2. SYNOPSIS

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

Name of Finished Product: Denosumab

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

Title of Study: An Open-label, Single-arm, Extension Study to Evaluate the Long-term Safety of Denosumab (AMG162) in the Treatment of Bone Loss in Subjects Undergoing Androgen-Deprivation Therapy for Nonmetastatic Prostate Cancer

Investigator(s) and Study Center(s): This study was conducted at 81 centers in North America and Europe. Centers and principal investigators are listed in Appendix 3.

Publication(s): None.

Study Period: 18 February 2009 (first subject randomized) through 03 May 2012 (last subject end-of-study date)

Development Phase: 3

Introduction and Objectives: Prostate cancer is the most common malignancy among men in the United States (US) and Europe; estimates from the American Cancer Society indicate the likelihood of 241,740 new cases of prostate cancer in the US during 2012 with over 28,000 cases resulting in death (American Cancer Society, 2012). In Europe, estimates in 2006 indicated a probable 340,000 prostate cancer cases and over 87,000 deaths (Ferlay et al, 2007).

In men with prostate cancer, androgens, such as testosterone, have been shown to stimulate tumor growth (Hussain et al, 2006). Androgen deprivation therapy (ADT) through bilateral orchiectomy or treatment with gonadotropin-releasing hormone (GnRH) agonists is the standard first-line therapy for metastatic prostate cancer (Heidenreich et al, 2008; Loblaw et al, 2007). GnRH agonists are also frequently used to treat men with nonmetastatic prostate cancer (Sharifi et al, 2005). Androgen deprivation therapy improves both disease-free survival and overall survival in certain clinical settings, including adjuvant treatment for men with locally advanced prostate cancer treated with radiation therapy (Bolla, 1999; Bolla et al, 2002) and adjuvant therapy for men with lymph node-positive prostate cancer treated with radical prostatectomy and pelvic lymphadenectomy (Messing et al, 1999). Gonadotropin-releasing hormone agonists have been shown to decrease serum concentrations of testosterone by > 90% and estrogen by approximately 75% (Stoch et al, 2001; Smith et al, 2001). As a result of the reduction in estrogen levels with ADT, detrimental effects on the skeleton are expected and are increasingly recognized as an unmet medical concern (Body et al, 2007; Guise, 2006; Guise et al, 2007).

Accelerated bone loss in men with prostate cancer who are undergoing ADT is a significant concern (Daniell, 1997), with estimates of bone mineral density (BMD) losses ranging from 3% to 5% per year, and increased risk for fractures ranging from 13% to 53% (Ross and Small, 2002; Morote et al, 2007; Shahinian et al, 2005; Smith et al, 2005; Melton et al, 2003; Daniell, 1997). Based on retrospective studies (Daniell, 1997; Melton et al, 2003), as well as on large-claims databases, an accompanying increased fracture risk of approximately 50% (from 12.4% to 19.7% over 4 years) has also been described (Shahinian et al, 2005; Smith et al, 2005).

Denosumab is a fully human monoclonal antibody with high affinity and specificity for RANK ligand (RANKL). Denosumab binds to human RANKL and neutralizes its activity resulting in an inhibition of osteoclast formation, function, and survival. Previous studies have demonstrated that denosumab decreases markers of bone resorption and bone formation and increases BMD. Denosumab is approved in the US for the treatment of bone loss in men with osteoporosis at high risk for fracture; based on the double-blind results of Study 20040138, denosumab is approved for the treatment of bone loss due to hormone ablation therapy in men with nonmetastatic prostate cancer in the US, European Union (EU), and 29 other countries.

The primary objective of this study was to describe the long-term safety and tolerability of up to 5 years of denosumab administration (ie, 3 years under Study 20040138 and 2 years under the current open-label study [20080537]) by assessing adverse events, immunogenicity, and safety laboratory parameters. The current study was a 2-year open-label extension (OLE) study; all eligible subjects were those who had completed the 36-month double-blind treatment period of Study 20040138. Subjects who declined participation in this OLE were invited to continue in the long-term (2 years) off-treatment safety follow-up phase of 20040138, where no investigational product was administered.

Results from the 36-month treatment period of Study 20040138 were previously presented in the clinical study report (CSR) dated 15 October 2008. Results of the 24-month off-treatment safety follow-up phase of Study 20040138 were previously presented in the CSR dated 16 December 2010.

Methodology:

This was an international, multicenter, single-arm, 24-month, OLE study designed to evaluate the safety and tolerability of denosumab after up to 5 years' administration to men who had been undergoing ADT (bilateral orchiectomy or GnRH agonists) as treatment for nonmetastatic prostate cancer. Eligible subjects were those who had previously participated in Study 20040138, a placebo-controlled, double-blind phase 3 study, and who had provided signed informed consent. Subjects who satisfied the eligibility criteria were enrolled into this study to receive open-label denosumab at a subcutaneous (SC) dose of 60 mg every 6 months (Q6M) for up to 2 years (including those subjects who had previously been randomized to the placebo group in Study 20040138), with dosing occurring on day 1, month 6, month 12, and month 18; subjects returned for the end-of-study (EOS) visit at month 24.

During this OLE study, all subjects were required to take daily supplements of calcium (approximately 1000 mg elemental calcium) and vitamin D (≥ 400 IU). Safety was assessed by adverse event incidence, by changes in safety laboratory analytes (ie, serum chemistry), and by antidenosumab antibody analysis.

Number of Subjects Anticipated: Approximately 500 to 800 subjects

Number of Subjects Enrolled: A total of 384 subjects were enrolled to receive denosumab in this OLE study (198 subjects previously randomized to denosumab in Study 20040138 [hereafter referred to as the denosumab/denosumab group]; 186 subjects previously randomized to placebo [placebo/denosumab group]).

Sex: 384 men (100%)

Age (mean [SD]): 74 (6.9) years of age overall (denosumab/denosumab: 74 [6.6] years; placebo/denosumab: 73 [7.1] years)

Ethnicity (Race): 326 (84.9%) white or Caucasian; 43 (11.2%) Hispanic/Latino; 14 (3.6%) black or African American; 1 (0.3%) Japanese

Diagnosis and Main Criteria for Eligibility: Eligible subjects were men who provided signed informed consent and had participated in Study 20040138 (which had enrolled men ≥ 18 years of age with histologically confirmed prostate cancer who had an Eastern Cooperative Oncology Group [ECOG] performance status of 0, 1, or 2, and who had undergone bilateral orchiectomy or initiated ADT with GnRH agonists [with the expectation that they would continue with ADT for ≥ 12 months]).

Investigational Product, Dose and Mode of Administration, Manufacturing Lot Number: All subjects in this OLE study received SC denosumab 60 mg Q6M (manufacturing lot numbers are presented in Listing 1-1.2). Denosumab was provided as a sterile, preservative-free liquid in single-use glass vials containing 60 mg denosumab per mL of [redacted] mM sodium acetate at pH [redacted], containing [redacted]% sorbitol in water for injection.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: None; all subjects received denosumab during the study.

Duration of Treatment: Subjects who enrolled in this OLE study were offered denosumab for up to 2 years; when taking into account the duration of denosumab exposure during Study 20040138, the maximum potential exposure to denosumab was approximately 5 years across both studies (for patients who received denosumab during the blinded phase).

Study Endpoints: The primary and secondary endpoints are safety endpoints, as specified in the protocol (Appendix 1).

Primary Endpoints: For subjects previously treated with denosumab in Study 20040138 who will have received denosumab for up to 5 years upon completion of this OLE study:

- Subject incidence of treatment-emergent adverse events
- Subject incidence of treatment-emergent serious adverse events
- Changes in safety laboratory analytes (ie, serum chemistry)
- Subject incidence of antidenosumab antibody (binding and neutralizing) formation

Secondary Endpoints: For subjects previously treated with placebo in Study 20040138 who will have received denosumab for up to 2 years upon completion of this OLE study:

- Subject incidence of treatment-emergent adverse events
- Subject incidence of treatment-emergent serious adverse events
- Changes in safety laboratory analytes (ie, serum chemistry)
- Subject incidence of antidenosumab antibody (binding and neutralizing) formation

Exploratory Endpoint:

[redacted]

Statistical Methods: Analyses of data collected during the OLE phase of the study are summarized in this section. Subjects in this analysis set were analyzed according to the actual treatment received in Study 20040138 (ie, subjects who received ≥ 1 dose of denosumab were analyzed in the denosumab group regardless of the randomized treatment assignment). For the determination of all safety variables, the OLE baseline value was the latest recorded measurement on or prior to the day of the first dose of open-label denosumab.

Safety endpoints were analyzed using the safety analysis set for the OLE, which included all subjects who received ≥ 1 dose of open-label denosumab. The subject incidence of adverse events was tabulated by system organ class, preferred term, severity grade, seriousness, and relationship to treatment. Subject-year adjusted incidence rates were summarized for adverse events and serious adverse events. The following adverse events of interest are summarized separately: hypocalcemia, positively adjudicated osteonecrosis of the jaw (ONJ), infections (including skin infections leading to hospitalization), new primary malignancy, adverse events potentially associated with hypersensitivity, eczema, cataracts, and cardiovascular disorders.

Clinical laboratory parameters were summarized using descriptive statistics and/or shift tables. The proportion of subjects developing antidenosumab antibodies was calculated.

[redacted]

Summary of Results:

Subject Disposition:

A total of 384 subjects were enrolled and all 384 (100%) subjects received ≥ 1 dose of denosumab in this OLE (198 subjects previously randomized to denosumab in Study 20040138; 186 subjects previously randomized to placebo). Ninety-five subjects (53 [27%] denosumab/denosumab; 42 [23%] placebo/denosumab) withdrew from the study, and

83 subjects (44 [22.2%] denosumab/denosumab; 39 [21.0%] placebo/denosumab) discontinued denosumab treatment. Overall, 289 (75%) subjects completed the OLE study (145 [73%] denosumab/denosumab, 144 [77%] placebo/denosumab).

Efficacy Results: Efficacy was not a component of this study.

Safety Results: A total of 384 subjects received ≥ 1 dose of denosumab (n = 199 denosumab/denosumab; n = 185 placebo/denosumab).

In total, 69.3% of subjects in the denosumab/denosumab group and 66.5% of subject in the placebo/denosumab group experienced ≥ 1 adverse event during the study, with the most frequently experienced adverse events (≥ 5% in either treatment group [denosumab/denosumab, placebo/denosumab]) being constipation (6.5%, 8.6%), urinary tract infection (6.5%, 3.2%), arthralgia (5.5%, 6.5%), back pain (5.5%, 4.3%), nausea (5.5%, 4.3%), anemia (5.5%, 3.8%), cataracts (5.0%, 3.8%), and pain in extremity (4.5%, 5.9%). Most of the adverse events in both groups were categorized as being either mild or moderate in severity.

The incidence of treatment-related adverse events was 4.5% (9 subjects) in the denosumab/denosumab group and 5.9% (11 subjects) in the placebo/denosumab group. The most common (≥ 2 subjects overall [ie, both treatment groups combined]) treatment-related adverse events were (denosumab/denosumab, placebo/denosumab) cellulitis (1 subject, 2 subjects), cataract (1 subject each group), peripheral edema (1 subject each group), and rash (1 subject each group).

In the denosumab/denosumab and placebo/denosumab groups, 12 subjects (6.0%) and 6 subjects (3.2%), respectively, had adverse events that led to their withdrawal from the study. None of the adverse events leading to study discontinuation was considered by the investigator to be related to denosumab.

Fifty-one subjects (25.6%) in the denosumab/denosumab group and 45 subjects (24.3%) in the placebo/denosumab group experienced serious adverse events. The most common (≥ 3 subjects overall) serious adverse events (denosumab/denosumab; placebo/denosumab) were congestive cardiac failure (0 subjects; 5 subjects [2.7%]), cerebrovascular accident (2 [1.0%]; 3 [1.6%]), prostate cancer (2 [1.0%]; 3 [1.6%]), hematuria (3 [1.5%]; 1 [0.5%]), anemia (2 [1.0%]; 2 [1.1%]), pneumonia (2 [1.0%]; 2 [1.1%]), acute renal failure (2 [1.0%]; 1 [0.5%]), cellulitis (1 [0.5%]; 2 [1.1%]), clostridium difficile colitis (1 [0.5%]; 2 [1.1%]), transient ischemic attack (1 [0.5%]; 2 [1.1%]), and respiratory failure (0; 3 [1.6%]). There appeared to be no evidence of clustering of serious adverse events within any given system organ class or high-level group term in either treatment group.

A total of 26 subjects (14 [7.0%] subjects in the denosumab/denosumab group; 12 [6.5%] subjects in the placebo/denosumab group) experienced fatal adverse events by the end of 24 months, with the most frequently reported fatal adverse events being myocardial infarction (2 [1.0%] subjects) in the denosumab/denosumab group; and respiratory failure (3 [1.6%] subjects) and prostate cancer (2 [1.1%] subjects) in the placebo/denosumab group. In the opinion of the investigators, none of the fatal outcomes was related to denosumab.

Overall, there were no clinically important imbalances seen in adverse events of interest between treatment groups. Of the predefined adverse events of interest, there were no adverse events of hypocalcemia. One subject (denosumab/denosumab group) experienced an adverse event of ONJ that was adjudicated as positive. This subject (who received a total of 10 doses of denosumab across both the double-blind study and this OLE) received IV zoledronic acid 4 mg once every 4 weeks for approximately 7 months during the study, in violation of the protocol, and had a tooth extraction approximately 3 months prior to the onset of ONJ.

Subject incidences of infection, cataract, malignancy, cardiac disorders, vascular disorders, eczema, and adverse events potentially associated with hypersensitivity were similar between treatment groups. New primary malignancies were reported for 11 subjects (5.5%) in the denosumab/denosumab group and 4 subjects (2.2%) in the placebo/denosumab group (Table 9-4); none of the adverse events of malignancy was considered by the investigator to have

a causal relationship with denosumab, and the distribution of new malignancies did not cluster to any specific tumor types or locations.

Serum calcium levels were similar over time in both study groups. Both groups had nearly identical mean calcium concentrations at baseline and month 24. No subjects had Common Terminology Criteria for Adverse Effects (CTCAE) grade $\geq$ 2 low serum calcium values during the study. No other consistent trends in serum chemistry parameters were indicative of a treatment effect for denosumab. Denosumab was not associated with clinically significant changes in vital signs.

Conclusions:

Denosumab at a SC dose of 60 mg Q6M was generally well tolerated during this OLE study in men with nonmetastatic prostate cancer, regardless of whether subjects received denosumab for up to 2 years or for up to 5 years. The incidence of adverse events, treatment-related adverse events, serious adverse events, fatal adverse events, and adverse events of interest was generally similar between subjects treated with denosumab for up to 2 years and those treated with denosumab for up to 5 years. No subjects experienced hypocalcemia. One subject in the denosumab/denosumab group experienced an adverse event of ONJ that was adjudicated as positive; this subject, who was exposed to denosumab for 5 years, received concomitant administration of bisphosphonate IV zoledronic acid (in violation of the protocol) for 7 months and had a tooth extraction 3 months prior to the onset of ONJ.