SYNOPSIS

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

Name of Finished Product: XGEVA®

Name of Active Ingredient: denosumab (AMG 162)

Title of Study: An Open-label, Single-arm Extension Study to Evaluate the Long-term Safety of Denosumab in the Treatment of Bone Metastases in Subjects with Advanced Cancer or Multiple Myeloma

Investigator(s) and Study Center(s): This study was conducted at 17 centers in the Czech Republic and United Kingdom. Centers and investigators are listed in Appendix 3.

Publication(s): None.

Study Period: This clinical study report (CSR) includes results from 07 September 2009 (first subject enrolled in the open-label extension [OLE] phase) to 28 February 2012 (last subject completion date of the OLE). Results from the respective double-blind treatment/extension phases for Studies 20050136 (breast cancer) and 20050103 (prostate cancer) have been previously reported, as have the results for subjects enrolled in the OLE phases of these studies at sites outside of the Czech Republic and United Kingdom.

Development Phase: 3

Introduction and Objectives:

Prostate cancer is diagnosed each year in over a half million men worldwide and constitutes the second most common cause of cancer-related death in men from Western industrialized countries. Up to 75% of patients with advanced prostate cancer develop bone metastases. Bone is also the most frequent site of distant metastasis of breast cancer, accounting for approximately 40% of all first metastases; up to 80% of stage IV breast cancer patients eventually develop disease in the bone. Skeletal metastasis is characterized by increased osteoclast activity and is associated with significant skeletal morbidity (ie, skeletal-related events [SREs]). Bisphosphonates, such as zoledronic acid (Zometa®), have been shown to inhibit osteoclast activity and reduce the incidence of SREs in patients with bone metastases. RANK ligand (RANKL) is an essential mediator of osteoclast formation, function, and survival. Inhibition of RANKL has been shown to have greater antiresorptive effects compared with bisphosphonates. Denosumab is a fully human monoclonal antibody that inhibits RANKL and osteoclast-mediated bone resorption.

The primary objective of double-blind Studies 20050136 (breast cancer) and 20050103 (prostate cancer) was to determine if denosumab was noninferior to zoledronic acid with respect to the first on-study SRE (pathologic fracture, radiation to bone [including the use of radioisotopes], surgery to bone, or spinal cord compression) in subjects with advanced cancer and bone metastases. The secondary objectives were to determine if denosumab was superior to zoledronic acid with respect to the first on-study SRE and the first-and-subsequent on-study SRE (multiple event analysis), and to assess the safety and tolerability of denosumab compared with zoledronic acid. Respective results have been previously reported in the primary analysis CSRs and the double-blind extension (DBE) CSRs for these studies; these results demonstrated that denosumab, administered at a dose of 120 mg subcutaneously (SC) once every 4 weeks (Q4W), significantly reduced the risk of developing SREs compared with zoledronic acid and had a favorable safety profile in subjects with hormone-refractory prostate cancer (Study 20050103), and in subjects with breast cancer (Study 20050136).

The primary objective of this OLE study was to describe the safety and tolerability of denosumab administration as measured by adverse events, immunogenicity, and safety laboratory parameters in subjects who had previously received either zoledronic acid or denosumab. The current report summarizes safety results and patient-reported outcomes (PRO) from the OLE

phases of Studies 20050136 and 20050103. This report also includes an analysis of overall survival for the entire study, including data from the double-blind and OLE treatment phases.

Methodology: This was the OLE phase of two phase 3, randomized, double-blind, active-controlled studies that compared denosumab with zoledronic acid in the treatment of bone metastases in subjects with advanced cancer. All subjects received denosumab during the OLE phase; subjects were initially randomized in a blinded manner to one of the following treatment groups:

- 120 mg denosumab SC and placebo for zoledronic acid intravenously (IV) Q4W, or
- placebo for denosumab SC and zoledronic acid IV at a dose of 4 mg (equivalent creatinine clearance adjusted dose in subjects with baseline creatinine clearance ≤ 60 mL/min) Q4W

Daily supplementation with ≥ 500 mg calcium and ≥ 400 IU vitamin D was strongly recommended, unless the subject developed documented hypercalcemia (albumin-adjusted serum calcium > 2.9 mmol/L [> 11.5 mg/dL] or ionized calcium > 1.5 mmol/L) on study.

Because denosumab was determined to be superior to zoledronic acid (based on the primary efficacy and safety analyses) in subjects with hormone-refractory prostate cancer (Study 20050103) and in subjects with breast cancer (Study 20050136), all subjects undergoing Q4W-scheduled assessments (including those who had been randomized to the zoledronic acid treatment group) were offered open-label denosumab at a dose of 120 mg SC Q4W for up to 2 years or until denosumab became commercially available (whichever occurred first); subjects who did not participate in this OLE phase were followed for survival for up to 2 years after the last dose of blinded investigational product.

An additional phase 3 double-blind study, Study 20050244, was conducted in subjects with advanced cancer (excluding breast cancer and prostate cancer) or multiple myeloma; however, denosumab did not achieve superiority over zoledronic acid—subjects in Study 20050244 were, therefore, not eligible for participation in the current OLE study.

For subjects at study centers in the United Kingdom and Czech Republic, this OLE was conducted under the current protocol number (Study 20080540) per Health Authority request; in other countries, the OLE phase was conducted under a parent study (ie, protocol number 20050103 or protocol number 20050136) (results reported separately).

During the OLE phase, adverse events, serum chemistry, SREs (reported by the investigator only), concomitant medications, antidenosumab antibodies, and PROs (specifically, the Brief Pain Inventory-Short Form [BPI-SF]) were evaluated at regular, prespecified intervals (as presented in the Schedule of Assessments of the clinical protocol [Appendix 1 of this report]).

Number of Subjects Planned: No formal statistical testing was planned. Subjects who were enrolled in Studies 20050103 or 20050136 and who met the eligibility criteria for the OLE were eligible to participate.

Number of Subjects Enrolled: A total of 35 subjects were enrolled in this OLE to receive open-label denosumab, which included 18 subjects previously randomized to denosumab in the referent double-blind studies (12 subjects from Study 20050103 and 6 subjects from Study 20050136 [hereafter referred to as the denosumab/denosumab group]); and 17 subjects previously randomized to zoledronic acid (10 subjects from Study 20050103 and 7 subjects from Study 20050136 [zoledronic acid/denosumab group]).

Sex: 22 men (62.9%) and 13 women (37.1%)

Age (mean [SD]): 61.3 (11.9) years of age, overall (denosumab/denosumab: 61.1 [13.0] years; zoledronic acid/denosumab: 61.6 [11.1] years)

Ethnicity (Race): 34 (97.1%) white or Caucasian, 1 (2.9%) black or African American

Diagnosis and Main Criteria for Eligibility: Subjects who were enrolled in Study 20050103 or 20050136 and who had provided signed, informed consent were eligible for participation in the study.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: All subjects received SC denosumab 120 mg Q4W (manufacturing lot numbers: [redacted], and [redacted] [Listing 1-1.2]). Denosumab was provided as a sterile, preservative-free liquid in single-use, 3.0-mL glass vials containing 1.7 mL of 70 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.

Duration of Treatment: Subjects were to receive denosumab until the subject had access to commercially available denosumab, or for a period of up to 2 years.

Study Endpoints: This synopsis CSR contains an analysis of the following endpoints that were specified in Statistical Analysis Plan (dated 17 April 2012), provided in Appendix 2.

- Subject incidence of treatment-emergent adverse events
- Changes in chemistry laboratory values
- Changes in ECOG status
- Incidence of antidenosumab antibody (binding and neutralizing) formation
- Total number of deaths
- Brief Pain Inventory–Short Form (BPI-SF) pain scores

Statistical Methods: Safety endpoints were analyzed using the safety analysis set, comprising 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, serious adverse events, and adverse events with a Common Toxicity Criteria Adverse Events (CTCAE; version 3.0) grade of 3, 4, or 5. The following adverse events of interest are discussed 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, cardiovascular disorders, and osteonecrosis outside the jaw; preferred terms used in the search strategy are listed in Appendix 5. New primary malignancies were identified by clinical review of malignancy preferred terms from the neoplasm system organ class. Infections were assessed using all preferred terms reported in the infections and infestations system organ class, and cardiovascular events were assessed using all preferred terms reported in the cardiac disorders and vascular disorders system organ classes.

Clinical laboratory parameters were summarized using descriptive statistics and/or shift tables. ECOG performance status scores and changes from open-label baseline ECOG scores were summarized. The proportion of subjects developing antidenosumab antibodies was calculated and listed.

The total number of deaths in the entire study (ie, the respective blinded treatment phase and the OLE phase) was summarized using the full analysis set (ie, all subjects who were randomized in the study); subjects were analyzed according to their randomized treatment assignment.

Descriptive statistics for recorded values and change from open-label baseline in BPI-SF worst pain score and pain interference score were presented by visit using the PRO analysis subset (comprising all subjects who participated in the OLE phase of the study and who had ≥ 1 open-label PRO assessment). Based on the BPI-SF worst pain score, the proportion of subjects with moderate/severe pain (worst pain score > 4) was summarized, as was the proportion of subjects with a clinically meaningful worsening of pain (≥ 2-point increase) from OLE baseline.

Summary of Results:

Subject Disposition: In total, 35 subjects (18 subjects previously randomized to denosumab; 17 subjects previously randomized to zoledronic acid) provided informed consent to receive denosumab in the OLE phase (Table 14-1.2). The distribution of subjects in the OLE phase of the study by country, site, and geographic region is provided in Table 14-1.3 to Table 14-1.5.

All 35 enrolled subjects received ≥ 1 dose of denosumab; of those who received denosumab during the referent double-blind treatment phase, the median (Q1, Q3) cumulative denosumab exposure across all study phases (double-blind and OLE) was 34.3 months (30.4, 44.9) with a minimum exposure of 24.8 months and a maximum exposure of 57.9 months (Table 14-5.2). Among denosumab/denosumab- and zoledronic acid/denosumab-designated subjects, median (Q1, Q3) exposures to denosumab during the OLE phase (only) were 9.5 (4.7, 16.6) and 16.7 (11.3, 22.1) months, respectively (Table 14-5.1).

The OLE phase of the study was completed by 8 subjects (22.9%), which included 3 subjects in the denosumab/denosumab group and 5 subjects in the zoledronic acid/denosumab group (Table 14-1.1). A total of 27 subjects (77.1%) discontinued from the OLE phase of the study (15 subjects denosumab/denosumab, 12 subjects zoledronic acid/denosumab), with the most common reasons for study discontinuation being death (28.6%), withdrawal of consent (11.4%), disease progression (11.4%), and administrative decision (11.4%).

No subjects in either group had protocol deviations during the OLE (Table 14-1.6).

Safety Results:

Most of the subjects in the denosumab/denosumab (14 subjects [77.8%]) and zoledronic acid/denosumab (14 subjects [82.4%]) groups experienced ≥ 1 treatment-emergent adverse event during their participation in the OLE phase, with adverse events being most commonly categorized within the system organ classes (denosumab/denosumab, zoledronic acid/ denosumab) of gastrointestinal disorders (61.1%, 47.1%), musculoskeletal and connective tissue disorders (55.6%, 58.8%), general disorders and administration site conditions (44.4%, 58.8%), infections and infestations (38.9%, 52.9%) and nervous system disorders (44.4%, 35.3%) (Table 14-6.2.1). By preferred term, the most frequently experienced adverse events were fatigue (6 subjects in the denosumab/denosumab group; 3 subjects in the zoledronic acid/denosumab group), anemia (6; 1), nausea (5; 1), and back pain (4; 2) (Table 14-6.3.1). Subject year-adjusted rates of adverse events are included in Table 14-6.4.1 and Table 14-6.5.1.

The investigator considered adverse events to be possibly related to denosumab in 6 (33.3%) subjects in the denosumab/denosumab group and in 4 (23.5%) subjects in the zoledronic acid/denosumab group (Table 14-6.2.5). By preferred term, the most frequently experienced treatment-related adverse events (> 1 subject in either group [denosumab/denosumab; zoledronic acid/denosumab]) were hypocalcemia (2 subjects; 1 subject) and osteonecrosis of the jaw (ONJ) (1 subject; 2 subjects) (Table 14-6.3.5). Of note, 1 additional subject in the denosumab/denosumab group ([redacted]) experienced an adverse event that was recorded by the investigator as (preferred term) "osteonecrosis"; however, this event (CTCAE grade 2), which was serious and considered by the investigator to be related to investigational product, met Amgen's predefined definition for ONJ and was subsequently adjudicated positive as ONJ (ie, 2 subjects in each group experienced ONJ [Listing 1-2.8]). Positively adjudicated events of ONJ are discussed below within the Adverse Events of Interest section.

The subject incidence of treatment-emergent adverse events with a CTCAE grade ≥ 3 was 12 subjects (66.7%) in the denosumab/denosumab group and 8 subjects (47.1%) in the zoledronic acid/denosumab group, with the most commonly reported (> 1 subject in either group [denosumab/denosumab; zoledronic acid/denosumab]) of these events being fatigue (4 subjects; 0 subjects), anemia (3; 0), cachexia (2; 1), and ONJ (1; 2) (Table 14-6.3.8). Grade ≥ 3 adverse events considered by the investigator to be possibly related to denosumab were reported for 2 subjects (11.1%) in the denosumab/denosumab group and for 3 subjects (17.6%) in the zoledronic acid/denosumab group; the only treatment-related grade ≥ 3 adverse event experienced by > 1 subject across both groups was ONJ (1 subject [5.6%] in the denosumab/denosumab group, 2 subjects [11.8%] in the zoledronic acid/denosumab group)

(Table 14-6.2.9 and Table 14-6.3.9). Subject year-adjusted rates of grade ≥ 3 adverse events are summarized in Table 14-6.4.3 and Table 14-6.5.3.

Serious adverse events were experienced by 10 subjects (55.6%) in the denosumab/denosumab group and by 8 subjects (47.1%) in the zoledronic acid/denosumab group, with the most common serious adverse events being cachexia (2 subjects and 1 subject, respectively) and ONJ (2 subjects each group [includes 1 subject with a serious adverse event of "osteonecrosis," as described above]); no other serious adverse event was experienced by > 1 subject in either group (Table 14-6.2.2 and Table 14-6.3.2). Subject year-adjusted rates of serious adverse events are included in Table 14-6.4.2 and Table 14-6.5.2. Narratives for all serious adverse events are provided in Appendix 6.

A total of 8 subjects (5 [27.8%] denosumab/denosumab; 3 [17.6%] zoledronic acid/denosumab) had fatal adverse events (Table 14-6.1); of these events, none was considered by the investigator to have a causal relationship with denosumab (Table 14-6.3.14). Fatal adverse events (denosumab/denosumab; zoledronic acid/denosumab) included cachexia (2 subjects; 1 subject), hepatic failure (1; 0), malignant neoplasm (1; 0), metastatic prostate cancer (1; 0), cardiac failure (0; 1), and death (0; 1) (Table 14-6.2.7 and Table 14-6.3.7). Narratives for all fatal adverse events are included in Appendix 6.

Three subjects in each group experienced adverse events that resulted in discontinuation of denosumab (Table 14-6.1 and Table 14-6.2.4); these adverse events (denosumab/denosumab, zoledronic acid/denosumab) were ONJ (1 subject, 2 subjects), general physical health deterioration (1, 0), osteonecrosis (1, 0), and hypocalcemia (0, 1) (Table 14-6.3.4). Of these, the 3 events of ONJ and the 1 event of osteonecrosis (all of which were adjudicated positive as ONJ, as discussed above) met the criteria of serious adverse events (Table 14-6.3.11).

Two subjects in the denosumab/denosumab group (0 in the zoledronic acid/denosumab group) withdrew from the study in response to an adverse event. Adverse events leading to subject withdrawal from the study were ONJ (1 subject) and general physical health deterioration (1 subject) (Table 14-6.2.3 and Table 14-6.3.3). Of these events, the event of ONJ met the criteria of a serious adverse event (Table 14-6.2.10 and Table 14-6.3.10) and was considered by the investigator to be related to denosumab (Table 14-6.3.15); no other adverse event leading to withdrawal from the study was serious or considered to be related to denosumab.

Adverse Events of Interest

The following adverse events were summarized separately: hypocalcemia, positively adjudicated ONJ, adverse events of infections (including skin infections leading to hospitalization), osteonecrosis outside the jaw, new primary malignancy, adverse events potentially associated with hypersensitivity, eczema, and cardiovascular disorders.

Hypocalcemia: Adverse events of hypocalcemia were reported for 2 (11.1%) subjects in the denosumab/denosumab group (1 of which experienced 4 hypocalcemia events) and for 1 (5.9%) subject in the zoledronic acid/denosumab group (Table 14-6.12.1, Listing 1-2.3). All adverse events of hypocalcemia were considered by the investigator to be related to denosumab (Table 14-6.3.5). None of the adverse events of hypocalcemia met the criteria of a serious adverse event (Table 14-6.12.3), none required correction with IV calcium (Table 14a-6.14), and none was associated with signs of or symptoms of acute hypocalcemia (eg, tetany, paresthesias) (Listing 1-2.1). No event of hypocalcemia resulted in subject withdrawal from the study (Table 14-6.3.3); however, 1 subject ([redacted]; zoledronic acid/denosumab) experienced an adverse event of hypocalcemia that resulted in discontinuation of denosumab (Table 14-6.3.4; Listing 1-2.10). None of the adverse events of hypocalcemia was reported as being fatal (Table 14-6.2.7).

Positively Adjudicated ONJ: Adverse events were identified for adjudication by the ONJ adjudication committee by information entered on the oral examination case report form, searches of the adverse event dataset using a predefined list of oral-related MedDRA preferred terms (see Appendix 5), and by additional clinical review of all adverse events constituting potential ONJ cases. After positive adjudication by the ONJ adjudication committee, these events are referred to as positively adjudicated ONJ, rather than the adverse event preferred term of

osteonecrosis of the jaw discussed in the previous adverse event section. Adverse events of ONJ were adjudicated positive for 2 subjects in each group (denosumab/denosumab: 11.1%; zoledronic acid/denosumab: 11.8%) (Table 14-6.11.2). All 4 subjects had a history of [redacted], and/or use of a [redacted]; in addition, 1 subject in the denosumab/denosumab group and 2 subjects in the zoledronic acid/denosumab group had [redacted] within the year prior to the respective onsets of ONJ (Appendix 6 and Listing 1a-2.8.2). Three of the subjects with events of positively adjudicated ONJ required treatment that included surgical intervention (which included tooth extraction, sequestrectomy, debridement, and curettage). The remaining subject ([redacted]) with positively adjudicated ONJ was not hospitalized, required no surgical treatments, and was managed conservatively (eg, with mouth rinses and antibiotics). This subject (denosumab/denosumab), a [redacted], had a grade-4 serious adverse event that triggered adjudication of ONJ; the reason for categorizing the event as CTCAE grade-4 severity was not specified (Appendix 6). The 3 remaining cases of positively adjudicated ONJ were CTCAE grade 2 (Listing 1-2.7).

For both subjects in the denosumab/denosumab group with positively adjudicated ONJ, response to the respective events included discontinuation of denosumab treatment; for the subject with grade-4 ONJ (discussed above), intervention also included withdrawal from the study. Of the 2 subjects in the zoledronic acid/denosumab group with positively adjudicated ONJ, 1 required discontinuation of denosumab; the remaining subject had "other" listed as the consequent action taken (Listing 1-2.7).

Based on information available as of 11 June 2012, the adjudicated-positive ONJ adverse events were considered to be resolved (defined as complete mucosal coverage of exposed bone) for 1 subject in each group (Listing 1a-2.8.2).

Osteonecrosis Outside the Jaw: One subject had an adverse event recorded as (preferred term) "osteonecrosis," an event that was subsequently adjudicated positive as ONJ. No subject had an event of osteonecrosis outside the jaw (Listing 1-2.1)

Infection: Seven subjects (38.9%) in the denosumab/denosumab group and 9 (52.9%) subjects in the zoledronic acid/denosumab group experienced adverse events categorized within the system organ class of infections and infestations (Table 14-6.2.1). The most common adverse events of infection (denosumab/denosumab, zoledronic acid/denosumab) were oral candidiasis (2 subjects, 0 subjects), pharyngitis (0 subjects; 2 subjects), and herpes zoster (1 subject in each group). One adverse event in the system organ class of infection met the criteria of a serious adverse event: 1 subject ([redacted]) in the denosumab/denosumab group experienced a serious adverse of urosepsis (CTCAE grade 3) that required hospitalization (Listing 1a-2.5); the event was not considered by the investigator to have a causal relationship with denosumab.

Adverse events of skin infection were reported by 2 subjects (11.1%) in the denosumab/denosumab group and by 1 subject (5.9%) in the zoledronic acid/denosumab group (Table 14-6.10.2). These adverse events (none being experienced by > 1 subject) included erysipelas (denosumab/denosumab), skin infection (denosumab/denosumab), and cellulitis (zoledronic acid/denosumab); none was a serious adverse event (Table 14-6.10).

New Primary Malignancy: No subject in either group experienced an adverse event of new primary malignancy (Table 14-6.8).

Hypersensitivity: Adverse events potentially associated with hypersensitivity were reported for 2 (11.1%) subjects in the denosumab/denosumab group (allergic dermatitis, eczema), and for 2 subjects in the zoledronic acid/denosumab group (face edema, photosensitivity allergic reaction) (Table 14-6.13.1, Table 14-6.13.2). None of the adverse events potentially associated with hypersensitivity were reported as being serious, none resulted in discontinuation of denosumab or subject withdrawal from the study, and all events of hypersensitivity were of mild or moderate severity (Listing 1-2.9).

Eczema: Two (11.1%) subjects in the denosumab/denosumab group (none in the zoledronic acid/denosumab group) experienced an adverse event of eczema (Table 14-6.9). These events, allergic dermatitis and eczema, are discussed above in the hypersensitivity subsection.

Cardiovascular Disorders: Adverse events in the MedDRA cardiac disorders system organ class were reported for 1 subject in the denosumab/denosumab group (atrial fibrillation) and for 2 subjects in the zoledronic acid/denosumab group (atrial fibrillation and palpitations in 1 subject, cardiac failure in 1 subject [a fatal adverse event; [redacted]]) (Table 14-6.2.1, Listing 1-2.1). Of these events, 1 event of atrial fibrillation (zoledronic acid/denosumab) and the event of cardiac failure (zoledronic acid/denosumab) each resulted in hospitalization and met the criteria of a serious adverse event. None of the adverse events in the system organ class of cardiac disorders resulted in discontinuation of denosumab or subject withdrawal from the study, and none was considered by the investigator to be related to denosumab.

Two subjects in the zoledronic acid/denosumab group (none in the denosumab/denosumab group) experienced a total of 3 adverse events categorized within the vascular disorders system organ class; these events included both hypertension and life-threatening jugular vein thrombosis in 1 subject ([redacted]), and lymphedema in 1 subject (Table 14-6.2.1). Of these events, the event of jugular vein thrombosis was serious (Table 14-6.2.2). None of the vascular disorder adverse events resulted in discontinuation of denosumab or subject withdrawal from the study, and none was considered by the investigator to be related to denosumab.

Laboratory Data

Antidenosumab Antibody Assays: Of the 34 subjects (n = 17 in each group) who were tested for antidenosumab antibodies, 1 subject ([redacted]; denosumab/denosumab) tested positive for antidenosumab binding antibodies to denosumab on day 1 of the OLE phase (Table 14-8.1.1, Listing 1-2.17); the sample was negative for neutralizing activity (Appendix 8). This subject had been previously treated with denosumab in Study 20050103, and all previous samples had been negative for antidenosumab binding antibodies. Subsequent samples were not available for this subject. Adverse events that occurred subsequent to the detection of day-1 antidenosumab antibodies in this subject included an ECOG worsening from a score of 2 to > 3 on study day 129, and a fatal event of cachexia (verbatim term: *malignant kachexia*) on study day 143 (Listing 1-2.18 and Appendix 6). Neither event was considered by the investigator to be related to denosumab. The Clinical Immunology Report is provided in Appendix 8.

Serum Chemistry: Laboratory values and changes in laboratory parameters are presented in Table 14-7.1.1 through Table 14-7.19.2, and in Figure 14-1.1 through Figure 14-1.10. Shifts in toxicity grades for laboratory parameters are presented in Table 14-7.20.1 through Table 14-7.20.14. Grade 3 or higher laboratory values are summarized in Table 14-7.21.1. Subject incidence of albumin-adjusted calcium CTCAE grade $\geq$ 2 and shifts from baseline $\geq$ 2 are summarized in Table 14-7.21.2 to Table 14-7.21.4.

Expected decreases in serum calcium and phosphorus occurred. Albumin-adjusted serum calcium concentrations remained relatively uniform (no median percent change in either direction > 2%) until week 25, when median (Q1, Q3) percent changes from OLE baseline decreased by 4.2% (-4.4%, 2.5%; n = 9 subjects) in the denosumab/denosumab group and by 3.1% (-5.1%, 1.0%; n = 10 subjects) in the zoledronic acid/denosumab group (Table 14-7.1.5, Figure 14-1.1). Although these decreases in albumin-adjusted serum calcium were evident, median values remained within the normal laboratory reference range throughout the study (Figure 14-1.5 and Table 14-7.1.1). One subject (denosumab/denosumab) had an albumin-adjusted calcium value that decreased from normal at OLE baseline to grade 2 at study day 512 (Table 14-7.21.4; Listing 1-2.22); for this subject, the abnormally low calcium value appeared to be transient (ie, concentrations were within the normal range at all time points both before and after the abnormal value).

Two subjects in the denosumab/denosumab group (0 in the zoledronic acid/denosumab group) had decreases in phosphorus levels from CTCAE grade 0 at OLE baseline to a maximum of CTCAE grade 3; no subject in either group had a grade-4 serum phosphorus decrease in either group (Table 14-7.20.10). There were no obvious trends within either the denosumab/denosumab or zoledronic acid/denosumab groups indicative of denosumab-related effects on other laboratory parameters (Table 14-7.20.1 through Table 14-7.20.14; Table 14-7.21.1).

Performance Status

While several subjects had a worst overall ECOG performance status that worsened by 1 grade (n = 4 denosumab/denosumab; n = 2 zoledronic acid/denosumab), 2 grades (n = 1 denosumab/denosumab; n = 0 zoledronic acid/denosumab), or 3 grades (1 subject in each group), overall changes in ECOG performance status did not appear to be indicative of a treatment-related effect (Table 14-8.4.1 and Table 14-8.4.2). In several cases, worsening ECOG grades were reported as adverse events (preferred term: *general physical health deterioration*), of which none was considered by the investigator to have a causal relationship with denosumab (Listing 1-2.1).

Overall Survival:

For subjects enrolled in the OLE treatment phase, the overall survival was similar between treatment groups, with the survival rate being 67% (12 subjects) in the denosumab/denosumab group and 77% (13 subjects) in the zoledronic acid/denosumab group (Table 14-4.16).

Patient-reported Outcomes:

Brief Pain Inventory – Short Form (BPI-SF) Pain Score

At baseline of the OLE phase, the mean (SD) worst pain score was 3.5 (3.0) in the denosumab/denosumab group and 3.6 (2.5) in the zoledronic acid/denosumab group (Table 14-2.2). Thereafter, mean BPI worst pain scores were generally consistent during the OLE phase (Table 14-4.3 and Table 14-4.8); however, the small and varying number of subjects with BPI-SF values at each time point precludes meaningful interpretation. Similar results were noted for "pain interference" scores (Table 14-4.7 and Table 14-4.12).

Up to 6 subjects in the denosumab/denosumab group and 7 subjects in the zoledronic acid/denosumab group had moderate/severe pain (worst pain score > 4) at ≥ 1 study visit during the OLE phase (Table 14-4.14); however, at any given time point, ≤ 3 subjects in either group had a clinically meaningful worsening (≥ 2-point increase) from OLE baseline in worst pain score (Table 14-4.13).

Conclusions:

Denosumab, at a SC dose of 120 mg Q4W, was generally well tolerated during this OLE study by subjects with advanced cancer and bone metastases. The median exposures to denosumab in the OLE treatment phase among subjects previously treated with denosumab or zoledronic acid in the parent studies were 9.5 and 16.7 months, respectively; for subjects previously treated with denosumab in the double-blind phase, the median cumulative exposure to denosumab (double-blind and OLE phases combined) was 34.3 months (maximum = 58 months). No new safety signals were identified during the OLE phase.