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 Subjects with Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma

Investigator(s) and Study Center(s): This study was conducted at 321 centers in 33 countries. Study centers and investigators are listed in Attachment 3.

Publication(s): Henry D, von Moos R, Vadhan-Raj S, et al. A double-blind, randomized study of denosumab versus zoledronic acid for the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. Presented at: the ECCO 15-34th ESMO Multidisciplinary Congress, September 21, 2009; Berlin, Germany. Abstract 20LBA.

Study Period: This report contains data collected from 21 June 2006 (date that the first subject was enrolled) to 21 October 2009 (study completion date), which includes data from the primary blinded treatment phase through the extended blinded treatment phase and survival follow-up through the study completion date. Results from the survival follow-up period after the study completion date will be reported separately.

Development Phase: 3

Introduction and Objectives: Bone is the most frequent site for cancer metastasis, with incidence rates as high as 75%. Also, patients with multiple myeloma typically have myeloma bone disease, which is characterized by diffuse osteolysis and multiple osteolytic lesions (95% to 100% incidence). Bone metastases and osteolytic bone destruction in multiple myeloma are characterized by increased osteoclast activity and are 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 advanced cancer or multiple myeloma.

The primary objective of this study was to determine if denosumab is noninferior to zoledronic acid with respect to the first on-study SRE (pathologic fracture, radiation therapy to bone [including the use of radioisotopes], surgery to bone, or spinal cord compression) in subjects with advanced cancer and bone metastases (or lytic bone lesions from multiple myeloma). 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]

Efficacy results from the primary analysis are reported in Table 1. Results from the primary blinded treatment phase, which were summarized separately, demonstrated that denosumab administered at a dose of 120 mg SC Q4W was noninferior to zoledronic acid in the time to first

on-study SRE. A 4-month longer median time to first on-study SRE was observed in the denosumab group. Denosumab was also well tolerated during the primary blinded treatment phase.

Methodology: This is an international phase 3, randomized, double-blind, active-controlled study comparing denosumab with zoledronic acid in the treatment of bone metastases in subjects with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. Subjects were randomized in a blinded manner to 1 of the following treatment groups.

- 120 mg denosumab subcutaneously (SC) and zoledronic acid placebo intravenously (IV) every 4 weeks (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 tumor type (non-small cell lung cancer or multiple myeloma or other), previous SRE (yes or no), and systemic anticancer therapy (eg, chemotherapy, biologic therapy or hormonal therapy, 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 primary 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. The open-label extension phase for this study was not initiated. Therefore, subjects ended blinded treatment at the end of the double-blind extension phase and are being followed for survival for 2 years after the last dose of blinded investigational product.

During the treatment phase, adverse events, clinical laboratory parameters, SREs, concomitant medications (including analgesic use), antidenosumab antibodies, vital signs, healthcare utilization, and PROs (including BPI-SF) were evaluated at regular, prespecified intervals. Three measures of disease progression were evaluated: (1) disease progression in bone (determined by blinded, central radiology reads from one reviewer using predominantly Q12W skeletal surveys), (2) overall disease progression (determined by the investigator throughout the study and reported on a specific CRF that required documentation of the methods used to determine disease progression), and (3) overall survival determined throughout the study. 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.

Number of Subjects Planned: 1690 subjects (845 subjects per treatment group)

Number of Subjects Enrolled: A total of 1779 subjects were enrolled in the study. Of these subjects, 889 were randomized to receive denosumab and 890 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. Three subjects randomized to denosumab met this criterion. Therefore, the number of subjects enrolled and randomized in this study is reported in this document as 1776 (886 denosumab, 890 zoledronic acid) (Table 14-1.2).

Sex: 636 (35.8%) women, 1140 (64.2%) men (Table 14-2.1)

Mean (SD) Age: 59.9 (11.1) years (Table 14-2.1)

Ethnicity (Race): 1540 (86.7%) white or Caucasian, 85 (4.8%) Hispanic/Latino, 80 (4.5%) Asian, 49 (2.8%) black or African American, 4 (0.2%) Japanese, 2 (0.1%) American Indian or Alaska Native, 16 (0.9%) other (Table 14-2.1)

Diagnosis and Main Criteria for Eligibility: Eligible subjects met the following criteria: adult with histologically or cytologically confirmed advanced cancers including solid tumors, multiple myeloma, and lymphoma, current or prior radiographic evidence of ≥ 1 bone metastasis (or lytic bone lesion from multiple myeloma); 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 (for treatment of bone metastases/osteolytic lesions).

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Subjects randomized to denosumab received denosumab 120 mg SC and zoledronic acid placebo IV Q4W during the treatment phase. Denosumab was provided as a sterile, preservative-free liquid in blinded-label, 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. A listing of lot numbers for denosumab and zoledronic acid placebo by subject is provided in Listing 1-1.2.

Duration of Treatment: Subjects received either denosumab or zoledronic acid (reference therapy) in a blinded fashion up to completion of the efficacy and safety analyses. The median (Q1, Q3) duration of exposure during the entire blinded treatment phase was 6.78 (3.15, 15.54) months (mean [SD] = 9.93 [8.53] months) for the denosumab group and 6.47 (3.02, 14.09) months (mean [SD] = 9.58 [8.30] months) for the zoledronic acid group, which included the exposure during the primary analysis blinded treatment phase (median [Q1, Q3]: 6.78 [3.15, 14.09] months [mean {SD} = 9.23 {7.40} months] denosumab, 6.47 [3.02, 13.40] months [mean {SD} = 8.91 {7.24} months] zoledronic acid) (Table 14-5.1 and Table 14-5.1 of the Study 20050244 Primary Analysis Clinical Study Report).

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch 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 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. A listing of lot numbers for zoledronic acid and denosumab placebo by subject is provided in Listing 1-1.2.

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 entire 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 double-blind extension phase. Data from the entire blinded treatment phase (including the primary blinded treatment phase and the double-blind extension phase) were included in the analyses. Efficacy analyzed at the end of the entire 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 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 non-inferiority; results of the Cox model were used directly to determine whether or not denosumab was 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 approach was used.

[redacted]

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. In addition, an ad hoc analysis was performed using a Fisher's exact test to assess differences between groups in subject incidence of MedDRA preferred terms for adverse events and serious adverse events. 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, 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 Fisher'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]

Summary of Results:

Subject Disposition:

A total of 1776 subjects were enrolled and randomized into the study, with 886 subjects randomized to denosumab and 890 subjects randomized to zoledronic acid (Table 14-1.2). Randomization was stratified by tumor type (non-small cell lung cancer [39%], multiple myeloma [10%], other [51%]), previous SRE (50%), and systemic anti-cancer therapy (84%); randomization was balanced between treatment groups within each stratum (Table 14-1.10). Of the randomized subjects, 1756 received ≥ 1 dose of investigational product (878 denosumab, 878 zoledronic acid) (Table 14-1.3). As of the study completion date, 86% of subjects in the denosumab group and 85% of subjects in the zoledronic acid group had withdrawn from investigational product. Including subjects who never received investigational product, approximately 86% in each treatment group had withdrawn from the study (Table 14-1.2, Table 14-1.3).

The overall incidence of eligibility deviations was low for both treatment groups (1.9% for each group) (Table 14-1.9). The most frequently reported deviations (denosumab, zoledronic acid) were prior malignancies or viral infection (0.6%, 0.6%) and prior use of IV bisphosphonates (0.3%, 0.6%). Three subjects (2 randomized to denosumab, 1 randomized to zoledronic acid) had a screening procedure performed before providing informed consent (Listing 1-1.5). 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. One less subject in the denosumab group ([redacted]) had an eligibility deviation in this analysis, compared with the primary analysis. In the primary analysis, this subject was reported as having screening laboratory samples taken before providing informed consent; however, the date of these samples was found to be in error and was corrected prior to the database lock for this analysis. Since the corrected date showed that the subject had all samples taken after providing informed consent, this eligibility deviation was removed from the database for this analysis. An additional subject in the zoledronic acid group was identified as having an eligibility deviation due to prior bisphosphonate administration following the primary analysis snapshot.

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

Efficacy endpoints were assessed over the entire blinded treatment phase (eg, primary and extended blinded treatment phases) using the full analysis set, which included 1776 subjects (886 denosumab, 890 zoledronic acid) (Table 14-1.12). Sensitivity analyses were conducted for the primary and secondary endpoints using the per protocol analysis set, which included 1745 subjects (872 denosumab, 873 zoledronic acid). Results for the primary and secondary endpoints from the entire blinded treatment phase are listed in Table 1 below. Results from the primary blinded treatment phase for this study are also included in Table 1 for reference; detailed results from the primary efficacy analysis are provided in the Study 20050244 primary analysis clinical study report, dated 26 January 2010. [redacted]

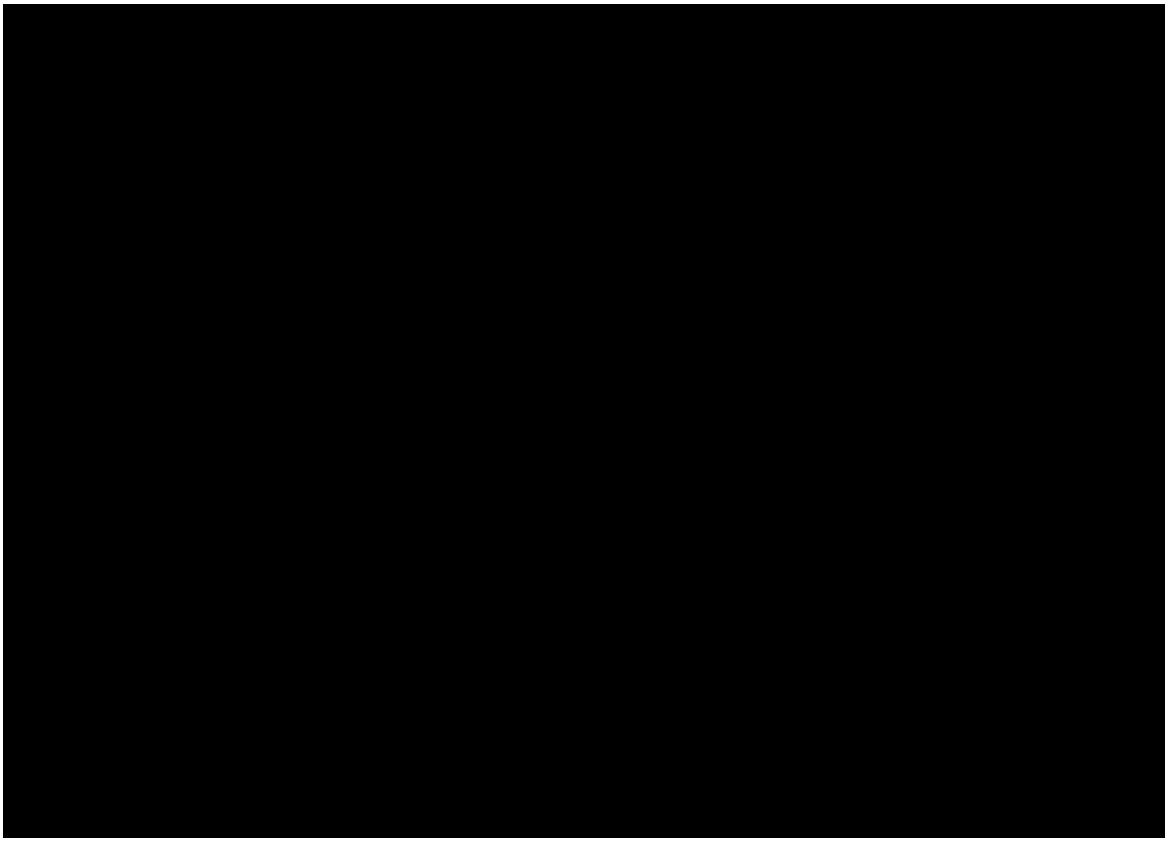
Efficacy results from the entire blinded treatment analysis for all endpoints were entirely consistent with those from the analysis of the primary blinded treatment phase of the study. Denosumab reduced the risk of developing a first on-study SRE by 16% compared with zoledronic acid (p = 0.0006 for noninferiority, p = 0.0300 [unadjusted] and 0.0600 [adjusted] for superiority); this level of reduction did not reach statistical significance for superiority

(Table 14-4.0.1). Results were consistent for the per protocol analysis set (p = 0.0015 for noninferiority and p = 0.0596 [unadjusted] for superiority) and the full analysis set with actual strata (p = 0.0346 [unadjusted] for superiority), thus supporting the primary results (Table 14-4.1.2, Table 14-4.1.3). The median time to first on-study SRE was 19.0 months (579 days) for the denosumab group and 15.9 months (485 days) for the zoledronic acid group (Table 14-4.2.1, Figure 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 = 0.8939) (Table 14-4.2.16).

The rate ratio (95% CI) for the time to first-and-subsequent on-study SREs was 0.88 (0.76, 1.01) with a p-value of 0.0779 (multiple-event analysis using Anderson-Gill model) (Table 14-4.3.1, Figure 2). Results were consistent when all events were included in the analysis (ie, no 21-day window applied) (rate ratio [95% CI] of 0.87 [0.75, 1.01]; p = 0.0753 [unadjusted] for superiority), thus supporting the primary analysis (Table 14-4.3.4). Results were consistent using the per-protocol analysis set and the full analysis set with actual strata, thus supporting the primary results (Table 14-4.3.2 and Table 14-4.3.3, respectively).

Results of subgroup analyses of time to first SRE and time to first-and-subsequent SRE by age, gender, race, region, previous SRE, tumor type (categorized using the randomization strata of non-small cell lung cancer, multiple myeloma, or other and categorized by all solid tumors, multiple myeloma, and individual solid tumor type), and systemic anticancer therapy were consistent with those observed from the analysis of the primary blinded treatment phase of the study (Table 14-4.2.9 to Table 14-4.2.15, Table 14-4.2.18, Table 14-4.3.8 to Table 14-4.3.14).

Exploratory Efficacy Endpoints



[redacted]

SYNOPSIS

Name of Sponsor: Amgen Inc

Name of Finished Product: Denosumab (AMG 162)

Name of Active Ingredient: Fully human monoclonal antibody to RANKL

Title of Study: A Randomized, Double-blind, Multicenter Study of Denosumab Compared With Zoledronic Acid (Zometa®) in the Treatment of Bone Metastases in Subjects With Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma

Investigator(s) and Study Center(s): This study was conducted at 321 sites in 33 countries. Study centers and investigators are listed in Attachment 2.

Publication(s): Henry D, von Moos R, Vadhan-Raj S, et al. A double-blind, randomized study of denosumab versus zoledronic acid for the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. Presented at the ECCO 15-34th ESMO Multidisciplinary Congress, September 21, 2009; Berlin, Germany. Abstract 20LBA.

Henry DH, Costa L, Goldwasser F, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. J Clin Oncol. 2011;29:1125-1132.

Study Period: This report presents survival data collected over the entire study period, including the double-blind treatment phase and the survival follow-up phase, from 21 June 2006 (date that the first subject was enrolled) to 24 August 2011 (survival follow-up phase completion date).

Development Phase: 3

Introduction and Objectives: Bone is the most frequent site for cancer metastasis, with incidence rates as high as 75%. In addition, patients with multiple myeloma typically have myeloma bone disease, which is characterized by diffuse osteolysis and multiple osteolytic lesions (95% to 100% incidence). Bone metastases and osteolytic bone destruction in multiple myeloma are characterized by increased osteoclast activity and are associated with significant skeletal morbidity (ie, skeletal-related events [SREs]). Bisphosphonates such as zoledronic acid (Zometa®) have been show 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, and RANKL inhibition has greater antiresorptive effects compared with bisphosphonates. Denosumab is a fully human monoclonal antibody that inhibits RANKL and osteoclast-mediated bone resorption and represents a new treatment for complications from bone metastases in patients with advanced cancer or multiple myeloma.

The primary objective of this study was to determine if denosumab is noninferior to zoledronic acid with respect to the first on-study SRE (pathologic fracture, radiation therapy to bone [including the use of radioisotopes], surgery to bone, or spinal cord compression) in subjects with advanced cancer and bone metastases (or lytic bone lesions from multiple myeloma). The secondary objectives were to determine if denosumab is superior to zoledronic acid with respect to first on-study SRE, to determine if denosumab is superior to zoledronic acid with respect to the first-and-subsequent on-study SRE (multiple event analysis), and to assess the safety and tolerability of denosumab compared with zoledronic acid.

[redacted]

[redacted]

Results from the primary double-blind treatment phase demonstrated that denosumab administered at a dose of 120 mg subcutaneously (SC) every 4 weeks (Q4W) was noninferior to zoledronic acid in the time to first on-study SRE. Denosumab reduced the risk of first SRE by 16%: a 4.2 month longer median time to first on-study SRE was observed in the denosumab group, compared with the zoledronic acid group, for the primary analysis ($p = 0.0007$ for noninferiority; $p = 0.0309$ [unadjusted] and 0.0619 [adjusted] for superiority) (Study 20050244 primary analysis clinical study report [CSR], 26 January 2010). Denosumab was well tolerated during the entire blinded treatment period, which ended on 21 October 2009 (Study 20050244 double-blind extension [DBE] CSR, 16 February 2010).

This report includes survival data from the entire study, including the double-blind treatment phase and the survival follow-up phase.

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 subjects with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. Approximately 1690 subjects were to be randomized 1:1 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 tumor type (non-small cell lung cancer, multiple myeloma, or other), previous SRE (yes or no), and systemic anticancer therapy (eg, chemotherapy, biologic therapy, or hormonal therapy, yes or no). Within each stratum, subjects were randomized using an equal allocation ratio of 1:1. Stratification for tumor type was bounded, limiting the enrollment to the non-small cell lung cancer stratum to 60% and the multiple myeloma stratum to 10% of the total study population.

Each subject received blinded investigational product up to completion of the primary 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. Per protocol, an open-label extension phase for this study was to be initiated if denosumab demonstrated a positive benefit:risk profile compared with zoledronic acid; the open-label phase was not initiated because denosumab demonstrated efficacy that was non-inferior, but not superior, to zoledronic acid. Subjects ended blinded treatment at the end of the double-blind extension phase (21 October 2009) and were followed for survival for 2 years after the last dose of blinded investigational product.

During the survival follow-up phase, study procedures were limited to collection of survival follow-up information by clinic visit or telephone contact every 12 weeks (± 14 days) for 2 years of the subject's end-of-study visit. A serum sample to evaluate for the presence of antidenosumab antibodies was to be obtained 24 weeks (approximately 6 months) after the end-of-study visit. Per protocol, no adverse event data were collected.

Number of Subjects Planned: 1690 subjects (845 subjects per treatment group)

Number of Subjects Enrolled: A total of 1779 subjects were enrolled in the study. Of these, 889 were randomized to receive denosumab and 890 were randomized to receive zoledronic acid. Prior to unblinding, the decision was made to exclude from all analyses any subjects for whom IRB review activities and oversight were not ensured. Three subjects randomized to denosumab met this criterion. Therefore, the number of subjects enrolled and randomized in this study is reported in this document as 1776 (886 denosumab, 890 zoledronic acid).

Sex: 636 (35.8%) women, 1140 (64.2%) men

Mean (SD) Age: 59.9 (11.1) years

Ethnicity (Race): 1540 (86.7%) white or Caucasian, 85 (4.8%) Hispanic/Latino, 80 (4.5%) Asian, 49 (2.8%) black or African American, 4 (0.2%) Japanese, 2 (0.1%) American Indian or Alaska Native, 16 (0.9%) other

Diagnosis and Main Criteria for Eligibility: Eligible subjects met the following criteria: adult with histologically or cytologically confirmed advanced cancers (including solid tumors, multiple myeloma, and lymphoma); current or prior radiographic evidence of ≥ bone metastasis (or lytic bone lesion from multiple myeloma); Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; adequate organ function; life expectancy ≥ 6 months; and no current or prior exposure to any IV or oral bisphosphonates (for treatment of bone metastases/osteolytic lesions).

Investigational Product, Dose and Mode of Administration, Manufacturing Lot Number: None during the survival follow-up phase.

Duration of Treatment: Subjects received either denosumab or zoledronic acid (reference therapy) in a blinded fashion through the primary double-blind treatment phase and the blinded extension phase. No treatment was provided during the 2-year survival follow-up phase.

Reference Therapy, Dose and Mode of Administration, Manufacturing Lot Number: None during the survival follow-up phase.

Study Endpoints

Endpoints: The efficacy and safety endpoints are presented in the protocol in Attachment 1. These endpoints were analyzed and reported in the primary analysis and DBE CSRs. This synopsis report contains an analysis of the following:

- total number of deaths
- incidence of antidenosumab antibody (binding and neutralizing) formation

Statistical Methods: The total number of deaths during the entire study, including the blinded treatment phase and survival follow-up phase, was summarized using the full analysis set (ie, all subjects who were randomized in the study). The survival data were analyzed using the Cox proportional hazards model and the Kaplan-Meier estimates were presented graphically. Subjects were analyzed according to their randomized treatment assignment. The proportion of subjects developing antidenosumab antibodies was calculated. In addition, adverse events that occurred during the double-blind treatment phase, but were reported during the survival follow-up phase, are listed. New potential events of osteonecrosis of the jaw (ONJ) that were reported and adjudicated positive by an independent expert panel after the double-blind treatment phase was completed are listed.

Summary of Results:

Subject Disposition: A total of 1776 subjects were enrolled and randomized into the study, with 886 subjects randomized to denosumab and 890 subjects randomized to zoledronic acid (Table 14-1.1). Of those subjects, 793 subjects (44.7%) entered the survival follow-up phase at

some point during the study: 401 subjects (45.3%) in the denosumab group and 392 subjects (44.0%) in the zoledronic acid group. Ninety subjects entered the survival follow-up phase before the DBE end date and were still ongoing in the survival follow-up phase on or after the DBE end date (21 October 2009) (ongoing on/after DBE end date, Table 14 -1.1). Further details are available in Table 14-1.1.

Overall Survival: [redacted]

New Reported Adverse Events: Per protocol, no adverse event data were collected during the survival follow-up phase. However, some adverse events that occurred during the double-blind treatment phase were reported after the data cutoff date for the DBE CSR and are presented in Listing 14-2. The events were consistent with those reported in the primary analysis CSR dated 26 January 2010 and the DBE CSR dated 16 February 2010.

Osteonecrosis of the Jaw: Although adverse event data were not collected, per protocol, during the survival follow-up period, 3 potential events of ONJ (1 in the denosumab group and 2 in the zoledronic acid group) were reported to Amgen and adjudicated positive during the survival follow-up phase (Listing 14-1). Narratives for the 3 ONJ cases are included in Attachment 4.

Antidenosumab Antibodies: Binding antibodies to denosumab were detected in 1 subject at baseline, but were not detected in any subjects post-baseline during the entire study (Table 14-8.1). No neutralizing antibodies were detected.

Conclusions:

Overall survival, including the double-blind treatment phase and the survival follow-up phase, was similar between the denosumab and zoledronic acid treatment groups.
