects (3.0%), respectively, had adverse events leading to withdrawal from the study; none of the adverse events leading to study discontinuation was experienced by > 1 subject in either treatment group.

The incidence of serious adverse events was 8% in both treatment groups; there was no evidence of clustering of serious adverse events within any given system organ class or high-level group term in either treatment group. Serious adverse events reported for > 1 denosumab-treated subject were osteoarthritis, radius fracture, cerebral ischemia, cerebrovascular accident, arthralgia, and atrial fibrillation; these serious adverse events were each experienced by 2 (0.5%) denosumab-treated subjects. In the risedronate treatment group, the most frequently reported serious adverse events (2 subjects each) were breast cancer and coronary artery stenosis; all other serious adverse events were experienced at an incidence of 1 subject each. One subject died during the study (risedronate group) as a result of an adverse event of cardiac arrest considered by the investigator to be unrelated to investigational product.

Overall, there were no significant imbalances noted in adverse events of interest. Of the predefined adverse events of interest, there were no adverse events of hypocalcemia, positively adjudicated osteonecrosis of the jaw (ONJ), fracture-healing complications, or positively adjudicated atypical femoral fractures. Adverse events potentially associated with hypersensitivity were more frequently observed among risedronate-treated subjects (3.5% [15 subjects]) than among denosumab-treated subjects (1.9% [8 subjects]%); in the risedronate group, 1 subject experienced a serious adverse event of anaphylactic shock that the

investigator considered to have no causal relationship with investigational product. Rates (denosumab, risedronate) of infection (23%, 21%), bacterial cellulitis (1% each), malignancy (1%, 2%), cardiac disorders (3%, 2%), vascular disorders (6%, 4%), eczema (1% each), and acute pancreatitis (0.2%, 0.5%) were similar between treatment groups.

Serum samples for antidenosumab antibody testing were collected at day 1 and month 12. Of the 429 samples, 1 subject was positive for pre-existing nonneutralizing antidenosumab binding antibodies in the baseline sample. This sample was tested in the bioassay and was negative for neutralizing activity towards denosumab; this subject's EOS sample was negative for antidenosumab binding antibodies. No samples were positive for antidenosumab antibodies at month 12.

Serum calcium levels were similar over time in both treatment groups. Both treatment groups had identical mean calcium concentrations at baseline (2.45 mmol/L) and month 12 (2.47 mmol/L). No subjects had Common Terminology Criteria for Adverse Effects (CTCAE) grade ≥ 2 low serum calcium values during the study. No other consistent trends in serum chemistry or hematology parameters were indicative of a treatment effect for either denosumab or risedronate. Neither denosumab nor risedronate was associated with clinically significant changes in vital signs.

Conclusions: Denosumab 60 mg Q6M reduced bone turnover and increased BMD at all measured skeletal sites to a greater extent than risedronate. Denosumab, based on treatment-satisfaction scores and given the low incidence of withdrawal due to adverse events, was generally well tolerated; no new safety risks safety risks were identified in this open-label study. [redacted]