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 Ibandronate in Postmenopausal Women Sub-optimally Treated with Daily or Weekly Bisphosphonates

Investigator(s) and Study Center(s): This study was conducted at 74 centers in the United States and Europe. Centers and principal investigators are listed in Appendix 4.

Publication(s): None.

Study Period: 29 July 2009 (first subject randomized) through 09 November 2011 (last subject end-of-study date)

Development Phase: 3b

Objectives:

Primary:

The primary objective was to evaluate the change in total hip bone mineral density (BMD) at 12 months in postmenopausal women transitioning from previous daily or weekly bisphosphonate therapy to denosumab 60 mg subcutaneous (SC) once every 6 months (Q6M) compared to that in subjects transitioning to ibandronate 150 mg oral (PO) monthly (QM).

Secondary:

The secondary objective of the study was to evaluate the effects of transitioning to denosumab 60 mg SC Q6M in comparison to transitioning to ibandronate 150 mg PO QM on:

- Serum C-telopeptide (CTX1) levels at 1 month (in a subset of patients)
- BMD at the femoral neck at 12 months
- BMD at the lumbar spine at 12 months

Safety Objective:

To evaluate safety and tolerability measured by evaluating adverse events, laboratory analytes, and antidenosumab antibodies, over 12 months.

Exploratory:

[redacted]

Methodology: This was a multicenter, randomized, open-label, parallel-group study in postmenopausal women with low BMD who had previously been treated for osteoporosis with bisphosphonate therapy. Approximately 800 subjects were randomized (1:1) to receive either SC administrations of denosumab 60 mg Q6M (total of 2 injections) or ibandronate 150 mg PO QM. The treatment duration was 12 months. All potential subjects attended a screening visit to establish eligibility and to have low BMD confirmed by dual-energy x-ray absorptiometry (DXA) scans. 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 ibandronate 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 (≥ 500 mg elemental calcium) and vitamin D (≥ 800 IU). Safety was assessed by adverse event monitoring, by changes in laboratory parameters and vital signs results, and by antidenosumab antibody analysis.

Substudy: A bone marker substudy was conducted in a subset of subjects for analysis of type-1 serum C-telopeptide (CTX1) at month 1 [redacted] It was estimated that approximately 250 subjects would have serum CTX1 collected.

Number of Subjects Planned: 800

Number of Subjects Enrolled: 833

Number of Subjects Planned for Bone Marker Substudy: 250

Number of Subjects Enrolled in Bone Marker Substudy: 280

Diagnosis and Main Criteria for Eligibility: Postmenopausal women with osteoporosis who had received their first prescription of daily or weekly bisphosphonate therapy ≥ 1 month prior to screening. In addition, eligible subjects had either discontinued bisphosphonate treatment ≥ 1 month prior to screening or were still receiving treatment but had demonstrated insufficient adherence to their 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:

Oral ibandronate tablets (manufacturing lot numbers are provided in Appendix 18) were provided in a box containing two blister cards, with each card containing three 150-mg tablets. Ibandronate does not require any special storage conditions. The inactive ingredients for 150-mg ibandronate tablets include lactose monohydrate, povidone, cellulose (microcrystalline), crospovidone, steric acid, silica (colloidalanhydrous), hypromellose, titanium dioxide E171, talc, and macrogol 6000.

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]

Safety:

- Adverse event incidence
- Changes in safety laboratory analytes (serum chemistry, hematology) from baseline to month 12
- Changes in vital signs
- Subject incidence of antidenosumab antibodies

Statistical Methods:

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, 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 ibandronate.

Safety analyses were performed on all subjects who received ≥ 1 dose of investigational product. 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, 833 subjects were enrolled and randomized to receive either denosumab (n = 417) or ibandronate (n = 416); of these, 821 (99%) received ≥ 1 dose of investigational product (411 subjects in the denosumab group; 410 subjects in the ibandronate group). A total of 79 subjects (9.5%) withdrew from the study (denosumab: 19 [5%]; ibandronate: 60 [14%]), with the most commonly cited reasons for study discontinuation being withdrawal of consent (denosumab: 9 [2%]; ibandronate: 19 [5%]) and adverse event occurrence (denosumab: 4 [1%]; ibandronate: 13 [3%]). In the denosumab group, none of the adverse events leading to study discontinuation was experienced by > 1 subject; among ibandronate-treated subjects, the only adverse event leading to withdrawal from the study that was experienced by > 1 subject was arthralgia, experienced by 2 subjects. Overall, 754 (91%) subjects completed the study (398 [95%] denosumab-treated subjects; 356 [86%] ibandronate-treated subjects).

Baseline Demographics:

Sex: 100% women

Age (mean [SD]): 67 (8.0) years of age, overall (denosumab: 67 [8.1] years; ibandronate: 66 [7.8] years)

Ethnicity/Race: Denosumab: 348 (83.5%) white/Caucasian; 54 (12.9%) Hispanic/Latino; 6 (1.4%) Native Hawaiian/Other Pacific Islander; 3 (0.7%) black/African American; 3 (0.7%) Asian; 2 (0.5%) American Indian/Alaska Native; 1 (0.2%) other.

Ibandronate: 361 (86.8%) white/Caucasian, 42 (10.1%) Hispanic/Latino; 4 (1.0%) Asian; 4 (1.0%) black/African-American; 3 (0.7%) Native Hawaiian or Other Pacific Islander; 2 (0.5%) other.

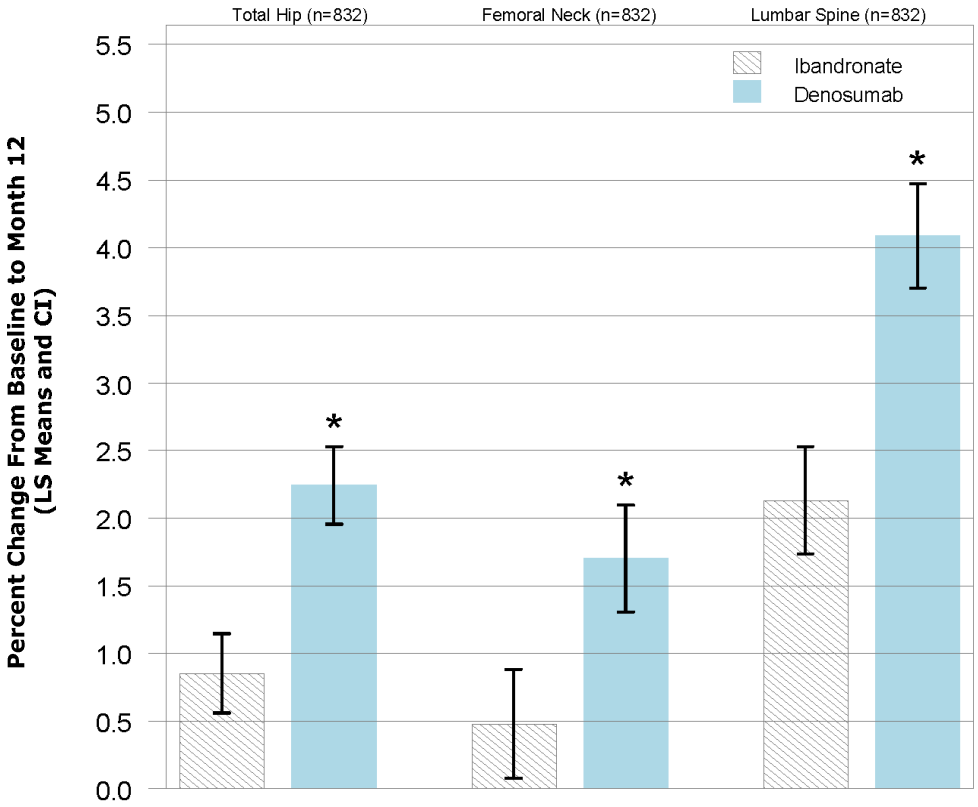
Efficacy Results:

Relative to ibandronate (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 1.4% ($p < 0.0001$; 95% CI: 1.0%, 1.8%). Denosumab also significantly increased BMD at all other skeletal sites measured, compared with ibandronate, with mean differences between treatment groups of 1.2% and 2.0% 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. When primary and secondary endpoints were analyzed by subgroups—including by age group, prior bisphosphonate treatment (duration of use, time since initial prescription, time since discontinuation), and previous osteoporotic fractures—the results demonstrated that denosumab's effect on total hip, lumbar spine, and femoral neck BMD remained both consistent and significantly greater than ibandronate's effects at month 12.

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)



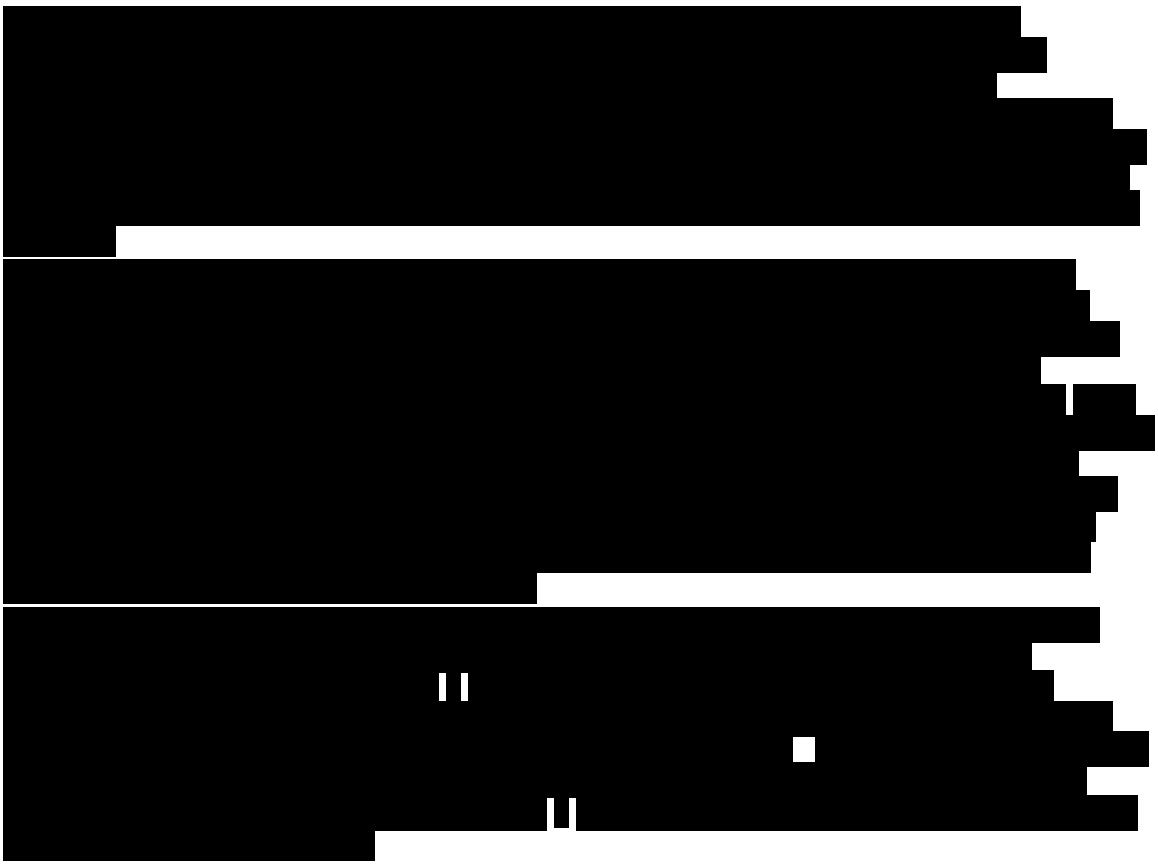
* Indicates significance at the 5% level without multiplicity adjustments.

Source: Figure 14-4.5.1

Bone Turnover Marker Substudy Results:

A total of 247 subjects (denosumab =134; ibandronate = 113) were included in the bone turnover marker substudy. At month 1, concentrations of the bone-resorption marker serum CTX1 exhibited median (Q1, Q3) percent change decreases from baseline in both the denosumab (-81.1% [-88.0%, -70.9%]) and ibandronate (-35.0% [-51.9%, -15.3%]) treatment groups; however, denosumab was associated with significantly greater ($p < 0.0001$) decreases from baseline in serum CTX1 than those noted among subjects treated with ibandronate. [redacted]

OS-MMAS Reliability and Construct Validity and Patient-reported Outcome Scores:



Safety Results:

A total of 821 subjects received ≥ 1 dose of either denosumab (n = 411) or ibandronate (n = 410), constituting the Safety Analysis Set.

Overall, the subject incidences of adverse events were balanced between treatment groups. A total of 245 subjects (59.6%) in the denosumab group and 230 subjects (56.1%) in the ibandronate group experienced ≥ 1 adverse event during the study, with the most frequently experienced adverse events (≥ 4% in either treatment group [denosumab, ibandronate]) being arthralgia (6.1%, 5.6%), upper respiratory tract infection (5.1%, 2.2%), and urinary tract infection (3.4%, 4.6%). Most of the adverse events in both groups were categorized as being either mild or moderate in severity.

The incidence of treatment-related adverse events was 8.5% in the denosumab group and 12.9% in the ibandronate group. The most common (≥ 4 subjects overall) treatment-related adverse events were (denosumab, ibandronate) arthralgia (6 subjects, 5 subjects), gastroesophageal reflux disease (1 subject, 6 subjects), headache (1 subject, 5 subjects), myalgia (2 subjects, 3 subjects), dyspepsia (2 subjects, 3 subjects), nausea (1 subject, 4 subjects), constipation (2 subjects, 2 subjects), flatulence (2 subjects, 2 subjects), upper abdominal pain (0 subjects, 4 subjects), and pruritus (3 subjects, 1 subject).

In the denosumab and ibandronate groups, 4 subjects (1%) and 12 subjects (3%), respectively, had adverse events leading to withdrawal from the study. In the denosumab group, none of the adverse events leading to study discontinuation was experienced by > 1 subject; among ibandronate-treated subjects, the only adverse event leading to withdrawal from the study that was experienced by > 1 subject was arthralgia, experienced by 2 subjects.

Thirty-nine subjects (10%) in the denosumab group and 22 subjects (5%) in the ibandronate group experienced serious adverse events. Serious adverse events reported for > 1 subject in the denosumab treatment group included congestive cardiac failure as well as chest pain (3 subjects each event), and diverticulitis, atrial fibrillation, bradycardia, sick sinus syndrome, and

cerebrovascular accident (2 subjects each event). In the ibandronate treatment group, none of the serious adverse events was experienced by > 1 subject. 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. One subject died during the study (ibandronate group) as a result of a gunshot wound.

Overall, there were no significant imbalances seen in adverse events of interest between treatment groups. Of the predefined adverse events of interest, there were no adverse events of osteonecrosis of the jaw (ONJ), fracture healing complications, atypical femoral fractures, or acute pancreatitis reported during the study. Subject incidences of hypocalcemia, infection, malignancy, cardiac disorders, vascular disorders, and adverse events potentially associated with hypersensitivity were similar between treatment groups. Eczema was reported for 7 subjects (1.7%) in the denosumab group and 2 subjects (0.5%) in the ibandronate group; none of the adverse events of eczema met the criteria of a serious adverse event.

Antidenosumab antibody testing revealed that none of the samples for the 411 denosumab-treated subjects were positive for antidenosumab binding antibodies.

Serum calcium levels were similar over time in both treatment groups. Both treatment groups had identical mean calcium concentrations at baseline (2.43 [0.09] mmol/L) and month 12 (2.46 [0.10] 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 ibandronate. Neither denosumab nor ibandronate 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 ibandronate. Denosumab was generally well tolerated, and was associated with a lower incidence of withdrawals due to adverse events than ibandronate; no new safety risks were identified in this open-label study. [redacted]. Subjects treated with denosumab also demonstrated greater treatment satisfaction and improvement in gastrointestinal symptoms, compared to ibandronate.