SYNOPSIS

Name of Sponsor: Amgen Inc and Daiichi Sankyo Co., Ltd.

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 Breast Cancer

Investigators and Study Centers: This study was conducted at a total of 322 centers in 35 countries. Study centers and investigators are listed in Attachment 2.

Publication: Stopeck A, Body JJ, Fujiwara Y, et al. Denosumab versus zoledronic acid for the treatment of breast cancer patients with bone metastases: results of a randomized phase 3 study. Presented at: the ECCO 15-34th ESMO Multidisciplinary Congress, September 22, 2009; Berlin, Germany.

Study Period: This clinical study report (CSR) includes results from 27 April 2006 (date that the first subject was enrolled) to 20 July 2009 (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: Bone is the most frequent site of metastasis of breast cancer, accounting for approximately 40% of all first metastases; up to 80% of stage IV breast cancer patients eventually develop disease in the bone. Skeletal metastasis is characterized by increased osteoclast activity and is associated with significant skeletal morbidity (ie, skeletal-related events [SREs]). Bisphosphonates, such as zoledronic acid (Zometa®), have been shown to inhibit osteoclast activity and reduce the incidence of SREs in patients with bone metastases. RANK ligand (RANKL) is an essential mediator of osteoclast formation, function, and survival. Inhibition of RANKL has been shown to have greater antiresorptive effects compared 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 breast cancer.

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 to bone [including the use of radioisotopes], surgery to bone, or spinal cord compression) in subjects with advanced breast 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]

[redacted]

Results from the primary blinded treatment phase, which were summarized separately, demonstrated that denosumab administered at a dose of 120 mg SC Q4W significantly reduced the risk of developing SREs compared with zoledronic acid and had a favorable safety profile in subjects with breast cancer and bone metastasis. 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 subjects with advanced breast cancer. 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 previous SRE (yes or no), prior oral bisphosphonate use (yes or no), current chemotherapy (defined as within 6 weeks before randomization) (yes or no), and region (Japan or other countries). 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 (20050136); 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; this survival follow-up phase is being conducted under the current protocol number.

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]. Vital signs and on-study healthcare utilization were also evaluated for all subjects, and serum denosumab concentration levels were obtained from a subset of approximately 180 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] were evaluated at regular, prespecified intervals.

Number of Subjects Planned: 1960 subjects (980 subjects per treatment group)

Number of Subjects Enrolled: A total of 2049 subjects were enrolled in the study. Of these subjects, 1026 were randomized to receive denosumab and 1023 were randomized to receive zoledronic acid. Prior to unblinding, the decision was made to exclude subjects from all analyses when properly documented informed consent was not obtained. Three subjects met this criterion (Listing 1-1.8). Therefore, the number of subjects enrolled and randomized in this study is reported in this document as 2046 (1026 denosumab, 1020 zoledronic acid) (Table 14-1.2).

Sex: 2029 (99.2%) women, 17 (0.8%) men (Table 14-2.1)

Mean (SD) Age: 56.7 (11.5) years (Table 14-2.1)

Ethnicity (Race): 1635 (79.9%) white or Caucasian, 139 (6.8%) Japanese, 118 (5.8%) Hispanic/Latino, 69 (3.4%) Asian, 51 (2.5%) black or African American, 2 (< 0.1%) Native Hawaiian/Pacific Islander, 32 (1.6%) other (Table 14-2.1)

Diagnosis and Main Criteria for Eligibility: Eligible subjects met the following criteria: adult with histologically or cytologically confirmed breast adenocarcinoma, 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 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 1-1.2.

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 (blinded treatment phase). The median (Q1, Q3) duration of exposure for the entire blinded treatment phase was 19.06 (9.23, 24.21) months (mean [SD] = 17.03 [8.90] months) for the denosumab group and 18.43 (9.10, 24.57) months (mean [SD] = 16.94 [9.22] months) for the zoledronic acid group, which included the exposure during the primary analysis blinded treatment phase (median [Q1, Q3]: 16.46 [9.23, 21.09] months [mean {SD} = 15.34 {7.47} months] denosumab, 16.48 [9.10, 21.22] months [mean {SD} = 15.23 {7.73} months] zoledronic acid) (Table 14-5.1, Study 20050136 Primary Analysis CSR). Since denosumab was determined to be superior compared with zoledronic acid based on the primary efficacy and safety analyses, 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, which ever 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 1-1.2.

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 extended-blinded treatment phase. Data from the entire 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 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 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 approach 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. In addition, an ad hoc analysis was performed using a Fisher's exact test to assess differences between groups in the 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, 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]

[redacted]

Summary of Results:

Subject Disposition:

A total of 2046 subjects were enrolled into the study, with 1026 subjects randomized to denosumab and 1020 subjects randomized to zoledronic acid (Table 14-1.10). Randomization was stratified by previous SRE (37%), current chemotherapy (40%), previous oral bisphosphonate use (4%), and Japanese region (7%); randomization was balanced between treatment groups within each stratum. Of the randomized subjects, 2033 received ≥ 1 dose of investigational product (1019 denosumab, 1014 zoledronic acid) (Table 14-5.1). As of the blinded treatment phase data cutoff date, 65.0% and 63.4% of subjects in the denosumab and zoledronic acid groups, respectively, had discontinued from investigational product (Table 14-1.3); 65.7% and 62.2% in the denosumab and zoledronic acid groups, respectively, had discontinued from the study (Table 14-1.2).

The overall incidence of eligibility deviations was low for both treatment groups (0.7% denosumab, 1.1% zoledronic acid) (Table 14-1.9). The most frequently reported deviations were prior malignancies or viral infection (0.3%, 0.2%) and current or prior use of IV bisphosphonates (0.0%, 0.6%). One subject ([redacted]) randomized to denosumab had the screening laboratory sample drawn before providing informed consent (Listing 1-1.5 and data on file). This subject was appropriately consented before any other study assessments were conducted; therefore, it was considered appropriate to include this subject in the efficacy and safety analyses.

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 2046 subjects (1026 denosumab, 1020 zoledronic acid). Sensitivity analyses were conducted using the per protocol analysis set, which included 2029 subjects (1017 denosumab, 1012 zoledronic acid) (Table 14-1.13). Results for the primary and secondary endpoints from the entire 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 efficacy analysis are provided in the Study 20050136 primary analysis CSR, dated 29 October 2009.

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 significantly reduced the risk of developing a first on-study SRE by 18% compared with zoledronic acid ($p < 0.0001$ for noninferiority and $p = 0.0096$ for superiority) (Table 1 and Figure 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 32.4 months (987 days) for denosumab and 27.4 months (834 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 = 0.6680) (Table 14-4.2.16).

Denosumab significantly reduced the risk of developing first-and-subsequent on-study SREs by 22% compared with zoledronic acid (excluding subsequent events occurring < 21 days from a previous SRE; p value = 0.0008) (Table 14-4.3.1 and Figure 2). 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 14-4.3.2 and Table 14-4.3.3). In addition, results were consistent when all events were included in the analysis (ie, no 21-day window applied; rate ratio [95% CI] of 0.80 [0.68, 0.93], p = 0.0031), thus supporting the primary analysis (Table 14-4.3.4).

Exploratory Endpoints

[redacted]

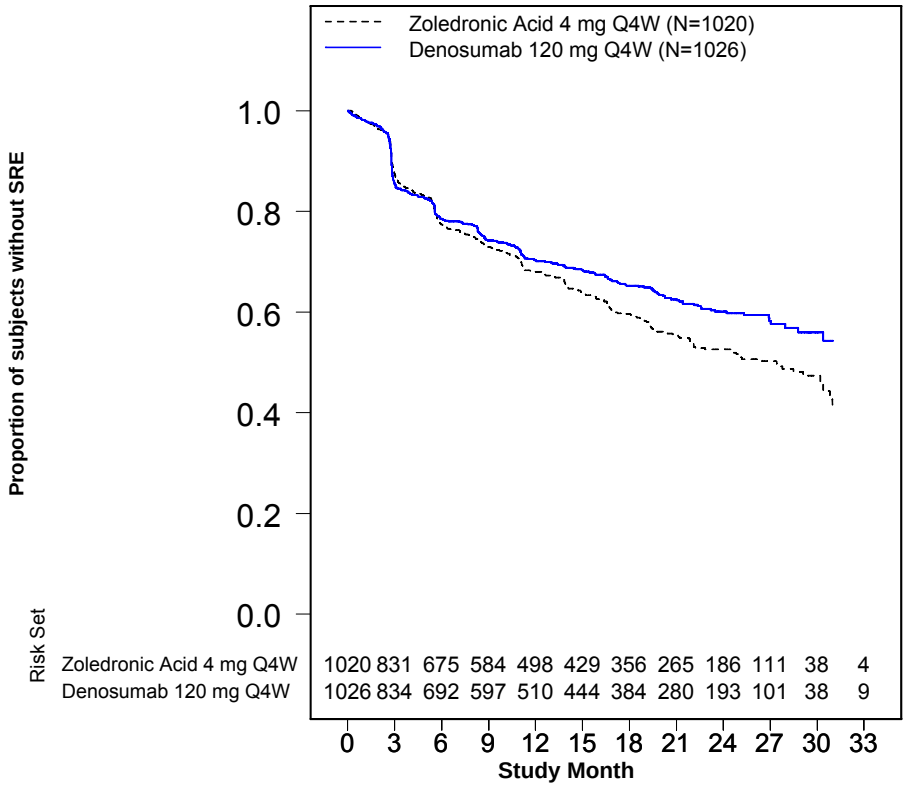
Table 1. Summary of Efficacy Endpoint Results from the Primary Blinded Treatment Phase (Primary Analysis) and the Entire Blinded Treatment Phase

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)	< 0.0001	< 0.0001	0.82	(0.71, 0.95)	< 0.0001	< 0.0001
Time to first on-study SRE (superiority)	0.82	(0.71, 0.95)	0.0101	0.0101	0.82	(0.71, 0.95)	0.0096	0.0096
Time to first and subsequent on-study SRE	0.77	(0.66, 0.89)	0.0006	0.0012	0.78	(0.68, 0.90)	0.0008	0.0016
[redacted]								

HCM = hypercalcemia of malignancy; SRE = skeletal-related event
[a] Hazard ratio or rate ratio < 1 favors denosumab
[b] Primary analysis through 06 March 2009
[c] Entire blinded treatment analysis through 20 July 2009

Primary Analysis Results Source: Table 14-4.0.1, Table 14-4.5, Table 14-4.6, Table 14-4.15, Table 14-4.16.1, Table 14-4.16.2, Table 14-4.17, and Table 4-1.105 of the Study 20050136 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 14-4.16.1, Table 14-4.16.2, Table 14-4.17, and Table 14A-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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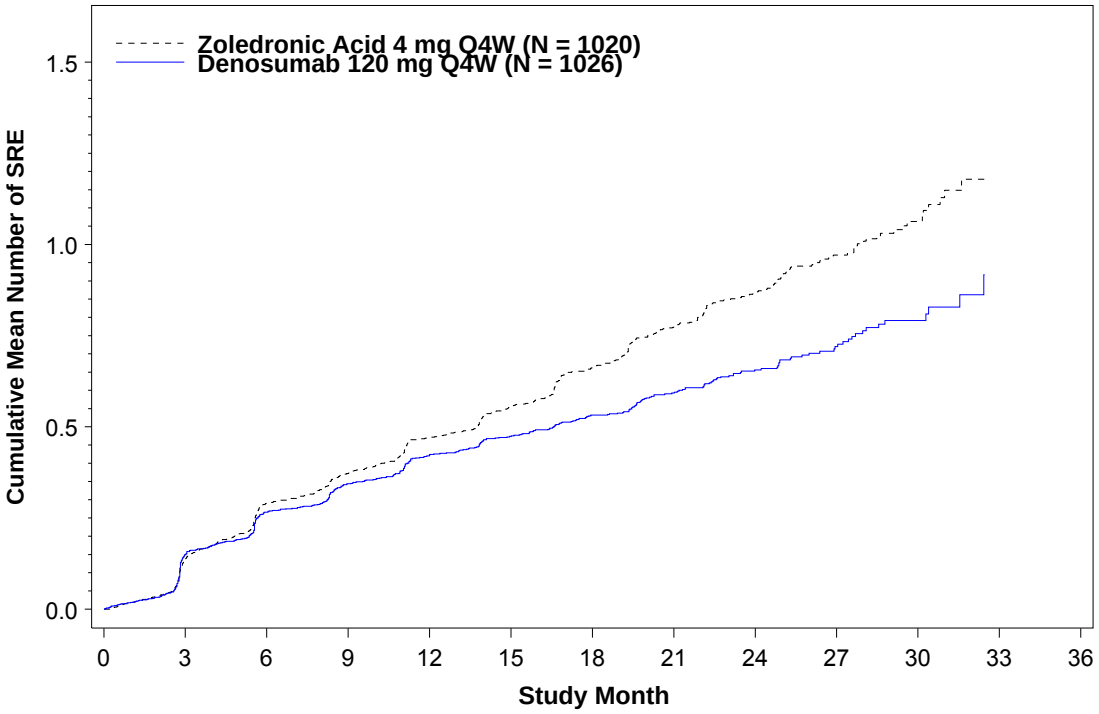
Output: g14-04_001_001_timeto_km_sre.cgm (Date Generated: 14DEC2009:15:04:30)
Source Data: adam.aslef

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.
Curves were displayed up to the last event time

Program: /stat/amg162/b_mets/20050136/analysis/extension/graphs/program/g_sre_cummean.sas
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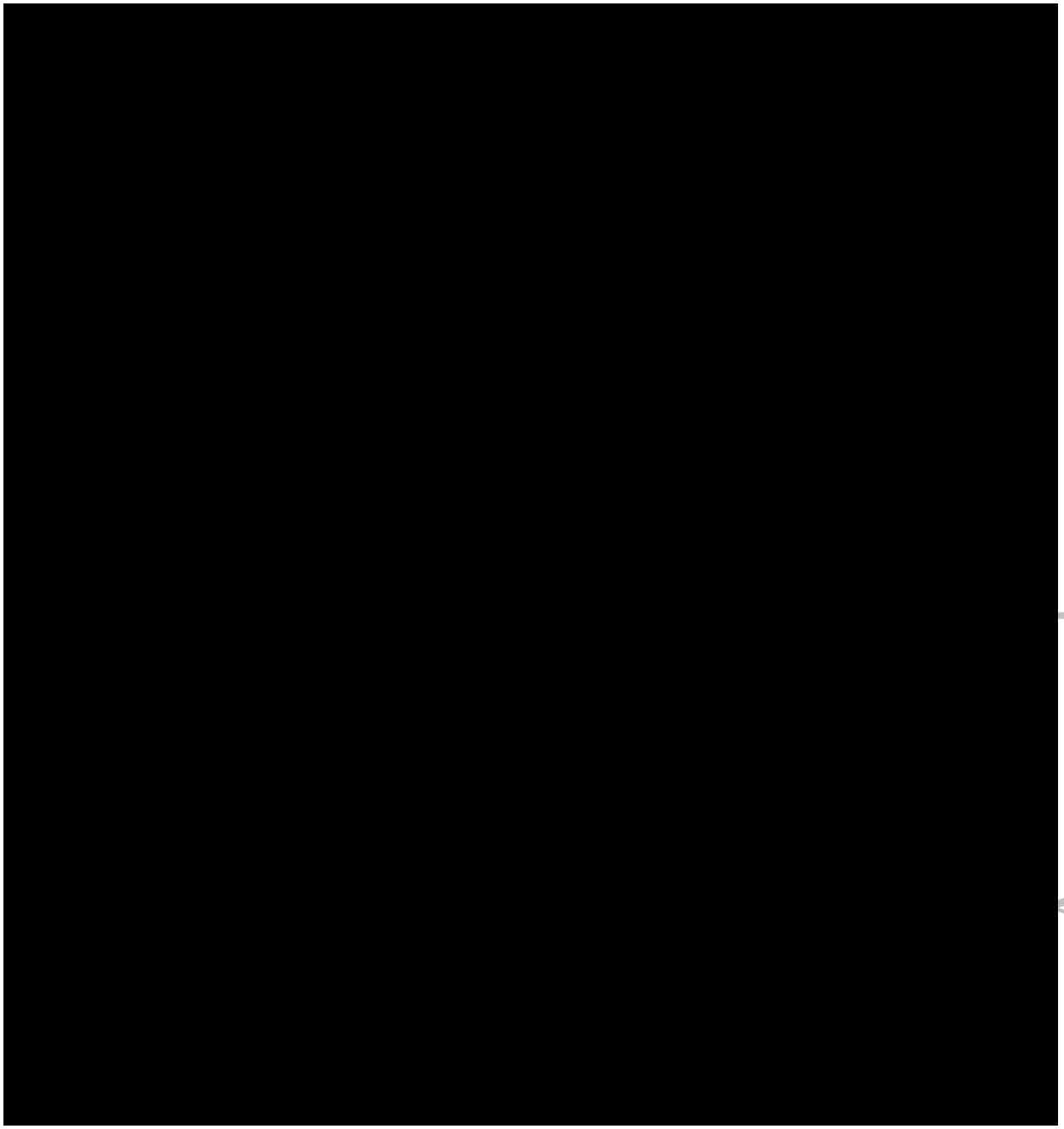
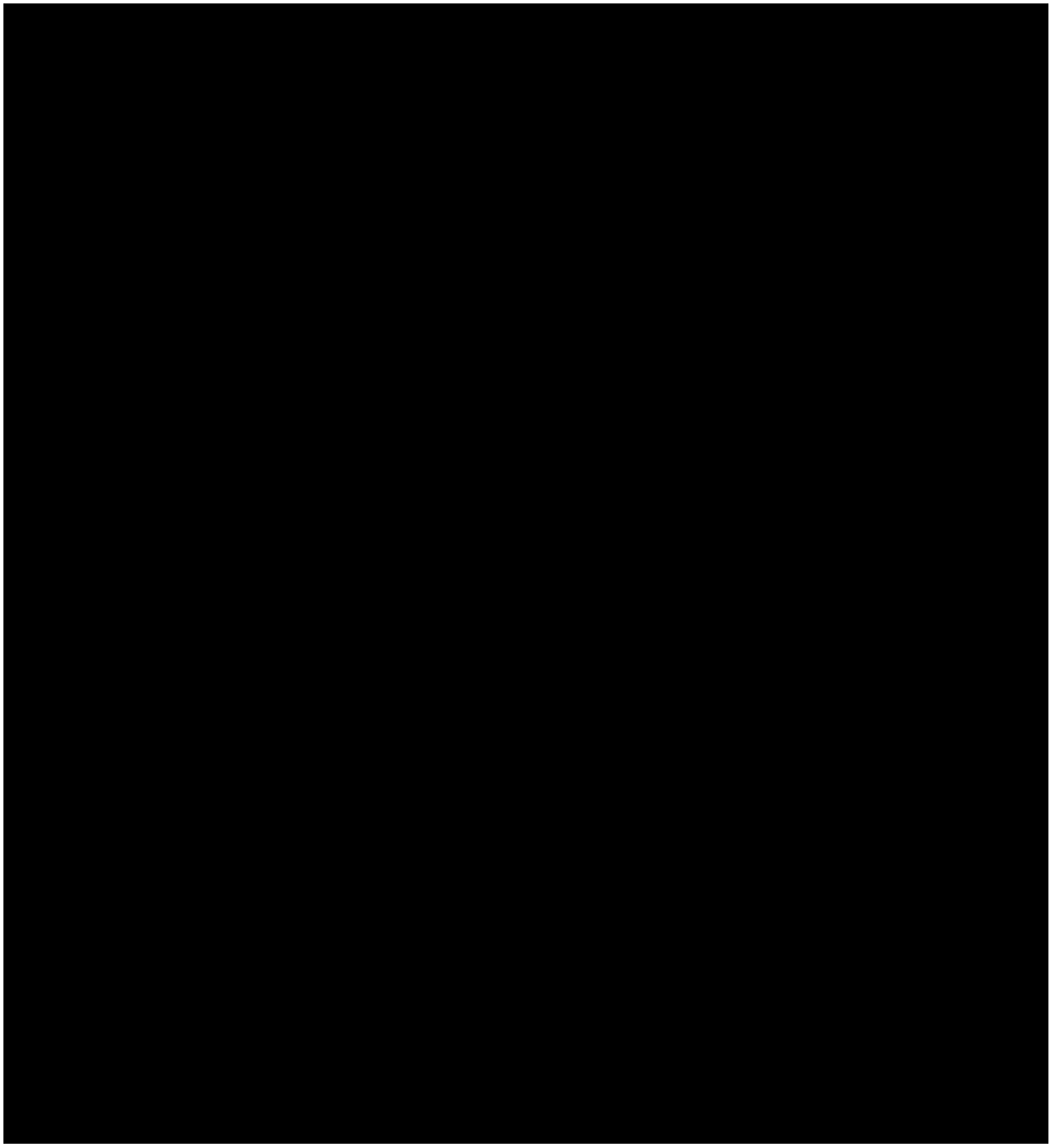
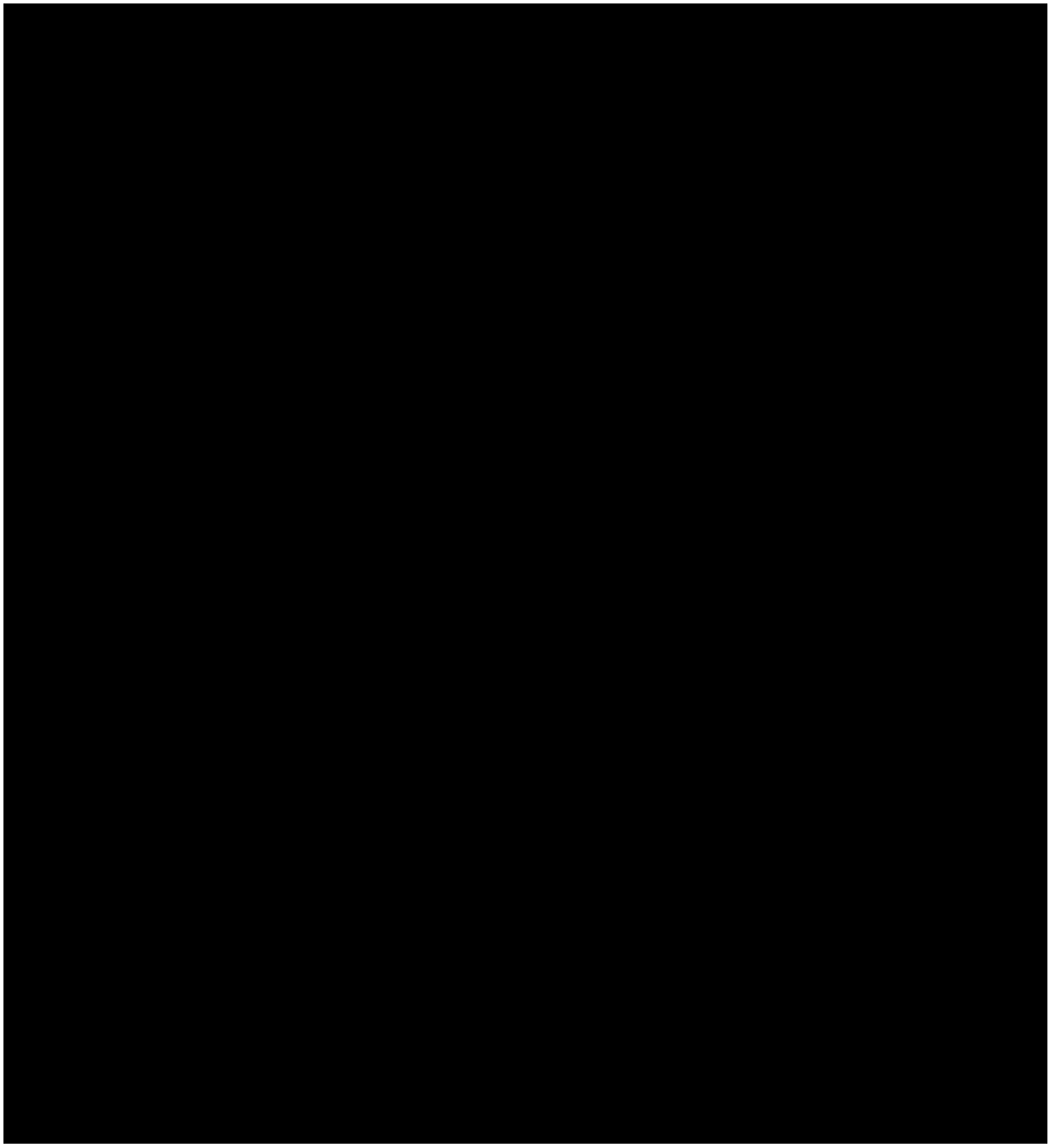
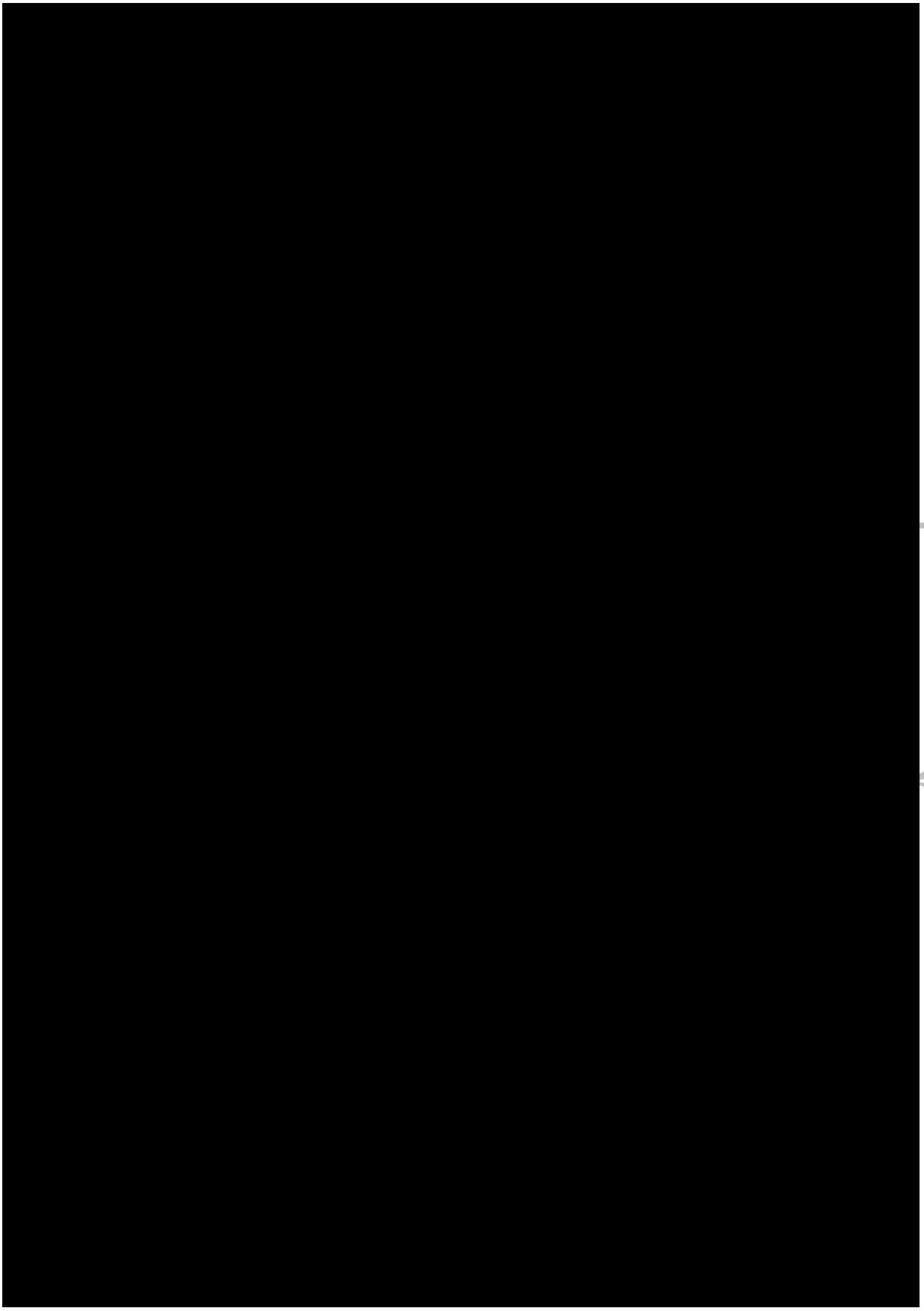


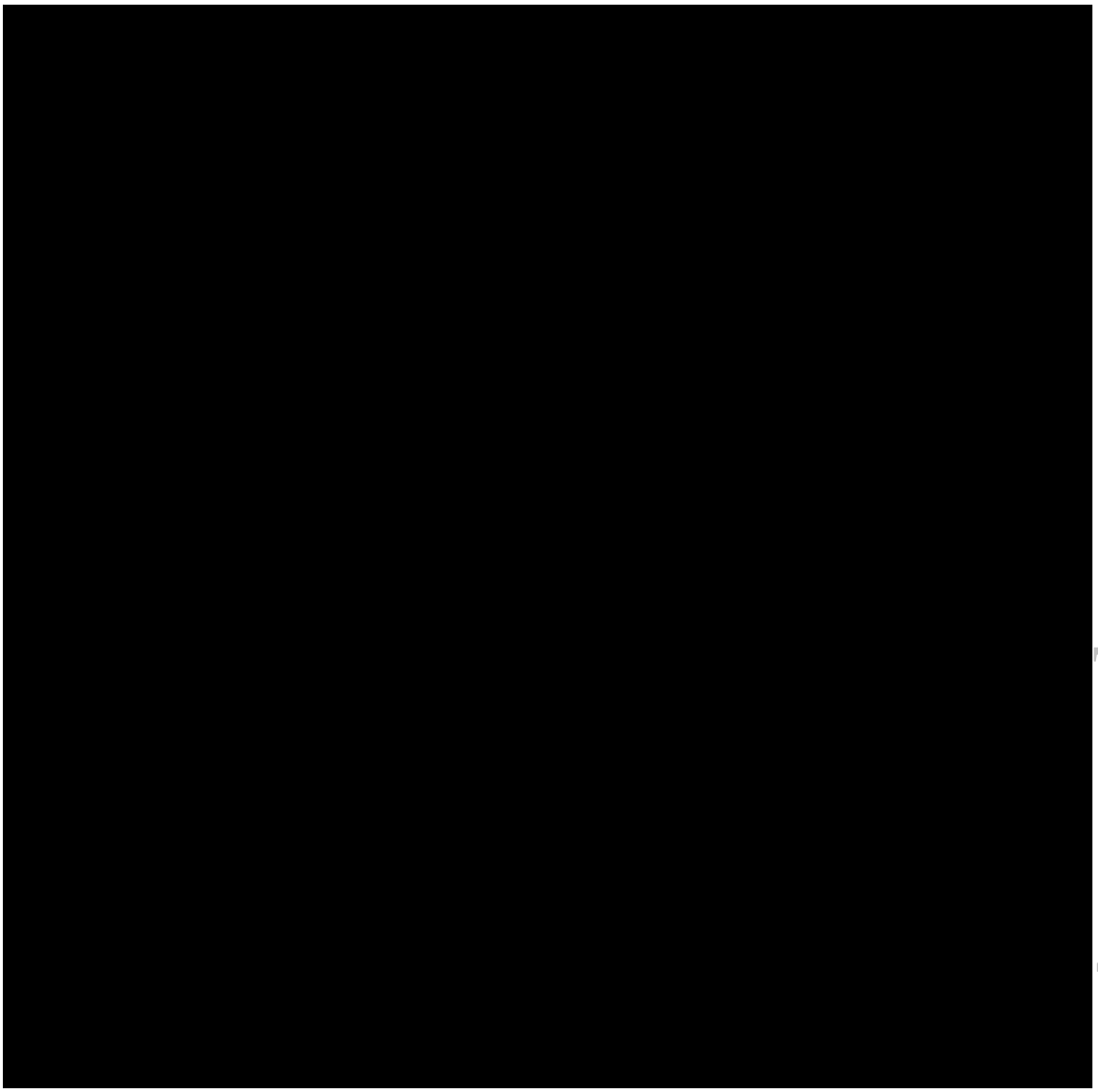




[redacted]

[redacted]





Safety Results:

Safety endpoints were assessed over the entire blinded treatment phase using the safety analysis set, which included 2033 subjects (1020 denosumab, 1013 zoledronic acid) (Table 14-1.13).

The safety profile of denosumab over the entire blinded treatment analysis phase was consistent with that of the primary blinded treatment phase. A total of 981 (96.2%) subjects in the denosumab group and 987 (97.4%) subjects in the zoledronic acid group had ≥ 1 treatment-emergent adverse event (Table 14-6.1). The most common adverse events reported in either group were nausea (36.3% denosumab, 39.9% zoledronic acid), fatigue (31.0%, 33.5%), arthralgia (25.8%, 29.8%), back pain (25.4%, 28.2%), diarrhea (24.5%, 21.9%), dyspnea (23.6%, 19.9%), vomiting (22.2%, 24.9%), decreased appetite (21.4%, 19.8%), pain in extremity (21.1%, 23.4%), asthenia (20.5%, 21.4%), headache (20.4%, 22.2%), anemia (20.1%, 24.4%), bone pain (19.9%, 24.6%), constipation (19.2%, 21.2%), and pyrexia (18.0%, 25.8%) (Table 14-6.2.1 and Table 14-6.3.1). An ad hoc comparison between treatment groups of all adverse event preferred terms using a Fisher's exact test was performed. Adverse events associated with acute phase reaction (pyrexia, bone pain, arthralgia, pain, chills, and hyperthermia) and adverse events

associated with renal toxicity (renal failure, blood urea increased) were higher in the zoledronic acid treatment group (Figure 14A-9.2.1). Also higher in the zoledronic acid group were anemia, aspartate aminotransferase increased, lumbar vertebral fracture, hypercalcemia, alanine aminotransferase increased, edema, blood alkaline phosphatase increased, skin hyperpigmentation, bronchospasm, and ear infection. The greater incidence of events of hypercalcemia in the zoledronic acid group (1.8% denosumab, 3.8% zoledronic acid) may reflect less suppression of bone turnover compared with denosumab. Mouth hemorrhage, vocal cord paralysis, periodontal disease, wheezing, toothache, hypocalcemia, and dyspnea were more frequent in the denosumab group than the zoledronic acid group. With the exception of hypocalcemia, which is discussed below, no causal relationship could be established with denosumab for any of these events. Events of mouth hemorrhage and periodontal disease were confounded by pre-existing comorbidities or concomitant medications, including prior chemotherapy. One subject with periodontal disease in each treatment group also had a positively-adjudicated event of ONJ. The subject incidence of high level group terms that included the preferred terms for wheezing (bronchial disorders, excluding neoplasms), dyspnea (respiratory disorders NEC), and vocal cord paralysis (cranial nerve disorders, excluding neoplasms) were similar between treatment groups, showing that differences between treatment groups observed for an individual preferred term are not indicative of an overall trend. A review of the dyspnea cases showed that more subjects in the denosumab group had a history of [redacted] at baseline. 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.

Serious adverse events were reported for 489 (47.9%) subjects in the denosumab group and 509 (50.2%) subjects in the zoledronic acid group (Table 14-6.1). The most common serious adverse events reported in either group were dyspnea (5.9% denosumab, 3.8% zoledronic acid), metastases to central nervous system (5.1%, 4.7%), vomiting (3.3%, 3.4%), anemia (2.8%, 3.3%), hepatic failure (2.8%, 1.9%), pleural effusion (2.6%, 2.8%), pyrexia (2.5%, 3.0%), respiratory failure (2.5%, 2.0%), metastases to liver (2.4%, 3.3%), general physical health deterioration (2.3%, 1.7%), nausea (2.3%, 2.5%), diarrhea (2.2%, 1.7%), pneumonia (2.1%, 2.6%), osteonecrosis (2.0%, 1.1%), breast cancer (1.9%, 2.0%), febrile neutropenia (1.9%, 2.2%), and dehydration (1.6%, 2.6%) (Table 14-6.2.2 and Table 14-6.3.2). An ad hoc comparison between treatment groups of all serious adverse event preferred terms using a Fisher's exact test was performed. A greater incidence of serious renal failure, serious acute renal failure, hypercalcemia, and hypokalemia was observed in the zoledronic acid group (Figure 14A-9.2.2). Serious adverse events of dyspnea were more frequent in the denosumab group. Narratives for all serious adverse events are included in Attachment 6.

A total of 230 (22.5%) subjects in the denosumab group and 242 (23.9%) subjects in the zoledronic acid group had fatal adverse events while on study (Table 14-6.1). Fatal adverse events were generally associated with progression of disease (Table 14-6.2.7 and Table 14-6.3.7) [redacted]. Narratives for all fatal adverse events are included in Attachment 6.

One hundred seven (10.5%) subjects in the denosumab group and 136 (13.4%) subjects in the zoledronic acid group had adverse events leading to withdrawal from investigational product (Table 14-6.1, Table 14-6.2.4, and Table 14-6.3.4). Fifty-four (5.3%) subjects in the denosumab group and 77 (7.6%) subjects in the zoledronic acid group had adverse events leading to study withdrawal (Table 14-6.1, Table 14-6.2.3, and Table 14-6.3.3). Narratives for all adverse events leading to withdrawal from investigational product are included in Attachment 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 for zoledronic acid. Preferred terms used to search for adverse events of hypocalcemia, skin infections, potential cases of ONJ, new primary malignancies, eczema, and adverse events potentially associated with hypersensitivity, renal toxicity, or acute phase reaction are listed in Attachment 5. New primary malignancies were determined using a search strategy of malignancy preferred terms from the neoplasm system organ class, which excluded terms for benign malignancies, recurrent malignancies, and disease progression (terms associated with breast cancer or metastases). 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.

The subject incidence of adverse events of hypocalcemia was 6.1% for the denosumab group and 3.7% for the zoledronic acid group (Table 14-6.14.1 and Table 14-6.14.2). Fifty-seven percent of the events in the denosumab group and 46% of the events in the zoledronic acid group occurred in the first 6 months after the first dose of investigational product (Table 14-6.6.1 and Listing 1-4.3). The majority of subjects (44 of 62 subjects [71%] denosumab, 26 of 37 subjects [70%] zoledronic acid) had a single event of hypocalcemia (Listing 1-4.3). Fourteen (1.4%) subjects in the denosumab group and 8 (0.8%) subjects in the zoledronic acid group had an adverse event of hypocalcemia and received IV calcium (Table 14A-6.16.3). Hypocalcemia was reported as serious in 0.6% of subjects in the denosumab group and 0.2% of subjects in the zoledronic acid group (Table 14-6.3.2 and Listing 1-4.2) and led to discontinuation from study in 0.2% of subjects in the denosumab group and < 0.1% of subjects in the zoledronic acid group (Table 14-6.3.3). No adverse events of hypocalcemia were reported as fatal (Table 14-6.14.1 and Table 14-6.3.7).

The overall subject incidence of adverse events of infection was 48.2% and 50.0% for denosumab and zoledronic acid, respectively (Table 14-6.2.1). The overall subject incidence of serious adverse events of infection was 7.9% and 8.5% for denosumab and zoledronic acid, respectively (Table 14-6.2.2). The subject incidence of adverse events and serious adverse events of skin infection was 4.3% (denosumab), 3.8% (zoledronic acid) and 0.9% (denosumab), and 0.5% (zoledronic acid), respectively (Table 14-6.12.2 and Table 14-6.12.1).

Adverse events adjudicated positive for ONJ were reported with a similar frequency for denosumab (2.5%) and zoledronic acid (1.8%), with p = 0.2861 (Table 14-6.13.2). Twenty-four of 26 (92%) subjects in the denosumab group and 15 of 18 (83%) subjects in the zoledronic acid group had a history of [redacted], and/or use of a [redacted], the majority of which (14 and 13 subjects, respectively) had [redacted] (Attachment 6 and data on file). In the denosumab and zoledronic acid groups, respectively, 5 (19%) and 3 (17%) subjects were receiving or had received antiangiogenic medications, 19 (73%) and 14 (78%) subjects were receiving or had received chemotherapy, and 0 and 5 (28%) subjects had previously received bisphosphonates (previous IV zoledronic acid for 2 subjects in the zoledronic acid group and oral bisphosphonates for the other 3 subjects). Of the subjects who had positively adjudicated ONJ events, 18 of 26 subjects in the denosumab group and 8 of 18 subjects in the zoledronic acid group withdrew from investigational product due to ONJ; the remaining 8 and 10 subjects in the denosumab and zoledronic acid groups, respectively, continued investigational product despite ONJ (Listing 1-4.9 and Listing 1-4.11). The adjudicated positive ONJ adverse event was considered resolved by the investigator for 10 and 6 subjects in the denosumab and zoledronic acid groups, respectively, according to information available as of 04 January 2010.

The subject incidence of new primary malignancies was 0.5% in the denosumab group and 0.6% in the zoledronic acid group (Table 14-6.9). Adverse events and serious adverse events in the system organ class cardiac disorders were reported for 10.9% (denosumab), 11.8% (zoledronic acid) and 3.8% (denosumab), 4.8% (zoledronic acid) of subjects, respectively (Table 14-6.2.1 and Table 14-6.2.2). Adverse events and serious adverse events in the system organ class vascular disorders were reported for 26.0% (denosumab), 26.9% (zoledronic acid) and 2.2%

(denosumab), 3.3% (zoledronic acid), respectively (Table 14-6.2.1 and Table 14-6.2.2). Fifty-eight (5.7%) subjects in the denosumab group and 50 (4.9%) subjects in the zoledronic acid group reported adverse events potentially associated with hypersensitivity (Table 14-6.15.1 and Table 14-6.15.2). Overall, there was no temporal relationship between the occurrence of these events and initiation of investigational product, and 76% of subjects in the denosumab group and 80% of subjects in the zoledronic acid group who experienced adverse events potentially associated with hypersensitivity reported a single event (Listing 1-4.10). Adverse events with the preferred term drug hypersensitivity were causally associated with concomitant medications (eg, taxol). Adverse events categorized as eczema were balanced between treatment groups (3.3% in each treatment group) (Table 14-6.11).

Adverse events of renal toxicity were reported for a higher number of subjects in the zoledronic acid group (5.4% denosumab, 9.4% zoledronic acid) (Table 14-6.10). Adverse events potentially associated with acute phase reaction occurred during the first 3 days of treatment for 10.7% of subjects in the denosumab group and 28.2% of subjects in the zoledronic acid group (Table 14-6.8.3).

Of the 1008 subjects tested for antidenosumab antibodies, 1 subject tested positive for binding, non-neutralizing antibodies to denosumab at week 49 (Attachment 9).

Expected decreases in serum calcium, phosphorus, and total alkaline phosphatase occurred; decreases in median serum calcium were mild and transient. A lower incidence of hypercalcemia was observed in the denosumab group compared with the zoledronic acid group (denosumab: 0.3% grade 3 and 0.4% grade 4, zoledronic acid: 1.2% grade 3 and 0.9% grade 4) (Table 14-7.48.2). 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 92 subjects who participated in the pharmacokinetic substudy, received ≥ 1 dose of denosumab, and had ≥ 1 valid denosumab serum concentration level (Attachment 1). The mean serum denosumab concentration at the 1-month (week 5) visit was 9660 ng/mL. Exposures, based on trough serum concentrations, increased as anticipated, with approximately 2-fold higher mean serum concentrations (20700 ng/mL) observed at 6 months (week 25) after the first dose. Mean trough serum concentrations obtained 6 to 24 months during study treatment (weeks 25 to 97) were similar (range: 20700 to 23100 ng/mL), consistent with a lack of change in pharmacokinetics with time.

Conclusions:

This study represents a dataset in a total of 2046 randomized subjects. Overall, the results for the entire blinded treatment phase in this population of patients with advanced breast 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 significantly reduces the risk of developing SREs compared with zoledronic acid and had a favorable safety profile in subjects with breast cancer and bone metastasis.

2. SYNOPSIS

Name of Sponsor: Amgen Inc and Daiichi Sankyo Co., Ltd.

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 Breast Cancer

Investigator(s) and Study Center(s): This study was conducted at a total of 222 centers in 33 countries. Study centers and investigators are listed in Appendix 3.

Publication(s): Stopeck A, Lipton A, Martin M, et al. Denosumab in Patients With Breast Cancer and Bone Metastases Previously Treated with Zoledronic Acid or Denosumab: Results from the 2-Year Open-Label Extension Treatment Phase of a Pivotal Phase 3 Study. Presented at: San Antonio Breast Cancer Symposium, December 6-10, 2011; San Antonio, TX.

Study Period: This clinical study report (CSR) includes results from 21 July 2009 (first subject enrolled in open-label extension [OLE] phase) to 20 July 2011. Final results from subjects who participated in the country-specific Protocol Amendment 4b, which allowed subjects to continue open-label denosumab beyond 2 years until denosumab was approved and available for sale in the subject's country or until another mechanism was identified to provide denosumab to ongoing subjects, are reported separately in Appendix 10 of this report and include results through the completion of the study (04 April 2012). Results from the double-blind treatment phase have been reported previously.

Development Phase: 3

Introduction and Objectives: Bone is the most frequent site of metastasis of breast cancer, accounting for approximately 40% of all first metastases; up to 80% of stage IV breast cancer patients eventually develop disease in the bone. Skeletal metastasis is characterized by increased osteoclast activity and is associated with significant skeletal morbidity (ie, skeletal-related events [SREs]). Bisphosphonates, such as zoledronic acid (Zometa®), have been shown to inhibit osteoclast activity and reduce the incidence of SREs in patients with bone metastases. RANK ligand (RANKL) is an essential mediator of osteoclast formation, function, and survival. Inhibition of RANKL has been shown to have greater antiresorptive effects compared with bisphosphonates. Denosumab is a fully human monoclonal antibody that inhibits RANKL and osteoclast-mediated bone resorption.

The primary objective of the double-blind phase of this study was to determine if denosumab was noninferior to zoledronic acid with respect to the first on-study SRE (pathologic fracture, radiation to bone [including the use of radioisotopes], surgery to bone, or spinal cord compression) in subjects with advanced breast cancer and bone metastases. The secondary objectives were to determine if denosumab was superior to zoledronic acid with respect to the first on-study SRE and the first-and-subsequent on-study SRE (multiple-event analysis), and to assess the safety and tolerability of denosumab compared with zoledronic acid. These objectives and the exploratory objectives were fully described in the primary analysis CSR (29 October 2009) and the double-blind extension (DBE) CSR (19 February 2010).

Results from the primary blinded treatment phase 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 favorable safety profile in subjects with breast cancer and bone metastasis. These findings were supported by the results for the entire blinded treatment phase (primary analysis plus DBE).

This report summarizes patient reported outcomes (PRO) and safety results from the OLE phase of the study. Safety results from the OLE phase in subjects who participated in the country-

specific Protocol Amendment 4b are included in Appendix 10. This report also includes an analysis of overall survival for the entire study.

Methodology: This was an open-label extension (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 subjects with advanced breast cancer. All subjects received denosumab during the OLE phase; subjects were initially randomized during the DBE phase 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.

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.

Because denosumab was determined to be superior compared with zoledronic acid, based on the primary efficacy and safety analyses, all subjects undergoing Q4W scheduled assessments were offered open-label denosumab at a dose of 120 mg SC Q4W for up to 2 years, including those who had been randomized to the zoledronic acid treatment group. 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 (20050136); in the United Kingdom and Czech Republic, the OLE phase was conducted under Protocol 20080540 per Health Authority request. Subjects who did not participate in OLE treatment were followed for survival for up to 2 years after the last dose of blinded investigational product. This CSR includes safety and PRO results from Study 20050136 for the OLE phase and an analysis of overall survival for the entire study; results from 13 subjects included in Study 20080540 will be reported separately in the CSR for that study protocol. In addition, 71 subjects were enrolled in the country-specific (8 countries) Protocol Amendment 4b, which allowed subjects in Study 20050136 to continue the OLE beyond 2 years until denosumab was approved and available for sale in the subject's country, or until another mechanism was identified to provide denosumab to ongoing subjects. The 2-year OLE data from the 71 subjects are analyzed in this OLE CSR; the 2-year data plus the OLE continuation under the country-specific Protocol Amendment 4b are analyzed in Appendix 10.

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

Number of Subjects Planned: 1960 subjects (980 subjects per treatment group)

Number of Subjects Enrolled: For the double-blind treatment phase of the study, a total of 2046 subjects (1026 denosumab, 1020 zoledronic acid) were randomized and reported in the primary analysis CSR.

A total of 752 subjects completed DBE and 667 subjects continued into the OLE phase of the study (of these, 325 subjects received denosumab in the double-blind phase and 342 subjects received zoledronic acid in the double-blind phase) (Table 14-1.1 and Table 14-2.1).

Sex: 660 (99.0%) women, 7 (1.0%) men

Age: Mean (±SD) was 56.0 (11.2) years

Ethnicity (Race): 528 (79.2%) white or Caucasian, 63 (9.4%) Japanese, 39 (5.8%) Hispanic/Latino, 13 (1.9%) black or African American, 13 (1.9%) Asian, 11 (1.6%) other

Diagnosis and Main Criteria for Eligibility: Eligible subjects met the following criteria: adult with histologically or cytologically confirmed breast adenocarcinoma, 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. Informed consent was obtained prior to beginning the OLE phase of the study.

Investigational Product, Dose and Mode of Administration, Manufacturing Lot Number: All subjects in the OLE phase and the continuation of the OLE phase under Protocol Amendment 4b received denosumab 120 mg SC Q4W. Denosumab was provided as a sterile, preservative free liquid, 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]. Lot numbers for denosumab used in the OLE phase of the study are provided in Listing 1-1.1.

Duration of Treatment: The median (range) duration of exposure for the entire blinded treatment phase was 19.1 months (0.1, 36.5) for the denosumab group and 18.4 months (0.3, 38.6) for the zoledronic acid group (DBE CSR, Table 14-5.1). Subjects who continued in the OLE phase of the study were offered denosumab for up to an additional 2 years. Protocol Amendment 4b allowed for an additional 10 months of study participation. Thus, the maximum potential exposure to denosumab in this study was approximately 5 years and 10 months.

Reference Therapy, Dose and Mode of Administration, Manufacturing Lot Number: None for the OLE phase of the study.

Study Endpoints: The efficacy and safety endpoints of the study are presented in the protocol in 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 02 August 2011) 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:

- total number of deaths

Patient Reported Outcomes:

- Brief Pain Inventory – Short Form (BPI-SF) “worst” pain score
- Analgesic Quantification Algorithm (AQA) score

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. The open-label baseline values were used to determine changes from baseline for ECOG, PRO, and all safety variables.

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, seriousness, and relationship to treatment. Subject-year adjusted incidence rates were summarized for adverse events, serious adverse events, and Common Toxicity Criteria Adverse Events (CTCAE) version 3.0 grades ≥ 3 adverse events. The following adverse events are discussed separately: hypocalcemia, positively adjudicated osteonecrosis of the jaw (ONJ), osteonecrosis excluding the jaw, infections (including skin infections leading to hospitalization), new primary malignancy, adverse events potentially associated with hypersensitivity, eczema, and cardiovascular disorders. 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, version 14.1 for the OLE CSR, and version 15.0 for the OLE continuation under Protocol Amendment 4b) 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, potential cases of ONJ, osteonecrosis excluding the jaw, eczema, 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 baseline ECOG scores were summarized. The proportion of subjects developing antidenosumab antibodies was calculated.

The total number of deaths on study 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 the Kaplan-Meier method.

Descriptive statistics for recorded values and change from open-label baseline in BPI-SF worst pain score were presented by visit using the PRO analysis set, which consisted of all subjects who participated in the OLE phase of the study and had at least 1 open-label PRO assessment. The proportion of subjects with ≥ 2-point increase in BPI-SF "worst" pain score and the proportion of subjects with > 4-point "worst" pain score were summarized. Changes in analgesic use were summarized using a shift table as an ad-hoc analysis. The analyses were based on the observed data.

Summary of Results:

Subject Disposition:

A total of 2046 subjects were enrolled and randomized into the study, with 1026 subjects randomized to denosumab and 1020 subjects randomized to zoledronic acid (Table 14-1.1). Of these, 752 subjects (366 denosumab and 386 zoledronic acid) completed the double-blind portion of the study. A total of 667 subjects enrolled in the OLE phase of the study, including 325 subjects who received denosumab in the blinded treatment phase (here forward referred to as denosumab/denosumab) and 342 subjects who received zoledronic acid in the blinded treatment phase (here forward referred to as zoledronic acid/denosumab). A total of 674 subjects (345 denosumab/denosumab and 329 zoledronic acid/denosumab) entered survival follow-up at any time during the study (Table 1-1.1.3).

The 2-year OLE phase of the study was completed by 194 subjects (29.1%) (94 subjects [28.9%] denosumab/denosumab and 100 subjects [29.2%] zoledronic acid/denosumab); 74 subjects (11.1%) (42 subjects [12.9%] denosumab/denosumab and 32 subjects [9.4%] zoledronic acid/denosumab) were ongoing and intended to continue in the study under Protocol Amendment 4b as of the data cut-off (20 July 2011) for this report (Table 14-1.1). After the data cut-off, it was discovered that although 74 subjects intended to continue in the study under Protocol Amendment 4b, only 71 subjects continued. A total of 399 subjects (59.8%) discontinued from the OLE phase of the study (189 subjects [58.2%] denosumab/denosumab, 210 subjects [61.4%] zoledronic acid/denosumab). The most common reasons for study discontinuation were death (16.6%), disease progression (15.4%), and adverse event (11.2%). 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.

The total number of subjects who received ≥ 1 dose of denosumab in the double-blind treatment phase and/or the OLE phase was 1019 subjects (Table 14a-5.2). Among these subjects, the median (Q1, Q3) cumulative denosumab exposure across all study phases was 19.1 months (9.2, 32.2) with a minimum of 0.1 months and a maximum exposure of 60 months. Of the

subjects enrolled in the OLE phase, 652 subjects received ≥ 1 dose of denosumab (318 denosumab/denosumab, 334 zoledronic acid/denosumab) (Table 14-5.1). The median (Q1, Q3) exposure to denosumab during the OLE phase only was 17.6 months (8.3, 23.0) with a minimum of 0 months and a maximum of 23.7 months in the denosumab/denosumab group and 16.3 months (7.4, 22.8) with a minimum of 0.5 months and a maximum of 23.3 months in the zoledronic acid/denosumab group.

The overall incidence of protocol deviations during the OLE phase was low for both groups (2 subjects [0.6%] denosumab/denosumab, 1 subject [0.3%] zoledronic acid/denosumab) (Table 14-1.6).

Safety Results:

A total of 283 subjects (89.0%) in the denosumab/denosumab group and 303 subjects (90.7%) in the zoledronic acid/denosumab group had ≥ 1 treatment-emergent adverse event (Table 14-6.1). The most common adverse events during the OLE phase (denosumab/denosumab, zoledronic acid/denosumab) were nausea (22.6%, 23.1%), fatigue (22.0%, 22.2%), and back pain (20.8%, 16.8%) (Table 14-6.3.1). Subject-year adjusted rates of adverse events are included in Table 14-6.4.1 and Table 14-6.5.1. The investigator considered the adverse events as possibly related to denosumab in 70 subjects (22.0%) in the denosumab/denosumab group and 68 subjects (20.4%) in the zoledronic acid/denosumab group (Table 14-6.2.5). The preferred term of osteonecrosis of the jaw was the most common adverse event considered by the investigator as possibly related to denosumab (denosumab/denosumab: 12 subjects [3.8%]; zoledronic acid/denosumab: 18 subjects [5.4%]) (Table 14-6.3.5). Positively adjudicated events of ONJ are discussed below with the events of interest.

The subject incidence of grade ≥ 3 treatment-emergent adverse events was 165 subjects (51.9%) in the denosumab/denosumab group and 187 subjects (56.0%) in the zoledronic acid/denosumab group (Table 14-6.3.8). The most commonly reported grade ≥ 3 treatment-emergent adverse events were anemia (8.2%, 5.7%), neutropenia (7.2%, 3.6%), and dyspnea (6.0%, 4.2%). The investigator considered the grade ≥ 3 adverse events as possibly related to denosumab in 11 subjects (3.5%) in the denosumab/denosumab group and 19 subjects (5.7%) in the zoledronic acid/denosumab group (Table 14-6.2.9 and Table 14-6.3.9). The preferred term of osteonecrosis of the jaw was the most common grade ≥ 3 adverse event considered by the investigator as possibly related to denosumab (denosumab/denosumab: 2 subjects [0.6%] zoledronic acid/denosumab: 9 subjects [2.7%]) (Table 14-6.3.9). Subject-year adjusted rate of grade ≥ 3 adverse events are included in Table 14-6.4.3 and Table 14-6.5.3.

A total of 126 subjects (39.6%) in the denosumab/denosumab group and 133 subjects (39.8%) in the zoledronic acid/denosumab group had a serious adverse event (Table 14-6.1 and Table 14-6.2.2). The most common serious adverse events (denosumab/denosumab, zoledronic acid/denosumab group) were metastases to central nervous system (1.9%, 5.1%), hepatic failure (2.5%, 3.3%), and pleural effusion (2.8%, 2.7%) (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 included in Appendix 6.

A total of 48 subjects (15.1%) in the denosumab/denosumab group and 61 subjects (18.3%) in the zoledronic acid/denosumab group had fatal adverse events during the OLE phase of the study (Table 14-6.1). Fatal adverse events were generally associated with progression of disease (Table 14-6.2.7 and Table 14-6.3.7) and none were considered by the investigator as possibly related to denosumab (Table 14-6.3.14). Narratives for all fatal adverse events are included in Appendix 6.

A total of 48 subjects (15.1%) in the denosumab/denosumab group and 55 subjects (16.5%) in the zoledronic acid/denosumab group had adverse events leading to discontinuation of denosumab (Table 14-6.1 and Table 14-6.2.4). The most common adverse events that led to discontinuation of denosumab (denosumab/denosumab, zoledronic acid/denosumab) were the preferred terms of osteonecrosis of the jaw (2.2%, 4.5%) and breast cancer metastatic (0.6%, 1.5%) (Table 14-6.3.4). Serious adverse events that led to discontinuation of denosumab were reported for 19 subjects (6.0%) in the denosumab/denosumab group and 26 subjects (7.8%) in

the zoledronic acid/denosumab group (Table 14-6.2.11). The most common serious adverse events that led to discontinuation of denosumab were the preferred terms of breast cancer metastatic (0.6%, 1.2%) and osteonecrosis of the jaw (0.6%, 1.2%) (Table 14-6.3.11). A total of 46 subjects (14.5%) in the denosumab/denosumab group and 43 subjects (12.9%) in the zoledronic acid/denosumab group had adverse events that led to study withdrawal (Table 14-6.2.3 and Table 14-6.3.3). Serious adverse events that led to study withdrawal were reported for 21 subjects (6.6%) in the denosumab/denosumab group and 20 subjects (6.0%) in the zoledronic acid/denosumab group (Table 14-6.2.10).

Events of Interest

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

Hypocalcemia: The subject incidence of adverse events of hypocalcemia was 3.8% (12 subjects) in the denosumab/denosumab group and 2.7% (9 subjects) in the zoledronic acid/denosumab group (Table 14-6.12.1). Of the 21 subjects with hypocalcemia, 12 subjects had single events (denosumab/denosumab: 8 subjects; zoledronic acid/denosumab: 4 subjects) (Listing 1-2.3). Four subjects (33.3%) in the denosumab/denosumab group and 2 subjects (22.2%) in the zoledronic acid/denosumab group had an adverse event of hypocalcemia and received IV calcium (Table 1-1.6.1). Hypocalcemia was reported as serious in 3 subjects (0.9%) in the denosumab/denosumab group and 0 subjects in the zoledronic acid/denosumab group (Table 14-6.12.3 and Listing 1-2.2). Hypocalcemia led to discontinuation of study in 1 subject in the denosumab/denosumab group (Table 14-6.3.3). No adverse events of hypocalcemia were reported as fatal (Table 14-6.2.7).

Positively Adjudicated ONJ: Adverse events were identified as positively adjudicated ONJ events 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. These events are referred to as positively adjudicated ONJ, rather than the preferred term of osteonecrosis of the jaw discussed in the previous adverse event section. Adverse events of ONJ were adjudicated positive in 6.3% (20 subjects) in the denosumab/denosumab group and 5.4% (18 subjects) in the zoledronic acid/denosumab group (Table 14-6.11.2). Nineteen of 20 subjects (95%) in the denosumab/denosumab group and 16 of 18 subjects (89%) in the zoledronic acid/denosumab group had a history of [redacted], and/or use of a [redacted], and among these, 8 subjects from each treatment group had [redacted] (Appendix 6 and Listing 1-6.105.1). Fourteen (37%) of the subjects with events of positively adjudicated ONJ required no surgical treatments and were managed conservatively (eg, with mouth rinses and antibiotics). All the 24 subjects (63%) who had surgical treatments underwent limited surgical procedures only (ie, sequestrectomy, debridement, and curettage) (Listing 1-6.105.1). Of the 38 subjects with positively adjudicated ONJ, 1 subject (3%) presented with a grade 4 event, 8 subjects (21%) presented with grade 3 events, 16 subjects (42%) presented with grade 2 events, and 13 subjects (34%) presented with grade 1 events; there were no grade 5 events (Listing 1-2.7). Subject [redacted] had a grade 4 adverse event that triggered adjudication of ONJ. The subject was a [redacted] (zoledronic acid/denosumab) who died due to disease progression 2 months after [redacted] ONJ diagnosis, but was never hospitalized for ONJ; the reason for the categorization of the event as grade 4 event was not specified.

Of the subjects who had positively adjudicated ONJ events, 11 of 20 subjects (55%) in the denosumab/denosumab group and 15 of 18 subjects (83%) in the zoledronic acid/denosumab group discontinued denosumab due to ONJ; the remaining 9 subjects (45%) and 3 subjects (17%) in the denosumab/denosumab and zoledronic acid/denosumab groups, respectively, continued denosumab despite ONJ (Listing 1-2.7 and Listing 1-2.11).

The adjudicated positive ONJ adverse event was considered resolved based on the Amgen definition of complete mucosal coverage of exposed bone for 2 subjects (10%) in the

denosumab/denosumab group and 5 subjects (28%) in the zoledronic acid/denosumab group, according to information available as of 01 February 2012 (Listing 1-2.7 and Listing 1-6.105.1).

The subject incidence of positively adjudicated ONJ adverse events during the entire study period (ie, blinded treatment phase and OLE phase) was 4.7% (48/1020) in the denosumab/denosumab group and 3.8% (38/1013) in the zoledronic acid/denosumab group (Appendix 10, Table 14-6.11.6 4b).

Osteonecrosis Excluding the Jaw: One subject (Subject [redacted]) in the zoledronic acid/denosumab group had a nonserious adverse event of osteonecrosis of right knee (Listing 1-2.1).

Infection: The subject incidence of adverse events of infection was 42.5% (135 subjects) in the denosumab/denosumab group and 40.4% (135 subjects) in the zoledronic acid/denosumab group (Table 14-6.2.1). The most commonly reported adverse events of infection in the denosumab/denosumab group or the zoledronic acid/denosumab group, respectively, were nasopharyngitis (7.2%, 6.6%), urinary tract infection (6.0%, 6.9%), and influenza (4.1%, 6.0%). The overall subject incidence of serious adverse events of infection was 6.9% (22 subjects) in the denosumab/denosumab group and 3.6% (12 subjects) in the zoledronic acid/denosumab group (Table 14-6.2.2). The most common serious adverse events of infection in the denosumab/denosumab or the zoledronic acid/denosumab group, respectively, were sepsis (1.3%, 0.3%) and pneumonia (0.6%, 0.6%). The subject incidence of skin infection was 2.8% (9 subjects) in the denosumab/denosumab group and 2.4% (8 subjects) in the zoledronic acid/denosumab group (Table 14-6.10.2). The subject incidence of serious adverse events of skin infection was 0.9% (3 subjects) in the denosumab/denosumab group and 0.3% (1 subject) in the zoledronic acid/denosumab group (Table 14-6.10).

New Primary Malignancies: The subject incidence of new primary malignancies was 0.6% (2 subjects) in the denosumab/denosumab group and 0.3% (1 subject) in the zoledronic acid/denosumab group (Table 14-6.8). New primary malignancies included a grade 3 adverse event of renal cancer (Subject [redacted]) and a grade 1 adverse event of squamous cell carcinoma of skin (Subject [redacted]) in the denosumab/denosumab group, and a grade 3 adverse event of germ cell cancer (Subject [redacted]) in the zoledronic acid/denosumab group (Listing 1-2.1). None of the events were considered by the investigator as related to denosumab (Listing 1-2.1) or resulted in death (Table 14-6.3.7).

Hypersensitivity: The subject incidence of adverse events potentially associated with hypersensitivity was 16.0% (51 subjects) in the denosumab/denosumab group and 16.8% (56 subjects) in the zoledronic acid/denosumab group (Table 14-6.13.1 and Table 14-6.13.2). Two subjects had a serious adverse event potentially associated with hypersensitivity (Listing 1-2.9). Subject [redacted] (denosumab/denosumab group) had a serious adverse event of grade 3 bronchospasm on day 314 (20 days from previous dose) that resolved 5 days later; the investigator considered the event as not related to denosumab. Subject [redacted] (zoledronic acid/denosumab group) had a serious adverse event of grade 3 hypersensitivity (allergic reaction) on day 20 (20 days from previous dose). The subject developed a rash on the ear and lower leg and was hospitalized on the same day for skin eruption and exanthema (Appendix 6). The event decreased to a grade 1 hypersensitivity 8 days after the event started; the investigator considered the event as possibly related to denosumab and to carbamazepine and the subject discontinued the study.

Eczema: The subject incidence of adverse events categorized as eczema was 3.8% (12 subjects) in the denosumab/denosumab group and 3.9% (13 subjects) in the zoledronic acid/denosumab group (Table 14-6.9). None of the adverse events categorized as eczema were serious (Table 14-6.3.2) or resulted in discontinuation of denosumab (Table 14-6.2.4). Two subjects in the denosumab/denosumab group had an adverse event categorized as eczema that was considered by the investigator as possibly related to denosumab (Table 14-6.2.5).

Cardiovascular Disorders: The subject incidence of adverse events in the cardiac disorders system organ class was 9.4% (30 subjects) in the denosumab/denosumab group and 6.3% (21 subjects) in the zoledronic acid/denosumab group (Table 14-6.2.1). Serious adverse events in the cardiac disorders system organ class were reported for 9 subjects (2.8%) in the

denosumab/denosumab group and 6 subjects (1.8%) in the zoledronic acid/denosumab group (Table 14-6.2.2). The subject incidence of adverse events in the vascular disorders system organ class was 19.2% (61 subjects) in the denosumab/denosumab group and 13.5% (45 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 5 subjects (1.6%) in the denosumab/denosumab group and 5 subjects (1.5%) in the zoledronic acid/denosumab group (Table 14-6.2.2).

Laboratory Data

Antibody Data: Of the 630 subjects tested for antidenosumab antibodies, 3 subjects tested positive for binding (including Day 1), non-neutralizing antibodies to denosumab (Listing 1-2.17). Subsequent samples were negative for binding antibodies; therefore, the immune responses were transient in these 3 subjects. There was no evidence of an altered safety profile found in subjects who tested positive for antidenosumab binding antibodies when compared to the safety profile of subjects who tested negative. In addition to the 630 subjects tested for antidenosumab antibodies, 2 subjects tested negative subsequent to the database lock (Appendix 9). Further information is available in the Clinical Immunology Report in Appendix 8.

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

Expected decreases in albumin-adjusted calcium and phosphorus occurred (Table 14-7.1.2 and Table 14-7.14.2); decreases in albumin-adjusted serum calcium were mild (median percent change from baseline of approximately 2% or less) (Table 14-7.1.5). No grade 3 decreases in albumin-adjusted serum calcium occurred; one subject in each treatment group (0.3%) had a single occurrence of a grade 4 decrease in albumin-adjusted serum calcium (Table 14-7.20.1 and Table 14-7-21.3). The subject incidence of grade 3 serum phosphorus decreases was 7 subjects (2%) in the denosumab/denosumab group and 12 subjects (4%) in the zoledronic acid/denosumab group. No subject had a grade 4 serum phosphorus decrease in either group (Table 14-7.20.10). No other changes indicative of a treatment-related effect were observed in clinical laboratory parameters for either treatment group.

Additional laboratory results from the double-blind treatment phase were received after finalization of the DBE CSR for 5 sets of results from 5 subjects; these data are included in Appendix 9.

ECOG

ECOG performance status by visit is summarized in Table 14-8.4.1 and changes from baseline in ECOG performance status are summarized in Table 14-8.4.2. In the denosumab/denosumab group, 176 subjects (58.9%) and 112 subjects (37.5%) had an ECOG performance status of 0 and 1, respectively, at baseline (Table 14-8.4.1). In the zoledronic acid/denosumab group, 157 subjects (51.8%) and 130 subjects (42.9%) had an ECOG performance status of 0 and 1, respectively. For the majority of subjects, the best overall ECOG performance status was the same as their baseline status (denosumab/denosumab: 227 subjects [80.2%]; zoledronic acid/denosumab: 227 subjects [79.1%]). The worst overall ECOG performance status was generally the same as baseline (denosumab/denosumab: 167 subjects [59.0%]; zoledronic acid/denosumab: 168 subjects [58.5%]) or an increase of 1 (denosumab/denosumab: 76 subjects [26.9%]; zoledronic acid/denosumab: 87 subjects [30.3%]) (Table 14-8.4.2).

Efficacy Results:

Overall Survival

During the entire study, 52.3% (537 subjects) in the denosumab group and 51.5% (525 subjects) in the zoledronic acid group died. Overall survival was similar between treatment groups: the Kaplan Meier estimate of median survival was 34.4 months (95% CI: 31.5 to 39.3) for the denosumab/denosumab group and 34.2 months (95% CI: 31.0 to 37.6) for the zoledronic acid/denosumab group (Table 14-4.16 and Figure 14-2.1). Five subjects (3 subjects in the denosumab/denosumab group and 2 subjects in the zoledronic acid/denosumab group) who continued in the OLE beyond 2 years under the country-specific Protocol Amendment 4b died. The Kaplan Meier estimate of median survival did not change with the 5 additional deaths that occurred during OLE continuation under Protocol Amendment 4b (Appendix 10, Table 14-4.16 4b and Figure 14-2.1 4b).

Patient Reported Outcomes:

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

At baseline of the OLE phase, the mean (SD) "worst" pain score was 3.07 (2.69) in the denosumab/denosumab group and 3.23 (2.67) in the zoledronic acid/denosumab group (Table 14-2.2).

Over the 2 year treatment period, mean BPI pain scores and mean changes in BPI pain scores were generally similar between the denosumab/denosumab group and zoledronic acid/denosumab group for "worst" pain (Table 14-4.3 and Table 14-4.8), as well as for the other BPI scores of "pain you have right now" (Table 14-4.4 and Table 14-4.9), "pain severity" (Table 14-4.6 and Table 14-4.11), "pain interference with general activity" (Table 14-4.5 and Table 14-4.10), and "pain interference" (Table 14-4.7 and Table 14-4.12).

At each study visit, fewer than 25% of subjects in the denosumab/denosumab group or the zoledronic acid/denosumab group reported a clinically meaningful worsening (≥ 2 point increase) from baseline of "worst" pain (Table 14-4.13). During at least 1 visit during the OLE phase, 50% of subjects in the denosumab/denosumab group and 51% of subjects in the zoledronic acid/denosumab group reported pain improvement (≥ 2 point decrease of "worst" pain from baseline) (Table 1-1.4.3.1). At each study visit, fewer than 40% of subjects in the denosumab/denosumab group or the zoledronic acid/denosumab group had moderate/severe pain ("worst" pain score > 4) (Table 14-4.14).

Analgesic Score

At baseline of the OLE phase, mean (SD) analgesic use was 1.4 (2.2) in the denosumab/denosumab group and 1.6 (2.3) in the zoledronic acid/denosumab group (Table 14-4.1). The change from baseline analgesic score was small (mean change: 0 to 0.4) in the denosumab/denosumab group and the zoledronic acid/denosumab group at each study visit (Table 14-4.1 and Table 14-4.2); therefore, no adjustment for analgesic use was required in the analysis of BPI-SF pain scores. Very few (≤ 5%) subjects who had no/low analgesic use at baseline shifted to strong opoid during the OLE phase (Table 1-1.4.7).

Conclusions:

Denosumab was generally well tolerated during the OLE phase at a dose of 120 mg Q4W in subjects with advanced breast cancer and bone metastases; cumulative exposure to denosumab in this study was up to 5 years. No new safety signals were noted during the OLE phase. The incidence of hypocalcemia was 3.8% (12/318) in the denosumab/denosumab group and 2.7% (9/334) in the zoledronic acid/denosumab group. Positively adjudicated ONJ was 6.3% (20/318) in the denosumab/denosumab group and 5.4% (18/334) in the zoledronic acid/denosumab group during the OLE phase and 4.7% (48/1020) in the denosumab/denosumab group and 3.8% (38/1013) in the zoledronic acid/denosumab group during the entire study. The incidence of these adverse events was similar, regardless of whether subjects were previously exposed to denosumab or zoledronic acid during the blinded phase of the study. Overall survival for the

entire study was also similar between the denosumab/denosumab and zoledronic acid/denosumab treatment groups.