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

Name of Finished Product:
Denosumab (AMG 162)

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

Title of Study:
A Randomized, Double-Blind Study to Compare the Efficacy of Treatment with Denosumab versus Alendronate Sodium in Postmenopausal Women with Low Bone Mineral Density

Investigators and Study Centers:
This was a multicenter study conducted at 86 centers in North America (49 in the United States and 7 in Canada), Western Europe (4 in Denmark, 4 in Belgium, 5 in Germany, 5 in Spain, and 4 in the United Kingdom), Australia (4), and Latin America (2 in Brazil and 2 in Argentina).

Publications:
None as of the date of this report.

Study Period:
26 April 2006 (first subject enrolled) through 07 December 2007 (last subject's end-of-study visit)

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, and neutralizes the activity of, human RANKL. In a phase 2 study in postmenopausal women with low bone mineral density (BMD, assessed by dual energy x-ray absorptiometry [DXA]) ($-4.0 \leq$ T-score ≤ -1.8 for the spine or $-3.5 \leq$ T-score ≤ -1.8 for the total hip or femoral neck), denosumab administration for up to 4 years increased mean BMD at the lumbar spine, total hip, femoral neck, hip trochanter, distal 1/3 radius, and total body (without head).

The primary objective of the study was to evaluate the effect of denosumab compared to alendronate sodium on percent change from baseline in BMD at the total hip as measured by DXA at 12 months in postmenopausal women.

The secondary objectives were to evaluate the effect of denosumab compared to alendronate on (1) percent change from baseline in BMD at the distal 1/3 radius, hip trochanter, femoral neck, and lumbar spine at 12 months and (2) safety and tolerability by evaluating adverse events, laboratory parameters, and vital signs over 12 months.

Tertiary objectives were to evaluate the effects of denosumab compared to alendronate on (1) serum bone turnover markers (type 1 C-telopeptide [CTX1] and procollagen type 1 N-telopeptide [P1NP]) at 1, 3, 6, 9 and 12 months and (2) percent change from baseline in BMD at the total hip, distal 1/3 radius, hip trochanter, femoral neck, and lumbar spine as measured by DXA at 6 months. Exploratory objectives were to evaluate the effects of denosumab compared to alendronate on (1) change from baseline in utility score measured by the EuroQol-5 Dimensions (EQ-5D) at 6 and 12 months, (2) to determine the reliability and validity of the Preference and Satisfaction Questionnaire (PSQ), and (3) to determine patient reported preference and satisfaction for the weekly pill and the 6-month injection.

Methodology:
This international, multicenter, randomized, double-blind, active controlled, double-dummy, parallel-group study compared the efficacy of denosumab (60 mg subcutaneously [SC] every 6 months [Q6M]) for the improvement of BMD to that of alendronate (70 mg orally [PO] every week [QW]) in postmenopausal women with BMD T-scores ≤ -2.0 at either the lumbar spine or total hip. Subjects were randomized (1:1) in a blinded fashion to receive either denosumab plus

placebo for alendronate or alendronate plus placebo for denosumab for 12 months. All subjects received daily calcium (≥ 500 mg) and vitamin D (≥ 400 IU) supplementation. Subject safety was monitored on an ongoing basis throughout the trial by a Data Monitoring Committee (DMC).

Number of Subjects Planned:
1100 (550 in each treatment group)

Number of Subjects Enrolled:
A total of 1189 subjects were enrolled in the study and were randomized (1:1) to receive denosumab plus placebo for alendronate (594 subjects) or alendronate plus placebo for denosumab (595 subjects).

Sex: 100% women

Mean (SD) Age: 64.4 (8.5) years

Ethnicity (Race): 84% white or Caucasian, 11% Hispanic or Latino, 1% black or African American, 1% Asian, < 1% Japanese, < 1% American Indian or Alaska Native, < 1% Native Hawaiian or other Pacific Islander, and < 1% other

Diagnosis and Main Criteria for Eligibility:
Subjects were postmenopausal women with low BMD (T-score ≤ -2.0 at the lumbar spine or total hip), ambulatory, in general good health, not receiving medications that affect bone metabolism, and free from any underlying conditions that may result in abnormal bone metabolism.

Duration of Treatment:
12 months

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number:
Denosumab was provided as a sterile, clear, colorless, preservative-free liquid in glass vials containing 60 mg denosumab per mL of 10 mM sodium acetate and 5% sorbitol in water for injection, with a pH of 5.2. One mL of blinded investigational product was administered SC at day 1 and at month 6. Lot numbers for denosumab used in this study were 049A055815 and 049A061751.

Subjects who received active denosumab also received placebo for alendronate. The placebo for alendronate contained the same ingredients, microcrystalline cellulose and magnesium stearate, as the commercially available 70-mg tablet of alendronate sodium. The placebo also contained pregelatanized starch, colloidal silicon dioxide, and crospovidone in place of anhydrous lactose and croscarmellose sodium, respectively. Also the active ingredient (alendronate monosodium salt trihydrate) was omitted. One tablet of blinded investigational product was taken PO QW. The sponsor tracking numbers for placebo for alendronate used in this study were 099D068395, 099D076782, 099D082785, and 099D089962.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number:
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 PO QW. Sponsor tracking numbers for alendronate used in this study were 099D068392, 099D076780, 099D082790, and 099D089960.

Subjects who received active alendronate also received placebo for denosumab. Placebo for denosumab was provided in vials 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 month 6. The lot number for placebo for denosumab used in this study was 049A037350.

Study Endpoints

Primary Efficacy Endpoint:

- Percent change from baseline in total hip BMD at 12 months

Secondary Efficacy Endpoints:

- Percent change from baseline in BMD at the 1/3 distal radius, hip trochanter, femoral neck, and lumbar spine at 12 months

Tertiary Efficacy Endpoints:

- Percent change from baseline in serum bone turnover markers (type 1 collagen C-telopeptide [CTX1] and procollagen type 1 N-telopeptide [P1NP]) at 1, 3, 6, 9, and 12 months
- Percent change from baseline in BMD at the total hip, 1/3 distal radius, hip trochanter, femoral neck, and lumbar spine at 6 months

Safety Endpoints:

- Adverse event incidence
- Actual values and changes in safety laboratory analytes (serum chemistry, hematology)
- Serum chemistry and hematology laboratory shifts between baseline and the most extreme value during the study
- Actual values and changes from baseline in vital signs at each scheduled visit
- Subject incidence of antidenosumab antibody formation

Exploratory Endpoints:

- Subject incidence of level of BMD response (percent change from baseline $\leq$ 0%, > 0% to 3%, and > 3%) in lumbar spine, total hip, and femoral neck BMD at 6 and 12 months
- Change from baseline in the EQ-5D health state index score at 6 and 12 months
- Change from baseline in the EQ-5D visual analog scale (VAS) at 6 and 12 months
- Proportion of patient reported preference (weekly pill versus 6-month injection)
- Proportion of patient reported satisfaction (weekly pill versus 6-month injection)
- Subject incidence of clinical fractures during the 12 months of evaluation period

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 or ordinal categorical). Frequencies and percentages were presented for nominal categorical variables.

The primary, secondary, and tertiary efficacy endpoints were tested using inferential analysis. The approach for handling multiplicity for the primary and secondary hypotheses included both a hierarchical testing strategy and the Hochberg procedure.

Statistical inferences of the treatment effects on the secondary hypotheses were only to be made when denosumab was concluded noninferior to alendronate with respect to mean percent change in total hip BMD at month 12 at the 1-sided significance level of 0.025. All the secondary hypotheses were tested simultaneously (including superiority hypothesis testing of total hip, distal 1/3 radius, and hip trochanter BMD as well as noninferiority hypothesis testing of hip trochanter, femoral neck, and lumbar spine BMD) and the Hochberg procedure was employed to control the overall type I error for the secondary hypotheses in order to maintain the overall 1-sided significance level at 0.025.

The approach for handling multiplicity within each of the bone turnover markers (CTX1 and P1NP) used the Hochberg methodology within percent change in each marker across the multiple evaluations (months 1, 3, 6, 9, and 12). This adjustment controlled the 2-sided error rate at 5% within each of the bone turnover markers, but this adjustment was independent of controlling the overall error rate for the primary hypothesis and 6 secondary hypotheses (ie, percent changes in BMDs at 12 months).

Safety was characterized by tabulating adverse event incidence by system organ class and preferred term (coded using Medical Dictionary for Regulatory Authorities [MedDRA] version 9.0); 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; and subject incidence of antidenosumab antibody appearance (negative/positive).

Summary of Results:

Subject Disposition:
A total of 1189 subjects were enrolled into the study, with 594 subjects randomized to the denosumab group and 595 subjects to the alendronate group. Of the 1189 subjects enrolled into the study, 1179 subjects (593 denosumab, 586 alendronate) received at least 1 dose of active investigational product. Ninety-four percent of subjects in the denosumab group and 93% of subjects in the alendronate group completed the study.

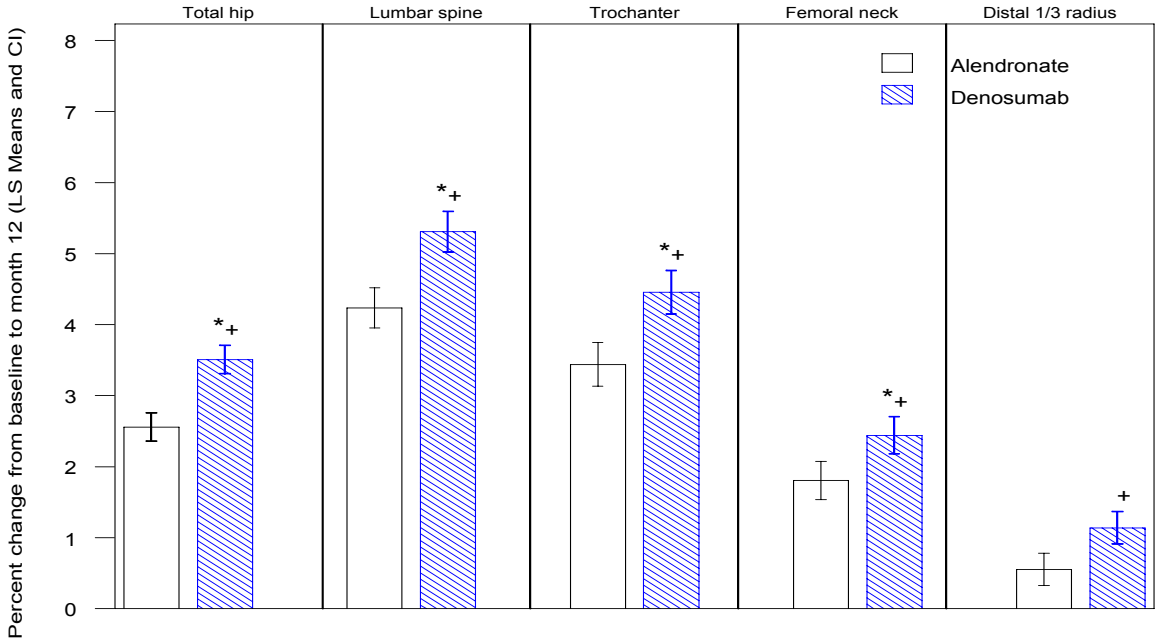
Efficacy Results:
All primary and secondary efficacy endpoints (including testing for both noninferiority and superiority of denosumab) were met with statistical significance (Figure 1). At month 12, the mean percent change in total hip BMD was 3.5% in the denosumab and 2.6% in the alendronate group (1-sided $p < 0.0001$). Since noninferiority for this primary efficacy endpoint was met, the prespecified secondary endpoints were inferentially evaluated. Results of superiority testing were statistically significantly in favor of denosumab for the total hip, hip trochanter, and distal 1/3 radius at month 12 (1-sided $p \leq 0.0001$ after multiplicity adjustment). While not prespecified, superiority testing at the lumbar spine and femoral neck also demonstrated that the denosumab-treated subjects showed greater gains in BMD compared with the alendronate-treated subjects at month 12 (1-sided $p \leq 0.0001$ after multiplicity adjustment with all BMD efficacy endpoints). Furthermore, at month 6 (the earliest timepoint measured), the differences in BMD gains at all measured site also were significant ($p \leq 0.0014$). A greater percentage of denosumab subjects had a > 3% increase in BMD at the total hip by 12 months than alendronate subjects (62% denosumab, 39% alendronate; $p < 0.0001$), a finding that also was observed at the

lumbar spine (77% denosumab, 65% alendronate; $p < 0.0001$) and femoral neck (42% denosumab, 34% alendronate; $p = 0.0003$).

Clinical fractures were reported by the investigators for 18 subjects (3%) in the denosumab group and 13 subjects (2%) in the alendronate group.

Subjects who received denosumab, as compared with those who received alendronate, had significantly greater decreases in serum concentrations of CTX1 from baseline at months 1, 3, 6, and 9 ($p \leq 0.0001$); at month 12, the decreases in serum CTX1 concentrations were similar for both treatment groups. Subjects who received denosumab, as compared with those who received alendronate, also had significantly greater decreases in serum concentrations of P1NP from baseline at months 1, 3, 6, 9, and 12.

Figure 1. Bone Mineral Density by DXA Percent Change From Baseline at Month 12
Least Squares Means and 95% CIs From ANCOVA Model
(Primary Efficacy Subset, LOCF)



Least squares means with 95% CIs based on ANCOVA models adjusting for treatment, baseline value, machine type, and baseline value-by-machine type interaction
*** Indicates significance of non-inferiority test after multiplicity adjustments at one-sided 2.5% level**
+ Indicates significance of superiority test after multiplicity adjustments at one-sided 2.5% level
The prespecified non-inferiority margins of percent changes from baseline in total hip, lumbar spine, femoral neck, and hip trochanter BMD at 12 months are 1.22%, 2.29%, 1.04%, and 1.65%, respectively.
The non-inferiority tests were prespecified for the total hip, lumbar spine, hip trochanter, and femoral neck.
The superiority tests were only prespecified for the total hip, hip trochanter, and distal 1/3 radius.

Source Data: adam.abmdxa
Output: g14-02_008_001_ci_dxa_pchg_barp_locf_p.cgm (Date Generated: 01MAY2008:16:48:49)
Program: /stat/amg162/osteo/20050141/analysis/final/adhoc/program/g_ci_dxa_pchg_barp.s

ANCOVA = analysis of covariance; LOCF = last observation carried forward

Patient-reported Outcome Results:
No between-group differences were observed for the change from baseline in utility score measured by the EQ-5D at 6 and 12 months. 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. Both convergent and divergent validity of the PSQ was demonstrated. The questionnaire proposed for use in future studies retained 2 individual preference items and 3 scales (eg, satisfaction, pill-bother, and injection-bother).

Safety Results:
A total of 1179 subjects (593 randomized to denosumab, 586 randomized to alendronate) received active 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 also were similar between treatment groups.

At least 1 adverse event was reported by 480 subjects (81%) in the denosumab group and 482 subjects (82%) in the alendronate group; most of these events were mild to moderate in severity. The 3 most frequent adverse events were (denosumab, alendronate) arthralgia (12.6%, 9.6%), nasopharyngitis (7.6%, 7.3%), and back pain (7.1%, 9.6%). The incidences of treatment-related (investigator attributed) events were 17.0% in the denosumab group and 18.3% in the alendronate group. The most frequent treatment-related adverse events (ie, incidence $\geq$ 1% in either treatment group) were (denosumab, alendronate) dyspepsia (3.0%, 2.9%), arthralgia (1.9%, 0.9%), headache (1.7%, 0.9%), gastroesophageal reflux disease (1.2%, 1.5%), and nausea (0.7%, 1.9%). No events of hypocalcemia were reported as adverse events by the investigators. A similar proportion of subjects in each treatment group had adverse events of infection (37.3% in the denosumab group and 35.7% in the alendronate group). Serious events within the neoplasms system organ class also were balanced between treatment groups (1.3% denosumab, 1.0% alendronate).

The proportions of subjects who discontinued investigational product (denosumab 4.4%, alendronate 3.8%) or withdrew from study (denosumab 1%, alendronate 2%) due to adverse events were similar between the treatment groups. Serious adverse events were reported for 34 subjects (6%) in the denosumab group and 37 subjects (6%) in the alendronate group. Most serious adverse events were reported with an incidence of 1 subject, and no serious adverse events were considered related to treatment in the denosumab group. Two subjects died during the study (1 subject in the denosumab group from cardio-respiratory arrest and 1 subject in the alendronate group from metastatic neoplasm).

No trends in serum chemistry or hematology parameters were noted other than modest, expected decreases in serum calcium, phosphorus, and total alkaline phosphatase. One subject in the denosumab group experienced asymptomatic grade 2 hypocalcemia (defined as 1.75 to < 2 mmol/L as per CTCAE v3.0) at month 1 (1.8 mmol/L), which normalized at subsequent visits. No subjects in the alendronate group experienced grade 2 or higher hypocalcemia. Three subjects in the denosumab group had grade 3 or 4 increases in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) values, concurrent with acute hepatitis in 1 subject and statin use in the other 2 subjects. Elevated AST and ALT values subsequently returned to either to normal (2 subjects) or to grade 1 (1 subject). One subject in the denosumab group experienced a grade 3 increase in creatinine at the last scheduled visit.

No subject in the denosumab group developed antibodies to denosumab.