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 for 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 Aromatase Inhibitor Therapy for Nonmetastatic Breast Cancer

Investigator(s) and Study Center(s): This was a multicenter study conducted at 50 centers in the United States and 3 centers in Canada. Study centers and principal investigators are listed in Appendix 4.

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

Study Period: 04 October 2004 (first subject enrolled) to 11 May 2007 (last subject completed month-24 assessment). The 24-month safety follow-up period is ongoing.

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 (RANKL). Denosumab binds to, and neutralizes the activity of, human RANKL. Denosumab has the potential to be an effective treatment for the bone loss associated with aromatase inhibitor therapy in patients with breast cancer.

The primary objective of this study was to determine whether denosumab compared with placebo preserved lumbar spine bone mineral density (BMD) during aromatase inhibitor therapy in subjects with nonmetastatic breast cancer after 12 months.

The secondary objectives were to assess the effect of denosumab compared with placebo on BMD of the total hip and femoral neck and the safety and pharmacokinetics of denosumab in subjects with nonmetastatic breast cancer undergoing aromatase inhibitor therapy.

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Methodology: This was a multicenter, randomized, double-blind, placebo-controlled study in subjects with nonmetastatic breast cancer who were undergoing aromatase inhibitor therapy. Subjects were randomized (1:1) to receive either 60 mg denosumab or placebo SC once every 6 months for a total of 4 doses during the treatment period of 24 months. Randomization was stratified by the duration of aromatase inhibitor therapy (≤ 6 months vs > 6 months). All subjects received daily calcium and vitamin D supplements. Adverse events, the incidence of fracture, concomitant medications were evaluated predose and at months 1, 3, 6, 12, 15, 18, and 24 months after initiation of investigational product or at the early-termination visit; clinical laboratory parameters and vital signs were measured at the same time points, with the exception of months 3 and 15. Dual x-ray absorptiometry (DXA) of the spine, femoral neck, and total hip was performed at baseline, months 1, 3, 6, and 12, and at the early-termination/month-24 visit; DXA of the total body and radius was performed at baseline, month 12, at the early-termination/month-24 visit; x-rays were taken at baseline and month 24. Bone turnover markers were assessed at baseline, at months 1, 6, and 12, and at the early-termination/month-24 visit.

Serum samples were obtained before and during the treatment period for assessment of denosumab concentrations, anti-denosumab antibodies, and exploratory biomarkers. An external data monitoring committee (DMC) monitored subject safety on an ongoing basis for the duration of the 24-month treatment period.

Number of Subjects Planned: 208 subjects (104 subjects in each treatment group)

Number of Subjects Enrolled: A total of 252 subjects were enrolled and randomized to receive denosumab (127 [50%]) or placebo (125 [50%]). Ninety-three subjects (37%) were in the $\leq$ 6 months of aromatase inhibitor therapy stratum, and 159 subjects (63%) were in the $>$ 6 months of aromatase inhibitor therapy stratum.

Sex: 100% women

Age: Mean (SD): 59.5 (9.3) years

Race/Ethnicity: 93% white, 3% Hispanic, 1% black, 1% Asian, 1% other

Diagnosis and Main Criteria for Eligibility: Eligible subjects met the following criteria: women $\geq$ 18 years of age with the ability to provide informed consent who had histologically or cytologically confirmed early-stage, estrogen-receptor-positive adenocarcinoma of the breast; Eastern Cooperative Oncology Group (ECOG) score of 0 or 1; no distant metastases; completed treatment pathway (surgery, chemotherapy, radiation, and/or hormone therapy); currently on or initiating aromatase inhibitor therapy for the duration of the study; 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; no recent exposure to bisphosphonates or other medications known to influence bone metabolism; were not receiving concurrent anti-neoplastic agents; did not have recurrent disease; and had not experienced fracture after the age of 25. Eligible subjects had a lumbar spine, total hip, and/or femoral neck BMD T-score of -1.0 to -2.5 (low bone mass); none of these anatomic sites could have been in the BMD range corresponding to a T-score of $<$ -2.5 (Appendix H of the protocol provided in Appendix 1); and had $\geq$ 2 evaluable vertebrae for DXA assessments.

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. Manufacturing lot numbers are provided in Listing 14-5.1.

Duration of Treatment: This 48-month study includes a 24-month treatment period (with last dose administered at month 18) and a 24-month safety follow-up period. The 24-month safety follow-up period is ongoing.

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 in glass vials. The appearance and formulation of the placebo was identical to denosumab, with the exception of the active protein content. Manufacturing lot numbers for placebo are provided in Listing 14-5.1.

Study Endpoints

Primary

The primary endpoint was the percentage change in lumbar spine BMD from baseline to month 12.

Secondary

Secondary endpoints were the following:

- percentage change in lumbar spine BMD from baseline to month 6
- percentage change in total hip and femoral neck BMD from baseline to months 6 and 12

Safety

Safety endpoints were the subject incidence of adverse events; changes in safety laboratory parameters and vital signs; formation of anti-denosumab antibodies; and serum denosumab concentrations.

Exploratory

[redacted]

Statistical Methods:

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

Efficacy

The primary and secondary efficacy endpoints were analyzed for all randomized subjects who had observations for the relevant endpoint at baseline and at least once at or before the relevant time point. Analysis of the primary and secondary BMD endpoints employed an analysis of covariance (ANCOVA) model using the last observation value carried forward (LOCF) imputation. Primary conclusions on the efficacy of denosumab were made using the difference of the point estimates for the least-squares mean and the 2-sided 95% confidence interval (CI) for the treatment difference (denosumab - placebo) at month 12.

Sensitivity analyses were conducted to further evaluate results of analyses of the primary endpoint. These included ANCOVA models using the mean-of-the-other-group (MOTH) imputation for missing 12-month BMD values, the per-protocol analysis set with no imputation of missing values, and LOCF imputation using the actual strata rather than the as-randomized strata. An additional sensitivity analysis was conducted using a likelihood-based repeated-measures model that included treatment group, stratum, baseline BMD value, machine type, baseline BMD value and machine type interaction, visit, and visit-by-treatment interaction as fixed effects.

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Safety

Safety endpoints were analyzed for all subjects who received ≥ 1 dose of investigational product; subjects were analyzed according to actual treatment received rather than randomized treatment assignment (ie, a subject who received denosumab, regardless of randomized treatment assignment, was included in the denosumab group). The subject incidence of each adverse event was tabulated by system organ class and preferred term. Clinical laboratory parameters were summarized using descriptive statistics and/or shift tables. Vital signs, weight, and serum denosumab concentrations were summarized using descriptive statistics. The percentage of subjects developing anti-denosumab antibodies was tabulated.

Summary of Results:

This report provides results for the 24-month treatment period of the study. As of the date of this report, the 24-month safety follow-up period is ongoing.

Subject Disposition:

A total of 252 subjects were randomized (127 randomized to receive denosumab, 125 randomized to receive placebo). Randomization was stratified by duration of aromatase inhibitor therapy at study entry; 93 subjects (47 denosumab, 46 placebo) were in the ≤ 6 months of aromatase inhibitor therapy stratum, and 159 subjects (80 denosumab, 79 placebo) were in the > 6 months of aromatase inhibitor therapy stratum. Of the 252 subjects enrolled in the study, 249 subjects (125 denosumab, 124 placebo) received at least 1 dose of investigational product. Eighty-three percent of subjects in the denosumab group and 79% of subjects in the placebo group completed the 24-month treatment period.

Efficacy Results:

All primary and secondary efficacy endpoints were met with statistical significance. Treatment with denosumab statistically significantly increased BMD, as assessed by DXA, at the lumbar spine, total hip, and femoral neck at months 6 and 12 ($p < 0.0001$) (Figure 2-1). Significant increases in BMD were observed both in primarily trabecular (lumbar spine) and predominantly cortical (femoral neck) bone sites. Of the anatomic sites evaluated in the primary and secondary endpoints, the magnitude of the percentage increase in BMD relative to placebo was greatest at the lumbar spine at month 12 (least squares means of the percentage changes from baseline to month 12 were 4.8% in the denosumab group compared with –0.7% in the placebo group), a magnitude of change (ie, >3%) that is considered clinically meaningful. The effect of denosumab was rapid and sustained throughout the 24-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, including month 1 (with the exception of the month-1 femoral neck assessment, which showed no change in the denosumab group). Sensitivity analyses of the primary and secondary endpoints confirmed the results of the primary analysis.

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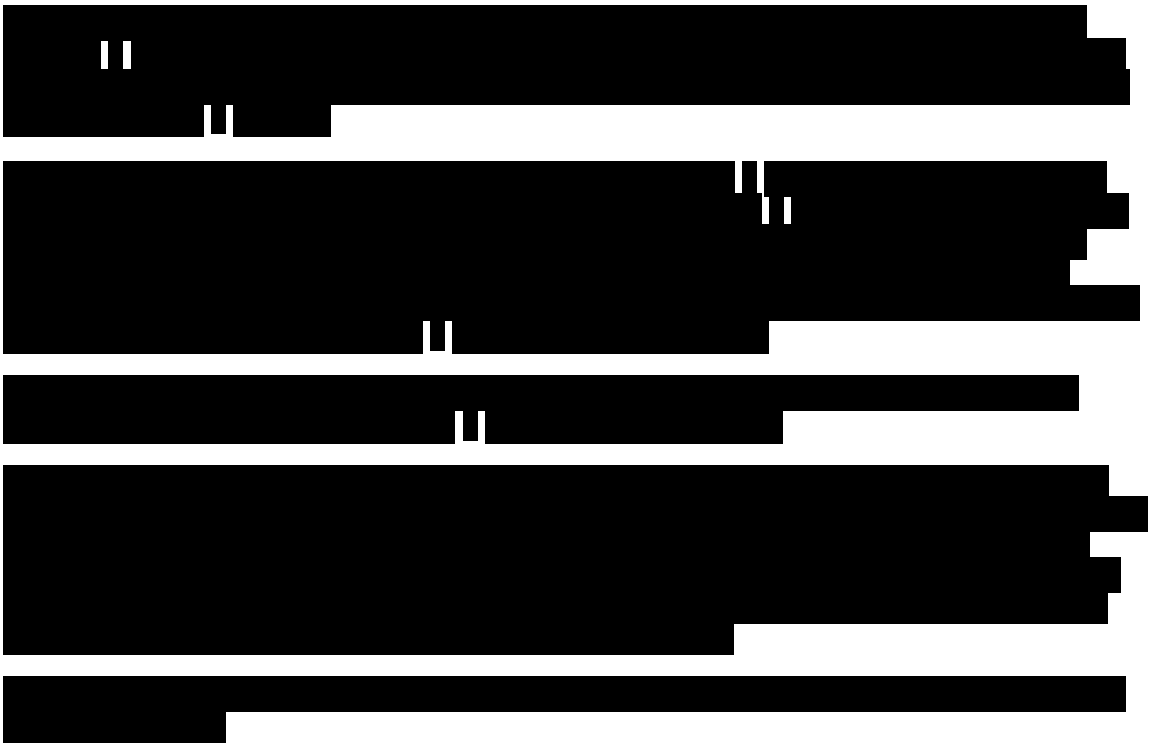
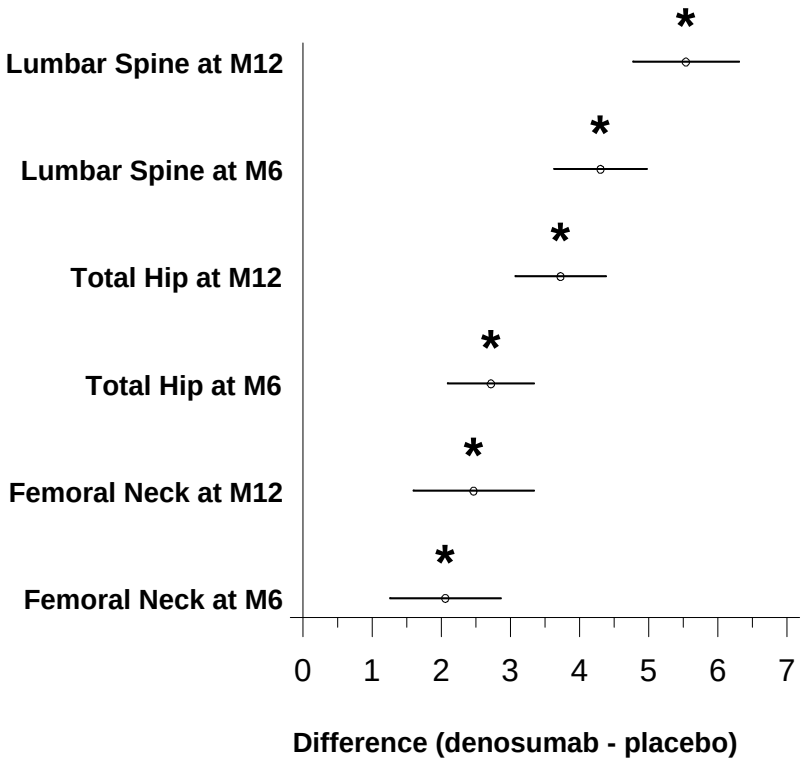


Figure 2-1. Primary and Secondary Endpoints – Percentage Changes in BMD From Baseline – Least Squares Means and Confidence Intervals (ANCOVA Model, Primary Efficacy Subset, LOCF Imputation)



Least squares means with 95% CIs based on ANCOVA model including treatment, stratification factor, baseline value, machine type, and baseline value-by-machine type interaction.
*** Indicates endpoints that were significant at the nominal 5% level for the overall comparisons**
P-values for secondary endpoints are adjusted with Hochberg's procedure for multiple comparisons.

Program: /stat/amg162/halt/20040135/analysis/mon24/graphs/program/g_ci_lsm_adj_pchg.sas
Output: g4-02_001_001_cilsm_adj_av_l.cgm (Date Generated: 19SEP2007:10:45:33)
Source Data: adam.abmdx

Safety Results:

Two hundred forty-nine subjects (129 who received denosumab, 120 who received placebo) received ≥ 1 doses of investigational product and were included in safety analyses.

The overall adverse event profile was similar in the denosumab and placebo groups and was consistent with what would be expected for subjects with breast cancer who were receiving adjuvant aromatase inhibitor therapy. The incidence of adverse events was similar between treatment groups (91% denosumab, 90% placebo). The most common adverse events were (denosumab, placebo) arthralgia (24%, 25%), pain in extremity (15%, 12%), back pain (14%, 13%), fatigue (13%, 14%), constipation (12%, 9%), cough (10%, 4%), and insomnia (9%, 12%). No adverse events of hypocalcemia were reported. The incidence of adverse events considered potential clinical manifestations of hypocalcemia (hypoesthesia and paresthesia) was 6% in the denosumab group and 3% in the placebo group. Adverse events in the neoplasms system organ class were reported for 15% of subjects in the denosumab group and 8% of subjects in the placebo group. Most of these events were not malignant in nature; the incidence of malignant disease progression (breast cancer) was 3% in both treatment groups (4 subjects in the denosumab group, 3 subjects in the placebo group), with a single new primary malignancy

(gastric cancer) reported for a subject in the placebo group. Adverse events in the infections and infestations system organ class were reported for 36% of subjects in the denosumab group and 32% of subjects in the placebo group, with no discernable pattern of differences between treatment groups in the type or severity of infectious events.

The proportion of subjects who withdrew from investigational product because of adverse events was similar between treatment groups (2% denosumab, 4% placebo). No subject withdrew from investigational product because of a serious or treatment-related adverse event.

The incidence and type of serious adverse events were consistent what would be expected for subjects with breast cancer who were receiving adjuvant aromatase inhibitor therapy. No serious adverse event was considered related to treatment with investigational product. Serious adverse events were reported for 19 subjects (15%) in the denosumab group and 11 subjects (9%) in the placebo group. No single system organ class or type of adverse event accounted for the higher incidence of serious adverse events in the denosumab group. Notably, by preferred term, most serious adverse events were reported for no more than 1 subject each. The only serious adverse events reported for 2 subjects in either treatment group were (denosumab, placebo) osteoarthritis (2 [2%], 0) and cholelithiasis (0, 2 [2%]). By system organ class, serious adverse events that were reported for 2 or more subjects in the denosumab group compared with the placebo group were the following: musculoskeletal and connective tissue disorders (4 [3%], 1 [1%]), neoplasms (benign, malignant, and unspecified, including cysts and polyps) (4 [3%], 2 [2%]), and infections and infestations (3 [2%], 1 [1%]). Serious adverse events in the musculoskeletal system organ class were primarily osteoarthritis and arthritis and occurred in subjects with a history of arthritis. Serious adverse events in the neoplasms system organ class were all events of disease progression (breast cancer) or nonmalignant neoplasms (1 new primary malignancy [gastric cancer] was reported as a nonserious adverse event for a subject in the placebo group). Serious infections were infrequent (2% denosumab, 1% placebo); 1 of the serious infectious events in the denosumab group (labyrinthitis), although classified as infectious, was attributed by the investigator to treatment with trastuzumab.

The proportion of subjects who had adverse events of grade 3 (Common Terminology Criteria for Adverse Events [CTCAE version 3.0]) or higher was the same (23%) in both treatment groups.

One subject in each treatment group died during the study; both deaths were attributed to disease progression (breast cancer) and were not considered related to investigational product.

Treatment-related adverse events were reported with a similar incidence between treatment groups (25% denosumab, 26% placebo). No treatment-related adverse event was serious. The most common treatment-related adverse events were (denosumab, placebo) pain in extremity (2%, 4%), arthralgia (5%, 2%), bone pain (1%, 4%), fatigue (2%, 2%), and pain (3%, 1%).

Expected decreases in serum calcium, phosphorus, and total alkaline phosphatase occurred; these decreases tended to be mild and were not associated with clinical sequelae. The incidence of hypocalcemia (reported as a laboratory value) was 2% in both treatment groups; all of these subjects had grade 1 hypocalcemia.

Two subjects (2%) in the denosumab group developed postdose binding antibodies to denosumab, and 1 subject (1%) in the placebo group tested positive for pre-existing binding antibodies to denosumab. Antibodies were non-neutralizing and transient in all subjects. No evidence of an effect of the presence of anti-denosumab antibodies on safety, efficacy, or pharmacokinetic profiles was observed.

Pharmacokinetic Results:

The mean serum denosumab concentration at month 1 (20 to 34 days postdose) was 5890 ng/mL. Mean serum concentrations at months 3 and 15 (approximately 3 months postdose) were 1730 and 1430 ng/mL, respectively, and were comparable. In addition, the mean trough concentrations 6 months postdose, ranging from 50 to 116 ng/mL, were consistent through month 24, indicating that the pharmacokinetics of denosumab did not change with time and that

there was no accumulation with repeated dosing. High intersubject variability in exposure was observed, consistent with observations in other denosumab studies (eg, phase 3 osteoporosis prevention Study 20040132).

Conclusions:

This study demonstrated that denosumab was generally well tolerated and effectively increased both trabecular and cortical BMD in subjects with breast cancer who were receiving aromatase inhibitor therapy. [redacted]