1. TITLE PAGE

Protocol Title	A Multi-Center, Randomized, Open-Label Study to Assess the Immunogenicity and Safety of Denosumab in Prefilled Syringe Compared to Vial in Subjects with Low Bone Mineral Density
Investigational Product	Denosumab (AMG 162)
Indication.	Treatment of Osteoporosis
Brief Description	This study was a multicenter, randomized, open-label study designed to evaluate the safety of denosumab in a prefilled syringe (PFS) compared with denosumab in a vial Subjects received one 60-mg subcutaneous (SC) injection given every 6 months (Q6M), the total study duration was 1 year (a total of 2 injections) All subjects enrolled must have successfully completed Study 20050141 Study 20050141 was an international, multicenter, randomized, double-blind, active controlled, double-dummy, parallel group study that compared the efficacy of denosumab (60 mg SC Q6M) in a vial with alendronate (70 mg orally [PO] every week [QW]) for changes of bone mineral density (BMD) 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 SC plus placebo for alendronate PO or alendronate PO plus placebo for denosumab SC for 12 months Subjects were instructed to take supplemental elemental calcium (≥ 500 mg daily) and vitamin D (≥ 400 IU daily) in both studies
Study Sponsor	Amgen Inc , Thousand Oaks, California
Protocol No ·	20060237
IND No	9837
Study Phase·	3b
Study Initiation Date	30 May 2007 (first subject enrolled)
Data Cutoff Date	09 September 2008 (last subject completed last assessment)
Principal Investigators	This was a multicenter study conducted at 32 study centers in the United States and Canada Study centers and principal investigators are listed in Appendix 4
Clinical Study Manager	Deborah Lium, Amgen Inc , Thousand Oaks, CA Tel (805) 447-7151, Fax· (805) 480-9075
Good Clinical Practice	This study was conducted in accordance with principles of United States (Food & Drug Administration), Canadian, and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines Essential documents will be retained in accordance with ICH GCP
Report Date	02 February 2009

2. SYNOPSIS

Name of Sponsor:
Amgen Inc

Name of Finished Product:
Denosumab (AMG 162)

Name of Active Ingredient:
Fully human monoclonal antibody

Title of Study:
A Multi-Center, Randomized, Open-Label Study to Assess the Immunogenicity and Safety of Denosumab in Prefilled Syringe Compared to Vial in Subjects with Low Bone Mineral Density

Investigators and Study Centers: This was a multicenter study conducted at 32 study centers in the United States and Canada Study centers and principal investigators are listed in Appendix 4

Publications:
None

Study Period:
30 May 2007 (first subject enrolled) to 09 September 2008 (last subject completed last assessment)

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 compare the immunogenicity profiles of denosumab using a prefilled syringe (PFS) and denosumab using a vial at 6 months in postmenopausal women with low bone mineral density (BMD)

The secondary objectives were to compare the immunogenicity profiles of denosumab using PFS and vial at 12 months and to describe the safety outcomes of denosumab using PFS administration in postmenopausal women with low BMD Denosumab (for either the PFS or the vial) was manufactured at Amgen Colorado (ACO), a facility planned to supply commercial material

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Methodology:
This was a multicenter, randomized, controlled, open-label study in postmenopausal women with low BMD receiving denosumab either using a PFS or a vial Only subjects who had successfully completed Study 20050141 ("A Randomized, Double-Blind Study to Compare the Efficacy of Treatment with Denosumab versus Alendronate Sodium in Postmenopausal Women with Low Bone Mineral Density"), which enrolled postmenopausal women with BMD T-scores ≤ 2 0 at either the lumbar spine or total hip, were eligible to participate in this study

If subjects did not complete all screening and day 1 (first day of dosing) procedures on the day of the month-12 visit for Study 20050141, they were required to do so within 30 days of that month 12 visit Upon meeting all eligibility criteria, subjects were randomized in a 1 1 ratio to receive subcutaneous (SC) injection of denosumab 60 mg using either a PFS or a vial The randomization was stratified by Study 20050141 treatment group (denosumab or alendronate) After the first dose of investigational product was administered, subjects were followed for 12 months All subjects were required to take supplemental elemental calcium (at least 500 mg daily) and vitamin D (at least 400 IU daily) during the study

Number of Subjects Planned: Approximately 300 subjects

Number of Subjects Enrolled:
A total of 311 subjects were enrolled in this study following completion of Study 20050141, these subjects were randomized (1:1) to receive denosumab 60 mg from a vial (155 subjects) or a PFS (156 subjects)

Sex: 100% women

Age: 62.7 (8.7) years

Ethnicity (Race): 82% white or Caucasian, 14% Hispanic or Latino, 2% black or African American, 2% Asian, < 1% Japanese, and < 1% American Indian or Alaska Native.

Diagnosis and Main Criteria for Eligibility:
Subjects were postmenopausal women with low BMD (T-score ≤ -2.0 at the lumbar spine or total hip), who successfully completed and received all SC investigational product doses (denosumab or placebo) in Study 20050141. Subjects must not have received any proscribed therapies, which were the same as those for Study 20050141 and included therapies for the treatment of osteoporosis or therapies that altered bone metabolism.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number:
Denosumab was provided as a sterile, clear, colorless, preservative free liquid in PFS and glass vials. The formulation for denosumab vial was 60 mg denosumab per mL formulated with 10 mM Sodium Acetate, 5% Sorbitol in Water for Injection, with a pH of 5.2. The formulation for denosumab PFS was identical to that of the vial with the addition of 0.01% polysorbate 20.

One mL of investigational product was administered SC at day 1 and at month 6. Manufacturing lot numbers are provided in Appendix 18.

Duration of Treatment:
The entire study was 12 months in duration.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number:
Not applicable

Study Endpoints

Primary Endpoint:

- proportion of subjects that develop antidenosumab antibodies at 6 months

Secondary Endpoints:

- proportion of subjects that develop antidenosumab antibodies at 12 months
- proportion of subjects that develop neutralizing antibodies against denosumab at 12 months
- subject incidence of adverse events and serious adverse events by system organ class and preferred term
- changes in safety laboratory analytes (serum chemistry and hematology) from baseline at 1, 6, and 12 months and shifts between baseline and the worst post-baseline value

Exploratory Endpoint:

- percent change in lumbar spine, total hip, femoral neck, and trochanter BMD at 12 months

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Statistical Methods: The focus of the statistical analysis was estimation and no formal statistical testing procedures were performed. The primary analysis was to estimate the difference in the proportion of subjects who developed antidenosumab antibodies between subjects receiving denosumab using either the PFS or vial at the month 6 visit.

Subject incidence rates of antidenosumab antibodies during the study were tabulated. The corresponding 95% confidence interval was constructed. Subject incidence of adverse events was summarized by system organ class and by preferred term (coded using Medical Dictionary

for Regulatory Activities [MedDRA] version 11.0) Ongoing adverse events that had onset dates during Study 20050141 and continued during this study were not included in the adverse event summaries (since they had already been reported in Study 20050141). Recorded values and changes from baseline in the laboratory variables (serum chemistry and hematology) also were summarized at each visit, laboratory shift tables from the baseline value to the worst value during the study were provided The subject incidences of all grade 3 and 4 laboratory toxicities were provided

Continuous endpoints were summarized descriptively using the mean, standard deviation, minimum, median, maximum, and the number of nonmissing observations Frequencies and percentages were presented for binary or categorical endpoints

Summary statistics for the percent change from baseline to month 12 in BMD at the lumbar spine, total hip, femoral neck, and trochanter also were reported

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Summary of Results:

Subject Disposition:
A total of 311 subjects were enrolled into the study, with 155 subjects randomized to receive denosumab using the vial and 156 subjects randomized to receive denosumab using the PFS Of the 311 subjects enrolled into the study, 283 subjects (91% overall) completed the study, 141 subjects (91%) randomized to receive the vial and 142 subjects (91%) randomized to receive the PFS. Twenty-eight subjects (9% overall) did not complete the study (9% in each treatment group)

Antibody Assay Results:
A total of 297 subjects (146 subjects who received denosumab using the vial and 151 subjects who received denosumab using the PFS) had a baseline and ≥ 1 postbaseline antibody sample available and were tested for antidenosumab antibodies. One hundred forty subjects who received treatment using the vial and 146 subjects who received treatment using the PFS had antibody results at month 6 and 139 subjects who received treatment using the vial and 140 subjects who received treatment using the PFS had antibody results at month 12 All subjects tested negative for binding antibodies at baseline, month 1, month 6, and month 12 As no subjects had positive antidenosumab antibodies, no risk difference in the incidences of binding denosumab antibodies were observed between subjects who received the vial and PFS during this study, the 95% confidence interval was: -0 7%, 0 7% at months 6 and 12

Safety Results:
A total of 310 subjects (154 randomized to receive investigational product using the vial, 156 subjects using the PFS) received investigational product and were evaluated for safety

One hundred four subjects (67.5%) who received denosumab using the vial and 121 subjects (77 6%) who received denosumab using the PFS experienced at least 1 adverse event, most of these events were mild to moderate in severity.

The 3 most frequent adverse events were (vial, PFS) arthralgia (7 1%, 8 3%), back pain (5.8%, 7 1%), and upper respiratory tract infection (3 2%, 6 4%). The incidences of treatment-related (investigator attributed) events were 5 2% for subjects who received denosumab using the vial and 11 5% for subjects who received denosumab using the PFS No treatment-related adverse event was experienced by more than 1 subject

The incidence of serious adverse events (7 subjects [4 5%] using the vial and 12 subjects [7 7%] using the PFS) and withdrawals from investigational product due to adverse events (3 subjects [2%] vial, 2 subjects [1%] PFS) were similar between the 2 groups

Five subjects (3 subjects using the vial and 2 subjects using the PFS) had serious adverse events that were considered by the investigator as possibly related to treatment, they were breast cancer, endometrial cancer, and vaginal cancer experienced by 1 subject each who received denosumab using the vial and aortic stenosis and pancreatic carcinoma experienced by 1 subject each who received denosumab using the PFS No subjects died during the study

No consistent trends in serum chemistry of hematology parameters were noted One subject who received denosumab using the PFS reported an adverse event of hypocalcemia 245 days after the first dose and 55 days after the last dose of investigational product, and was judged unlikely to be related to investigational product because of the time since the last dose

Exploratory BMD Results:
An exploratory analysis of percent change from baseline in BMD showed similar gains for both treatment groups at all anatomical locations