2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: Denosumab (AMG 162)

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

Title of Study: A Randomized, Open Label, Active Controlled Study of AMG 162 in Subjects with Advanced Cancer Currently Being Treated with Intravenous Bisphosphonates

Investigator(s) and Study Center(s): This was a multicenter study conducted at 26 centers (9 in the United States, 2 in Canada, 7 in Europe, and 8 in Mexico). For the extension phase, subjects participated at 10 centers (2 in the United States, 1 in Canada, 3 in Europe, and 4 in Mexico). The study centers and principal investigators participating in the extension phase are listed in Appendix 2.

Publications: A complete list of publications is provided in Appendix 5.

Clinicaltrials.gov identifier: NCT00104650.

Study Period: The first subject was enrolled on 02 December 2004, the last subject completed the last 105-week visit (extension phase) on 19 May 2009, and the last subject completed the last 137-week visit (extension phase follow-up) on 04 January 2010.

Development Phase: 2

Introduction and Objectives: Skeletal complications associated with bone metastases are a result of osteoclast-mediated bone destruction. RANKL is an essential mediator of osteoclast function, formation, and survival. Denosumab is a fully human monoclonal antibody that inhibits RANKL and osteoclast-mediated bone resorption. Urinary N-telopeptide (uNTX) is a biochemical marker of bone resorption. Elevated levels of uNTX have been associated with an increased risk for skeletal complications in patients with bone metastases. Intravenous (IV) bisphosphonates are a common treatment for patients with bone metastases and have been shown to delay the onset of skeletal-related events (SREs). During the clinical development of bisphosphonates (eg, zoledronic acid, pamidronate, ibandronate), suppression of uNTX was predictive of a subsequent delay in the onset of SREs (fracture, radiation to bone, surgery to bone, or spinal cord compression).

The treatment phase of this study focused on the effect of denosumab administered subcutaneously (SC) once every 4 weeks (Q4W) or once every 12 weeks (Q12W) compared with IV bisphosphonate on uNTX levels as a marker for the biologic activity of denosumab. At the end of the treatment phase, subjects had the opportunity to enroll in a 105-week extension phase (approximately 2 years). Upon enrollment in the extension phase, subjects who were randomized to the denosumab groups during the treatment phase continued to receive that treatment (180 mg Q4W or 180 mg Q12W). Subjects who were randomized to the IV bisphosphonate group switched to denosumab 180 mg Q4W during the extension phase. All subjects were followed for 32 weeks after completing treatment.

The primary objective for the treatment phase was to determine the effectiveness of denosumab in reducing uNTX (corrected for creatinine levels; hereinafter referred to as uNTX/Cr) to below 50 nM/mM in subjects with advanced cancer and bone metastases (including subjects with multiple myeloma and bone disease) who had uNTX/Cr levels > 50 nM/mM during prestudy IV bisphosphonate treatment. The secondary objective for the treatment phase was to characterize the safety profile of denosumab when administered SC at 180 mg Q4W or Q12W as

compared with IV bisphosphonates administered Q4W. [redacted] The evaluation of these objectives has been fully described in the treatment phase clinical study report dated 15 July 2008.

[redacted]

Methodology: This was a multicenter, randomized, open-label, active-controlled, parallel-group, multidose study in subjects with advanced cancer and bone metastases (including subjects with multiple myeloma and bone disease) who had uNTX/Cr levels > 50 nM/mM during prestudy IV bisphosphonate therapy. The study consisted of a treatment phase and an optional extension phase. In the treatment phase, subjects were randomized (1:1:1 ratio) to receive either denosumab 180 mg Q4W or denosumab 180 mg Q12W, or to continue on IV bisphosphonate Q4W for 25 weeks. Randomization was stratified by cancer type (breast, prostate, solid tumor [except lung]/multiple myeloma) and screening uNTX (50 to 100 nM/mM or > 100 nM/mM) using an equal allocation ratio. Data collected during the treatment phase were reported in the clinical study report dated 15 July 2008.

Subjects who completed the initial 25-week treatment period and enrolled in the extension phase were assigned to 1 of 2 denosumab treatment arms, based upon their initial randomization assignment. Subjects randomized to receive either denosumab 180 mg Q4W or IV bisphosphonate during the initial 25-week treatment period received denosumab 180 mg SC Q4W and subjects randomized to denosumab 180 mg SC Q12W during the initial 25-week treatment period continued to receive denosumab 180 mg SC Q12W in the extension phase. In the extension phase, subjects were treated for up to 105 weeks (2 years) and were followed for 32 weeks after completing treatment.

During both the treatment and extension phases, adverse events, clinical laboratory parameters, SREs, concomitant medications, and bone turnover markers were evaluated at regular, prespecified intervals. Serum samples were also obtained for assessment of denosumab concentrations and antidenosumab antibodies. Subject safety was monitored during both the treatment and extension phases by the sponsor. Data from the 105-week extension phase (and 32-week extension phase follow-up) are reported in this document.

Number of Subjects Planned: 135 subjects (45 in each treatment group).

Number of Subjects Enrolled: A total of 111 subjects were enrolled in the study and were randomized to receive denosumab (74 subjects in both denosumab groups combined) or IV bisphosphonate (37 subjects).

Nineteen subjects (17% of those randomized in the treatment phase) continued on study in the extension phase; 7 subjects received denosumab 180 mg Q12W and 12 subjects (8 randomized to denosumab 180 mg Q4W and 4 randomized to IV bisphosphonates) received denosumab 180 mg Q4W. Seven of the 19 subjects (1 [14%] subject who received denosumab 180 mg Q12W and 6 [50%] who received denosumab 180 mg Q4W) completed the extension phase (ie, through week 105 in the extension phase). Five subjects (all who received denosumab 180 mg Q4W) completed the extension phase follow-up. Demographic data presented below reflect the subjects enrolled in the extension phase.

Sex:

Denosumab 180 mg Q12W: 4 (57%) female, 3 (43%) male
Denosumab 180 mg Q4W groups combined: 8 (67%) female, 4 male (33%)

Age (Median [range]):

Denosumab 180 mg Q12W (n = 7): 62.0 (range: 55 to 81 years)
Denosumab 180 mg Q4W groups combined (n = 12): 61.5 (range: 44 to 73 years)

Ethnicity (Race):

Denosumab 180 mg Q12W: 4 (57%) White, 3 (43%) Hispanic/Latino
Denosumab 180 mg Q4W groups combined: 7 (58%) White, 4 (33%) Hispanic/Latino, 1 (8%) Native Hawaiian/other Pacific Islander

Diagnosis and Main Criteria for Eligibility: To be eligible to enroll in the extension phase, subjects met the following key eligibility criteria: completed the treatment phase and currently enrolled in Study 20040114; Eastern Cooperative Oncology Group (ECOG) score of 0, 1, or 2; adequate organ function; no more than 2 prior SREs; and no condition requiring oral surgery or dental/oral surgery that was not healed. For subjects randomized to the IV bisphosphonate arm during the treatment phase, uNTX/Cr levels had to be > 50 nM/mM at 1 measurement obtained within 4 weeks of enrollment into the extension phase. For subjects randomized to denosumab during the treatment phase, ≤ 25 weeks had to have passed between last dose of denosumab and enrollment into extension phase.

Investigational Product, Dose and Mode of Administration, Manufacturing Lot Number: Denosumab was administered SC at doses of 180 mg Q4W or Q12W. Denosumab was provided as a sterile, clear, colorless, preservative-free liquid in glass vials. The product formulation was 60 mg denosumab per mL of [redacted] mM sodium acetate and [redacted]% sorbitol at pH [redacted]. A listing of lot numbers and the individual subjects receiving each lot number used in the extension phase is provided in Listing 1E-1.2. A listing of lot numbers and the individual subjects receiving each lot number used in the treatment phase was provided in the treatment phase clinical study report dated 15 July 2008.

Duration of Treatment: Up to 25 weeks during the treatment phase and up to 105 weeks during the extension phase.

Reference Therapy, Dose and Mode of Administration, Manufacturing Lot Number: During the treatment phase, the active-control therapy was a commercially available IV bisphosphonate (eg, pamidronate, zoledronic acid) administered according to the product insert. There was no comparator arm during the extension phase. During the extension phase, subjects who had received IV bisphosphonate during the treatment phase were eligible to receive a fixed dose of denosumab 180 mg (SC) every 4 weeks.

Study Endpoints

This report summarizes the extension phase endpoints, which included the following:

- subject incidence of treatment-emergent adverse events,
- change from baseline in laboratory assessments including hematology and serum chemistry values,
- number of study subjects experiencing SREs,
- [redacted]

Statistical Methods:

Efficacy
The extension phase primary efficacy subset included all subjects who were enrolled on the extension phase, received at least 1 dose of extension phase investigational product, and had extension phase baseline measurements of uNTX/Cr and at least 1 extension phase

post-baseline measurement of uNTX/Cr. [redacted]

For the extension phase, the extension phase safety subset (defined below) was used to summarize the proportion of subjects experiencing SREs.

Safety
Safety endpoints were analyzed using the extension phase safety subset, which included all subjects who were enrolled to the extension phase. The subject incidence of each adverse event was tabulated by system organ class, preferred term, severity, 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 of Results:

Subject Disposition:

A total of 111 subjects were enrolled into the study, with 72% of subjects in the denosumab groups and 68% of subjects in the IV bisphosphonate group completing 25-weeks of the treatment phase. Of the 78 subjects completing the 25-week treatment phase, 19 subjects (17% of those randomized to the study initially) participated in the extension phase; 7 subjects received denosumab 180 mg Q12W and 12 subjects (8 randomized to denosumab 180 mg Q4W and 4 randomized to IV bisphosphonates) received denosumab 180 mg Q4W. Seven of these 19 subjects (1 [14%] who received denosumab Q12W and 6 [50%] who received denosumab Q4W) completed 105 weeks of treatment in the extension phase. Five of the 7 subjects (all 5 subjects received denosumab Q4W) completed the 32-week extension phase follow-up.

During the extension phase, 12 of 19 subjects withdrew from the study (6 [86%], 4 [50%], and 2 [50%] subjects administered denosumab Q12W, denosumab Q4W continuation, and denosumab Q4W transitioned from IV bisphosphonate, respectively). Nine of the 12 subjects that withdrew in the extension phase died (3, 4, and 2 subjects, respectively). The remaining 3 subjects were in the denosumab Q12W group and withdrew due to administrative decision, adverse event (physical health deterioration), and other (participation in a phase 1 study).

During the extension phase follow-up, 2 subjects withdrew from the study (1 [14%], 0 [0%], and 1 [25%], respectively). The reasons for discontinuation in the extension phase follow-up were death (1 subject who received denosumab Q12W during the extension phase) and lost to follow-up (1 subject who received denosumab Q4W transitioned from IV bisphosphonate during the extension phase).

Efficacy Results:

One subject in each treatment group (1 subject who received denosumab Q12W, 1 subject who received denosumab Q4W continuation, and 1 subject who received denosumab Q4W transitioned from IV bisphosphonate) reported an SRE during the extension phase. The median time to first on-study SRE could not be estimated due to the large proportion of subjects in each treatment group (80% of subjects who received denosumab Q12W, 86% of subjects who received denosumab Q4W continuation, and 67% of subjects who received denosumab Q4W transitioned from IV bisphosphonate) who were censored at week 105 because they did not experience an SRE.

[redacted] By weeks 53 and 105, few subjects had evaluable uNTX/Cr values. Individual uNTX/Cr values at each visit are provided in Listing 1E-3.1. Changes in uNTX/Cr values were not summarized due to the small number of subjects in each treatment group.

Safety Results:

All 19 subjects (7 denosumab Q12W, 8 denosumab Q4W continuation, 4 denosumab Q4W transitioned from IV bisphosphonate) that transitioned to the extension phase received investigational product. All subjects experienced at least 1 adverse event during the extension phase or extension phase follow-up. The most frequent adverse events were fatigue (2 [29%] denosumab Q12W, 4 [50%] denosumab Q4W continuation, 1 [25%] denosumab Q4W transitioned from IV bisphosphonate), nausea (0%, 4 [50%], 1 [25%]), abdominal pain (1 [14%], 4 [50%], 0%), anemia (4 [57%], 4 [50%], 0%), asthenia (1 [14%], 2 [25%], 2 [50%]), decreased appetite (0%, 3 [38%], 1 [25%]), back pain (1 [14%], 2 [25%], 1 [25%]), bone pain (1 [14%], 1 [13%], 2 [50%]), constipation (2 [29%], 2 [25%], 1 [25%]), headache (2 [29%], 1 [13%], 2 [50%]), pain in extremity (2 [29%], 1 [13%], 2 [50%]), and diarrhea (3 [43%], 2 [25%], 0%). Treatment-related adverse events were reported for 1 subject in each treatment group. One subject receiving denosumab Q12W withdrew from the extension phase due to an adverse event (general physical health deterioration).

Serious adverse events were reported for 5 (71%), 6 (75%), and 2 (50%) subjects in the denosumab Q12W, denosumab Q4W continuation, and denosumab Q4W transitioned from IV bisphosphonate groups, respectively, during the extension phase and extension phase follow-up. Eleven of these serious adverse events (4, 5, and 2 subjects in the denosumab Q12W, denosumab Q4W, and denosumab Q4W transitioned from IV bisphosphonate groups, respectively) occurred during the extension phase and 2 of these serious adverse events (1 subject who received denosumab 180 mg Q12W and 1 subject who received denosumab 180 mg Q4W) occurred during the extension phase follow-up. Abdominal pain and hepatic failure were the only serious adverse events reported by more than 1 subject in a treatment group (both events were reported by 2 subjects in the denosumab Q4W continuation group and no subjects in either the denosumab Q12W or denosumab Q4W transitioned from IV bisphosphonate groups). One subject in the denosumab Q12W group reported a treatment-related serious adverse event (osteonecrosis, described below). One subject receiving denosumab Q12W withdrew from the extension phase due to a serious adverse event (general physical health deterioration).

Fatal adverse events were reported for 4 (57%), 5 (63%), and 2 (50%) subjects in the denosumab Q12W, denosumab Q4W, and denosumab Q4W transitioned from IV bisphosphonate groups, respectively. None of the fatal adverse events were considered treatment-related by the investigator. Ten of the 11 deaths were attributed to disease progression (3 subjects who received denosumab Q12W, 5 subjects who continued on denosumab Q4W, and 2 subjects who transitioned from IV bisphosphonates to denosumab Q4W). In 1 subject (who received denosumab Q12W), the cause of death was pulmonary edema that had developed in the setting of a possibly newly diagnosed lymphoma. Nine of the 11 deaths (3, 4, and 2 subjects in the denosumab Q12W, denosumab Q4W continuation, and denosumab Q4W transitioned from IV bisphosphonate groups, respectively) occurred during the extension phase and 2 deaths (1 subject who received denosumab Q12W and 1 subject who received denosumab Q4W) occurred during the extension phase follow-up.

Hypocalcemia was reported as an adverse event for 3 subjects (1 subject in each treatment group). These events were mild or moderate in severity and resolved with administration of calcium supplementation. One subject receiving denosumab Q12W had an adjudicated positive event of osteonecrosis of the jaw that began approximately 2 years after the start of the study. No treatment was administered for the event, and the subject died approximately 1 month later; the event was ongoing at the time of death.

Other than changes in serum calcium expected from the pharmacologic action of denosumab, no changes indicative of a treatment- or dose-related effect were observed in clinical laboratory parameters.

Conclusions:

Nineteen of the 111 subjects who were enrolled to the study continued to the extension phase. One subject in each treatment group reported an SRE during the extension phase. [redacted]. Denosumab 180 mg administered SC either Q12W or Q4W was generally well-tolerated by subjects with advanced cancer and bone metastases, including subjects who were previously treated with IV bisphosphonates.