SYNOPSIS

Name of Sponsor: Amgen Inc

Name of Finished Product: not applicable

Name of Active Ingredient: denosumab (AMG 162)

Title of Study: A Randomized, Double-Blind, Multicenter Study of Denosumab Compared with Zoledronic Acid (Zometa®) in the Treatment of Bone Metastases in Men with Hormone-Refractory Prostate Cancer

Investigators and Study Centers: This study was conducted at a total of 342 centers in 39 countries. Study centers and investigators are listed in Attachment 3.

Publication(s): Fizazi K, Carducci MR, Smith R, et al. A randomized phase III trial of denosumab versus zoledronic acid in patients with bone metastases from castration-resistant prostate cancer [abstract]. *J Clin Oncol* 2010;28:18s. Abstract LBA4507.

Study Period: This clinical study report (CSR) includes results from 12 May 2006 (date that the first subject was enrolled) to 26 February 2010 (extended blinded treatment phase data cutoff date). Results from the ongoing open-label treatment phase (including survival follow-up for subjects not receiving open-label denosumab) will be reported separately.

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. 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 to bisphosphonates. Denosumab is a fully human monoclonal antibody that inhibits RANKL and osteoclast-mediated bone resorption. Thus, denosumab represents a new and potentially efficacious treatment for complications from bone metastases in patients with hormone-refractory prostate cancer.

The primary objective of this study was to determine if denosumab is noninferior to zoledronic acid (Zometa®) with respect to the first on-study occurrence of an SRE in men with hormone-refractory prostate cancer and bone metastases. The secondary objectives were to determine if denosumab is 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.

[redacted]

Results from the primary blinded treatment phase, which were summarized separately, demonstrated that denosumab administered at a dose of 120 mg subcutaneously (SC) every 4 weeks (Q4W) significantly reduced the risk of developing SREs compared with zoledronic acid and had a positive benefit:risk profile in subjects with hormone refractory (castrate-resistant) prostate cancer and bone metastases. Efficacy results from the primary analysis are reported in Table 1.

Methodology: This was an international, phase 3, randomized, double-blind, active-controlled study comparing denosumab with zoledronic acid in the treatment of bone metastases in men with hormone-refractory prostate cancer. Subjects were randomized in a blinded manner to 1 of the following treatment groups.

- *120 mg denosumab SC and zoledronic acid placebo intravenously (IV) Q4W, or*
- *denosumab placebo 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.*

Randomization was stratified by previous SRE (yes or no), PSA level (< 10 ng/mL or ≥ 10 ng/mL), and current chemotherapy (defined as within 6 weeks before randomization) (yes or no). Within each stratum, subjects were randomized using an equal allocation ratio of 1:1. Each subject received blinded investigational product up to completion of the efficacy and safety analyses (blinded treatment phase). 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 or > 11.5 mg/dL or ionized calcium > 1.5 mmol/L) on study.

Since denosumab was determined to be superior compared with zoledronic acid, based on the primary efficacy and safety analyses (see Efficacy and Safety Results synopsis sections), all subjects undergoing Q4W-scheduled assessments were offered open-label denosumab at a dose of 120 mg SC Q4W for up to 2 years or until denosumab is commercially available, whichever comes first. For subjects at all study centers, except in the United Kingdom and Czech Republic, the open-label phase is being conducted under the current protocol number (20050103); in the United Kingdom and Czech Republic, the open-label extension phase is being conducted under protocol number 20080540 per Health Authority request. Subjects who did not enroll in this open-label extension phase are being followed for survival for 2 years after the last dose of blinded investigational product.

During the blinded treatment phase, adverse events, clinical laboratory parameters, SREs, concomitant medications (including analgesic use), antidenosumab antibodies, and [redacted] were evaluated at regular, prespecified intervals. [redacted] and serum denosumab concentration levels were obtained from a subset of approximately 150 subjects at selected centers. An external, independent data monitoring committee (DMC) reviewed safety and efficacy data at regular intervals during the blinded treatment phase. Results from the open-label treatment phase will be reported separately. During the open-label treatment phase, adverse events, serum chemistry, SREs, concomitant medications (including analgesic use), antidenosumab antibodies, and [redacted]) are evaluated at regular, prespecified intervals.

Number of Subjects Planned: 1870 subjects (935 subjects per treatment group)

Number of Subjects Enrolled: A total of 1904 subjects were enrolled in the study. Of these subjects, 951 were randomized to receive denosumab, and 953 were randomized to receive zoledronic acid. Prior to unblinding, the decision was made to exclude subjects from all analyses when IRB review activities and oversight were not ensured. One subject randomized to denosumab and 2 subjects randomized to zoledronic acid met this criterion (Listing 1-5.1 and Listing 1-1.1). Therefore, the number of subjects enrolled and randomized in this study is reported in this document as 1901 (950 denosumab, 951 zoledronic acid) (Table 14-1.1 and Table 14-1.3).

Sex: 1901 (100%) men (Table 14-2.1)

Age: mean 70.8 (SD 8.6) years (Table 14-2.1)

Ethnicity (Race): 1639 (86.2%) white or Caucasian, 102 (5.4%) Hispanic/Latino, 73 (3.8%) black or African American, 48 (2.5%) Asian, 2 (0.1%) Hawaiian/Pacific Islander, 37 (1.9%) other (Table 14-2.1)

Diagnosis and Main Criteria for Eligibility: Eligible subjects met the following criteria: men ≥ 18 years of age with histologically confirmed, hormone-refractory prostate cancer; current or prior radiographic evidence of ≥ 1 bone metastasis; Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; adequate organ function; life expectancy ≥ 6 months; and no current or prior exposure to any IV bisphosphonates or oral bisphosphonates administered for treatment of bone metastases.

Investigational Product, Dose and Mode of Administration, Manufacturing Lot Number: Subjects randomized to denosumab received denosumab 120 mg SC and zoledronic acid placebo IV Q4W during the blinded treatment phase and will receive denosumab 120 mg SC Q4W during the open-label treatment phase. Denosumab was provided as a sterile, preservative-free liquid in blinded-label (blinded treatment phase only), single-use, 3.0-mL glass vials containing 1.7 mL of 70 mg denosumab per mL of [redacted] mM sodium acetate, [redacted]% sorbitol at a pH of [redacted]. Zoledronic acid placebo was provided in a blinded manner as a liquid formulation containing the inactive ingredients, 16 mM sodium citrate and 4.4% mannitol, at a pH of 6.2 to mimic the Zometa® brand of zoledronic acid. Lot numbers for denosumab and zoledronic acid placebo used in this study are provided in Listing 1-1.3.

Duration of Treatment: Subjects received either denosumab or zoledronic acid (reference therapy) in a blinded fashion up to completion of the primary efficacy and safety analyses (blinded treatment phase). The median (Q1, Q3) duration of exposure for the blinded treatment phase was 11.99 (5.55, 19.45) months (mean [SD] = 13.39 [9.26] months) for the denosumab group and 10.18 (4.86, 17.81) months (mean [SD] = 12.23 [8.97] months) for the zoledronic acid group, which included the exposure during the primary blinded treatment phase (median [Q1, Q3]: 11.86 [5.55, 18.17] months [mean {SD} =12.63 {8.38} months] denosumab, 10.15 [4.86, 16.56] months [mean {SD} = 11.59 {8.13} months] zoledronic acid) (Table 14-5.1 and Study 20050103 Primary Analysis CSR) and exposure during the extended blinded treatment phase (ie, from the primary analysis data cutoff date to the completion of the blinded efficacy and safety analyses). Since denosumab was determined to be superior compared with zoledronic acid based on the primary efficacy and safety analyses (see Efficacy and Safety Results synopsis sections), subjects undergoing Q4W-scheduled assessments were offered open-label denosumab at a dose of 120 mg SC Q4W for up to 2 years or until denosumab is commercially available, whichever comes first.

Reference Therapy, Dose and Mode of Administration, Manufacturing Lot Number: Subjects randomized to zoledronic acid received zoledronic acid 4 mg (adjusted for creatinine clearance) as a single, minimum 15-minute IV infusion and denosumab placebo SC Q4W during the blinded treatment phase. Zoledronic acid was supplied in a blinded manner as a sterile liquid concentration solution for infusion. The commercial form of zoledronic acid was not altered: each 5 mL of the zoledronic solution contained 4.264 mg of zoledronic acid monohydrate, corresponding to 4 mg zoledronic acid on an anhydrous basis; inactive ingredients included

220 mg mannitol, water for injection, and 24 mg sodium citrate. Denosumab placebo was provided in identical containers and was identical in formulation (excluding the protein content) to the active denosumab product. Lot numbers for zoledronic acid and denosumab placebo used in this study are provided in Listing 1-1.3.

Study Endpoints

Primary Efficacy

- *time to first on-study SRE (noninferiority)*

Secondary Efficacy

- *time to first on-study SRE (superiority)*
- *time to first-and-subsequent on-study SRE (superiority, using multiple-event analysis)*

Exploratory Efficacy

- [redacted]

[redacted]

Safety

- *subject incidence of treatment-emergent adverse events*
- *changes in laboratory values*
- *incidence of antidenosumab antibody (binding and neutralizing) formation*

Pharmacokinetic

- *denosumab serum concentration levels*

Statistical Methods:

Analyses of data collected during the blinded treatment phase are summarized in this section. All analyses from the primary blinded treatment phase, including any ad hoc analyses, were repeated at the end of the blinded treatment phase. Data from the blinded treatment phase (including the primary blinded treatment phase and the extended blinded treatment phase) were included in the analyses. Efficacy analyzed at the end of the blinded treatment phase was considered supportive to the primary analysis; therefore, no adjustments for multiplicity were made.

Primary and Secondary Efficacy Endpoints

The primary and secondary efficacy endpoints were analyzed using the full analysis set, which included all randomized subjects. Supportive analyses used the per-protocol analysis set, which included all subjects with a protocol-defined diagnosis and no major protocol violations who received ≥ 1 dose of active investigational product.

Time to first on-study SRE was analyzed using a Cox proportional hazards model, with treatment groups as the independent variable and stratified by factors used to balance randomization. This study was designed to be similar to the zoledronic acid registration studies in subject population, dose and administration of zoledronic acid, and endpoint definitions. The aim of having similarity in study designs was to achieve a similar zoledronic acid treatment effect compared with placebo as that observed in the historical studies. A synthesis approach was used for the noninferiority test for the primary endpoint. Testing for superiority proceeded after demonstration of noninferiority; results of the Cox model were used to determine whether or not denosumab is superior to zoledronic acid with respect to time to first on-study SRE. For time to first-and-subsequent on-study SRE (multiple-event analysis), the Andersen and Gill model was used.

Safety Endpoints

Safety endpoints were analyzed using the safety analysis set, which included all randomized subjects who received ≥ 1 dose of active investigational product; subjects in this analysis set were analyzed according to the treatment received, based on the first investigational product dose administered. The subject incidence of each adverse event was tabulated by system organ class, preferred term, severity, seriousness, and relationship to treatment. The following adverse events were summarized separately: hypocalcemia, adverse events of infections (including skin infections leading to hospitalization), osteonecrosis of the jaw (ONJ), new primary malignancy, eczema, and cardiovascular disorders, and adverse events potentially associated with hypersensitivity, renal toxicity, or acute phase reaction. The incidence of positively adjudicated ONJ events was compared between treatment groups using a Fischer's exact test. Clinical laboratory parameters and vital signs were summarized using descriptive statistics and/or shift tables. The proportion of subjects developing antidenosumab antibodies was calculated.

Exploratory Endpoints

[redacted]

[redacted]

Summary of Results:

Subject Disposition:

A total of 1901 subjects were enrolled into the study, with 950 subjects randomized to denosumab and 951 subjects randomized to zoledronic acid (Table 14-1.13). Randomization was stratified by previous SRE (24%), PSA level < 10 ng /mL (15%), and current chemotherapy (14%); randomization was balanced between treatment groups within each stratum (Table 14-1.10). Of the randomized subjects, 1888 received ≥ 1 dose of investigational product (943 denosumab, 945 zoledronic acid) (Table 14-1.13).

As of the blinded treatment phase data cutoff date, 81.4% and 84.5% of subjects who had received ≥ 1 dose of investigational product in the denosumab and zoledronic acid groups, respectively, had discontinued from investigational product (Table 14-1.3); 81.6% and 84.4% in the denosumab and zoledronic acid groups, respectively, had discontinued from the study (Table 14-1.1). The median time to withdrawal was 12.7 months (386 days) for denosumab and 11.2 months (342 days) for zoledronic acid (Table 1-4.102.1 and Figure 1-4.102.1). The most frequently cited reasons for withdrawal were death (32.8% denosumab, 30.6% zoledronic acid), study consent withdrawn (16.1%, 18.1%), disease progression that precluded continuation of treatment (13.4%, 12.9%), adverse event (6.6%, 4.7%), subject request (6.1%, 9.0%), and other (3.8%, 4.7%) (Table 14-1.1). Other reasons for withdrawal were reported for < 2% of subjects in each treatment group. A clinical review was performed to determine the underlying reason for study consent withdrawn/subject request. In most cases, reasons for study consent withdrawn/subject request were unknown, and, where reasons were known, the incidence was similar between groups.

The overall incidence of eligibility deviations was low for both treatment groups (4.7% denosumab, 4.0% zoledronic acid) (Table 14-1.9). The most frequently reported deviations were that the [redacted]
Six subjects (3 subjects randomized to each treatment group) had screening procedures performed before providing informed consent (Listing 1-1.5 and data on file). These subjects were appropriately consented before any other study assessments were conducted; therefore, it was considered appropriate to include these subjects in the efficacy and safety analyses.

Two subjects in the denosumab group and 3 subjects in the zoledronic acid group had an eligibility deviation reported in the primary analysis but not in the current analysis (Listing 1-1.5 and Study 20050103 Primary Analysis CSR). In the primary analysis, 1 subject in the denosumab group ([redacted]) and 2 subjects in the zoledronic acid group ([redacted] and [redacted]) were reported as having central labs drawn before

providing informed consent; however, these sample dates or consent dates were found to be in error and were corrected prior to the database lock for this analysis. The corrected date showed that the subjects had all samples taken after providing informed consent. One subject in the denosumab group ( ) was reported as having a . One subject in the zoledronic acid group ( ) was reported as not having a serum testosterone level of < 50 ng/dL due to either surgical or chemical castration; however, the testosterone level at screening was confirmed to be 32.54 ng/dL, and the error was corrected prior to the database lock for this analysis. Therefore, eligibility deviations for these subjects were removed from the database for this analysis.

One additional subject in each group was identified as having an eligibility deviation compared to the primary analysis: denosumab and zoledronic acid did not provide written informed consent prior to a skeletal survey.

Slight differences in datasets used for the primary analysis and entire blinded treatment phase analysis may exist due to the change in number of eligibility deviations noted above.

Efficacy Results:

Primary and Secondary Endpoints

The primary and secondary endpoints were assessed over the entire blinded treatment phase (ie, primary and extended blinded treatment phases) using the full analysis set, which included 1901 subjects (950 denosumab, 951 zoledronic acid) (Table 14-1.13). Sensitivity analyses were conducted using the per protocol analysis set, which included 1876 subjects (936 denosumab, 940 zoledronic acid). Results for the primary and secondary endpoints from the blinded treatment phase are listed in Table 1 Results from the primary blinded treatment phase for this study are also included in Table 1 for reference; detailed results from the primary blinded treatment phase efficacy analysis are provided in the Study 20050103 primary analysis CSR, dated 23 April 2010.

Efficacy results from the blinded treatment analysis for all endpoints were entirely consistent with those from the analysis of the primary blinded treatment phase of the study. Denosumab significantly reduced the risk of developing a first on-study SRE by 17% compared with zoledronic acid (p = 0.0003 for noninferiority and p = 0.0139 for superiority) (Table 1). Results were consistent using the per-protocol analysis set and the full analysis set using the actual randomization strata, thus supporting the primary results (Table 14-4.1.2, Table 14-4.1.3, Table 14-4.2.2, and Table 14-4.2.3). The median time to first on-study SRE was 18.2 months (554 days) for denosumab and 15.1 months (460 days) for zoledronic acid (Table 14-4.2.1). Homogeneity testing for time to first on-study SRE showed no evidence of inconsistent effect across the 4 SRE components (pathological fracture, radiation to bone, surgery to bone, and spinal cord compression) (p = 0.6003) (Table 14-4.2.16).

Denosumab significantly reduced the risk of developing first-and-subsequent on-study SREs by 17% compared with zoledronic acid (excluding subsequent events occurring < 21 days from a previous SRE) (unadjusted p = 0.0073, adjusted p = 0.0139) (Table 1 and Figure 1). Results were consistent when all events were included in the analysis (ie, no 21-day window applied; rate ratio [95% CI] of 0.84 [0.72, 0.96], p = 0.0140), thus supporting the primary analysis (Table 14-4.3.4).

Exploratory Endpoints

[redacted]

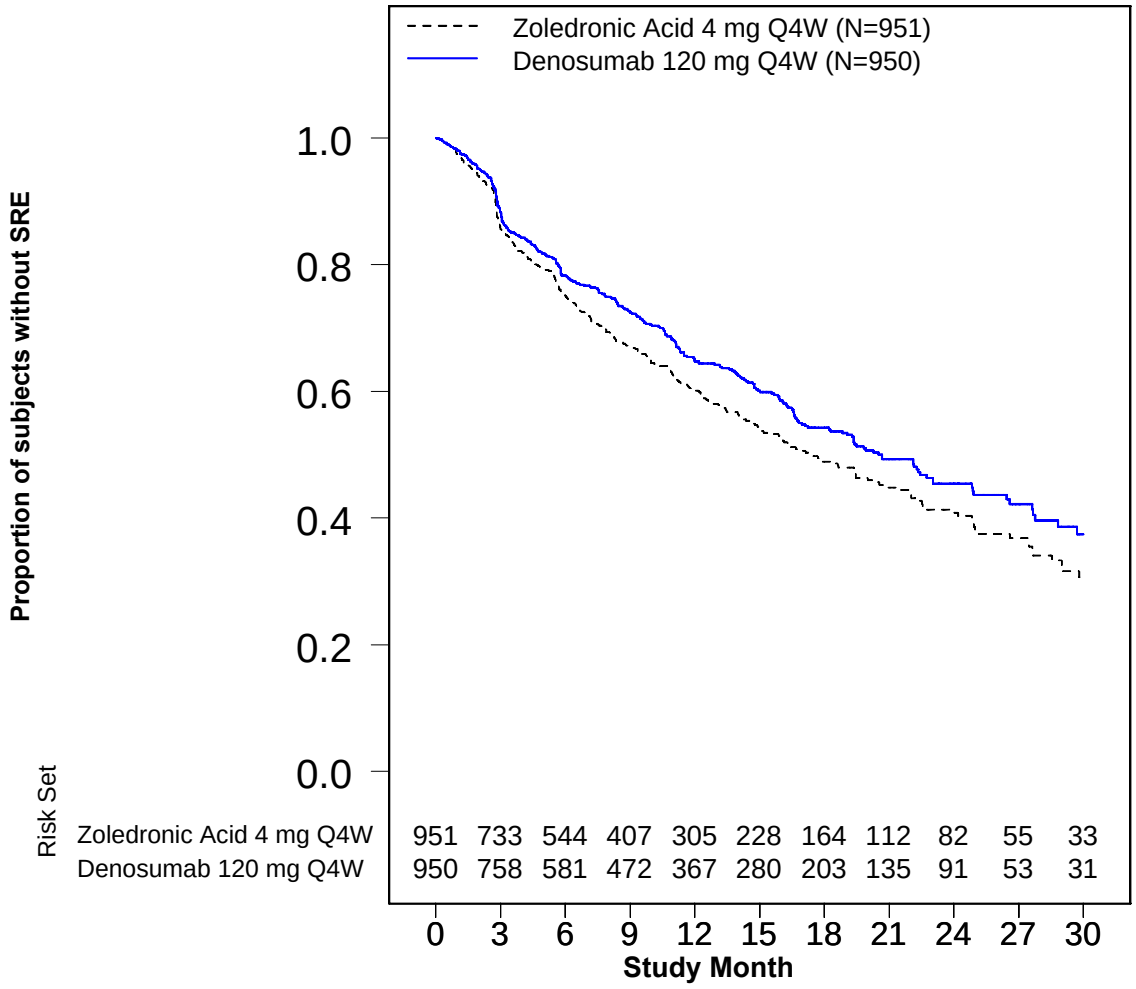
Table 1. Summary of Efficacy Endpoint Results from the Primary Blinded Treatment Phase (Primary Analysis) and the Entire Blinded Treatment Phase

Endpoint	Denosumab vs Zoledronic Acid Hazard Ratio or Rate Ratio[a] (Primary Analysis Results)[b]				Denosumab vs Zoledronic Acid Hazard Ratio or Rate Ratio[a] (Blinded Treatment Analysis Results)[c]			
	Pt Est	(95% CI)	p-value (unadjusted)	p-value (adjusted)	Pt Est	(95% CI)	p-value (unadjusted)	p-value (adjusted)
Time to first on-study SRE (noninferiority)	0.82	(0.71, 0.95)	0.0002	0.0002	0.83	(0.72, 0.96)	0.0003	0.0003
Time to first on-study SRE (superiority)	0.82	(0.71, 0.95)	0.0085	0.0085	0.83	(0.72, 0.96)	0.0139	0.0139
Time to first and subsequent on-study SRE	0.82	(0.71, 0.94)	0.0044	0.0085	0.83	(0.72, 0.95)	0.0073	0.0139
[redacted]								

HCM = hypercalcemia of malignancy; SRE = skeletal-related event
[a] Hazard ratio or rate ratio < 1 favors denosumab
[b] Primary analysis through 30 October 2009
[c] Entire blinded treatment analysis through 26 February 2010

Primary Analysis Results Source: Table 14-4.0.1, Table 14-4.1.1, Table 14-4.2.1, Table 14-4.3.1, Table 14-4.5, Table 14-4.6, Table 14-4.15, Table 14-4.17, Table 14-4.16.1, Table 14-4.16.2, and Table 4-4.8 of the Study 20050103 Primary Analysis CSR
Blinded Treatment Analysis Results Source: Table 14-4.0.1, Table 14-4.5, Table 14-4.6, Table 14-4.15, Table 14-4.17, Table 14-4.16.1, Table 14-4.16.2, and Table 14-4.8

Figure 1. Time to First On-study SRE
Kaplan-Meier Curves (Full Analysis Set)



N = Number of subjects randomized

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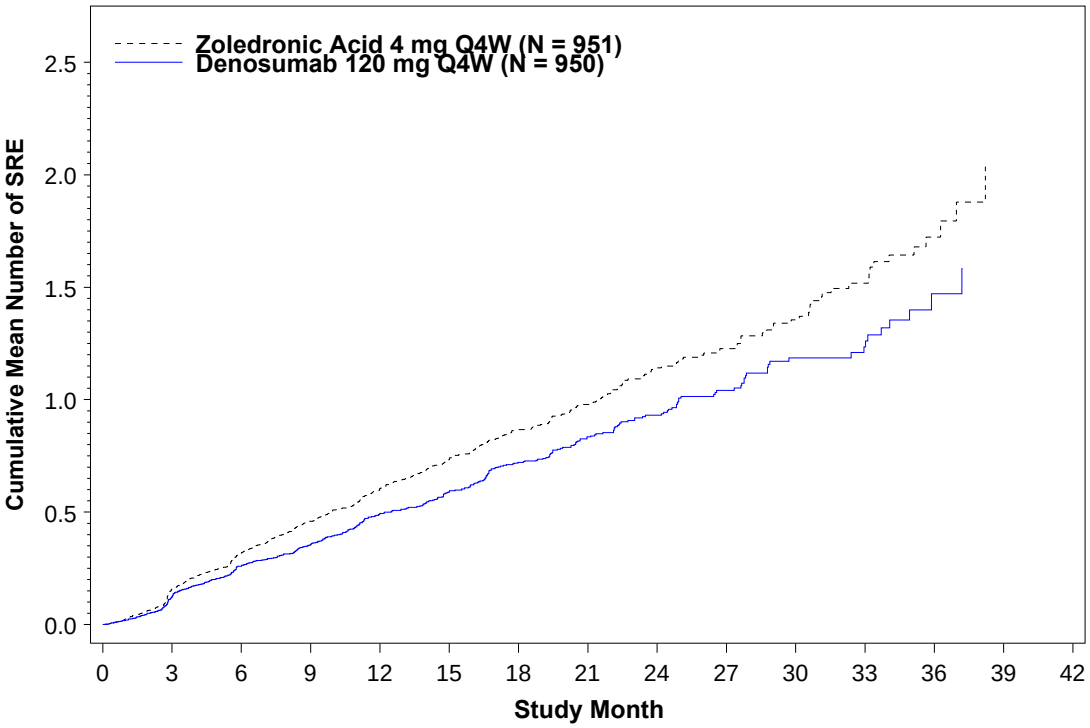
Source Data: adam.aslef

Figure 2. Cumulative Mean Number of SREs Kaplan-Meier Curves (Full Analysis Set)



N = Number of subjects randomized
Only events occurring >= 21 days after the previous event are counted.

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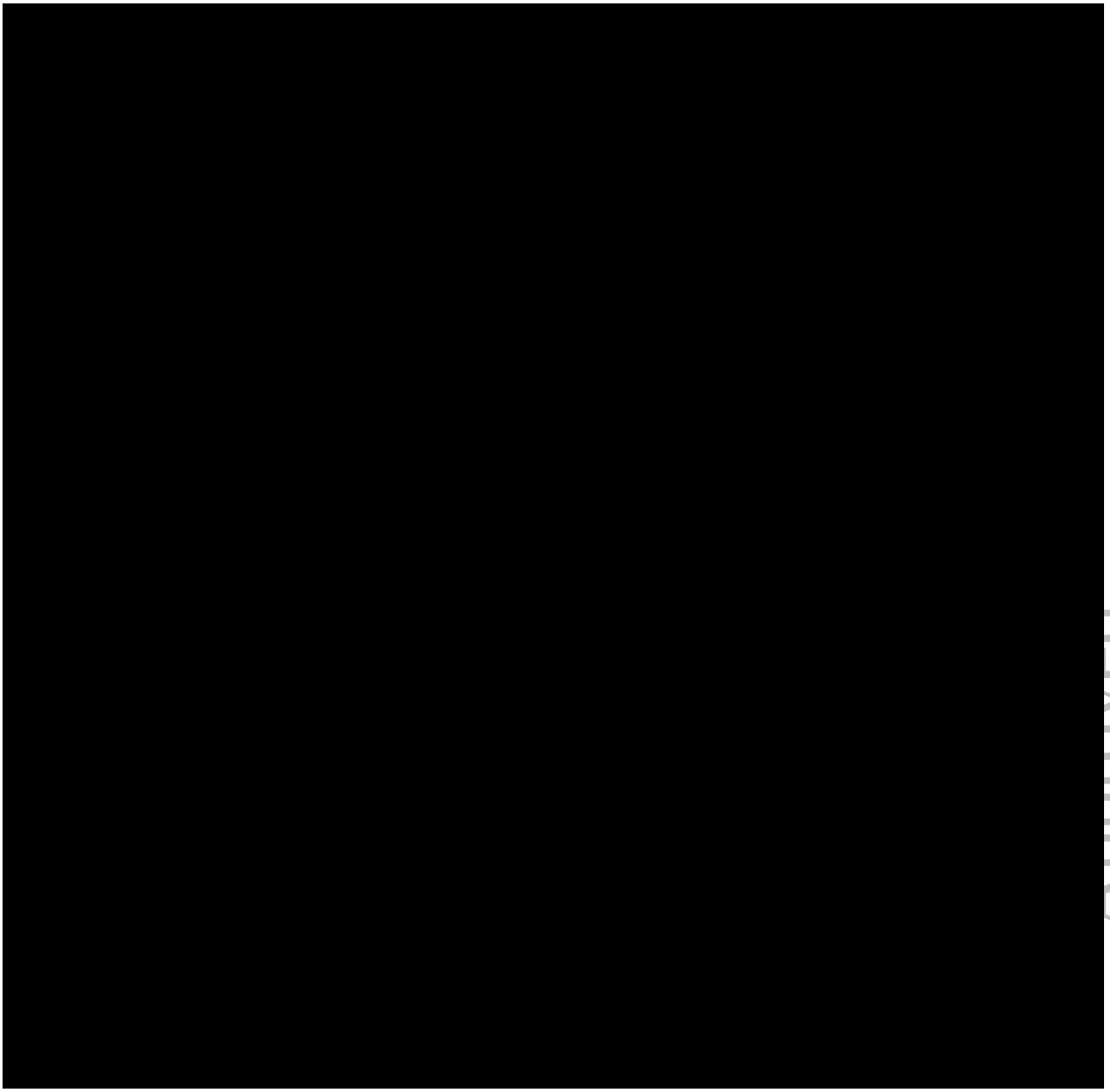
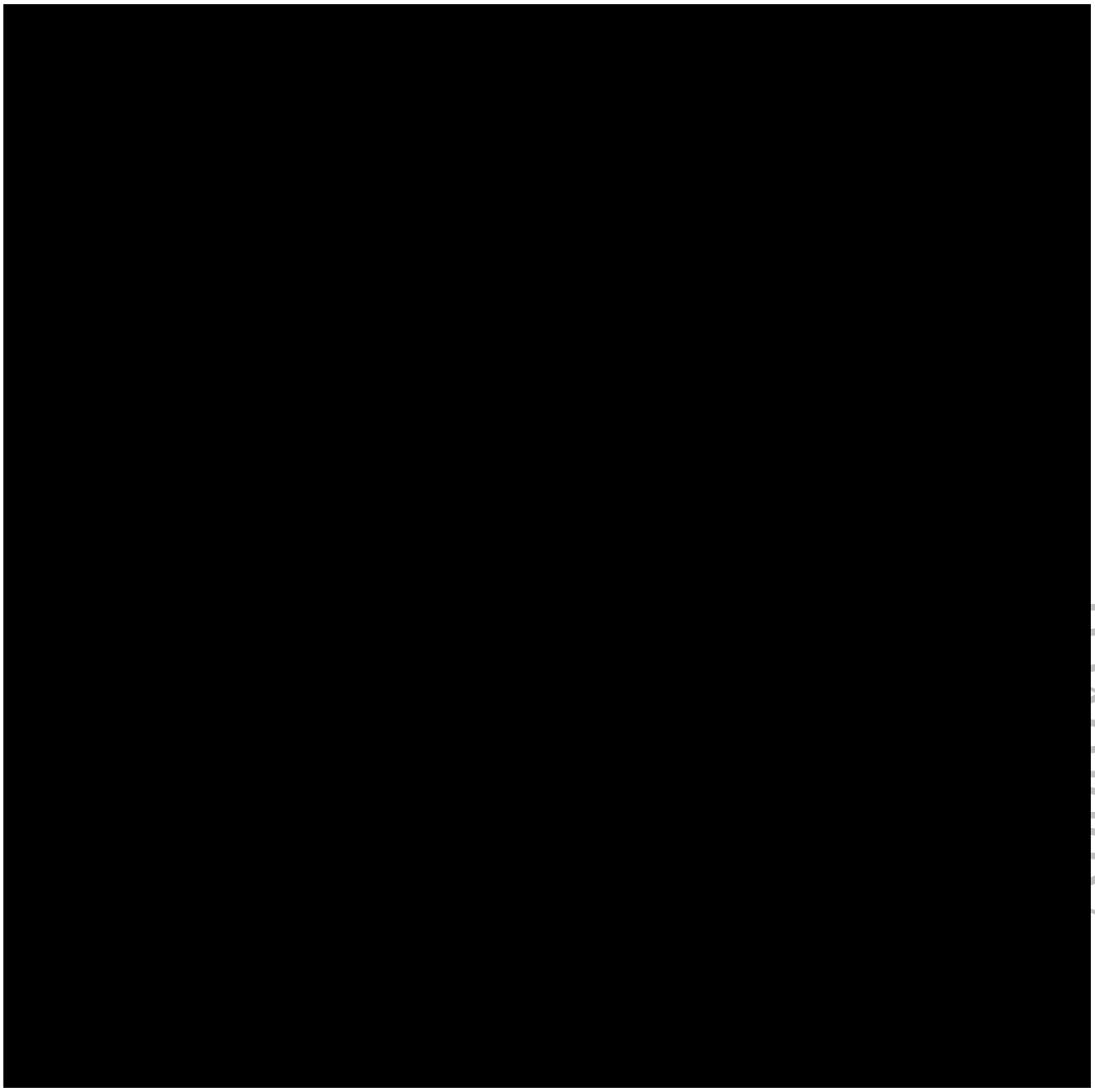
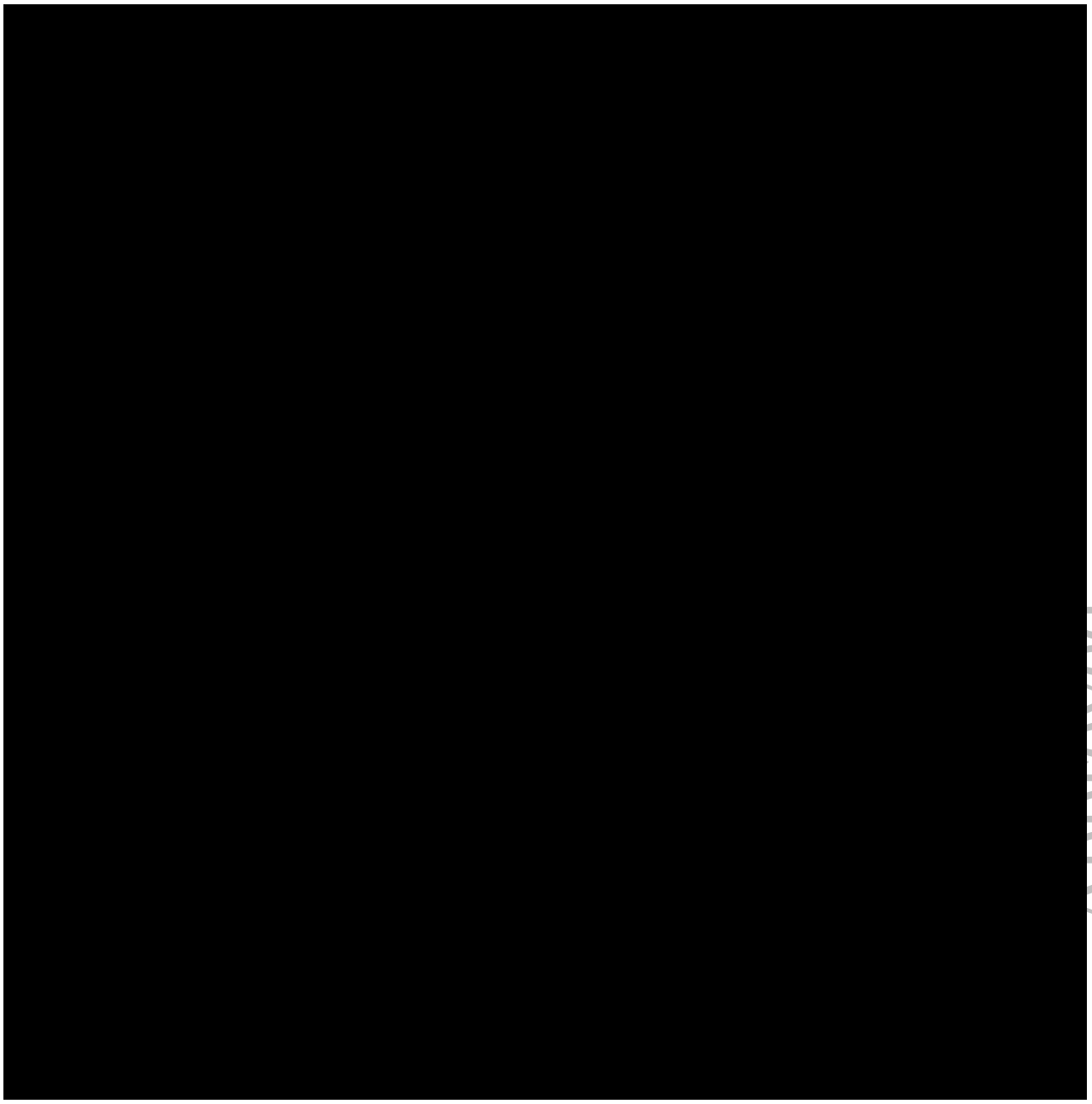
[redacted]







[redacted]

[redacted]

[redacted]

[redacted]

Safety Results:

Safety endpoints were assessed over the entire blinded treatment phase using the safety analysis set, which included 1888 subjects who received ≥ 1 active dose of investigational product (943 denosumab, 945 zoledronic acid) (Table 14-1.13).

A total of 923 (97.9%) subjects in the denosumab group and 920 (97.4%) subjects in the zoledronic acid group had ≥ 1 treatment-emergent adverse event (Table 14-6.1.1). The most common adverse events reported by subjects in either group were anemia (38.0% denosumab, 37.0% zoledronic acid), back pain (32.8%, 30.9%), nausea (29.3%, 26.7%), decreased appetite (29.1%, 29.6%), fatigue (27.8%, 24.1%), asthenia (26.5%, 26.0%), constipation (25.9%, 27.7%), bone pain (25.3%, 26.1%), peripheral edema (21.6%, 18.9%), arthralgia (21.4%, 22.5%), and pain in extremity (21.2%, 21.3%) (Table 14-6.1.3). A comparison between treatment groups of all adverse event preferred terms using a Fisher's exact test was performed. This analysis does not include any adjustments for multiplicity and should be considered exploratory in nature. Seven events (pyrexia, influenza-like illness, myalgia, chills, cognitive disorder, increased blood glucose, and cholelithiasis,) were higher in the zoledronic acid group than the denosumab group (Figure 14-51.1). Twenty-three events (duodenitis, xerosis, drug hypersensitivity, fractured ischium, ilium fracture, hypercalcemia, oral herpes, blood alkaline phosphatase, tooth abscess, cerebrovascular accident, vision blurred, sinusitis, osteonecrosis, stomatitis, hypophosphatemia, influenza, pleural effusion, increased PSA, hyperhidrosis, thoracic vertebral fracture, muscle spasms, dyspnea, and hypocalcemia) were higher in the denosumab group compared with the zoledronic acid group. Of these, adverse events of hypersensitivity, cerebrovascular accident, infections, hypocalcemia, and clinical laboratory evaluations of albumin-adjusted calcium, phosphorus, and alkaline phosphatase are discussed below in specific sections. For the remaining events, as pathological fractures (including fractured ischium, ilium fracture, and thoracic vertebral fracture) were 1 component of the composite SRE endpoint, these events are discussed above under Efficacy Results. [redacted]. Two events of tooth abscess occurred in subjects in the denosumab group who also had positively adjudicated events of ONJ, which are discussed below (Listing 1-4.1 and Listing 1-4.9). All events of duodenitis were mild in severity, not serious, and occurred in subjects receiving either a concomitant (anti-inflamatory) medication or with a history of [redacted] disease that predisposed the subject to duodenitis. All events of xerosis were mild or moderate in severity and not serious; none resulted in discontinuation of investigational product, and none recurred after resolution. All events of vision blurred were mild to moderate in severity, were not associated with cataracts, and the majority resolved with no action taken and did not recur. Events of stomatitis were generally associated with chemotherapy administration. Only 1 serious adverse event of stomatitis occurred in a subject receiving zoledronic acid. Pleural effusion events were generally associated with disease progression. All but 1 event (grade 3) of hyperhidrosis for subjects in the denosumab group were mild to moderate in severity and not serious (Listing 1-4.1). No event of hyperhidrosis led to investigational product or study withdrawal, and on study androgen deprivation therapy usage was similar between treatment arms (Listing 1-4.1 and data on file at Amgen). Events of muscle spasms were mild to moderate in severity in all but 1 subject in the zoledronic acid group who had a severe event; no events were serious. Events of muscle spasm were associated with reductions in serum calcium in 7 of 55 subjects in the denosumab group and 2 of 29 subjects in the zoledronic acid group (Listing 1-4.1 and data on file at Amgen). There was no evidence of a temporal or causal association between dyspnea and administration of denosumab or zoledronic acid, and most events resolved in both treatment groups. Dyspnea is a nonspecific symptom that may result from a variety of conditions (eg, lung metastases or infection, cardiac failure, anemia, renal failure, anxiety). No known association exists between RANKL or osteoprotegerin and respiratory adverse events such as dyspnea. The remaining adverse events with a higher incidence in the denosumab group included oral herpes, which might be increased in patients undergoing chemotherapy, and sinusitis,for which there was no evidence to indicate a causal relationship to denosumab.

Serious adverse events were reported for 622 (66.0%) subjects in the denosumab group and 597 (63.2%) subjects in the zoledronic acid group (Table 14-6.1.1). The most common serious adverse events reported in either group were anemia (12.4% denosumab, 9.1% zoledronic acid), pneumonia (4.3%, 3.0%), asthenia (4.2%, 3.3%), dyspnea (4.2%, 3.1%), dehydration (3.9%, 2.1%), prostate cancer (3.7%, 5.9%), urinary retention (3.4%, 4.0%), urinary tract infection (3.4%, 3.3%), general physical health deterioration (3.4%, 3.1%), back pain (3.2%, 3.9%), bone pain (2.9%, 3.7%), renal failure (2.9%, 3.3%), hematuria (2.5%, 4.0%), and spinal cord compression (2.5%, 3.5%) (Table 14-6.2.2). [redacted]. Events of decreased performance status, neutropenia, dehydration, and anemia were not corroborated using objective monthly overall measures from each treatment group such as ECOG performance status or laboratory parameters of white blood cells, creatinine, and hemoglobin (Table 14-8.29.1 and Table 14-8.29.2, Table 14-7.27.1 and Table 14-7.27.2, Table 14-7.11.1 through Table 14-7.11.4, and Table 14-7.14.1 through Table 14-7.14.4). Further, based on a clinical review of neutropenia events, each serious adverse event was temporally related to the administration of a chemotherapeutic drug, most often docetaxel. [redacted]. Changes in calcium laboratory values and adverse events of hypocalcemia and positively adjudicated ONJ are discussed below. Serious adverse events of cerebrovascular accident occurred in 1.7% of subjects in the denosumab group and 0.5% of subjects in the zoledronic acid group (Table 14-6.2.2). Almost all of these subjects (> 90%) had at least 1 risk factor for cerebrovascular accident, including hypertension, dyslipidemia, and cardiac disease (data on file at Amgen). An evaluation of the high level group term for central nervous system vascular disorders, which encompasses all vascular events occurring in the central nervous system (such as cerebral hemorrhage and ischemic stroke), showed that the overall subject incidence was 4.3% in the denosumab group and 3.5% in the zoledronic acid group (Table 14A-6.1.3.2). Therefore, most of the events were confounded by risk factors, and the imbalance observed in the single preferred term of cerebrovascular accident was attenuated when other like terms are considered in the analysis. Narratives for all serious adverse events are included in Attachment 6.

A total of 305 (32.3%) subjects in the denosumab group and 298 (31.5%) subjects in the zoledronic acid group had fatal adverse events while on study (Table 14-6.4.2). Fatal adverse events were generally associated with progression of disease. As described above, [redacted] and cancer outcomes were balanced between treatment groups. Narratives for all fatal adverse events are included in Attachment 6.

One hundred fifty-seven (16.6%) subjects in the denosumab group and 141 (14.9%) subjects in the zoledronic acid group had adverse events leading to withdrawal from investigational product (Table 14-6.1.7). A higher incidence of events with the preferred terms of hypocalcemia (1.1% denosumab, 0% zoledronic acid) and osteonecrosis (1.6% denosumab, 0.6% zoledronic acid) leading to withdrawal from investigational product in the denosumab group accounts for the overall difference between treatment groups. Ninety-eight (10.4%) subjects in the denosumab group and 83 (8.8%) subjects in the zoledronic acid group had adverse events leading to study withdrawal (Table 14-6.1.6).

The following adverse events were prespecified and summarized separately according to the statistical analysis plan: hypocalcemia, adverse events of infections (including skin infections leading to hospitalization), ONJ, new primary malignancy, cardiovascular disorders, adverse events potentially associated with hypersensitivity, and eczema. In addition, adverse events potentially associated with renal toxicity and acute phase reaction were prespecified and summarized, since they are known side effects of zoledronic acid.

The subject incidence of adverse events of hypocalcemia was 13.3% for the denosumab group and 5.8% for the zoledronic acid group (Table 14-6.10.1). Of the subjects who had hypocalcemia, 66% in the denosumab group and 56% of the subjects in the zoledronic acid group had events that occurred in the first 6 months after the first dose of investigational product, likely due to the initial reduction in serum calcium observed with denosumab or zoledronic acid therapy (Table 14-6.10.1 and Table 14-6.1.11). The majority of subjects (82 of 125 [66%] subjects denosumab, 39 of 55 [71%] subjects zoledronic acid) had a single event of hypocalcemia (Listing 1-4.3). Forty-four (4.7%) subjects in the denosumab group and 15 (1.6%) subjects in the zoledronic acid group had an adverse event of hypocalcemia and received treatment with IV calcium (Table 1-6.109.11). Hypocalcemia was reported as serious in 2.7% of subjects in the denosumab group and 0.7% of subjects in the zoledronic acid group and led to discontinuation from study in 0.4% of subjects in the denosumab group and 0 subjects in the zoledronic acid group (Table 14-6.10.1, Table 14-6.2.2, and Table 14-6.1.6). No adverse events of hypocalcemia were reported as fatal (Table 14-6.10.1 and Table 14-6.4.2).

The overall subject incidence of adverse events of infection was 44.1% and 41.0% for denosumab and zoledronic acid, respectively (Table 14-6.1.2). The overall subject incidence of serious adverse events of infection was 14.8% and 12.7% for denosumab and zoledronic acid, respectively (Table 14-6.2.1). Serious adverse events of pneumonia occurred in 4.3% of subjects in the denosumab group and 3.0% of subjects in the zoledronic acid group (Table 14-6.2.2). Almost all of these events occurred in subjects with risk factors for pneumonia that included advanced age; medical history of [redacted]; or concomitant medications such as corticosteroids, chemotherapy, and opioids. The subject incidence of adverse events of skin infection was 3.3% in the denosumab group and 3.0% in the zoledronic acid group (Table 14-6.13.3); the subject incidence of serious adverse events of skin infection was 1.0% in the denosumab group and 1.1% in the zoledronic acid group (Table 14-6.13.4).

The incidence of adverse events adjudicated positive for ONJ was 2.4% in the denosumab group and 1.4% in the zoledronic acid group, with p = 0.0954 (Table 14-6.11.2). Eighteen of 23 (78%) subjects in the denosumab group and 11 of 13 (85%) subjects in the zoledronic acid group had a history of [redacted], and/or use of a [redacted], the majority of whom (16 and 8 subjects, respectively) had [redacted] (Attachment 6 and data on file at Amgen). In the denosumab and zoledronic acid groups, respectively, 1 (4.3%) and 0 subjects were receiving or had received antiangiogenic medications, and 15 (65%) and 9 (69%) subjects were receiving or had received chemotherapy (Attachment 6 and data on file at Amgen). One (4.3%) subject in the denosumab group and 0 subjects in the zoledronic acid group had previously received oral bisphosphonates (Listing 1-4.9 and Attachment 6). Of the subjects who had positively adjudicated ONJ events, 15 of 23 (65%) subjects in the denosumab group and 8 of 13 (62%) subjects in the zoledronic acid group withdrew from investigational product due to ONJ; 3 (13% denosumab, 23% zoledronic acid) subjects in each group continued investigational product despite ONJ (Listing 1-4.11). The remaining 5 (22%) and 2 (15%) subjects discontinued investigational product for other reasons. Of the subjects with positively adjudicated ONJ, 52% of subjects in the denosumab group and 31% of subjects in the zoledronic acid group had local gum or oral infection, and 57% of subjects in the denosumab group and 38% of subjects in the zoledronic acid group had surgical treatments for ONJ (data on file at Amgen). The majority of surgical procedures were limited in nature (ie, sequestrectomy debridement, curettage, and extraction) (11 of 13 subjects denosumab, 4 of 5 subjects zoledronic acid); few cases in either treatment group required bone resection (2 subjects denosumab, 1 subject zoledronic acid), indicating that the severity of ONJ was similar between treatment groups (data on file at Amgen). The adjudicated positive ONJ event was considered resolved by the investigator for 5 and 2 subjects in the denosumab and zoledronic acid groups, respectively, according to information available as of 01 June 2010 (data on file at Amgen).

The subject incidence of new primary malignancies was 1.9% in the denosumab group and 1.1% in the zoledronic acid group (Table 14-6.13.6). No single malignancy was reported in more than 2 subjects.

Adverse events and serious adverse events in the system organ class cardiac disorders were reported for 17.0% and 10.3% of subjects, respectively, in the denosumab group and17.7% and 11.1% of subject, respectively, in the zoledronic acid group (Table 14-6.1.2 and Table 14-6.2.1). Adverse events and serious adverse events in the system organ class vascular disorders were reported for 19.9% and 3.6% of subjects, respectively, in the denosumab group and 19.9% and 3.5% of subjects, respectively, in the zoledronic acid group (Table 14-6.1.2 and Table 14-6.2.1).

Forty--five (4.8%) subjects in the denosumab group and 38 (4.0%) subjects in the zoledronic acid group had adverse events potentially associated with hypersensitivity (Table 14-6.12.1). Overall, there was no temporal relationship between the occurrence of these events and initiation of investigational product. One subject in each treatment group had an adverse event potentially associated with hypersensitivity that led to discontinuation of investigational product, and 1 subject in each treatment group had an adverse event potentially associated with hypersensitivity that led to discontinuation from study (Listing 1-4.10). Most subjects experienced single events (80% denosumab, 84% zoledronic acid), indicating that the events did not recur with continued treatment with investigational product. Adverse events with the preferred term drug hypersensitivity were causally associated with other medications (eg, Taxol® [pacitaxel]) known to be associated with drug hypersensitivity reactions in all but 1 subject in the denosumab group and all subjects in the zoledronic acid group (Listing 1-4.10 and data on file at Amgen). Serious adverse events potentially associated with hypersensitivity were reported for 4 subjects in the denosumab group and 2 subjects in the zoledronic acid group (Listing 1-4.10).

Aggregated adverse events of eczema were similar between treatment groups (1.2% denosumab, 1.1% zoledronic acid) (Table 14-6.8.1).

Adverse events potentially associated with renal toxicity were reported for 15.6% of subjects in the denosumab group and 16.2% of subjects in the zoledronic acid group (Table 14-6.6.1). Adverse events potentially associated with acute phase reaction occurred during the first 3 days of treatment for 8.4% of subjects in the denosumab group and 17.8% of subjects in the zoledronic acid group (Table 14-6.7.3).

The subject incidence of adverse events of cataract in this study was 0.5% and 0.6% in the denosumab and zoledronic acid groups, respectively (Table 14-6.1.3).

Of the 821 subjects tested for antidenosumab antibodies, 2 subjects tested positive for binding, non-neutralizing antibodies to denosumab post-baseline (1 at week 25 and 1 at week 49) (Table 14-8.9.1, Listing 1-4.71, and Attachment 9).

Expected decreases in serum calcium, phosphorus, and total alkaline phosphatase occurred; median albumin-adjusted calcium values remained within the normal range throughout the study (Table 14-7.1.1, Table 14-7.19.1, and Table 14-7.4.1). Grade 3 low albumin-adjusted calcium values were reported in 40 (4.2%) subjects in the denosumab group and 12 (1.3%) subjects in the zoledronic acid group, and grade 4 low values were reported in 10 (1.1%) subjects in the denosumab group and 1 (0.1%) subject in the zoledronic acid group (Table 14-7.48.1). Grade 3 low phosphorus values were reported in 184 (19.5%) subjects in the denosumab group and 74 (7.8%) subjects in the zoledronic acid group, and grade 4 low values were reported in 11 (11.2%) subjects in the denosumab group and 3 (0.3%) subjects in the zoledronic acid group. The incidences of grade 1 to 4 elevated serum creatinine values based on central laboratory assessments were 20.7% for denosumab and 22.3% for zoledronic acid (Table 14-7.35.1). No other changes indicative of a treatment-related effect were observed in clinical laboratory parameters, vital signs, or ECOG performance status for either treatment group.

Pharmacokinetic Results:

The pharmacokinetic analysis set was comprised of 82 subjects who participated in the pharmacokinetic substudy, received ≥ 1 dose of denosumab, and had ≥ 1 valid denosumab serum concentration level. The mean trough serum denosumab concentration at the 1-month (week-5) visit was 7190 ng/mL. Exposures, based on trough serum concentrations, increased as anticipated, with approximately 2-fold higher mean serum concentrations (16400 ng/mL) observed at month 6 (week 25). Mean trough serum concentrations obtained during months 6 to 24 (weeks 25 to 97) were similar (range: 16100 to 17700 ng/mL), consistent with a lack of change in pharmacokinetics with time.

Conclusions:

This study represents a dataset in a total of 1901 randomized subjects. Overall, the results for the entire blinded treatment phase in this population of patients with advanced prostate cancer were consistent with those from the analysis of the primary blinded treatment phase of the study. Denosumab administered at a dose of 120 mg SC Q4W was superior to zoledronic acid in reducing the risk of developing an SRE and demonstrated a positive benefit:risk profile in subjects with hormone-refractory (castrate-resistant) prostate cancer.

SYNOPSIS

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

Name of Finished Product: XGEVA®

Name of Active Ingredient: denosumab (AMG 162)

Title of Study: A Randomized, Double-blind, Multicenter Study of Denosumab Compared With Zoledronic Acid (Zometa®) in the Treatment of Bone Metastases in Men with Hormone-Refractory Prostate Cancer

Investigator(s) and Study Center(s): This international study was conducted at 139 centers in 32 countries. Centers and investigators are listed in Appendix 3.

Publication(s): Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet*. 2011;377:813-822.

Study Period: This clinical study report (CSR) includes results from 01 March 2010 (first subject enrolled in the open-label extension [OLE] phase) to 27 February 2012 (last subject completion date of the OLE phase). Results from the double-blind treatment phase have been previously reported.

Development Phase: 3

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. 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 the double-blind phase of the study was to determine whether denosumab was noninferior to zoledronic acid with respect to the first on-study occurrence of an SRE in men with hormone-refractory prostate cancer and bone metastases. (An SRE was defined as pathological fracture [vertebral or nonvertebral], radiation therapy to bone [including the use of radioisotopes], surgery to bone, or spinal cord compression.) 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. These objectives and the exploratory objectives were reported in the primary analysis CSR (23 April 2010) and the double-blind extension (DBE) CSR (23 July 2010).

Results from the primary blinded treatment phase 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 men with hormone-refractory prostate cancer. These findings were supported by the results for the entire blinded treatment phase (primary analysis plus DBE).

To satisfy regional regulatory agency requirements for reporting the OLE results from individual studies, the current report summarizes safety results and patient-reported outcomes (PRO) from the OLE phase of the study. This report also includes an analysis of overall survival for the entire study, including data from the double-blind and OLE treatment phases of the study.

Methodology: This was the OLE phase of an international, phase 3, randomized, double-blind, active-controlled study comparing denosumab with zoledronic acid in the treatment of bone

metastases in men with hormone-refractory prostate 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 on-study hypercalcemia (albumin-adjusted serum calcium > 2.9 mmol/L [> 11.5 mg/dL] or ionized calcium > 1.5 mmol/L).

Because denosumab was determined to be superior to zoledronic acid, based on the primary efficacy and safety analyses, 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 is first occurring). For subjects at all study centers, except in the United Kingdom and Czech Republic, the open-label phase was conducted under the current protocol number (20050103); in the United Kingdom and Czech Republic, the open-label extension phase was conducted under protocol number 20080540 per Health Authority request. 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. Results from subjects who participated in Study 20080540 will be reported separately.

During the OLE phase, adverse events, serum chemistry, SREs (reported by the investigator only), concomitant medications (including analgesic use), antidenosumab antibodies, and PROs (specifically, the Brief Pain Inventory-Short Form [BPI-SF]) were evaluated at regular, prespecified intervals.

Number of Subjects Planned: 1870 subjects (935 subjects per treatment group) were planned for enrollment into the double-blind treatment phase; there was no predefined sample size for the OLE phase of the study.

Number of Subjects Enrolled: For the double-blind treatment phase of Study 20050103, a total of 1901 subjects (950 denosumab, 951 zoledronic acid) were randomized and reported in the primary analysis CSR.

A total of 323 subjects completed the DBE; of these, 281 subjects provided informed consent to receive denosumab in the OLE phase of the study (153 subjects previously randomized to denosumab [hereafter referred to as the denosumab/denosumab group]; 128 subjects previously randomized to zoledronic acid [zoledronic acid/denosumab group]) (Table 14-1.1 and Table 14-2.1).

Sex: 281 men (100%)

Age (mean [SD]): 70 (7.6) years of age, overall (denosumab/denosumab: 71 [7.9] years; zoledronic acid/denosumab: 70 [7.4] years)

Ethnicity (Race): 246 (87.5%) white or Caucasian, 11 (3.9%) black or African American, 12 (4.3%) Hispanic/Latino, 4 (1.4%) Asian, 8 (2.8%) other

Diagnosis and Main Criteria for Eligibility: To be eligible for participation in the initial double-blind phase, men ≥ 18 years of age with histologically confirmed, hormone-refractory prostate cancer were required to have radiographic evidence of ≥ 1 bone metastasis, an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, adequate organ function, a life expectancy ≥ 6 months, and no current or prior exposure to any IV bisphosphonates or oral bisphosphonates administered for treatment of bone metastases. Informed consent was obtained prior to participation in the OLE phase of the study.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: All subjects in the OLE phase received SC denosumab 120 mg Q4W (manufacturing lot numbers are presented in 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 during the OLE phase of the study.

Duration of Treatment: Subjects who continued in the OLE phase of the study were offered denosumab for up to an additional 2 years; when taking into account the duration of denosumab exposure during the entire blinded treatment phase, the maximum potential exposure to denosumab throughout the entire study was approximately 5.6 years.

Study Endpoints: The safety and efficacy endpoints of the study are presented in the protocol (Appendix 1). These endpoints were analyzed and reported in the primary analysis and DBE CSRs. This synopsis report contains an analysis of the following endpoints that were specified for the OLE phase of the study in Addendum 2 of the Statistical Analysis Plan (dated 28 February 2012), provided in Appendix 2.

Safety Endpoints:

- Subject incidence of treatment-emergent adverse events
- Changes in laboratory values
- Changes in ECOG status
- Incidence of antidenosumab antibody (binding and neutralizing) formation

Efficacy Endpoint:

- Total number of deaths

Patient Reported Outcomes (PRO):

- Brief Pain Inventory–Short Form (BPI-SF) pain scores
- Analgesic score (using the Analgesic Quantification Algorithm [AQA])

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 treatment received in the blinded treatment phase, which was based on the first investigational product dose administered in the blinded treatment phase. For the determination of changes from baseline for ECOG, PRO, and all safety variables during the OLE phase, 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 phase, 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, 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. The Medical Dictionary for Regulatory Activities (MedDRA) composite searches for hypocalcemia, events potentially associated with hypersensitivity, skin infections, and eczema have been updated since the time of the DBE CSR analyses to account for the updated MedDRA version (version 12.1 for the DBE CSR and version 14.1 for the OLE CSR) and to increase standardization across studies. The system organ classes for infections, cardiac disorders, and vascular disorders have been updated to account for the MedDRA version only. Preferred terms used to search for adverse events of hypocalcemia, skin infections (including skin infections resulting in hospitalization), potential cases of ONJ, eczema, osteonecrosis excluding the jaw, and adverse events potentially associated with hypersensitivity 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.

The total number of deaths in the entire study (ie, the 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. Overall survival was analyzed using Kaplan-Meier estimates.

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 had ≥ 1 open-label PRO assessment). The proportion of subjects with clinically significant pain worsening (≥ 2-point increase in BPI-SF worst pain score) and the proportion of subjects with moderate or severe pain (> 4-point worst pain score) were summarized by visit. The proportion of subjects shifting to strong opioid use from no/low opioid use at OLE baseline was summarized by visit.

Summary of Results:

Subject Disposition: In total, 1901 male subjects were randomized to receive either denosumab (950 subjects) or zoledronic acid (951 subjects) during the primary blinded treatment phase (Table 14-1.1); of these, 323 subjects (175 denosumab, 148 zoledronic acid) completed the double-blind phase of the study.

A total of 281 subjects provided informed consent to receive denosumab in the OLE phase of the study (153 subjects previously randomized to denosumab; 128 subjects previously randomized to zoledronic acid). The distribution of subjects in the OLE phase of the study by country, site, and geographic region are provided in Table 14-1.3 to Table 14-1.5. A total of 645 subjects (311 denosumab/denosumab and 334 zoledronic acid/denosumab) entered the survival follow-up phase of the study (Table 14-1.1.1).

The 2-year OLE phase of the study was completed by 68 subjects (24.2%), which included 42 subjects (27.5%) in the denosumab/denosumab group and 26 subjects (20.3%) in the zoledronic acid/denosumab group. A total of 213 subjects (75.8%) discontinued from the OLE phase of the study (111 subjects [72.5%] denosumab/denosumab, 102 subjects [79.7%] zoledronic acid/denosumab), with the most common reasons for study discontinuation being death (25.3%), withdrawal of consent (14.2%), disease progression (10.3%), and adverse event occurrence (10.3%) (Table 14-1.1).

Overall, 942 subjects received ≥ 1 dose of denosumab at any point during the study (ie, double-blind treatment phase and/or OLE phase); among these subjects, the median (Q1, Q3) cumulative denosumab exposure across all study phases was 12.0 months (5.6, 21.3) with a minimum exposure of 0.1 months and a maximum exposure of 67.2 months (Table 14-5.2).

During the OLE phase, 265 subjects received ≥ 1 dose of denosumab (147 denosumab/denosumab; 118 zoledronic acid/denosumab) (Table 14-5.1). Among denosumab/denosumab- and zoledronic acid/denosumab-designated subjects, median (Q1, Q3) exposures to denosumab during the OLE phase (only) were 12.0 (5.3, 22.1) and 12.0 (5.5, 20.5) months, respectively.

The overall incidence of protocol deviations during the OLE phase was low for both groups: 5 subjects (3.3%) in the denosumab/denosumab group, and 1 subject (0.8%) in the zoledronic acid/denosumab group. Deviations included use of bisphosphonates (a proscribed treatment) during the OLE phase (3 [2.0%] denosumab/denosumab, 1 [0.8%] zoledronic acid/denosumab) and receipt of temperature-compromised investigational product (2 denosumab/denosumab, 0 zoledronic acid/denosumab) (Table 14-1.6, Listing 1-1.3).

Safety Results:

Most subjects in the denosumab/denosumab (138 subjects [93.9%]) and zoledronic acid/denosumab (105 subjects [89.0%]) groups experienced ≥ 1 treatment-emergent adverse event during the OLE phase of the study, with events being most commonly categorized within the system organ classes (denosumab/denosumab, zoledronic acid/denosumab) of musculoskeletal and connective tissue disorders (62.6%, 49.2%), general disorders and administration site conditions (50.3%, 39.0%), gastrointestinal disorders (41.5%, 32.2%), and infections and infestations (39.5%, 28.0%) (Table 14-6.2.1). By preferred term, the most frequently experienced adverse events (denosumab/denosumab, zoledronic acid/denosumab) were anemia (23.1%, 22.0%), back pain (19.7%, 16.1%), asthenia (19.7%, 9.3%), and pain in extremity (17.7%, 14.4%) (Table 14-6.3.1; Table 14-6.3.17). 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 33 (22.4%) denosumab/denosumab-treated subjects and in 19 (16.1%) zoledronic acid/denosumab-treated subjects (Table 14-6.2.5). The preferred term of osteonecrosis of the jaw was the most common adverse event considered by the investigator as being possibly related to denosumab (denosumab/denosumab: 11 subjects [7.5%]; zoledronic acid/denosumab: 5 subjects [4.2%]) (Table 14-6.3.5). 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 87 subjects (59.2%) in the denosumab/denosumab group and 76 subjects (64.4%) in the zoledronic acid/denosumab group, with the most commonly reported of these events being anemia (10.9% and 11.0%, respectively), general physical health deterioration (6.1%, 3.4%), and back pain (3.4%, 5.1%) (Table 14-6.3.8). Grade ≥ 3 adverse events considered by the investigator to be possibly related to denosumab were reported for 9 subjects (6.1%) in the denosumab/denosumab group and 6 subjects (5.1%) in the zoledronic acid/denosumab group; the only treatment-related grade ≥ 3 adverse events experienced by > 1 subject across both groups were ONJ (4 subjects [2.7%], 2 subjects [1.7%]) and hypocalcemia (1 subject in each treatment 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.

Overall, 78 subjects (53.1%) in the denosumab/denosumab group and 63 subjects (53.4%) in the zoledronic acid/denosumab group experienced ≥ 1 serious adverse event (Table 14-6.1 and Table 14-6.2.2). The most common (≥ 7 subjects overall) serious adverse events (denosumab/denosumab, zoledronic acid/denosumab) were anemia (5.4%, 7.6%) and general physical health deterioration (4.8%, 2.5%) (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 29 subjects in each treatment group (19.7% denosumab/denosumab; 24.6% zoledronic acid/denosumab) had fatal adverse events (Table 14-6.1). Fatal adverse events (denosumab/denosumab, zoledronic acid/denosumab) were generally associated with progression of disease (eg, general health deterioration [4.1%, 1.7%], prostate cancer [2.0%, 1.7%]) (Table 14-6.2.7 and Table 14-6.3.7); none was considered by the investigator as being possibly related to denosumab (Table 14-6.3.14). Narratives for all fatal adverse events are included in Appendix 6.

Adverse events that resulted in the discontinuation of denosumab were experienced by 24 subjects (16.3%) in the denosumab/denosumab group and 11 subjects (9.3%) in the zoledronic acid/denosumab group (Table 14-6.1 and Table 14-6.2.4); the most common of these events were ONJ (4.1%, 2.5%), general physical health deterioration (2.0%, 0%), and osteomyelitis (1.4%, 0%) (Table 14-6.3.4). Serious adverse events that resulted in the discontinuation of denosumab were reported for 15 subjects (10.2%) in the denosumab/denosumab group and 3 subjects (2.5%) in the zoledronic acid/denosumab group, with general physical health deterioration (3 subjects [2.0%]) and osteomyelitis (2 subjects [1.4%]) being the most commonly reported of these events among denosumab/denosumab-treated subjects; no other serious adverse event resulting in denosumab discontinuation was experienced by > 1 subject within either treatment group (Table 14-6.3.11).

Twenty subjects (13.6%) in the denosumab/denosumab group and 10 subjects (8.5%) in the zoledronic acid/denosumab group withdrew from the study in response to an adverse event (Table 14-6.2.3 and Table 14-6.3.3); for 10 subjects (6.8%) in the denosumab/denosumab group and 3 subjects (2.5%) in the zoledronic acid/denosumab group, the events that led to withdrawal from the study were serious (Table 14-6.3.10).

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: Thirteen subjects (8 [5.4%] denosumab/denosumab, 5 [4.2%] zoledronic acid/denosumab) experienced adverse events of hypocalcemia (Table 14-6.12.1); of these subjects, 2 in the denosumab/denosumab group and 2 in the zoledronic acid/denosumab group required IV calcium administration (Table 14a-6.14). Hypocalcemia was reported as being serious for 1 subject (< 1%) in each treatment group (Listing 1-2.3); neither of these subjects ([redacted] [denosumab/denosumab] and [redacted] [zoledronic acid/denosumab]) had serious hypocalcemia events that were associated with signs or symptoms (eg, tetany, paresthesias) (Listing 1-2.1). None of the adverse events of hypocalcemia (serious or nonserious) necessitated discontinuation of denosumab or subject withdrawal from the study (Table 14-6.3.3 and Table 14-6.3.4). No adverse events of hypocalcemia were associated with a fatal outcome (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 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 terms discussed in the previous adverse event section. Adverse events of ONJ were adjudicated positive in 12 subjects (8.2%) in the denosumab/denosumab group and in 7 subjects (5.9%) in the zoledronic acid/denosumab group (Table 14-6.11.2). All 12 subjects in the denosumab/denosumab group and 6 of the 7 subjects (86%) in the zoledronic acid/denosumab group had a history of [redacted], and/or use of a [redacted]; of these subjects, 7 in the denosumab/denosumab group and 3 in the zoledronic acid/denosumab group had undergone [redacted] prior to the onset of ONJ (Appendix 6).

Nine (47%) of the subjects with events of positively adjudicated ONJ required no surgical intervention and were managed conservatively (eg, with mouth rinses and antibiotics) (Listing 1a-2.8.2). Ten subjects (52%) with events of positively adjudicated ONJ required surgical intervention; of these, 9 underwent limited surgical procedures only (ie, sequestrectomy, debridement, and curettage). The remaining subject ([redacted] required surgery that included partial resection of the right maxilla.

Of the 19 subjects with positively adjudicated ONJ, 1 subject (zoledronic acid/denosumab) presented with a CTCAE grade-4 event, 4 subjects (n = 3 denosumab/denosumab; n = 1 zoledronic acid/denosumab) presented with grade-3 events, 9 subjects (n = 5 denosumab/denosumab; n = 4 zoledronic acid/denosumab) presented with grade-2 events, and 6 subjects (n = 5 denosumab/denosumab; n = 1 zoledronic acid/denosumab) presented with grade-1 events; there were no grade-5 events (Listing 1-2.7). Subject [redacted] had a grade-4 serious adverse event that triggered adjudication of ONJ. This subject, a [redacted] in the zoledronic acid/denosumab group, had received 3 denosumab doses during the OLE phase by the time of the ONJ onset (Listing 1-2.8). The investigator described this subject's ONJ as grade 4 bone exposure; the subject was not hospitalized for the ONJ event (Appendix 6).

Of the subjects who had positively adjudicated ONJ events, 6 of 12 subjects (50%) in the denosumab/denosumab group and 4 of 7 subjects (57%) in the zoledronic acid/denosumab group discontinued denosumab due to ONJ (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 4 subjects (33%) in the denosumab/denosumab group and no subjects in the zoledronic acid/denosumab group (Listing 1a-2.8.2).

Infection: Infection adverse events were reported by 58 subjects (39.5%) in the denosumab/denosumab group and by 33 subjects (28.0%) in the zoledronic acid/denosumab group. The most commonly reported infection adverse events (denosumab/denosumab; zoledronic acid/denosumab) were urinary tract infection (14.3%; 7.6%), nasopharyngitis (4.1%; 0.8%), and pneumonia (3.4%; 2.5%) (Table 14-6.2.1). The overall subject incidence of serious adverse events of infection was 16.3% (24 subjects) in the denosumab/denosumab group and 5.1% (6 subjects) in the zoledronic acid/denosumab group (Table 14-6.2.2), with the most common serious adverse events of infection (denosumab/denosumab; zoledronic acid/denosumab) being pneumonia (2.7%, 2.5%), urinary tract infection (2.7%, 0.8%), and sepsis (2.7%, 0%). The subject incidence of skin infection was 3.4% (5 subjects) in the denosumab/denosumab group and 2.5% (3 subjects) in the zoledronic acid/denosumab group (Table 14-6.10.2); none of the events of skin infection met the criteria of a serious adverse event (Table 14-6.10).

Osteonecrosis Outside the Jaw: No subject in either treatment group had an event of osteonecrosis outside the jaw (Listing 1-2.1 and Listing 1a-2.8.2).

New Primary Malignancy: One subject (denosumab/denosumab; Subject [redacted]) had a new primary malignancy of CTCAE grade 1 bladder cancer (Table 14-6.8; Listing 1-2.2). This event was not considered by the investigator to have a causal relationship with investigational product.

Hypersensitivity: Adverse events potentially associated with hypersensitivity were reported for 5 subjects in both the denosumab/denosumab (3.4%) and zoledronic acid/denosumab (4.2%) groups (Table 14-6.13.1, Table 14-6.13.2). None of the adverse events potentially associated with hypersensitivity met the criteria of a serious adverse event, and all events of hypersensitivity were of mild or moderate severity (Listing 1-2.9). Such events among subjects in the denosumab/denosumab group consisted of rash in 4 subjects, and drug eruption, urticaria, and hypersensitivity (preferred term) in 1 subject each; of these events, 1 (rash) was considered by the investigator to be related to denosumab. In the zoledronic acid/denosumab group, adverse events potentially associated with hypersensitivity included rash and scrotal edema in 2 subjects each, and erythematous rash and facial swelling in 1 subject each; none was considered by the investigator to be related to investigational product.

Eczema: No subject in either group experienced an adverse event of eczema (Table 14-6.9).

Cardiovascular Disorders: Adverse events in the MedDRA cardiac disorders system organ class were reported for 18 subjects (12.2%) in the denosumab/denosumab group and for 8 subjects (6.8%) in the zoledronic acid/denosumab group (Table 14-6.2.1). Serious adverse events in the system organ class of cardiac disorders were reported for 6 subjects (4.1%) in the denosumab/denosumab group (cardiac failure [3 subjects]; cardiopulmonary failure [2 subjects]; angina pectoris [1 subject]; atrial fibrillation [1 subject]) and for 3 subjects (2.5%) in the zoledronic acid/denosumab group (cardiac failure [2 subjects]; acute myocardial infarction [1 subject]) (Table 14-6.2.2). Most adverse events in the cardiac disorders system organ class were considered by the investigator to be unrelated to investigational product; 1 subject in the zoledronic acid/denosumab group (Subject [redacted]) had concurrent (nonserious) events of myocardial fibrosis and diastolic dysfunction that were each considered to be related to investigational product (Listing 1-2.1).

The subject incidence of adverse events in the vascular disorders system organ class was 15.0% (22 subjects) in the denosumab/denosumab group and 11.0% (13 subjects) in the zoledronic acid/denosumab group (Table 14-6.2.1). Serious adverse events in the vascular disorders system organ class were reported for 4 subjects (2.7%) in the denosumab/denosumab group and for 3 subjects (2.5%) in the zoledronic acid/denosumab group (Table 14-6.2.2). One vascular disorder, a serious adverse event of intra-abdominal hemorrhage (Subject [redacted]; zoledronic acid/denosumab), was fatal; this event was not considered by the investigator to be related to investigational product (Listing 1-2.2).

Laboratory Data

Antidenosumab Antibody Assays: None of the 256 subjects (n = 143 denosumab/denosumab; n = 113 zoledronic acid/denosumab) tested positive for binding nonneutralizing antibodies to denosumab (Table 14-8.1.1, Listing 1-2.17). The Clinical Immunology Report is provided in Appendix 9.

Other Laboratory Analyses: Expected decreases in serum calcium and phosphorus occurred. In both groups, median decreases in albumin-adjusted serum calcium were mild (median percent change from OLE baseline of approximately 2% or less) (Table 14-7.1.5), and remained within the normal laboratory reference range throughout the study (Figure 14-1.5 and Table 14-7.1.1). Three subjects (2%) in the denosumab/denosumab group and 2 subjects (2%) in the zoledronic acid/denosumab group each had grade-3 decreases in albumin-adjusted serum calcium (Table 14-7.20.1 and Table 14-7-21.3). For these subjects, while the decreases were generally transient, 1 subject ([redacted]) in the denosumab/denosumab group had a grade-3 albumin-adjusted serum calcium (1.7 mmol/L on day 421) that further decreased to CTCAE grade 4 (1.4 mmol/L on day 505) before values returned to within the normal reference range at the next time point (Listing 1-2.22); this decrease to grade 4 in adjusted calcium was not reported as an adverse event (Listing 1-2.1). The number of subjects who had CTCAE grade $\geq$ 2 shifts (decreases) from baseline is provided in Table 14-7.21.3, and all grade ≥ 2 albumin-adjusted calcium values are summarized in Table 14-7.21.2.

Eleven (7%) subjects in the denosumab/denosumab group and 13 (11%) subjects in the zoledronic acid/denosumab group had decreases in phosphorus levels to CTCAE grade 3; no subject 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

In general, no changes indicative of a treatment-related effect were observed in the results for ECOG performance status for either treatment group (Table 14-8.4.1 and Table 14-8.4.2). The percentages of subjects with a baseline ECOG performance status of 0 was 39.6% in the denosumab/denosumab group and 38.8% in the zoledronic acid/denosumab group, and the percentages of subjects with a baseline ECOG performance status of 1 was 49.6% in the denosumab/denosumab group and 49.1% in the zoledronic acid/denosumab group (Table 14-8.4.1).

For the majority of subjects, the best overall ECOG performance status was the same as their OLE baseline status (denosumab/denosumab: 97 subjects [75.8%]; zoledronic acid/denosumab: 74 subjects [69.8%]) (Table 14-8.4.2). The worst overall ECOG performance status was generally the same as baseline (denosumab/denosumab: 70 subjects [54.7%]; zoledronic acid/denosumab: 56 subjects [52.8%]) or an increase of 1 (denosumab/denosumab: 41 subjects [32.0%]; zoledronic acid/denosumab: 28 subjects [26.4%]).

Efficacy Results:

Overall Survival

During the entire study, including the double-blind and OLE treatment phases, overall survival was similar between treatment groups (Figure 14-2.1): the percentage of subjects who had not died was 35.9% (341 subjects) in the denosumab group and 39.1% (372 subjects) in the zoledronic acid group. Kaplan Meier estimates of median survival were 590 days (95% CI: 543.0, 638.0) for the denosumab group and 586 days (95% CI: 549.0, 628.0) for the zoledronic acid group (approximately 19 months for subjects in each 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 3.04 (2.71) in the denosumab/denosumab group and 3.18 (2.79) in the zoledronic acid/denosumab group (Table 14-2.2). Thereafter, mean BPI worst pain scores were generally consistent for the duration of the OLE, and were comparable between treatment groups (Table 14-4.3 and Table 14-4.8). Similar results were noted for "pain interference" scores (Table 14-4.7 and Table 14-4.12).

The proportion of subjects in the OLE with a clinically meaningful pain worsening (≥ 2-point increase in worst pain score) from OLE baseline ranged from 13.7% to 29.2% among subjects in the denosumab/denosumab group, and from 11.1% to 36.3% in the zoledronic acid/denosumab group at each visit (Table 14-4.13). At any given visit, fewer than 39% of subjects had moderate/severe pain (worst pain score > 4), regardless of treatment group (Table 14-4.14). Clinically meaningful pain improvements (≥ 2-point decrease from the OLE baseline) were reported by 7.3% to 17.8% of subjects in the denosumab/denosumab group and by 10.1% to 22.6% of subjects in the zoledronic acid/denosumab group (Table 14-4.15).

Analgesic Score

At baseline of the OLE phase, mean (SD) analgesic use was 1.0 (1.9) in the denosumab/denosumab group and 1.0 (2.0) in the zoledronic acid/denosumab group (Table 14-4.1), where an analgesic score of 0 to 2 = no analgesics or weak opioid use and 3 to 7 = strong opioid use. At each visit, the proportions of subjects shifting from no/low analgesic use at OLE baseline to strong opioid were minimal in both the denosumab/denosumab group (0.0% to 5.3%) and zoledronic acid/denosumab group (0.0% to 6.7%) (Table 14-4.2.1). (See also, Appendix 8.)

Conclusions:

Denosumab, at a SC dose of 120 mg Q4W, was generally well tolerated during the OLE phase of this study in men with prostate cancer and bone metastases; the cumulative exposure to denosumab (blinded phase and OLE phase) was up to a maximum of 5.6 years. The median exposure to denosumab in the OLE phase of this study was 12 months (up to a maximum of 23 months). The incidence of hypocalcemia was 5.4% in the denosumab/denosumab group and 4.2% in the zoledronic acid/denosumab group. The incidence of positively adjudicated ONJ during the OLE phase was 8.2% in the denosumab/denosumab group and 5.9% in the zoledronic acid/denosumab group. Overall survival for the entire study was similar between the denosumab/denosumab and zoledronic acid/denosumab treatment groups.