2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: Not applicable

Name of Active Ingredient: Denosumab

Title of Study: A Randomized, Active-controlled Study of AMG 162 in Breast Cancer Subjects With Bone Metastasis Who Have Not Previously Been Treated With Bisphosphonate Therapy

Investigators and Study Centers: This study was conducted at 56 centers in Australia, Canada, the European Union, Mexico, and the United States. Study centers and principal investigators are listed in Appendix 4.

Publications:

Lipton A, de Boer R, Figueroa J, et al. Extended safety and efficacy analysis of denosumab in breast cancer patients with bone metastases without prior bisphosphonate therapy [abstract]. Presented at: San Antonio Breast Cancer Symposium; December 14-17, 2006; San Antonio, Texas. Available at: http://www.abstracts2view.com/sabcs06/sessionindex.php. Accessed 02 January 2007. Abstract 1069.

Lipton A, Alvarado D, de Boer R, et al. Randomized, active-controlled study of denosumab (AMG 162) in patients with bone metastases not previously treated with intravenous (IV) bisphosphonates (BP) [abstract]. *J Clin Oncol*. 2006;24(suppl):512.

Steger GG, Body J, Solal-Celigny P, et al. Denosumab suppresses bone turnover markers in breast cancer patients with bone metastases naïve to intravenous bisphosphonates regardless of antineoplastic treatment [abstract]. *Ann Oncol*. 2006;17:288-299. Abstract 998P.

Study Period: 08 September 2004 to 15 June 2006

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 destruction. 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 bisphosphonates are a common treatment for patients with bone metastases and have been shown to delay the onset of skeletal-related events. During the clinical development of bisphosphonates (eg, zoledronic acid, pamidronate, ibandronate), suppression of uNTx was predictive of subsequent delay in onset of skeletal-related events (fracture, radiation to bone, surgery to bone, or spinal cord compression). This study focused on the effect of denosumab compared with IV bisphosphonates on uNTx levels as a marker for the biologic activity of denosumab.

The primary study objective was to evaluate the effect of different doses and schedules of denosumab on the percentage change from baseline in urinary N-telopeptide (uNTx) at week 13 in subjects with breast cancer and bone metastasis who had not previously received IV bisphosphonate therapy. The secondary objectives were to characterize the safety profile and long-term efficacy on bone turnover markers of denosumab administered subcutaneously at doses of 30, 60, 120, or 180 mg, to evaluate the effect of denosumab on skeletal-related adverse events and hypercalcemia, and to evaluate the pharmacokinetic parameters of denosumab at different doses and schedules. [redacted]

[redacted].

Methodology: This was a multicenter, randomized, partially blinded, multidose, active-controlled, parallel-group study in subjects with breast cancer and bone metastases who had not previously received IV bisphosphonate therapy. Subjects were randomized to 1 of 6 treatment groups (approximately 40 subjects per group): denosumab at a dose of 30, 120, or 180 mg every 4 weeks (Q4W), denosumab 60 or 180 mg every 12 weeks (Q12W), or open-label IV bisphosphonate Q4W. Randomization was stratified by the treatment (chemotherapy or hormonal therapy; if both therapies were used, the therapy was classified as chemotherapy) subjects were receiving at study entry. Subjects participated in the study for 57 weeks: a 25-week treatment period followed by 3 post-treatment follow-up visits at weeks 33, 45, and 57.

Subjects were instructed to take daily calcium and vitamin D supplements. Vital signs, clinical laboratory parameters, the incidence of skeletal-related adverse events, concomitant medications use, and bone turnover markers were evaluated at regular, prespecified intervals throughout the study. Serum samples were obtained before, during, and after the treatment period for assessment of denosumab concentrations, anti-denosumab antibodies, and [redacted]. Subject safety was monitored by the sponsor on an ongoing basis for the duration of the study.

Number of Subjects Planned: 240 (40 subjects in each treatment group)

Number of Subjects Enrolled: 255 (212 denosumab, 43 IV bisphosphonate)

Sex: 255 (100%) women

Age (Mean [SD]):
All denosumab groups combined: 57.8 years (11.4) (range: 31 to 84)
IV bisphosphonate group: 52 years (10.7) (range: 36 to 81)

Ethnicity/Race:
All denosumab groups combined: 154 subjects (73%) white, 55 (26%) Hispanic, 1 (1%) Asian, 1 (1%) native Hawaiian or other Pacific islander; 1 (1%) other
IV bisphosphonate group: 25 (58%) white, 16 (37%) Hispanic, 1 (2%) Asian, 1 (2%) other

Diagnosis and Main Criteria for Eligibility: Eligible subjects met the following criteria: women ≥ 18 years of age; informed consent provided before any study-specific procedure was performed; ECOG score of 0, 1, or 2; histologically or cytologically confirmed breast adenocarcinoma; radiographic evidence (eg, magnetic resonance imaging, computed tomography, bone scan) of at least 1 bone metastasis; adequate organ function, as defined by protocol-specified criteria; no prior oral bisphosphonate use, total cumulative oral bisphosphonate use of ≤ 8 weeks and no oral bisphosphonate use in the 2 weeks before randomization or total cumulative oral bisphosphonate use of > 8 weeks and no oral bisphosphonate use in the 24 weeks before randomization; no changes in chemotherapy or hormonal therapy regimens or agents planned for the first 12 weeks on study.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Denosumab was administered SC at doses of 30, 120, or 180 mg Q4W or 60 or 180 mg Q12W. Denosumab was provided as a sterile, clear, colorless, preservative-free liquid in blinded-label glass vials. The formulation of the liquid was 30- or 60-mg denosumab per mL of [redacted] mM sodium acetate, and [redacted]% sorbitol in water for injection, with a pH of [redacted]. Manufacturing lot numbers are provided in Appendix 18.

Duration of Treatment: 25 weeks of investigational product administration followed by a 32-week post-treatment follow-up period, for a total of 57 weeks on study

Reference Therapies, Dose and Mode of Administration, Manufacturing Batch Numbers: The open-label active control medication was commercially available IV bisphosphonate,

administered according to the product insert. Bisphosphonate was formulated, packaged, and labeled according to local manufacturer and supplier procedures. Placebo (used in the denosumab treatment groups to maintain the dose and dosing interval blind) was provided in glass vials as a sterile, clear, colorless, preservative-free liquid. The appearance and formulation of placebo were identical to denosumab, with the exception of the active protein ingredient. Study centers were responsible for obtaining IV bisphosphonate and normal saline. Manufacturing lot numbers are provided in Appendix 18.

Study Endpoints

Primary

An adjustment in urinary N-telopeptide (uNTx) by urinary creatinine (uCr) levels was performed (uNTx/uCr). The adjusted value is designated as uNTx/Cr. The primary endpoint was the percentage change from baseline to week 13 in uNTx/Cr, defined as 100*(week 13uNTx/Cr – baseline uNTx/Cr / baseline uNTx/Cr).

Secondary Efficacy

- Percentage change from baseline to week 25 in uNTx/Cr
- Percentage change from baseline to week 13 and percentage change from baseline to week 25 in type 1 serum C-telopeptide (CTx), procollagen 1 N-terminal peptide (P1NP), tartrate-resistant acid phosphatase 5b (TRAP 5b), bone-specific alkaline phosphatase (BSAP), and/or osteocalcin
- Proportion of study subjects at week 13 and at week 25 achieving a $\geq$ 65% decrease in uNTx/Cr from baseline levels
- Time to a $\geq$ 65% decrease from baseline in uNTx/Cr
- Proportion of study subjects experiencing skeletal-related events and the time to first skeletal-related event. A skeletal-related event was defined as a bone fracture (vertebral or nonvertebral), surgery, radiation therapy to bone, or spinal cord compression
- Incidence of hypercalcemia

Safety

- Subject incidence of treatment-emergent adverse events
- Changes from baseline in laboratory assessments, including adjusted calcium levels and estimated glomerular filtration rate
- Subject incidence of anti-denosumab antibody formation

Pharmacokinetic

- Pharmacokinetic parameters for denosumab

Exploratory

- [redacted]
- [redacted]

Statistical Methods:

Efficacy

The primary and secondary efficacy analyses were conducted for all subjects who received ≥ 1 dose of denosumab or IV bisphosphonate and had baseline and ≥ 1 postbaseline measure of uNTx/Cr. The primary endpoint (percentage change in uNTx/Cr from baseline to week 13) was summarized using median percentage change (with 25th and 75th percentile, minimum, and maximum) and the mean percentage change and 95% confidence intervals (CI) for each treatment group, for all denosumab groups combined, and by randomization stratification factor and treatment group. For all efficacy endpoints, summary statistics and estimated confidence intervals for each treatment group and all treatment groups combined were used as the principal approach of statistical inference. Estimation of denosumab treatment effects were conducted using methods such as analysis of covariance (ANCOVA), the logistic regression model, and the Cox regression model, and statistical tests were performed for supportive evaluation of differences between treatment groups. The IV bisphosphonate group was included as a descriptive comparator to evaluate the effects of denosumab.

Safety

Safety endpoints were analyzed for all subjects who received ≥ 1 dose of denosumab or IV bisphosphonate. 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 percentages of subjects developing anti-denosumab antibodies were tabulated.

Pharmacokinetic

Pharmacokinetic analyses were conducted using noncompartmental pharmacokinetic methods for the subset of subjects in the safety analysis set who had ≥ 1 evaluable denosumab serum concentration-time profile. Estimates of noncompartmental parameters were generated using WinNonlin® Professional (version 4.1e).

Summary of Results:

Subject Disposition:

Two hundred fifty-five subjects were enrolled and randomized to receive denosumab or bisphosphonate (42 to 43 subjects in each treatment group); all but 1 subject received investigational product. Most subjects in all treatment groups completed the study (ie, attended the safety follow-up visit at week 57) (70% denosumab, 67% IV bisphosphonate). The most common reasons for not completing the study were death (13% denosumab, 14% IV bisphosphonate) and withdrawn consent (5% denosumab, 9% IV bisphosphonate). Most subjects in all treatment groups (87% denosumab groups combined, 84% IV bisphosphonate) completed all planned doses of investigational product, and no notable differences were observed in investigational product discontinuation rates among the groups (10% to 17% denosumab, 16% IV bisphosphonate).

Efficacy Results:

Results for the primary endpoint, percentage change from baseline to week 13 in uNTx/Cr, showed similar levels of uNTx/Cr suppression in the denosumab groups combined and IV bisphosphonate group, with a median percentage change in uNTx/Cr at week 13 of -73% in the denosumab groups and -78% in the IV bisphosphonate group. Although reductions were similar across treatment groups and doses, the denosumab 120-mg Q4W group demonstrated the

greatest median uNTx/Cr suppression (-74% 30 mg Q4W, -80% 120 mg Q4W, -71% 180 mg Q4W, -68% 60 mg Q12W, -71% 180 mg Q12W). In the Q12W treatment groups at week 13, some evidence of escape of uNTx/Cr suppression was noted at week 13.

At week 25, the median percentage change in uNTx/Cr from baseline continued to be similar in the denosumab groups combined (-75%) and IV bisphosphonate group (-71%). Median reductions in uNTx/Cr tended to be slightly greater in the denosumab groups than in the IV bisphosphonate group, with the exception of the 180-mg Q12W group (-79% 30 mg Q4W, -74% 120 mg Q4W, -77% 180 mg Q4W, -76% 60 mg Q12W, -60% 180 mg Q12W, -71% IV bisphosphonate).

In the post-treatment follow-up phase (weeks 25 to 57), there was evidence of increasing bone resorptive activity after discontinuation of denosumab, predominantly at weeks 45 and 57. At week 57, the median percentage change in uNTx/Cr was -21% in the denosumab groups combined and -30% in the IV bisphosphonate group. Note that subjects received their last dose of denosumab or IV bisphosphonate at week 25 and were permitted to receive treatment with IV bisphosphonates during the 32-week follow-up period.

Other secondary markers of bone resorption (serum CTx, P1NP, TRAP5b), formation (BSAP, osteocalcin), and osteoclast activity (TRAP5b) showed the same pattern, with similar reductions from baseline observed across treatments and doses. Median percentage reductions at week 13 in these secondary markers were as follows (denosumab groups combined, IV bisphosphonate): serum CTx (-85%, -80%), P1NP (-63%, -60%), TRAP5b (-59%, -41%), BSAP (-40%, -43%), and osteocalcin (-20%, -10%). At week 25, median percentage reductions were as follows (denosumab groups combined, IV bisphosphonate): serum CTx (-85%, -80%), P1NP (-71%, -66%), TRAP5b (-60%, -44%), BSAP (-51%, -49%), and osteocalcin (-35%, -28%).

Over the course of the study, 85% of subjects in the denosumab groups and 83% of subjects in the IV bisphosphonate group had a $\geq$ 65% decrease in uNTx/Cr from baseline. At week 13, the percentage of subjects who had a $\geq$ 65% decrease in uNTx/Cr from baseline was 55% in the denosumab groups combined (range: 48% to 65%) and 61% in the IV bisphosphonate group. At week 25, the percentage of subjects who had a $\geq$ 65% decrease in uNTx/Cr from baseline was similar in the denosumab treatment groups combined (52%; range: 36% to 61%) and IV bisphosphonate group (46%).

The median (95% CI) time to a $\geq$ 65% reduction in uNTx/Cr was similar across the treatment groups, with the exception of the denosumab 180-mg Q12W group, which had a longer time to $\geq$ 65% reduction in uNTx/Cr: 13 days (9, 29) 30 mg Q4W, 11 days (9, 15) 120 mg Q4W, 10 days (8, 29) 180 mg Q4W, 9 days (9, 16) 60 mg Q12W, 30 days (16, 58) 180 mg Q12W, 10 days (9, 55) IV bisphosphonate. Note that the sampling times for serum bone turnover markers (ie, approximately every 4 weeks from weeks 5 to 25) contributed to a lack of precision in the analysis of time to a $\geq$ 65% reduction in uNTx/Cr.

It should be noted that efficacy analyses conducted for time points corresponding to subject visits (eg, weeks 13 and 25) included subject data through the date of the week-13 or week-25 subject visit, which, because of the protocol-specified dosing guidelines, varied by subject and did not correspond precisely to 13 or 25 weeks on study. This occurred because the first dose was administered within 5 days of randomization, and subsequent doses were administered every 4 weeks thereafter, but may have deviated slightly from this schedule because of subject visit scheduling issues. In contrast, Kaplan-Meier analyses were based on the number of days subjects were on study after randomization. Thus, for example, because the week-13 subject visit most closely corresponded to study day 84, day 84 was used as the time point for Kaplan-Meier analyses.

By weeks 13 and 25, the incidence of skeletal-related events was similar in subjects who received denosumab (10% and 12%, respectively) and subjects who received IV bisphosphonates (14% and 16%, respectively). Most skeletal-related events (22/26 subjects

[85%] who had skeletal-related events in the denosumab groups, 6/7 subjects [86%] who had events in the IV bisphosphonate group) had occurred by week 13, indicating that skeletal-related events tended to occur earlier in the 25-week treatment period.

Although the median time to first skeletal-related event was not calculable because of the large proportion of subjects who had no skeletal-related events and therefore were censored, a Kaplan-Meier analysis showed that the estimated incidence rate of skeletal-related events was similar across the treatment groups at weeks 5, 9, and 13. By week 13, the estimated incidence of skeletal-related events was 9.3% (95% CI: 6.0%, 14.2%) in the denosumab groups combined and 10.1% (95% CI: 3.9%, 24.7%) in the IV bisphosphonate group. At week 17, the Kaplan-Meier estimated incidence of skeletal-related events continued to be similar in the denosumab groups combined (11.8% [95% CI: 8.1%, 18.1%]) and IV bisphosphonate group (18.2% [95% CI: 9.1%, 34.6%]) (week 17 was used for the Kaplan-Meier estimate because the small number of skeletal-related events and larger number of censored subjects after week 17 made week-17 estimates more reliable than those for week 25). No dose-related pattern was apparent in the denosumab groups in the Kaplan-Meier estimated incidence of skeletal-related events.

The incidence of hypercalcemia (an efficacy endpoint) reported as an adverse event (ie, clinically significant hypercalcemia) was 0%; no subject had an elevated calcium laboratory value $>$ grade 1.

Pharmacokinetic Results:

Exposure based on mean C_{max} and $AUC_{0\text{-}tau}$ values increased approximately dose proportionally in the 30-, 120-, and 180-mg Q4W treatment groups for the first, third, and fifth doses and for the 60- and 180-mg Q12W groups for the first and second doses. Approximately 2-fold accumulation was observed across all Q4W groups after the third and fifth doses, consistent with time-linear pharmacokinetics. The beta phase half-life values were similar on average across all Q4W and Q12W groups, ranging from approximately 26 to 35 days. High intersubject variability in exposure was observed for all dosing groups but was similar to that observed in previous denosumab studies (phase 1 Studies 20010123 and 20040176).

Safety Results:

Most subjects in all treatment groups had $\geq$ 1 adverse event during the study (200 subjects [95%] denosumab, 41 subjects [95%] IV bisphosphonate). Adverse events occurring with a $\geq$ 10% difference in incidence between the denosumab groups combined and the IV bisphosphonate group were asthenia (16% denosumab, 28% IV bisphosphonate), arthralgia (11% denosumab, 30% IV bisphosphonate), pyrexia (9% denosumab, 21% IV bisphosphonate), and myalgia (4% denosumab, 21% IV bisphosphonate). Fatal adverse events were reported for 32 subjects (15%) in the denosumab groups and 8 subjects (19%) in the IV bisphosphonate group; most deaths were due to the progression or complications of advanced breast cancer. Life-threatening adverse events were reported for 13 subjects (6%) in the denosumab groups and 2 subjects (5%) in the IV bisphosphonate group. Severe adverse events were reported for 82 subjects (39%) in the denosumab groups and 17 subjects (40%) in the bisphosphonate group. Serious adverse events were reported for a similar proportion of subjects in the denosumab and IV bisphosphonate groups (75 subjects [36%] and 15 subjects [35%], respectively).

Treatment-related adverse events (investigator attributed) were reported for a lower proportion of subjects in the denosumab groups combined (21%) than in the IV bisphosphonate group (30%). In the denosumab groups, all adverse events considered by the investigators to be related to treatment were reported as mild to moderate in severity. In the IV bisphosphonate group, 2 subjects had severe treatment-related adverse events. The most common treatment-related adverse events (investigator attributed) in the denosumab groups combined were (denosumab, IV bisphosphonate) headache (2%, 0%), injection-site pain (2%, 0%), asthenia (1%, 2%), bone pain (1%, 5%), fatigue (1%, 0%), arthralgia (1%, 7%), buttock pain (1%, 0%), constipation (1%, 0%), rash (1%, 2%), and vomiting (1%, 5%). In the IV bisphosphonate group, the most

commonly reported treatment-related adverse events were (denosumab, IV bisphosphonate) arthralgia (1%, 7%), pyrexia (1%, 7%), bone pain (1%, 5%), hypocalcemia (1%, 5%), vomiting (1%, 5%), and chills (0%, 5%). The overall profile of changes in serum calcium was similar in the denosumab and IV bisphosphonate groups, with grade 1 (albumin-adjusted) hypocalcemia reported for 14% of subjects who received denosumab and 9% of subjects who received IV bisphosphonate and grade 2 hypocalcemia reported for 7% of subjects in the denosumab groups and in the IV bisphosphonate groups. Grade 3 hypocalcemia was reported for 1 subject ($<$ 1%) in the denosumab 180-mg Q4W group.

Non-neutralizing, binding antibodies to denosumab were reported for 3 subjects (2 in the 120-mg Q4W group, 1 in the 180-mg Q4W group). The antibodies were transient for 2 of these subjects and were positive only at the last time point tested for 1 subject. No subject developed neutralizing antibodies to denosumab.

Conclusions:

Results from this study demonstrated that denosumab has biologic activity, as evidenced by the rapid and sustained suppression of uNTX/Cr to levels similar to IV bisphosphonate at all doses evaluated. In addition, the data provide evidence that denosumab has important clinical activity, as demonstrated by the similar time to first skeletal-related adverse events observed among subjects who received denosumab and IV bisphosphonate. Denosumab was well tolerated at all doses, with an overall profile of changes in calcium similar to that observed with IV bisphosphonates. Denosumab serum exposure increased approximately dose proportionally across the denosumab Q4W and Q12W groups, and multiple-dose data were consistent with time-linear pharmacokinetics. Beta phase half-life values also were similar across all doses and were similar to those observed in previous denosumab studies.