

Clinical Development & Medical Affairs

ZOL446

Clinical Trial Protocol CZOL446E2352

**A prospective, randomized, double-blind, stratified, multi-center, 2-arm trial of the continued efficacy and safety of Zometa<sup>®</sup> (every 4 weeks vs. every 12 weeks) in patients with documented bone metastases from breast cancer**

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## Amendment 4

### Amendment rationale

The purpose of this amendment is primarily to describe and provide the justification for a sample size re-estimation for study CZOL446E2352 [OPTIMIZE-2]. The re-estimated sample size for this study is reduced from a total of N=705 to a total of N=423 patients. As a result of the sample size re-estimation, it is now feasible to complete this study in a timely fashion.

This re-evaluation was prompted by the recently available, currently unpublished results of a similarly-designed, Novartis-sponsored local trial conducted in Italy (CZOL446EIT14 [ZOOM]). ZOOM was a Phase III prospective, randomized, single country, multicenter, open-label trial that assessed the efficacy and safety of Zometa every 12 weeks (Arm 1) vs. every 4 weeks (Arm 2) after pre-treatment for approximately one year with standard Zometa treatment (every 4 weeks) in breast cancer patients with bone lesions.

The primary analysis of ZOOM indicated that Zometa at a reduced dosing frequency (every 12 weeks) during the second year of Zometa therapy was not inferior to continuation of the standard dosing frequency (every 4 weeks). In the ITT population (N=423), the primary endpoint of skeletal morbidity rate (SMR; number of skeletal-related events [SREs]/patient/year) was met. Secondary endpoints, including the SRE rate, were consistent with the findings of the primary endpoint.

The ZOOM study provided important new data on the incidence of skeletal-related events (SREs) during the second year of Zometa therapy in this patient population. The pooled SRE rate was 15%, which was much lower than anticipated from the assumptions made in the protocol. This result in particular prompted a blinded, pooled analysis of the SRE rate in OPTIMIZE-2. At a cut-off date of December 10, 2010 (including only those patients who either completed or discontinued from the study) the pooled SRE rate in OPTIMIZE-2 was 21%. This was substantially lower than the assumptions for SRE rate made for the study design change at Amendment 2 of this protocol, which were 58% in the every 12 weeks arm, and 48% in the every 4 weeks arm. When the previously assumed SRE rate is adjusted to reflect the observed blinded, pooled SRE rate, there is a substantial impact on the sample size.

The sample size re-estimation is described in further detail in Section 6.2, "Sample size and power considerations." Except for the change in the assumed SRE rate, there are no other changes to the key statistical parameters; i.e., there is no change in the study power of 80%, the non-inferiority margin of 10%, or the one-sided alpha of 0.05. The new sample size (N=423) is substantially less than the prior sample size (N=705) that was estimated in Amendment 2. Based upon this information a decision was made to amend this protocol to reduce the sample size to approximately 423 patients.

The sample size re-estimation enables the timely completion of OPTIMIZE-2. In a meeting between Novartis and the FDA that was held in October 2011, FDA requested additional exploratory analyses of targeted safety events. These safety analyses are described in Section 6.1.6 "Safety evaluation" of this amended protocol.

Based on the enrollment as of January 18, 2012 (403 patients), and in consideration of the rate of enrollment over the past 12 months, it is anticipated that the number of patients enrolled in

the study at the time when this amendment is fully implemented will be very close to the amended sample size. At the time Amendment 4 is implemented (i.e., as soon as it is approved by the IRB), each site must stop enrollment of new patients into the study. However, all patients who are already enrolled when this amendment is fully implemented are to continue on study as per protocol until they have either completed the trial or discontinued from the study prematurely.

This protocol amendment also provides important new safety information to investigators on atypical femoral fractures. Such fractures have been reported in patients receiving Zometa. The collection of source documents related to potential cases, and independent adjudication of these potential cases is described. In parallel, the informed consent has been changed to inform patients of this risk.

In addition, denosumab (marketed as Xgeva<sup>®</sup> and Prolia<sup>®</sup>) has been added to the list of prohibited concomitant medications. This biologic agent has an anti-resorptive effect on bone that would interfere with the assessment of the effect of the study drug Zometa. Denosumab (Xgeva<sup>®</sup> and Prolia<sup>®</sup>) was approved by FDA after implementation of Amendment 3 to this protocol. It is a monoclonal antibody that inhibits the receptor activator of the nuclear factor-kappa-B ligand (RANKL).

### Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions. In addition to the changes to the protocol listed under Amendment 4 rationale, a high level list of changes is as follows:

- The list of abbreviations has been amended to include the abbreviations for atypical femoral fracture (AFF), Full Analysis Set (FAS), and Per Protocol Set (PPS). Punctuation errors were also corrected for the End of Study (EOS) abbreviation.
- In Section 3.1, the overall study design and associated figure have been amended to update the total number of patients to be randomized for this study. In addition, the disposition of patients when the amendment is implemented is defined.
- In Section 3.4.4, the list of prohibited concomitant medications has been amended to include denosumab (marketed as Xgeva<sup>®</sup> and Prolia<sup>®</sup>), or any commercial bisphosphonates, including Zometa<sup>®</sup> and Reclast<sup>®</sup> (zoledronic acid) or Aredia<sup>®</sup> (pamidronate), after randomization into the study.
- In Section 3.5.3, a new section has been added to describe the newly recognized safety risk of Atypical Subtrochanteric Femoral Fracture (AFF), collection of source documents, and independent adjudication of potential cases. The numbering for all subsections from Section 3.5.3.3 to Section 3.5.3.9 has been changed to account for this new section.
- In Section 6.1.1, Population definitions have been further defined. Major protocol deviation criteria have been added to clarify the Per Protocol Set (PPS).
- In Section 6.1.5.1, the following changes to the analysis plan are described:
  - A sensitivity analysis has been added to evaluate the impact of missing values on the non-inferiority analysis, using the “tipping-point” analysis method.

- The strata for pre-study bisphosphonate therapy have been clarified to include: zoledronic acid vs. pamidronate vs. both zoledronic acid and pamidronate in the stratified Cochran-Mantel-Haenszel analysis for the proportion of patients with at least one SRE.
- The last sentence of Section 6.1.5.1 “The sub-group analysis for SRE based on whether or not IV bisphosphonates were used prior to entering the study” has been deleted because all patients were required to have IV bisphosphonate treatment prior to entering the study.
- In Section 6.1.6, safety evaluation criteria have been included to account for all changes as a result of amendment 4.
  - Subgroup analyses of safety based on the type and duration of prior bisphosphonate exposure before entering the study.
  - Adverse events of special interest as requested by FDA, including: renal function deterioration, osteonecrosis of the jaw (ONJ), atrial fibrillation, and cardiac ischemic events. The adjudication results of potential atypical femoral fractures (Section 3.5.3.3) will be described in an exploratory analysis.
- In Section 6.2, sample size and power considerations have been updated to provide further detail to the description of the sample size re-estimation.
- Administrative correction of the description of the Brief Pain Inventory (BPI) in Section 7.2.2 of the protocol. The timing of pain recall is changed from “the last 7 days” to “the past 24 hours,” to be consistent with other study documents, including the CRF.
- The ZOL446E2352 informed consent has been updated to include information on Atypical Femoral Fractures (AFF), a newly recognized risk for patients receiving Zometa.

### **IRB/IEC/REB Approval**

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. All on-study patients must be re-consented with the revised informed consent form (ICF), which is provided with this protocol amendment.

### **Summary of previous amendments**

Please refer to Section 1 Introduction.

## List of abbreviations

AC	Adjudication Committee
AE	adverse event
AFF	atypical femoral fracture
ALT	alanine aminotransferase/glutamic pyruvic transaminase/GPT
ASBMR	American Society for Bone and Mineral Research
ASCO	American Society for Clinical Oncology
AST	aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	area under the curve
BC	Breast Cancer
b.i.d.	bis in diem/twice a day
BPI	brief pain inventory
C <sub>max</sub>	maximum concentration
CRF	Case Report/Record Form
CS&E	Clinical Safety and Epidemiology
CrCl	creatinine clearance
CR	Clinical Research
CRO	Contract Research Organization
CT	computed tomography
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group performance status
EOS	End of Study
FAS	Full Analysis Set
HCM	hypercalcemia of malignancy
IIT	intent to treat
i.v.	intravenous(ly)
IMS	Integrated Medical Safety
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
MM	multiple myeloma
MRI	magnetic resonance imaging
NOAEL	No Adverse Event Level
N-Tx	cross linked N-terminal telopeptide of type I collagen
o.d.	omnia die/once a day
ONJ	osteonecrosis of the jaw
p.o.	per os/by mouth/orally
PPS	Per Protocol Set
PTHrP	parathyroid hormone-related peptide
REB	Research Ethics Board
SAE	serious adverse event
SMR	skeletal morbidity rate
SOP	Standard Operating Procedure



SRE	skeletal related event
SUSARs	Suspected Unexpected Serious Adverse Reactions
TGF- $\beta$	transforming growth factor-beta
TIH	tumor induced hypercalcemia
WHO	World Health Organization

## 1 Introduction

Bone metastases are a common cause of morbidity in patients with advanced solid tumors of many types, including breast, prostate and lung cancer (Roodman 2004). The osteolytic bone lesions of multiple myeloma lead to similar morbidity (Roodman 2004). Of the more than 200,000 women diagnosed with breast cancer in the U.S. each year, about one third develop advanced disease. Sixty-five to 75% of these women develop bone metastases (Coleman 2001). Despite improvements in the primary treatment of these cancers, bone complications (pain, pathologic fracture, spinal cord compression, the need for palliative radiation or surgery to bone, and hypercalcemia of malignancy) continue to cause morbidity and adversely affect the quality of life for these patients. Currently available therapies are usually not able to cure patients with bone metastases. In addition to appropriate antineoplastic therapy, supportive treatments are given in order to reduce pain and improve the quality of life.

Bone metastases may present radiographically as primarily lytic, mixed, or blastic (sclerotic) lesions. There is a component of osteolysis even in bone metastases that appear as primarily blastic on imaging. The clinical complications of malignant osteolytic bone lesions primarily result from excessive bone resorption by osteoclasts. Growth factors released during bone resorption, such as transforming growth factor-beta (TGF- $\beta$ ), may enhance localized tumor growth in the bone microenvironment (Hauschka 1986, Pfeilschifter 1987, Yoneda 1995). In turn, secretion of factors such as parathyroid hormone-related peptide (PTHrP) by tumor cells stimulates osteoclast activity (Guise 1996, Guise 1998, Orr 2000). TGF- $\beta$  may directly stimulate the secretion of PTHrP by breast cancer cells (Kakonen et al 2002). In osteolytic lesions, the malignant activation of osteoclasts shifts the normal balance between bone resorption and formation in favor of bone resorption, ultimately resulting in destruction of bone (Roodman 2004).

Bisphosphonates are analogues of pyrophosphate that avidly bind to the mineralized portion of the bone matrix. Bisphosphonates are taken up by osteoclasts, and inhibit bone resorption by disrupting the function and survival of osteoclasts (Hughes 1995, Rogers 1996). The mechanism of action of nitrogen-containing bisphosphonates involves inhibition of the mevalonate pathway (Coxon et al 2000), specifically farnesyl diphosphate (FPP) synthase, and disruption of the prenylation of key intracellular signaling proteins (Rogers 2004). Preclinical data indicate that nitrogen-containing bisphosphonates also have direct effects on tumor cells in vitro, decreasing the proliferation of human breast cancer and multiple myeloma cell lines and inducing apoptosis of tumor cells (Shipman 1997, Aparicio 1998, Fromigue 1999, Fromigue 2000, Senaratne 2000, Tassone 2000).

Zometa<sup>®</sup> (zoledronic acid, 1-hydroxy-2-(1H-imidazol-1-yl)-phosphono-ethyl phosphonic acid) is a highly potent third generation bisphosphonate compound. In animal models, Zometa shows high affinity to the mineralized bone matrix and inhibits osteoclast-mediated bone resorption more effectively than earlier generation bisphosphonates, at doses that do not impair bone mineralization. This results in a favorable therapeutic index, i.e., ratio of antiresorptive activity to risk of osteomalacia (Green 1994, Green 1997).

Zometa 4 mg (infused intravenously over no less than 15 minutes) every 3 to 4 weeks is approved by the FDA in the United States, and corresponding regulatory agencies in Canada,

Europe, Australia, Asia, and Latin-America for the treatment of patients with documented bone metastases from solid tumors (breast, prostate, non-small cell lung cancer, and others), and in patients with multiple myeloma, in conjunction with standard antineoplastic therapy. In addition, Zometa 4mg as a single infusion over no less than 15 minutes is approved by the FDA in the U.S., and regulatory agencies in Canada, Europe, Australia, Japan, and Latin-America for the treatment of tumor-induced hypercalcemia (TIH).

### **Zometa: Clinical efficacy data**

Zometa has demonstrated efficacy and safety in phase II and phase III clinical trials. The phase II study was a randomized, double-blind study of 280 patients with malignant bone lesions associated with multiple myeloma or breast cancer (Berenson et al 2001). Patients were randomized to a 5-minute infusion of 0.4, 2.0, or 4.0 mg of Zometa, or a 2-hour infusion of 90 mg of pamidronate with the proportion of patients receiving radiation to bone as the primary efficacy variable. The nature and frequency of adverse events with Zometa and pamidronate were similar, and a 5-minute 4.0-mg Zometa infusion was equivalent to a 2-hour 90-mg pamidronate infusion as treatment for osteolytic metastases (Berenson et al 2001).

The phase III clinical program for Zometa consists of three prospective, randomized, controlled studies. [Study 0010] was a randomized, double-blind, double-dummy, 12-month study of 1,122 patients with at least one osteolytic bone lesion secondary to Durie-Salmon Stage III multiple myeloma or at least one bone metastasis secondary to Stage IV breast carcinoma (Rosen et al 2001). Patients were randomized to 15-minute 4-mg infusions of Zometa, or to 120-minute 90-mg infusions of pamidronate, while receiving standard antineoplastic therapy. Originally, the patients were randomized to receive either Zometa 4 mg, Zometa 8 mg or pamidronate. However, following a Renal Safety Advisory Board, the protocol was amended to increase renal safety. The infusion time for Zometa was increased from 5 to 15 minutes, the infusate volume was increased from 50 to 100 mL, all patients on 8 mg Zometa were switched to 4 mg (subsequently termed the 8/4 mg group) and creatinine monitoring was instituted.

Results for the 8-mg dose are not described because it did not offer further therapeutic benefit. The primary efficacy variable was the proportion of patients with at least one skeletal-related event (SRE) during the study period. SRE was defined as pathologic fracture, surgery to bone, radiation to bone for pain, or spinal cord compression. The secondary variables were time to first SRE, skeletal morbidity rate, multiple-event analysis, and hypercalcemia of malignancy (Rosen et al 2003a). Analysis of the primary endpoint at the end of the core phase of the study at 13 months showed that the results met the non-inferiority criteria based on a pre-defined non-inferiority margin, indicating that Zometa is at least as effective as pamidronate. The study also had an additional 12-month extension phase. Data from the entire study duration of 25 months demonstrated non-inferiority of Zometa compared with pamidronate. Tolerability was similar for the two drugs, with bone pain, nausea, and fatigue the most common adverse events. There was no significant difference between the renal safety profiles for Zometa and pamidronate (Rosen et al 2003a) after the renal safety amendments for Zometa were implemented.

Two additional phase III studies demonstrated the safety and efficacy of Zometa in patients with bone metastases associated with prostate cancer, and non-small cell lung cancer or other

solid tumors. Both of these trials contained an 8 mg arm which was reduced to 4 mg to increase renal safety. [Study 0039] (Saad et al 2002) was a phase III, double-blind, placebo-controlled, multicenter, 15-month parallel study that enrolled 422 patients with prostate cancer receiving antineoplastic therapy, and who had metastatic bone lesions and three consecutive rises in serum PSA level. Patients were randomized to 15-minute 4-mg infusions of Zometa or to placebo. In this study, Zometa reduced the proportion of patients with SREs during the study by 25%, when compared with placebo. [Study 0011] (Rosen et al 2003b) was a phase III double-blind, placebo-controlled, multicenter, 9-month parallel study in 507 patients with malignancies other than breast, prostate, or multiple myeloma, and documented bone metastases (257 patients received 15-minute 4-mg infusions of Zometa, and 250 patients received placebo every three weeks). This study demonstrated that Zometa mediated a significant delay to the first SRE and a significant reduction in the risk of developing SRE, compared to placebo. Both studies confirmed the safety profile of Zometa.

A phase III randomized, placebo-controlled trial of Zometa in Japanese women with bone metastases from breast cancer showed a significant reduction in skeletal complications (Kohno et al 2005). In this study, 228 women with bone metastases from breast cancer were randomly assigned to Zometa 4mg by 15-minute infusion every 4 weeks or placebo for one year. The skeletal related event (SRE) rate ratio at one year, excluding hypercalcemia of malignancy or prior fracture, was 0.61 ( $p = 0.027$ ). This indicated that Zometa reduced the SRE rate by 39% compared with placebo. The percentage of patients with at least one SRE was 49.6% for placebo, and 29.8% for Zometa-treated women. No significant decrease in renal function was observed in the Zometa-treated group compared with placebo. Data from this study provides additional evidence for efficacy and safety of Zometa for the treatment of bone metastases in women with breast cancer.

### **Zometa: Renal safety**

In animal safety studies, bisphosphonates, when given as a single high dose, or when given at a lower dose but with greater frequency (i.e., daily, every other or third day), have been shown to produce histological evidence of renal tubular injury. Renal changes may be evidenced by increased serum BUN and creatinine, decreased serum calcium, increased urine specific gravity, hematuria, proteinuria, and changes in the albumin to globulin ratio (Fleisch 1998). Safety data for Zometa in the rat and dog reflect this, showing lower renal no-adverse-event levels (highest observed dosage which did not produce renal injury, or NOAEL) with increasing dosing frequency, as summarized in Table 1-1.

**Table 1-1 Renal NOAEL's (mg/m<sup>2</sup>) of Zometa in rat and dog**

Regimen	Rat <sup>a</sup>	Dog
Acute (single dose)	9.4	40 <sup>b</sup>
Chronic		
Daily dosing x 90	0.18	0.20 <sup>b</sup>
Intermittent dosing	3.5 <sup>c</sup>	0.1 <sup>b,d</sup>
Every three weeks	---	0.1 - 0.25 <sup>e</sup>

a s.c. administration (bioequivalent to i.v. bolus)

b i.v. bolus

c q 3 days x 6

d q 2 or 3 days x 141

e 15-minute infusion, q x 3 wks for 6 months

There is a >4-fold safety margin for a single administration of the 4 mg (= 2.3 mg/m<sup>2</sup>) clinical dose of Zometa as compared to the rat and dog (Table 1-1). The clinical regimen of Zometa 4 mg every three to four weeks is supported by a chronic safety study in dogs where Zometa was administered every three weeks as a 15-minute infusion for 6 months. The no-effect level was 0.1 mg/kg (2 mg/m<sup>2</sup>), with only minimal findings based on histopathological examination at 0.25 mg/kg (5 mg/m<sup>2</sup>). Assuming that the dog renal NOAEL is in the range 0.1-0.25 mg/kg, this represents an approximately one- to two-fold safety margin for chronic dosing with 4 mg (= 2.3 mg/m<sup>2</sup>) Zometa in the clinic. Based on systemic exposure to drug infused over 15 minutes, the comparison between 0.1 mg/kg and 0.25 mg/kg dose in the dog and clinical 4 mg dose in the human was as follows: for C<sub>max</sub>: 398, 995, and 495 ng/mL, respectively; for AUC: 608, 1520, and 420 (ng x h)/mL, respectively, consistent with the one to two-fold margin established from the comparison by surface areas.

The “renal amendment” changes in the three pivotal safety and efficacy studies [Study 0010] (Rosen et al 2001), [Study 0011] (Rosen et al 2002), and [Study 0039] (Saad et al 2002) implemented a dose reduction from 8 mg to 4 mg, and increased the infusion time of Zometa from 5 minutes to 15 minutes. The amended clinical studies identified that Zometa 4 mg, given as a 15-minute infusion every 3 or 4 weeks, is an acceptable regimen. Table 1-2 summarizes the risk of experiencing a renal adverse event with different doses and infusion times.

Table 1-2 identifies risk reduction with the implementation of increased infusion time, and lowering the dose of Zometa from 8 mg to 4 mg. There is a small, residual renal risk compared to placebo or pamidronate for the clinical dose of 4 mg infused over 15 minutes. The degree of risk is of similar magnitude as for pamidronate and is managed by the monitoring of serum creatinine prior to each dose as specified in the drug label.

**Table 1-2 Hazards ratios and significance of clinically relevant serum creatinine increases for chronically administered drug (q 3 - 4 weeks)**

Study	Zometa 4 mg		Zometa 8 mg	
	4 mg/5 min	4 mg/15 min	8 mg/5 min	8 mg/15 min
Multiple myeloma and breast cancer [Study 0010]. (Rosen, et al 2001)	2.34 P=0.003*	1.01 P = NS*	3.58 P=0.001*	2.19 P=0.001*
Prostate cancer [Study 0039]. (Saad, et al 2002)	2.03 P=0.048**	1.11 P=NS**	4.02 P=0.001**	1.66 P=NS**
Lung cancer and other solid tumors [Study 0011]. (Rosen, et al 2002)	3.86 P=0.05**	1.56 P=NS**	2.88 P=NS**	1.91 P=0.08**

\* versus pamidronate; \*\* versus placebo; NS = not significant (P>0.1)

Source: [Rosen et al 2001](#), [Saad et al 2002](#), [Rosen et al 2002](#).

In terms of observed renal adverse events, Zometa 4 mg infused over 15 minutes showed a similar frequency of occurrence as Aredia<sup>®</sup> (pamidronate) 90 mg infused over 2 hours, with a total of 24/272 (8.8 %) of patients on Zometa and 22/268 (8.2 %) of patients on pamidronate experiencing clinically relevant increases in serum creatinine during chronic therapy ([Rosen et al 2001](#)). In patients with prostate cancer, renal function deterioration occurred in 15.2% of patients in the Zometa 4 mg/15 minute group, and in 11.5% of patients in the placebo group, with no significant difference in the time to renal function deterioration assessed by Kaplan-Meier analysis between the two groups ([Saad et al 2002](#)). In patients with lung cancer and other solid tumors, the incidence of clinically relevant deterioration of renal function occurred in 11% of patients receiving Zometa 4 mg/15 minutes and 7% of patients receiving placebo ([Rosen et al 2003b](#)).

In all three studies, patients with a serum creatinine > 3.0 mg/dL at baseline were excluded. A clinically relevant deterioration of renal function was defined as a change from baseline of ≥ 0.5 mg/dL for patients with normal (< 1.4 mg/dL) baseline serum creatinine, of ≥ 1.0 mg/dL for patients with abnormal (≥ 1.4 mg/dL) baseline serum creatinine, or at least a two-fold increase over baseline irrespective of baseline value. [Table 1-3](#) summarizes the increase from baseline serum creatinine. [Table 1-3](#) shows data on the incidence of clinically relevant deterioration of renal function in patients with normal and abnormal baseline serum creatinine.

**Table 1-3 Proportion of patients with normal<sup>1</sup> and abnormal<sup>2</sup> baseline function experiencing renal deterioration<sup>3</sup> on study**

Study	Zometa 4 mg		Zometa 8 mg	
	4 mg/5 min	4 mg/15 min	8 mg/5 min	8 mg/15 min
Multiple myeloma and breast cancer [Study 0010].	30/252 (12%) <sup>1</sup> 6/20 (30%) <sup>2</sup>	23/246 (9%) <sup>1</sup> 1/26 (4%) <sup>2</sup>	45/223 (20%) <sup>1</sup> 4/17 (24%) <sup>2</sup>	43/242 (18%) <sup>1</sup> 6/21 (29%) <sup>2</sup>
Prostate cancer [Study 0039].	14/84 (17%) <sup>1</sup> 8/27 (30%) <sup>2</sup>	10/82 (12%) <sup>1</sup> 4/10 (40%) <sup>2</sup>	29/93 (31%) <sup>1</sup> 11/27 (41%) <sup>2</sup>	14/68 (21%) <sup>1</sup> 4/19 (21%) <sup>2</sup>
Lung cancer and other solid tumors [Study 0011].	7/55 (13%) <sup>1</sup> 3/6 (50%) <sup>2</sup>	17/154 (11%) <sup>1</sup> 1/11 (9%) <sup>2</sup>	5/47 (11%) <sup>1</sup> 2/8 (25%) <sup>2</sup>	19/160 (12%) <sup>1</sup> 2/21 (10%) <sup>2</sup>

<sup>1</sup> normal renal function: baseline serum creatinine <1.4 mg/dL

<sup>2</sup> abnormal renal function: baseline serum creatinine ≥1.4 mg/dL; however, patients with baseline serum creatinine >3 mg/dL were excluded from studies

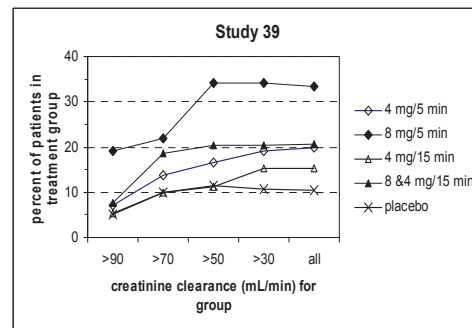
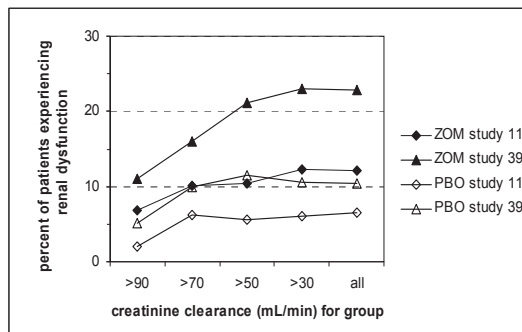
<sup>3</sup> change from baseline ≥0.5 mg/dL or > two-fold

The data in Table 1-3 suggest that patients with abnormal renal function at baseline, i.e. serum creatinine > 1.4, may be at increased risk of further renal dysfunction. Figure 1-1 breaks out the proportion of patients experiencing renal dysfunction (using the same criteria as specified in Table 1-3) by creatinine clearance at baseline. The left panel in Figure 1-1 shows the mean percentage of patients experiencing renal deterioration in studies 11 and 39, comparing all patients on Zometa versus all patients on placebo, irrespective of the study amendments adjusting dose and infusion time. The right panel in Figure 1-1 breaks [Study 0039] data into pre- and post switch from 5 min to 15 min infusion.

**Figure 1-1 Mean percentage of patients experiencing renal dysfunction (change from baseline >0.5 mg/dL or >two-fold increase) by baseline renal function, in comparison to placebo, in clinical trials with Zometa**

All patients included

Pre- and post-amendment changing infusion time from 5 minutes to 15 minutes



The pooled results from the two placebo-controlled studies [Study 0011] and [Study 0039] (left panel of Figure 1-1) indicate a trend towards a slightly higher percentage of renal dysfunction when on Zometa compared to placebo for patients with normal renal function at baseline. With greater renal impairment at baseline, there is a trend towards more renal



dysfunction during study, for both the placebo and active treatment groups. This trend is consistent across the pre- and post-amendment subgroups (right panel of [Figure 1-1](#)). [Figure 1-1](#) also shows that patients with prostate cancer, particularly when receiving Zometa 8 mg infused over 5 minutes ([\[Study 0039\]](#); see right panel of [Figure 1-1](#)), had a much greater frequency of renal impairment compared to patients with lung cancer or other solid tumors [\[Study 0011\]](#) when presenting with impaired baseline renal function.

For additional information on Zometa, please see the [\[Investigator's Brochure\]](#).

## Rationale

The duration of treatment in Zometa phase III clinical trials ranged from 21 to 25 months. The core phase of the studies had a duration of approximately one year. The patient dropout rates for [\[Study 0011\]](#) and [\[Study 0010\]](#) were relatively high, particularly between the respective core and extension phases. This was most likely due to the need for patients to re-consent prior to entering the extension phase. Thus, the data for core and extension phases in these trials does not conclusively demonstrate efficacy and safety of Zometa beyond one year of treatment.

In clinical practice, bisphosphonates are frequently used for an indefinite period of time. The American Society for Clinical Oncology (ASCO) guidelines for breast cancer and multiple myeloma recommend treatment until evidence of a substantial decline in a patient's general status ([Berenson 2002](#); [Hilner 2003](#)). These recommendations are based on the fact that skeletal complications can occur repeatedly over the disease course, and the assumption of continued risk for skeletal complications in the presence of bone metastases. However, definitive clinical data is lacking to demonstrate the continued efficacy and safety of Zometa treatment beyond one year. This issue is particularly relevant to patients with breast cancer, in whom survival with bone metastases typically exceeds one year.

Another consideration is that bisphosphonates accumulate in the skeleton when repeated doses are administered ([Cremers 2005](#)) [\[DM17/1993\]](#). They bind preferentially to active bone resorption sites, and are taken up by the osteoclast during bone resorption ([Sato 1991](#); [Azuma 1995](#)). Because of drug accumulation in bone, the pharmacological effect of bisphosphonates may persist for a longer period of time after chronic treatment is discontinued than after a single dose is administered. Therefore, it is possible that Zometa therapy for bone metastases, after one year of treatment on a dosing regimen of proven efficacy (every 3-4 weeks), may have continued efficacy with a regimen of reduced frequency of administration (every 12 weeks), or even complete discontinuation of drug. Neither of these strategies have been investigated clinically to date. The present study is designed to address these possibilities in women with documented bone metastases from breast cancer.

Markers of bone resorption are the most direct way to assess the pharmacologic effect of bisphosphonates ([Cremers 2005](#)). There is emerging evidence that markers of bone turnover are correlated with the extent of skeletal metastatic disease and tumor burden ([Demers 2000](#), [Lipton 2001](#)) and may have prognostic utility ([Berruti 2000](#), [Brown 2003](#)). Bone markers may be more elevated in patients with a blastic disease presentation than in patients with osteolytic lesions. There is also emerging data based on retrospective analysis of clinical studies that normalizing the bone marker concentration with antiresorptive therapy by bisphosphonates leads to a lower probability of skeletal related adverse events and may reduce pathological



fractures ([Brown et al 2005](#)). However, to date there has been no confirmation by prospective studies, of what constitutes appropriate normal ranges, how useful these biomarkers are to identify candidate populations or disease type (i.e., lytic, blastic or mixed metastases) for bisphosphonate therapy, and how to diagnose disease status and progression. In the absence of such studies, the current aim is to dose the bisphosphonate to achieve the maximum degree and duration of suppression of bone markers without unacceptable side effects.

In response to a request by the FDA, Novartis is investigating potential relationships between dose, pharmacokinetics, rate of bone turnover, and efficacy, using modeling techniques on all available pharmacokinetic (PK), pharmacodynamic (PD) and clinical outcome data [[Modeling and simulation plan in response to FDA request \(11-11-2004\)](#)]. The aim of such modeling is to predict the clinical outcome of various dose regimens of Zometa in cancer patients with bone metastases, especially after one year of the registered 4 mg every 3-4 week regimen. This investigation is a continuing work in progress, and all future PK and PD data will be incorporated into the pharmacokinetic/pharmacodynamic/clinical outcome model. At present, however, no long-term (> 1 month between dose administrations) pharmacokinetic and pharmacodynamic data of Zometa in cancer patients are available. Decreasing the dose frequency to every 12 weeks instead of every 4 weeks allows investigation of zoledronic acid PK and PD parameters during a longer period, which will eventually enable adequate long-term predictions of PK, PD and clinical outcome with different dose regimens.

Recently, case reports of osteonecrosis of the jaw (ONJ) associated with the use of oral and intravenous bisphosphonates have been published ([Marx 2003](#); [Ruggiero 2004](#)). These reports include cases of ONJ in cancer patients treated with Zometa. However, there has not been a consensus as to the precise definition of ONJ. The pathophysiology is poorly understood, and likely involves multiple factors. A causal relationship between bisphosphonates and ONJ in cancer patients has not been established. To date, there are no data regarding the incidence or natural history of ONJ in cancer patients from controlled clinical trials. The present study is an opportunity to investigate in a prospective, controlled trial, the possible occurrence of ONJ in patients with bone metastases from breast cancer who are on chronic Zometa therapy. The present trial is designed to monitor patients carefully for the possible occurrence of ONJ, and report such cases in an expedited fashion (within 15 days) to the FDA. For further information, see [Post-text supplement 1](#). (“Expert Panel Recommendations for the Prevention, Diagnosis, and Treatment of Osteonecrosis of the Jaws: June 2004”)

In summary, the present study will investigate the efficacy, safety, pharmacokinetics and pharmacodynamics of continued treatment with Zometa beyond one year in patients with documented bone metastases from breast cancer. Efficacy, safety, and pharmacodynamics will be assessed and compared among patients receiving Zometa every 4 weeks, or Zometa on a reduced dosing schedule (every 12 weeks). Pharmacokinetics will be assessed through sparse sampling in a subset of patients. The duration of treatment will be 48 weeks. The possible utility of a bone resorption marker (urine N-Telopeptide) to identify patients at higher risk of developing skeletal complications during the second year of Zometa therapy will be investigated. Safety monitoring will emphasize the detection and expedited reporting of possible cases of ONJ in this trial.

### **Amendment 1 rationale**

The previous design of this study required that patients should be pretreated with Zometa 4 mg every 3-4 weeks for 9 to 12 doses during the previous 10 to 12 months. Pre-screening data, however, showed that a high proportion of patients were ineligible for inclusion on the basis of too many or too few doses of Zometa, or a prior history of Aredia (pamidronate) therapy, during the defined pre-treatment period. Therefore, it was decided to widen the window for inclusion to allow patients to enter the trial if they received 9 to 20 doses of Zometa over the prior 10 to 15 months. In addition, the protocol has been amended to include patients pretreated with up to 3 doses of Aredia (pamidronate) during the prior 10 to 15 months, provided that they are on Zometa at the time of study entry.

A lateral skull x-ray was added to the Bone Survey in order to provide a more complete radiographic assessment of skeletal-related events, the key component to the primary and several of the secondary efficacy endpoints. Oral examinations were added at 6 months and end of study (EOS) in order to ensure that patients are appropriately screened for osteonecrosis of the jaw (ONJ). The clinical features for suspected ONJ were updated and clarified.

An interim analysis plan was added for the following purposes: 1) to discover early evidence of efficacy, and 2) to detect evidence of futility, that is, evidence of an outcome not consistent with the specific alternative hypothesis specified when the trial was planned.

All other changes to the protocol were administrative.

### **Amendment 2 rationale**

The changes to the protocol are being made to allow a sufficient number of patients to enroll in the study. This study's enrollment is extremely behind schedule. Screening logs from sites indicated there are two major issues: (1) Protocol currently excludes pre-treatment with Zometa > 15 months duration before study entry, and (2) the presence of a placebo arm.

The changes made with Amendment 1 widened the window of required prior Zometa dosing. There was a sample size of 1652 patients of which only 55 were randomized after 18 months. This Amendment will keep the lower limit requirement of 9 doses of IV bisphosphonate (either Zometa or Aredia or a combination of both) during the first 10 to 15 months of therapy, but remove the upper limit of duration of therapy (currently 15 months). Patients must be on Zometa at the time of study entry. The placebo arm will be removed, thus leaving the two

Zometa treatment arms: either treatment every 4 weeks or treatment every 12 weeks. Patients enrolled in the study prior to amendment 2 and randomized to the placebo arm will be switched to the every 4 week treatment arm through the IVRS system. This will be done without unblinding of the investigator, study staff, patient, or Novartis internally. With removal of the placebo arm, the rescue therapy will no longer be needed and therefore will also be removed. The patients who were enrolled into the placebo arm will be analyzed separately and will not be included in the efficacy analysis. Summary statistics will be provided for these patients.

In the new study design, the primary objective of the study will be to determine whether the efficacy of treatment with Zometa every 12 weeks is non-inferior to treatment with Zometa every 4 weeks, based on the SRE rate (the proportion of patients with at least one SRE during the study), using a one-sided test, with a significance level of 0.025.

The primary efficacy variable will be changed from “time-to-first SRE during the study period” to “the proportion of patients with at least one SRE during the study period.” The primary endpoint is changed because with the amended study design, the clinical relevance of time-to-first SRE is diminished for patients already on very long term therapy (> 15 months), but the proportion of patients with  $\geq$  one SRE during the study period remains clinically meaningful for all patients.

If the non-inferiority test is met, then the difference between the treatment with Zometa every 12-weeks and Zometa every 4-weeks will be tested using a two-sided test with a significance level of 0.05. The clinical margin for non-inferiority is 10%. If one Zometa treatment group is significantly better than the other, then that group will be declared superior.

The intent to treat (ITT) patient population is the primary analysis population. The per protocol population is the secondary analysis population. The non-inferiority should be claimed in both the ITT and the per protocol populations and the treatment difference should also be evaluated in both patient populations.

In order to balance the two treatment arms with this amended study design, the stratification procedure will be changed such that stratification will be based upon: (1) the duration of prior bisphosphonate therapy (10-15 months vs >15 months) and (2) urinary N-Tx/Cr value (> 100 nmol bone collagen equivalent (BCE)/mmol creatinine or  $\leq$  100 nmol BCE/mmol creatinine). Stratification will no longer be based on history of prior SRE.

No formal interim analysis is planned for the study. However, the DMC will monitor safety data every 6 months.

### **Amendment 3 rationale**

Although study enrollment has been significantly improved since Amendment 2, it is still extremely behind the original projection. In order to further accelerate study enrollment, Amendment 3 includes the following changes: (1) to include new study sites from worldwide; (2) to allow patients whose last pre-study dose of bisphosphonate is either Zometa<sup>®</sup> OR Aredia<sup>®</sup> (pamidronate) to participate in the study; (3) to redefine the baseline serum creatinine as the result obtained from the patient screening visit; and (4) to reduce the frequency of bone survey tests from once every 3 months to once every 6 months during the study. These

changes are expected to provide more benefits /convenience to patients, increase feasibility in trial operation, and continually retain a high quality of the study.

Slow enrollment is largely related to a progressive decline in the number of study sites, which are presently restricted to the U.S. Study sites typically close because of absence of activity. Although the causes for slow enrollment in the U.S. are probably multifactorial, it is likely that there are insufficient numbers of patients within the U.S. Clearly, the addition of new study sites, not only in the U.S., but also importantly in regions outside of the U.S., should help study enrollment.

Both Zometa and Aredia (pamidronate) are approved for the treatment of osteolytic bone metastases in women with breast cancer, pamidronate is the more commonly used first-line bisphosphonate for the study indication (treatment of women with documented bone metastases from breast cancer) in many countries worldwide. Although Amendment 2 allowed pamidronate as a pre-study i.v. bisphosphonate, interchangeably with Zometa, the requirement that the patient must receive Zometa for the last pre-study bisphosphonate dose is one of the major obstacles to study enrollment. Amendment 3 eases this requirement, allowing the last dose be either Zometa OR pamidronate before study randomization. Therefore, patients who have never been treated with Zometa will now have the opportunity to become eligible for this study. This change should not compromise the scientific merit of the study, data quality, or patient safety, because both drugs are approved for the osteolytic bone metastasis therapy in women with breast cancer, and are comparable with regard to skeletal-related events (SREs) and safety endpoints in treating breast cancer patients with bone metastases [Zometa study CZOL446E010] (Rosen et al 2003a). This change is not expected to adversely affect the results of pharmacokinetic (PK) sampling in the patients who participate in the PK sub- study within this trial.

Although it is not expected that the prior use of bisphosphonates (Zometa vs. pamidronate) will significantly impact the primary endpoint of the study (proportion of patients with SREs at 12 months) based on the above information, exploratory analysis will be performed to compare the two treatment groups with respect to the primary endpoint adjusting for the use of bisphosphonates (Zometa vs. pamidronate) prior to study entry.

The baseline serum creatinine in Amendment 2 (defined as the serum creatinine result obtained before the “first ever dose of Zometa, or approximately one year prior to study entry”) no longer applies to all patients in the study, because there is no upper limit to the duration of Zometa and/or pamidronate therapy prior to enrollment. In addition, when Amendment 3 is implemented, the “first ever” Zometa dose would be the first dose of study medication for those patients who received pamidronate only prior to randomization. The baseline serum creatinine is now defined as the result obtained from patient Screening (Visit 1), regardless of the patient prior Zometa and/or pamidronate treatment history, or the patient prior serum creatinine history. This is intended to simplify and standardize the baseline serum creatinine for all types of patients. The result of the baseline serum creatinine, as defined in Amendment 3, is the basis for determining what the Zometa/study drug dose should be, and whether the Zometa/study treatment should be withheld in the event of a rise in serum creatinine from baseline during the study.

In the original protocol, and through Amendment 2, a bone survey is scheduled every 3 months, and a radionuclide bone scan every 6 months during the study. Due to the change of

the primary efficacy endpoint in Amendment 2 and the poor patient compliance with the current bone survey schedule, a reduction in the frequency of bone surveys should make it easier for patients to comply with the bone survey schedule during the study, and enhance study enrollment when patients consider study requirements during the informed consent process. In Amendment 3, the frequency of bone survey tests is reduced from a quarterly to a semiannual basis. This reduced bone survey schedule applies to all patients in the study. This change reduces not only the number of bone survey tests, but also, in theory, the total amount of radiation exposure by 40%, which is an added benefit to patients. This change is not expected to impact the primary endpoint (the proportion of patients with at least one SRE during the study). However, it is possible that the detection of asymptomatic SREs could be delayed when the frequency of bone surveys is reduced. This change may therefore impact one of the secondary endpoints, time-to-first SRE. Asymptomatic SREs should be detected no longer than every 6 months. This change is unlikely to cause a systematic bias in the between-treatment group comparisons for SRE-related endpoints. This is because the same frequency of radiographic procedure applies to all patients in this randomized and double-blinded study. Certain procedures specified in the protocol should be able to minimize such a potential impact.

The other changes in Amendment 3 are either administrative or explanatory: clarification in respect of stratification factors on the duration of prior bisphosphonate (Zometa vs. pamidronate) therapy (10-15 months vs > 15 months); clarification of determination of study drug dose; clarification of the brief pain inventory (BPI) to be assessed at Visits 2, 3, 4, 5, 8, 11, and EOS; clarification of EOS; clarification of panoramic x-ray of jaw to be required at baseline only; clarification of oral examinations to be completed by dentists; clarification of the definition of a dentist; description of the independent adjudication of suspected ONJ cases by the ONJ Adjudication Committee (ONJ AC); clarification of the numerical rating for pain to be done only up to the first four months; clarification of SRE free survival to be analyzed for the time to first SRE during the study; addition of protocol adherence language; addition of Suspected Unexpected Serious Adverse Reaction (SUSARs) reporting language; change of Clinical Safety and Epidemiology Department to Integrated Medical Safety (IMS); update of the list of abbreviations; and changes in protocol authorship.

## **2 Study objectives**

### **2.1 Primary**

To determine the efficacy, as measured by the SRE rate (the proportion of patients with at least one SRE during the study see [Section 3.5.2](#)) of continued treatment with Zometa every 4 weeks vs. reduced Zometa dosing frequency (every 12 weeks) in patients with documented bone metastases from breast cancer, who have been pretreated with Zometa, or Aredia (pamidronate), or all sequential regimens of both for at least 9 doses during the first 10 to 15 months of treatment, and are on either Zometa or Aredia (pamidronate) at the time of study entry.

### **2.2 Secondary**

- To determine the effect of continued treatment with Zometa every 4 weeks vs. reduced Zometa dosing frequency (every 12 weeks) in patients with documented bone metastases

from breast cancer, who have been pretreated with Zometa, or Aredia (pamidronate), or all sequential regimens of both for at least 9 doses during the first 10 to 15 months of treatment, and are on either Zometa or Aredia (pamidronate) at the time of study entry on:

- Time to first SRE during the study
- Bone pain using the brief pain inventory (BPI) and analgesic consumption for each study group.
- The metabolic bone markers urine N-Telopeptide (N-Tx) and serum bone alkaline phosphatase in each group.
- The skeletal morbidity rate in each group
- To determine the relationships between dose, pharmacokinetics, rate of bone resorption biochemically assessed, presence or absence of prior SRE at study entry, and efficacy in patients with documented bone metastases from breast cancer, who have been pretreated with Zometa, or Aredia (pamidronate), or all sequential regimens of both for at least 9 doses during the first 10 to 15 months of treatment, and are on either Zometa or Aredia (pamidronate) at the time of study entry.
- To determine the safety of continued treatment with Zometa every 4 weeks vs. reduced Zometa dosing frequency (every 12 weeks) in patients with documented bone metastases from breast cancer, who have been pretreated with Zometa, or Aredia (pamidronate), or all sequential regimens of both for at least 9 doses during the first 10 to 15 months of treatment, and are on either Zometa or Aredia (pamidronate) at the time of study entry.

### **3 Investigational plan**

#### **3.1 Overall study design**

This is a prospective, double-blind, stratified, multicenter, two-arm clinical trial in patients with documented bone metastases from breast cancer pretreated with Zometa, Aredia (pamidronate), or a sequence of both for at least 9 doses during the first 10 to 15 months of treatment, and are on either Zometa or Aredia (pamidronate) at the time of study entry. Following a blinded sample size reassessment ([Section 6.2](#)), the target sample size for this study is N=423 patients. Patients are randomized on a 1:1 ratio to one year of continued treatment with Zometa every 4 weeks or Zometa every 12 weeks (with placebo infusion every 4 weeks for the intervening 8 weeks). Prior to Amendment 2, 55 patients were randomized into the study. The randomization ratio before Amendment 2 was 2:2:1 (Zometa every 4 weeks or Zometa every 12 weeks or Placebo). Consequently, approximately 11 (20%) of the 55 patients were randomized into the Placebo arm, and the remaining patients (approximately 44, or 80%) were randomized into one of the two Zometa treatment arms. Therefore the overall total number of patients to be entered will be approximately 423.

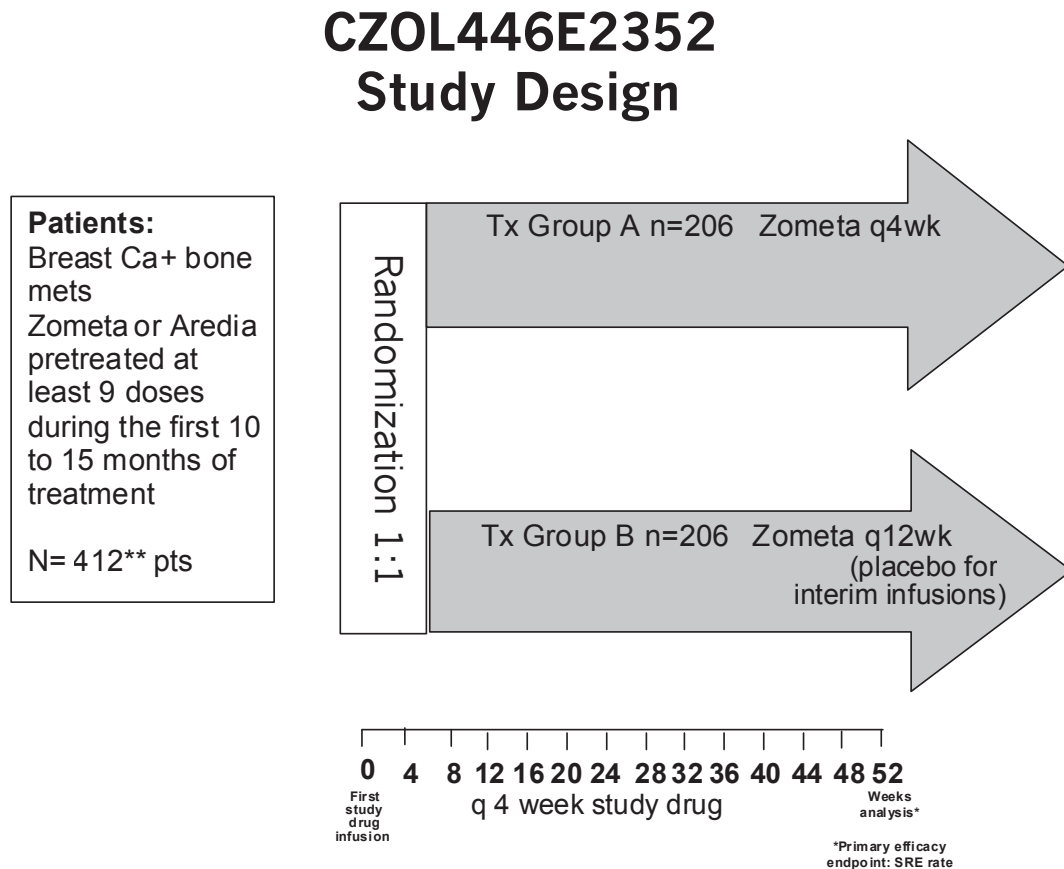
All patients randomized to the placebo arm prior to Amendment 2 will be switched to Zometa every 4 weeks, will be analyzed separately and will not be included in the efficacy analysis. The sample size estimation is based upon the assumptions described in [Section 6.2](#) of this protocol. Analysis will be done at 52 weeks, with a treatment duration of 48 weeks.

Except for the blinded sample size reassessment, no interim analysis for efficacy is planned.



At the time Amendment 4 is implemented (i.e., as soon as it is approved by the IRB), each site must stop enrollment of new patients into the study. However, all patients who are on study (i.e., randomized but not completed) at the time Amendment 4 is implemented should continue to participate (as specified in protocol [Section 3.4](#) and [Section 3.5](#)) until they have either completed or discontinued prematurely from the study.

**Figure 3-1 Study design**



\*\*Approximately 412 patients will be randomized into the two Zometa treatment arms. Prior to amendment 2, it was estimated that 11 patients were randomized into the placebo arm. Therefore the overall total number of patients entered will be approximately 423. All patients randomized to the placebo arm prior to Amendment 2 will be switched to Zometa every 4 weeks, will be analyzed separately and will not be included in the efficacy analysis

### 3.2 Discussion of design

The essential features of this study design are based upon discussions with and advice from the U.S. Food and Drug Administration (FDA). The study is intended to meet the FDA's request for Novartis to demonstrate the continued safety and efficacy of Zometa treatment beyond one year for the prevention of skeletal complications associated with solid tumor bone

metastases or multiple myeloma. It was agreed that the study population be restricted to patients with bone metastases from breast cancer.

In order to investigate whether there is continued efficacy of Zometa after one year of therapy in the study population, subjects pretreated with Zometa, or Aredia (pamidronate), or all sequential regimens of both for at least 9 doses during the first 10 to 15 months of treatment will be randomized to Zometa every 4 weeks or Zometa every 12 weeks. Patients must be on either Zometa or Aredia (pamidronate) at the time of study entry.

Recently it was shown that the pretreatment rate of bone resorption, assessed biochemically, predicts skeletal related events in patients with cancer and bone metastases (Brown 2005, Coleman 2005). Moreover, it has been shown that patients with a history of SREs are predisposed to subsequent SREs (Saad 2004).

The trial is also designed to address safety concerns related to reports of osteonecrosis of the jaw (ONJ) in cancer patients treated with Zometa. This concern will be addressed by careful monitoring for ONJ and expedited reporting (15-days) to the FDA of such events, should they occur in the study.

### 3.3 Study population

#### 3.3.1 Patient population

This study will investigate women with breast cancer complicated by bone metastases. This population was chosen due to their greater overall survival compared to patients with bone metastases from hormone-refractory prostate cancer and from lung cancer or other solid tumors (see table below).

Study	Cancer type	Median survival rate (years)
[Study 0010].	Breast	2.1
[Study 0039].	Prostate	1.4
[Study 0011].	Lung and other solid tumors	0.5

#### 3.3.2 Inclusion and exclusion criteria

##### Inclusion criteria

- Female patients  $\geq 18$  years of age
- Life expectancy of  $\geq 1$  year
- Ambulatory and ECOG status  $\leq 2$
- Histologically confirmed diagnosis of breast cancer with at least one bone metastasis confirmed by conventional radiograph of bone (plain film), CT or MRI scan.
- Pretreated with Zometa 4mg (or renally adjusted dose), or Aredia (pamidronate) 90mg, or all sequential regimens of both, for a minimum of 9 doses. The first 9 doses of IV bisphosphonate the patient received were within a window of 10-15 months. There is no upper limit on the number of doses or duration of treatment. The patient must be on either Zometa or Aredia (pamidronate) at the time of study entry. The last dose of either Zometa or Aredia (pamidronate) must be within 60 days of randomization.



- Patients willing and able to comply with expected study regimens and schedules.
- Written informed consent prior to any study procedures.

### Exclusion criteria

- The baseline serum creatinine (which is obtained at Screening Visit or Visit 1) > 3.0 mg/dL (265 µmol/L) or calculated (Cockcroft-Gault formula) creatinine clearance (CrCl) < 30 mL/min.
  - Cockcroft-Gault formula (Cockcroft and Gault 1976):  
$$\text{CrCl} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)} \times 0.85 \text{ (for female patients)}}{72 \times \text{serum creatinine (mg/dL)}}$$
- Current active dental problems including: ongoing infection of the teeth or jawbone (maxilla or mandibula); current exposed bone in the mouth; and current or prior diagnosis of osteonecrosis of the jaw (ONJ; see Section 3.5.3.1). See Dental Exam Guide for further information.
- Recent (within 8 weeks) or planned dental or jaw surgery (e.g., extraction, implants)
- Diagnosis of metabolic bone disease other than osteoporosis (e.g., Paget's disease of bone)
- Known hypersensitivity to Zometa
- Treatment with bisphosphonates other than Zometa or Aredia (pamidronate) at any time during the 12 months prior to Visit 1.
- Corrected serum calcium < 8.0 mg/dL (2.0 mmol/L) or ≥ 12.0 mg/dL (3.0 mmol/L) at Visit 1. The formula to be used is: Corrected serum calcium (mg/dL) = Patient's serum calcium (mg/dL) + 0.8 x (Midrange Albumin (g/dL) - Patient's Albumin (g/dL)). 4.0g/dL to be used for the Midrange Albumin.
- Treatment with other investigational drugs within 30 days prior to randomization.
- Any changes in antineoplastic therapy within 30 days prior to randomization.
- Pregnant patients (who have a positive serum pregnancy test prior to study entry) or lactating patients. Patients of reproductive potential not using effective methods of birth control (e.g., abstinence, oral contraceptives or implants, IUD, vaginal diaphragm or sponge, or condom with spermicide). Patients of childbearing potential require a negative serum pregnancy test at Visit 1 (Screening Visit).

### 3.3.3 Interruption or discontinuation of treatment

All interruptions, reductions, or any changes in study drug administration must be captured on the Dosage Administration Case Report Form.

If either study treatment or observations are discontinued, the reason will be recorded on the appropriate case report form. Patients withdrawn during the trial will not be replaced. Reasons that a patient may discontinue participation in a clinical study are considered to constitute one of the following:

1. adverse event(s), including diagnosis of ONJ as discussed in Section 3.5.3.1.
2. abnormal laboratory value(s), including:

- significant deterioration in renal function, as determined from local serum creatinine determination prior to infusion of investigational drug or reference therapy. See [Section 3.5.3.2](#) “Serum creatinine monitoring” for criteria
  - Hypercalcemia of malignancy (HCM), defined as a corrected serum calcium  $\geq 12.0$  mg/dL.
3. abnormal test procedure result(s)
  4. unsatisfactory therapeutic effect
  5. subject's condition no longer requires study treatment
  6. protocol violation
  7. withdrawal of patient consent
  8. lost to follow-up
  9. administrative problems
  10. death

For all patients whose treatment is discontinued prior to completing the trial, every effort must be made to complete all of the end-of-study evaluations. A final assessment at the time of the patient's withdrawal must be completed, together with an explanation of why the patient is discontinuing from study treatment. End-of-study evaluations include: physical, vital signs, laboratory assessments, ECOG, bone scan, pain score, analgesic score, assessment of SREs, adverse events, oral examination, and concomitant medications. All relevant information related to the reason for premature discontinuation including contributory factors must be included on the Study Completion CRF.

Every patient has the right to discontinue study participation at any time and may be discontinued from the study for any reason beneficial to his/her well being. All data generated up to the time of discontinuation from the study will be analyzed and the reason(s) for discontinuation will be recorded.

## **3.4 Treatments**

### **3.4.1 Investigational therapy and reference therapy**

#### **Dose and regimen**

- Zometa intravenous infusion according to dose table in [Section 3.4.2](#) over no less than 15 min every 4 weeks
- Zometa intravenous infusion according to dose table in [Section 3.4.2](#) over no less than 15 min every 12 weeks (patients will receive placebo infusions at 4-week intervals between the zoledronic acid infusions)

All patients will receive supplemental oral calcium (1000-2000 mg daily) and vitamin D (400-800 IU daily)

Randomization ratio: 1:1, i.e., the two treatment groups will have the same amount of patients in each.

### 3.4.2 Determination of study drug dose

All patients must have a serum creatinine level tested at Screening (Visit 1), which is analyzed by the central laboratory designated for this study. The baseline serum creatinine level is defined as the result obtained from Screening (Visit 1), regardless of prior Zometa and/or pamidronate dosing history, or prior serum creatinine history. This is suitable for all patients in order to simplify and standardize the baseline serum creatinine to be used as the basis for determining the Zometa/study drug dose, and for determining whether Zometa/study drug should be withheld during the study because of a rise in serum creatinine from baseline.

The Zometa/study drug dose to be used during the trial is determined by the baseline creatinine clearance, as calculated by the Cockcroft-Gault formula (see [Table 3-1](#)), using the serum creatinine obtained at Screening (Visit 1). For patients whose baseline creatinine clearance is normal (i.e., > 60 mL/min), the study dose of Zometa should be 4.0 mg for each infusion. In patients with mild to moderate renal impairment at baseline (i.e. calculated creatinine clearance 30-60 mL/min, using the serum creatinine obtained at Screening (Visit 1), a reduced dose of Zometa should be administered according to [Table 3-1](#) below. After the initial dose is determined, there should be no change to the Zometa/study drug dose during the trial.

It must be emphasized that serum creatinine should be repeated and the result should be reviewed before each study drug infusion. The baseline serum creatinine level obtained at Screening (Visit 1) is also the basis for determining whether or not subsequent study drug infusions should be withheld in the event of an increase in creatinine from baseline, as specified in [Section 3.5.3.2](#).

**Table 3-1 Recommended Zometa dose**

Baseline CrCl	Zometa Recommended Dose (mg)
>60	4.0
50 - 60	3.5
40 - 49	3.3
30 - 39	3.0

Baseline creatinine clearance (CrCl) is calculated by the Cockcroft-Gault equation:

$$\text{CrCl} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)} \{ \times 0.85 \text{ for female patients} \}}{[72 \times \text{serum creatinine (mg/dL)}]}$$

### Treatment cycle

The treatment cycle will be 4 weeks long. In order to allow for patient and office schedules, a window of ± 7 days will be allowed when arranging infusion/treatment visits. Subsequent infusions/visits shall always be scheduled based on the actual date of the most recent infusion, so that the length of time between infusions will not be less than 3 weeks or greater than 5 weeks (except in the case of dose withholding secondary to toxicities).

## Supply

Zometa will be provided by Novartis in plastic vials containing 4mg zoledronic acid in a 5 mL concentrate as a solution for infusion.

Matching placebo will be supplied as 5 mL of sterile water as a solution for infusion.

Calcium and vitamin D supplements will be provided by the investigative sites as open-label drug. Formulation is at the discretion of the investigator.

## Preparation

The zoledronic acid 4 mg/5 mL concentrate solution is not for direct infusion and has to be further diluted prior to the use. Prior to administration, the 5 mL of the concentrate solution must be diluted with 100 mL calcium-free infusion solution (0.9% sodium chloride solution or 5% glucose solution). The appropriate volume of the reconstituted zoledronic acid solution is 105 mL. The necessary infusion bags/bottles, containing either 100ml calcium free 0.9% sodium chloride or 5 % dextrose solution, that have to be used for the set up of the infusion will be provided by the study center. Glass bottles and infusion bags or tubing made from polyvinylchloride (PVC), polypropylene (PP) and polyethylene (PE) are appropriate for use with Zometa.

If not used immediately after dilution with infusion media, for microbiological integrity, the final solution must be placed in a refrigerator with a temperature between 2-8°C. The refrigerated solution should then be equilibrated to room temperature prior to administration. The total time between dilution, storage in a refrigerator, and end of administration of the infusion must not exceed 24 hours. Reconstituted zoledronic acid solutions must be administered in no less than a 15-minute intravenous infusion in a line separate from all other drugs.

A peripheral or central intravenous site is to be used for the study drug infusion. Study drug should be administered as a single intravenous solution in a line separate from all other drugs. The i.v. infusion will be preceded by and followed by a 10 ml normal saline flush of the intravenous line. In order to allow constant flow a vented infusion line should be used. Prior to application of the drug, the infusion line via a y-connector or other similar set-up will be flushed with approximately 10 ml of normal saline. Thereafter, the solution will be infused over a period of no less than 15 minutes. After emptying, approximately 3 mL of drug product solution may stay in the infusion bottle. Use at least 10 ml of normal saline to flush the infusion line.

A pharmacist or other qualified person will be responsible for the preparation of the i.v. The qualified person who prepares the drug to be infused must enter the appropriate drug preparation information requested on the sign off log for drug preparation. Documentation of trial-drug administration and amount infused will be maintained for every patient

Preparation of reduced Zometa dose solution: for patients with mild to moderate renal impairment (CrCl <60 mL/min) at baseline (baseline defined as the serum creatinine obtained at Screening):

Withdraw an appropriate volume of the 5 mL - study drug concentrate:

- 4.4 mL for 3.5 mg dose

- 4.1 mL for 3.3 mg dose
- 3.8 mL for 3.0 mg dose

The withdrawn concentrate must be diluted in 100 mL of sterile 0.9% sodium chloride, USP, or 5% dextrose injection, USP. The dose must be given as a single intravenous infusion over no less than 15 minutes.

Medication vial labels will comply with the legal requirements of the United States. They will supply no information about the patient, only the medication number. The storage conditions for study drug will be described on the medication label.

### 3.4.3 Treatment assignment

At Visit 1 the investigator or his/her staff will assign patients entering the study (for whom informed consent has been obtained) a unique patient number, by which they will be identified. This consists of a unique center number assigned by Novartis and the patient number assigned sequentially within the center at the screening visit (e.g., 00101). The patient number assigned at Visit 1 will be used by the patient for the period of that patient's trial participation. Once assigned to a patient, the patient number will not be reused. The investigator or his/her delegate will place a call to the Interactive Voice Response System (IVRS) at Visit 1 to register the patient into screening phase of the trial. If the patient fails to be randomized for any reason, the patient's number and reason for not being randomized will be entered on the Screening Log.

At Visit 2 all eligible patients will be allocated a randomization number that assigns them to one of the two treatment groups. The investigator or his/her delegate will call the IVRS and confirm that the patient fulfils all of the inclusion/exclusion criteria, and enter the answers to the two stratification questions. The stratification factors are the duration of IV bisphosphonate therapy (10-15 months and >15 months) prior to entering the study and the level of urinary N-Tx/Cr (>100 nmol bone collagen equivalent (BCE)/mmol creatinine or ≤ 100 nmol BCE/mmol creatinine) prior to the study. (If the urine N-Tx/Cr results are not available at the time of randomization, the investigator or his/her delegate will choose the ≤ 100 option when calling into IVRS. Once the results are received, the IVRS entry is to be updated accordingly.) The IVRS will assign a randomization number to the patient, which will be used to link the patient to one of the two treatment groups, and will specify a unique medication number for the first infusion of double-blind study drug to be dispensed to the patient. The medication number will be communicated to caller. Unique medication numbers will be assigned for subsequent infusions in a similar manner, after site personnel make a call to the IVRS to register each visit.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IVRS provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication randomization list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study drugs. All patients enrolled in the placebo arm of the study prior to

Amendment 2 will be switched to Zometa every 4 weeks treatment arm through the IVRS system while maintaining the double-blind. These patients will be analyzed separately and will not be included in the efficacy analysis.

## Blinding

Randomization will be performed by an IVRS vendor using a validated system that automates the random assignment of treatment groups to randomization numbers. The randomization scheme will be reviewed by a Biostatistics Quality Assurance Group and locked by them after approval.

Randomization data will be kept strictly confidential, accessible only to authorized persons, until the time of unblinding. At the conclusion of the trial, the occurrence of any emergency code breaks will be determined by IVRS. Only when the study has been completed, the data file verified, and the protocol violations determined will the drug codes be broken and made available for data analysis.

For details of the emergency procedure for unblinding of individual patients in cases of emergency see [Section 9.1.3](#). Emergency procedure for unblinding.

### 3.4.4 Concomitant therapy

Patients may receive:

- Non-experimental antineoplastic medications (e.g., chemotherapy and/or hormonal therapy). Such therapy can be initiated before or after randomization, and change of non-experimental antineoplastic medication while on study will be allowed. There should be no change to antineoplastic therapy within 30 days prior to randomization. All concomitant antineoplastic therapy will be recorded at baseline and during the study.
- Standard marketed cytokine/colony stimulating factors.
- Corticosteroid therapy utilized to prevent/treat chemotherapy-induced nausea/vomiting
- Doses of corticosteroids to treat spinal cord compression or other recognized indications
- Marketed drugs/therapies EXCEPT those that would be expected to affect osteoclast activity (e.g., calcitonin, mithramycin, and gallium nitrate).

Patients should NOT receive:

- Denosumab (Xgeva<sup>®</sup> or Prolia<sup>®</sup>)
- Any bisphosphonates, including commercial Zometa<sup>®</sup> or Reclast<sup>®</sup> (zoledronic acid) or Aredia (pamidronate), after randomization into the study.

All patients will receive supplemental oral calcium (1000-2000 mg daily) and vitamin D (400-800 IU daily).

Generic name, start and stop dates, dose, regimen, and reason for concomitant medications will be recorded.

### **3.4.5 Treatment compliance**

Interruptions in treatment may occur during the trial. Patients will be considered non-compliant, and withdrawn from the study, if more than two (2) consecutive study drug treatments are missed or if more than four (4) total treatments are missed during the entire study.

Records of study medication used, dosages administered, and intervals between visits will be kept during the study. Treatment accountability will be noted by the field monitor during site visits and at the completion of the trial.

## **3.5 Visit schedule and assessments**

### **3.5.1 Visit schedule**

There will be a total of 15 scheduled visits for a patient who completes this study: one (1) Screening Visit, thirteen (13) Treatment Visits, and one (1) End of Study Visit. Visits will occur as schematically shown in [Table 3-2](#) “Visit evaluation schedule.” Visits should be scheduled for as close to the same time of day as possible so that blood and urine samples are taken at the same time from visit to visit. Patient diary information will be collected by a touch-tone telephone system (IVRS). The patient diary IVRS evaluations will be performed at the times specified in the protocol, allowing a range of  $\pm 1$  day for each assessment. Note that patient diary IVRS is distinct from the registration, randomization, and study-blinding uses of IVRS.

#### **Screening visit (Visit 1)**

Between four weeks and one day prior to the first treatment visit, patients will undergo screening evaluations to determine eligibility for participation in the study. These evaluations will include:

- Written, informed consent
- Urine from second voided morning specimen to be sent to the central lab for N-Tx/Cr analysis to be performed prior to randomization for stratification purposes.
- Demographic information
- Contact IVRS to register patient into screening
- Relevant medical and surgical history/current medical conditions
- Diagnosis and extent of cancer
- History of prior cancer surgery
- History of prior antineoplastic medications (e.g., chemotherapy, hormonal therapy)
- History of prior radiation therapy
- History of prior concomitant medications
- History of prior SRE (see [Section 3.5.2](#), Skeletal Related Events); this information is to be used for stratification assignment
- Serum pregnancy test for all females of child-bearing potential
- Oral examination (see [Section 3.5.3.1](#))



- Panoramic x-ray of jaw (unless obtained during the previous 30 days; with films and report available)
- Physical examination (see [Section 3.5.3.9](#))
- Vital signs to include height, weight, body temperature, resting pulse and blood pressure
- Hematology and serum biochemistry to be sent to the central laboratory
- ECOG score (see [Section 7.2.4](#))
- Baseline Tc-99 bone scan (see [Section 3.5.2.2](#)) (unless obtained within the previous 30 days; with films and report available)
- Baseline bone survey (see [Section 3.5.2.1](#))
- Dispense calcium and vitamin D supplements to be started at least 1 day prior to randomization

If **all** inclusion/exclusion criteria are met, then patients will proceed to randomization and treatment phases of the protocol.

### **Treatment visits (Visits 2 through 14)**

#### Visit 2

Visit 2 will be the first randomized treatment visit, and will consist of the following activities:

- Contact IVRS to randomize patient and receive medication number
- Review current medical condition
- Review antineoplastic, radiation therapy and concomitant medications
- Vital signs to include weight, body temperature, resting pulse and blood pressure
- Serum creatinine to be sent to local laboratory with result needed PRIOR to study drug infusion (see [Section 3.5.3.2](#), can be done up to 72-hours prior to visit )
- Hematology and serum biochemistry to be sent to the central laboratory
- Urine (second morning void) N-Tx/Cr to be sent to the central laboratory.
- Serum bone-specific alkaline phosphatase, and other serum samples to be sent to the central laboratory
- ECOG score (see [Section 7.2.4](#))
- Brief Pain Inventory (see [Section 7.2.2](#))
- Train patient on IVRS for collection of weekly pain scores (see [Section 7.2.1](#))
- Analgesic score (see [Section 7.2.3](#))
- Study drug infusion unless prohibited by rise in serum creatinine (see [Section 3.4.1](#)). Record infusion start and stop times.
- PK sampling for those patients who consent for the PK sub-study (see [Section 3.5.5](#) Drug levels and pharmacokinetic assessments)

#### **Visits 3 through 14**

- Contact IVRS to record visit occurrence and receive medication number



- Record adverse events as needed (see [Section 3.5.3.4](#))
- Record concomitant medications as needed (see [Section 3.4.4](#))
- Record SREs as needed
- Record antineoplastic and radiation therapy as needed
- Physical examination at Visit 8 (see [Section 3.5.3.9](#))
- Vital signs to include weight, body temperature, resting pulse and blood pressure
- Serum creatinine to be sent to local laboratory with result needed PRIOR to study drug infusion (see [Section 3.5.3.2](#), can be done up to 72-hours prior to visit)
- Hematology and serum biochemistry to be sent to the central laboratory
- Urine (second morning void) N-Tx/Cr to be sent to central laboratory at Visits 5, 8, 11, and 14
- Bone specific alkaline phosphatase and serum samples to be sent to the central laboratory at Visits 5, 8, 11, and 14
- ECOG score at Visits 5, 8, and 11 (see [Section 7.2.4](#))
- Brief Pain Inventory (BPI) at Visits 3, 4, 5, 8, and 11 (see [Section 7.2.2](#))
- Remind patient to call IVRS to record weekly pain score through Visit 5 so they will record pain scores through Week 16 (see [Section 7.2.1](#))
- Analgesic score at Visits 3, 4, 5, 8, and 11 (see [Section 7.2.3](#))
- Bone scan at Visit 8 (see [Section 3.5.2.2](#)). The administration of study drug should take place after the bone scan has been completed, and not prior to the bone scan or between administration of the radionuclide tracer and the actual bone scan.
- Bone survey at Visit 8 (see [Section 3.5.2.1](#))
- Study drug infusion unless prohibited by rise in serum creatinine (see [Section 3.4.1](#)). Record infusion start and stop times.
- PK sampling at Visit 11 for those patients who consented to the PK sub-study (see [Section 3.5.5 Drug levels and pharmacokinetic assessments](#))
- Dispense calcium and vitamin D supplements as needed to be taken daily during treatment phase.
- Oral examination at Visit 8 (6 months) (see [Section 3.5.3.1](#))

### End of Study Visit

When a patient completes 48 weeks of treatment, or **discontinues treatment for any reason**, an end of study visit will be conducted. The visit procedures should be completed within four weeks of Visit 14 if the patient completes the study treatment period or within 4 weeks of the date that the patient is taken off the study. This visit will include the following assessments:

- Contact IVRS to record end of study for patient
- Record adverse events as needed (see [Section 3.5.3.4](#))
- Record SREs as needed
- Record concomitant medications as needed (see [Section 3.4.4](#))

- Record anti-neoplastic and radiation therapy as needed
- Physical examination (see [Section 3.5.3.9](#))
- Vital signs to include weight, body temperature, resting pulse and blood pressure
- Hematology and serum biochemistry to be sent to the central laboratory
- ECOG score (see [Section 7.2.4](#))
- Bone scan (see [Section 3.5.2.2](#))
- Bone survey (see [Section 3.5.2.1](#))
- Brief Pain Inventory (BPI) (see [Section 7.2.2](#))
- Analgesic score (see [Section 7.2.3](#))
- Oral examination (see [Section 3.5.3.1](#))

**Table 3-2 Evaluation and visit schedule**

Visit	Screening	Treatment (visits have a window of ±7days)														Follow-up
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	EOS <sup>11</sup>	
q 4 week study drug infusion/treatment week		1/0	2/4	3/8	4/12	5/16	6/20	7/24	8/28	9/32	10/36	11/40	12/44	13/48	52	
Evaluation / assessment																
Demography/informed consent	X															
IVRS contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Relevant med hist/current med cond'n	X	X														
Diagnosis and extent of cancer	X															
Prior antineoplastic or radiation therapy	X	X														
Concomitant medication - Prior	X	X														
Pregnancy test	X															
Oral examination <sup>2</sup>	X (baseline)		As required						X	As required						X
Panoramic x-ray of jaw <sup>2</sup> Panoramic x-ray of jaw <sup>2</sup>	X		As required													
Physical	X							X							X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum creatinine - local lab		X	X	X	X	X	X	X	X	X	X	X	X	X		
Serum biochemistry - central lab <sup>6</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology - central lab <sup>7</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine NTx/Cr <sup>8</sup>	X <sup>8a</sup>	X			X			X			X			X		
BSAP, Serum sample - central lab <sup>8a</sup>		X			X			X			X			X		
PK Sub-Study for consented patients <sup>14</sup>		X									X					
ECOG <sup>5</sup>	X	X			X			X			X				X	
Bone scan <sup>10</sup>	X (baseline)							X							X	
Bone Survey	X (baseline)							X							X	

Visit	Screening		Treatment (visits have a window of ±7days)												Follow-up
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	EOS <sup>11</sup>
q 4 week study drug infusion/treatment week		1/0	2/4	3/8	4/12	5/16	6/20	7/24	8/28	9/32	10/36	11/40	12/44	13/48	52
Evaluation / assessment															
BPI <sup>3</sup>		X	X	X	X			X			X				X
Numerical rating pain scale via IVRS <sup>3</sup>		X	X	X	X										
Analgesic score <sup>4</sup>		X	X	X	X			X			X				X
Randomization		X													
Study drug infusion <sup>13</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	
Dosing schedule for Z q 12 weeks		Z	Pbo	Pbo	Z	Pbo	Pbo	Z	Pbo	Pbo	Z	Pbo	Pbo	Z	
calcium and vitamin D supplements <sup>1</sup>	X	DISPENSE AS NEEDED													
Antineoplastic medication <sup>12</sup>		RECORD AS NEEDED													
Radiation therapy <sup>12</sup>		RECORD AS NEEDED													
SRE		RECORD AS NEEDED													
Adverse events		RECORD AS NEEDED													
Concomitant medication		RECORD AS NEEDED													
<sup>1</sup> Patients will be instructed to begin taking calcium and vitamin D supplements 1 day prior to randomization <sup>2</sup> Oral exam will be performed at screening/baseline, visit 8 and EOS visit. Panoramic X-ray of jaw will be performed at screening/baseline. If patient has a panoramic x-ray available within 30 days prior to starting the study, and can provide a copy to the study site, it will not be repeated. See <a href="#">Section 3.5.3.1</a> and Oral Examination Guide provided to site. Additional oral exams and panoramic x-ray will be performed during the study whenever a suspected ONJ SAE is reported. If a regularly scheduled oral exam is performed between visit 7 and visit 8 or between visit 14 and EOS visit, and the information is made available to the investigator, this exam can substitute the visit 8 or EOS visit exam respectively. <sup>3</sup> See <a href="#">Section 7.2.2</a> for the BPI (Brief pain Inventory) to assess bone pain BPI will be assessed at Visits 2, 3, 4, 5, 8, 11 and EOS visit. Numerical rating pain scale will be assessed weekly by IVRS for the first 4 months (through Visit 5). <sup>4</sup> See <a href="#">Section 7.2.3</a> for the analgesic score. <sup>5</sup> ECOG: Eastern Cooperative Oncology Group performance status, see <a href="#">Section 7.2.4</a> . <sup>6</sup> <b>Serum chemistry</b> (to be done <b>prior to study drug infusion</b> ): Calcium, albumin, sodium, chloride, potassium, bicarbonate, BUN, creatinine, glucose, phosphate, magnesium, alkaline phosphatase, bilirubin, total protein, AST, ALT, and LDH. <sup>6a</sup> Bone specific alkaline phosphatase will be measured at Visits 2, 5, 8, 11, and 14. The remaining <b>serum sample</b> will be stored for possible bone marker testing in future.) <sup>7</sup> Hematology: CBC with differential. A serum pregnancy test will be performed at Visit 1 for female patients of childbearing potential.															

Visit	Screening		Treatment (visits have a window of ±7days)												Follow-up
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	EOS <sup>11</sup>
q 4 week study drug infusion/treatment week		1/0	2/4	3/8	4/12	5/16	6/20	7/24	8/28	9/32	10/36	11/40	12/44	13/48	52
Evaluation / assessment															

<sup>8</sup> Urine sample (**second voided morning urine**; to be done **prior to study drug infusion**) for N-telopeptide, and creatinine. Sample will be stored for possible future testing).

<sup>8a</sup> Urine N-Tx/Cr at Visit 1 will be sent to central lab to determine value for stratification purposes. If the urine N-Tx/Cr results are not available at the time of randomization, the investigator or his/her delegate will choose the ≤ 100 option when calling into IVRS. Once the results are received, the IVRS entry is to be updated accordingly. See [Section 3.4.3](#).

<sup>9</sup> SRE (skeletal related events) to include at least one of the following: pathologic bone fracture, spinal cord compression, and surgery or radiation therapy to bone.

<sup>10</sup> Bone scan: see [Section 3.5.2.2](#). Bone survey see [Section 3.5.2.1](#).

<sup>11</sup> A study completion form will be completed any time a subject ends participation in the study.

<sup>12</sup> Initiation, change or termination of antineoplastic and/or radiation therapy during study allowed and to be documented.

<sup>13</sup> In patients who discontinue study medication, every effort should be taken to perform follow-up procedures according to a study schedule.

<sup>14</sup> Urine collection from start of infusion to 6 hours after start of infusion; serum samples at 0, 0.25 (end of infusion), 2 and 6 hours after start of infusion.

### 3.5.2 Efficacy assessments

#### Primary efficacy variable

- Proportion of patients who experience at least one SRE during the study period (SRE rate).

#### Secondary efficacy variables

- Time to first skeletal related event (SRE), defined as time (in days) from randomization to first occurrence of any SRE up to week 52 in the study. SRE includes any of the following events: pathologic bone fracture, radiation therapy to bone, surgery to bone, and spinal cord compression.
- Time to first individual type of SRE up to Week 52
- SRE free survival
- Skeletal morbidity rate
- Proportion of patients experiencing each individual type of SRE
- Bone pain score, assessed by:
  - the brief pain inventory (BPI, see [Section 7.2.2](#)) at Visits 2, 3, 4, 5, 8, 11, and EOS visit
  - numerical rating scale (see [Section 7.2.1](#)) weekly through Month 4 via the touch-tone telephone system (IVRS)
- Analgesic consumption as assessed by analgesic score (see [Section 7.2.3](#))
- Urinary N-Tx/Cr ratio and serum bone specific alkaline phosphatase

#### Skeletal-related events (SRE)

SRE is defined as pathologic bone fractures, radiation therapy or surgery to bone, and spinal cord compression.

**Pathologic fractures** are defined as bone fractures which occur spontaneously or which result from trivial trauma. A new vertebral compression fracture is defined as a decrease in total vertebral height, or anterior vertebral height, or posterior vertebral height of  $\geq 25\%$  from baseline (Visit 1). An old (pre-existing) vertebral compression fracture may be present at Visit 1. At Visit 1, a pre-existing vertebral compression fracture is defined as a decrease in total, or anterior, or posterior vertebral height of  $\geq 25\%$  as compared to a previous spinal film or as compared to an adjacent vertebrae. A further reduction in the total, or anterior, or posterior vertebral height of an old vertebral fracture by  $\geq 25\%$  during the study is to be classified as a new vertebral compression fracture. Each pathologic fracture (vertebral and non-vertebral, including rib fractures) is to be documented by a plain X-ray film during the study and is to be counted separately.

The investigator will have the responsibility of determining SREs related to vertebral fractures. Thus, old vertebral fractures will be determined by the investigator at Visit 1 by reviewing the baseline bone survey. New vertebral fractures will be determined by the investigator by reviewing serial bone surveys performed during the trial and by reviewing plain films or other

imaging procedures (e.g., CT or MRI of the spine) obtained between the scheduled bone surveys (it is anticipated that such imaging will be obtained for symptomatic vertebral compression fractures).

**Spinal cord compression** is caused by the impingement of tumor on the spinal cord and is associated with neurologic impairment and/or back pain. Compression usually originates from tumor involvement of the vertebrae when metastatic tumor expands posteriorly from the vertebral body or neural arch and compresses on the anterior aspect of the dural sac. If spinal cord compression occurs, each involved vertebral compression fracture (if present), in addition to the spinal cord compression event, will be recorded as an SRE. Spinal cord compression events are to be confirmed by appropriate radiographic studies [e.g. magnetic resonance imaging (MRI) or computed tomography (CT)].

All local radiographic studies must be copied and submitted to Novartis for archiving. Alternatively, images can be stored in digital format and submitted to Novartis for archiving.

**Surgery to bone events** include surgical procedures which are performed to set or stabilize pathologic fractures or areas of spinal cord compression, and surgical procedures which are performed to prevent an imminent pathologic fracture or spinal cord compression.

**Radiation therapy to bone events** include irradiation of bone to palliate painful lesions, to treat or prevent pathologic fractures, or to treat or prevent spinal cord compression. Each field of radiation therapy is to be considered a separate SRE for the purposes of this study. In addition, the use of intravenous strontium-89 (or other radioisotopes) for the treatment of metastatic bone pain will be considered an SRE and will be categorized as “radiation to bone”.

SREs which occurred prior to the administration of study medication will be recorded at Visit 1 (screening) on the Skeletal related events history case report form. The number of new or continuing events during the study will be recorded at each subsequent visit on the Skeletal related events case report form. Should a patient develop an SRE, that event and the treatment for that event will be recorded.

### 3.5.2.1 Bone surveys

All patients will undergo a radiographic bone survey at screening/baseline and Visits 8 and End of Study visit. This bone survey will consist of the following x-rays:

- AP and lateral cervical spine
- AP and lateral thoracic spine
- AP and lateral lumbar spine
- PA chest
- AP pelvis
- AP upper extremities, shoulder to elbow
- AP lower extremities, hip to knee
- Lateral skull

The purpose of the bone survey will be to record pathological fractures. All study investigators (PIs) should order appropriate x-rays (including bone surveys) at any time during the study when suspicious symptoms are reported.

### **3.5.2.2 Bone scans**

All patients will undergo radionuclide bone scans using Tc-99 during the study. Bone scans will occur at Visit 1 (screening/baseline), Visits 8, and End of Study visit. If a suspicious area is identified on bone scan, plain x-rays of the region in question will be performed for clarification.

### **3.5.3 Safety assessments**

Safety assessments will consist of monitoring and recording all adverse events, including serious adverse events, the regular monitoring of hematology, blood chemistry (including calculated creatinine clearance using the Cockcroft-Gault formula in [Table 3-1](#)), regular monitoring of vital signs, physical condition, body weight, and careful monitoring for the possible occurrence of osteonecrosis of the jaw (ONJ; see [Section 3.5.3.1](#)).

#### **3.5.3.1 Oral examinations**

Oral examinations will be done to document the patient's oral health status at Visits 1 (Screening/Baseline), 8 (6 Months), and EOS. This examination will be done by a dentist (defined as a practicing dentist, periodontist, oral and maxillofacial surgeon, but not a dental hygienist) following the procedures outlined in the Oral Examination Guide provided to all investigative sites. If a regularly scheduled oral exam is performed between Visit 7 and Visit 8 or between Visit 14 and EOS visit and the information is made available to the investigator, this exam can substitute the Visit 8 or EOS visit exam respectively. Patients will also have a panoramic x-ray of the jaw taken as part of screening/baseline procedures. If there is a panoramic x-ray available from within 30 days prior to starting the study, and the patient can make a copy of the images and report available to the study site, this test will not be repeated.

After study entry, any patient report of the following symptoms at interim visits will require a follow-up examination by a dentist to rule out ONJ prior to further study drug dosing:

- exposed bone in the oral cavity
- rough area on the jawbone
- “heavy jaw”, a dull aching sensation
- numbness/tingling of the jaw
- loosening of teeth
- tooth pain
- sudden change in the health of periodontal or mucosal tissue
- failure of oral mucosa to heal
- undiagnosed oral pain,
- soft tissue swelling, drainage or infection

At either regularly scheduled or additional (prompted by symptoms) oral exam, if “clinical features of suspected ONJ” are identified, the patient will be referred to a dentist knowledgeable in ONJ for examination, diagnosis, and treatment. A Dental Evaluation Form will be completed with detailed description of the event along with a panoramic x-ray. The clinical features of suspected ONJ are exposed bone in the maxillofacial area that occurs in



association with dental surgery or occurs spontaneously, with no evidence of healing. Please see the dental examination guide for further information.

If a diagnosis of ONJ is made, study medication will be stopped permanently, the patient will be discontinued from the study, and further treatment will be at the discretion of the patient's physician. The patient will be followed for outcome of ONJ. (See [Post-text supplement 1](#) for further information on the prevention, treatment and diagnosis of ONJ).

All such diagnosed cases of ONJ should be considered as "medically significant," irrespective of whether the event meets the definition of "serious adverse event (SAE)" under current health authority guidelines. These cases are therefore to be reported to Novartis CS&E as well as local health authorities under the guideline of SAE reporting (see [Section 9.1.1](#)).

Osteonecrosis of the jaw, and osteomyelitis at any skeletal site, should also be considered as medically significant and reported to Novartis CS&E as well as local health authorities under the guidance of SAE reporting (see [Section 9.1.1](#)).

If diagnosis of ONJ is **not** made, then the patient will be allowed to continue on the study at the discretion of the investigator.

All reported cases of suspected ONJ are to be reviewed by the ONJ Adjudication Committee (ONJ AC). The ONJ AC is an independent panel of academic dental professionals who are experts in the field of ONJ. The ONJ AC reviews submitted cases while remaining blinded to the study arm assignment. The adjudicated results of all reports of suspected cases of ONJ are to be reported to Novartis by the ONJ AC via completion of a case report form. The study site may be asked to collect additional dental information, dental records, dental x-ray films, photographs, pathology reports, or any other records which are a part of the evaluation of reports of suspected cases of ONJ.

The activities of the ONJ AC are conducted independently of the clinical care of patients with suspected ONJ in this trial. The adjudication process is for investigational purposes only and does not impact the obligation of investigators to report all suspected cases of ONJ, regardless of clinical severity, to Novartis IMS as well as local health authorities under the guidelines of SAE reporting (see [Section 9.1.1](#)). In addition, decisions regarding the ongoing clinical care of patients with suspected ONJ while the patients remain on this study should not be delayed or impacted by the adjudication process.

### **3.5.3.2 Serum creatinine monitoring**

Serum creatinine should be monitored in all patients treated with Zometa or placebo infusion prior to each dose. A 72-hour window for checking creatinine is allowed prior to the each study infusion. Elevations in serum creatinine above baseline values may require a delay in treatment.

Each pre-infusion serum creatinine during the study must be compared with the baseline serum creatinine (defined as the serum creatinine obtained at Screening/Visit 1) and should be managed as follows:

- If the patient's baseline serum creatinine (at Screening/Visit 1) was < 1.4 mg/dL, an increase of 0.5 mg/dL or more will require that the study drug be delayed until the patient's serum creatinine returns to no higher than 10% above the baseline value.

- If the patient's baseline serum creatinine (at Screening/Visit 1) was  $\geq 1.4$  mg/dL, then an increase in the serum creatinine of 1.0 mg/dL or more will require that the study drug be delayed until the patient's serum creatinine returns to no higher than 10% above the baseline value.
- Any doubling of the baseline serum creatinine (at Screening/Visit 1) will require that the study drug be delayed until the patient's serum creatinine returns to no higher than 10% above the baseline value.

**Zometa should be re-initiated at the same dose as that prior to treatment interruption.**

### **3.5.3.3 Evaluation of potential cases of atypical femoral fractures**

#### **Background**

Atypical subtrochanteric and diaphyseal femoral fractures have been reported in patients receiving bisphosphonate therapy, including Zometa. These fractures can occur after minimal or no trauma, anywhere in the femur from just below the lesser trochanter to just above the supracondylar flare. They are transverse or short oblique in orientation without evidence of comminution. Patients may experience thigh or groin pain weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. A number of case reports noted that patients were also receiving treatment with glucocorticoids (such as prednisone or dexamethasone) at the time of fracture. Causality with bisphosphonate therapy has not been established.

Any patient who presents with thigh or groin pain in the absence of trauma should be suspected of having an atypical fracture and should be evaluated. Discontinuation of Zometa therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment by the investigator. It is unknown whether the risk of atypical femur fracture continues after stopping therapy.

#### **Collection of targeted safety information**

In order to comply with a specific request by the FDA, and as a pharmacovigilance procedure, Novartis will search the clinical database for cases of potential atypical subtrochanteric femoral fracture that occurred during the course of the study. This search will be conducted in a way that maintains blinding of the assigned treatment arm to Novartis.

When a potential AFF event is identified, the site will be asked to collect all available source documents related to the event. Such source documents include, but are not limited to: relevant clinical notes, radiographs, operative reports, and pathology reports. Note that patients who have completed the study should NOT be contacted retrospectively by the investigator or other site staff in order to seek additional information related to the potential event.

### **Independent AFF data review and adjudication**

All available materials related to suspected cases of potential AFF will be reviewed and adjudicated by one or more blinded central reviewers who are expert in the diagnosis of AFF. The central reviewer(s) cannot otherwise participate in this study, and will function independently of Novartis. The central reviewer(s) will adjudicate each case sent for review, and provide the results to Novartis via completion of a case report form. The basis for adjudication will be the case definition of AFF as described in the American Society for Bone and Mineral Research (ASBMR) Task Force Report (Shane et al 2010). The details of the adjudication process and case report form will be approved by the central reviewer(s) and described in an AFF adjudication charter.

The central review and adjudication of suspected potential AFF cases will be conducted independently of the clinical care of the patients in the study. The ongoing clinical care of patients with potential AFF will remain the responsibility of the investigator during the course of the trial.

Of note, this study was not designed to capture the newly recognized safety risk of atypical femoral fractures (AFF). The processes of collection of source documents, review and adjudication of potential events will be introduced relatively late in the course of the trial, and will be initiated after the events of potential AFF have been reported. Therefore, the identification and adjudication of potential cases will be retrospective.

#### **3.5.3.4 Adverse events**

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded on the Adverse Event Case Report Form and followed as appropriate. An adverse event is any undesirable sign, symptom or medical condition occurring after starting study drug even if the event is not considered to be related to study drug. Study drug includes the drug under evaluation, and any reference or placebo drug given during any phase of the trial.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol). Adverse events (but not serious adverse events) occurring before starting study treatment but after signing the informed consent form are recorded on the Medical History/Current Medical Conditions Case Report Form. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant or require therapy, and are recorded on the Adverse Events Case Report Form under the signs, symptoms or diagnosis associated with them.

As far as possible, each adverse event will also be described by:

1. its duration (start and end dates),
2. the severity grade according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3
3. its relationship to the study drug (suspected / not suspected),
4. the action(s) taken and, as relevant, the outcome.

### 3.5.3.5 Serious adverse events

Information about all serious adverse events will be collected and recorded on the Serious Adverse Event Report Form. To ensure patient safety each serious adverse event must also be reported to Novartis within 24 hours of learning of its occurrence. A serious adverse event is an undesirable sign, symptom or medical condition which:

1. is fatal or life-threatening
2. requires or prolongs hospitalization
3. results in persistent or significant disability/incapacity
4. constitutes a congenital anomaly or a birth defect
5. is medically significant (**including a diagnosis of ONJ as per Section 3.5.3.1; or osteomyelitis at any skeletal site**), in that it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Events not considered to be serious adverse events are hospitalizations for the:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition. (e.g., scheduled inpatient chemotherapy treatment)
- treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen
- admission to a hospital or other institution for general care, not associated with any deterioration in condition
- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

Any serious adverse event occurring after the patient is randomized or begins taking study medication and until 4 weeks after the patient has stopped study participation must be reported.

Serious adverse events occurring more than 4 weeks after study discontinuation need only be reported if a relationship to the Novartis study drug (or therapy) is suspected. Instructions about completing initial and follow-up Serious Adverse Event Report Forms and sending them to Novartis are given in [Section 9.1.1](#). (Instructions for rapid notification of serious adverse events).

### 3.5.3.6 Pregnancies

Any pregnancy that occurs during study participation should be reported using a Clinical Trial Pregnancy Form. To ensure patient safety each pregnancy must also be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications. Instructions about completing initial and follow-up Clinical Trial Pregnancy Forms and sending them to Novartis are given in [Section 9.1.2](#). (Instructions for rapid notification of pregnancies).

### **3.5.3.7 Laboratory evaluations**

All laboratory evaluations will be done prior to study drug infusion at each treatment visit. Both a central and local laboratories will be used for this study. The site local laboratory will be used to evaluate pretreatment serum creatinine prior to each infusion of study drug. The central laboratory will be used for all other evaluations per the schedule in [Table 3-2](#).

The name of the central laboratory, and all details about collection, shipment of samples, reporting of results, and alerting of extreme values can be found in the laboratory folder supplied to the site.

#### **Hematology**

Hematology will include a complete blood count with differential and platelets.

#### **Blood chemistry**

Blood chemistry will include: calcium, albumin, sodium, chloride, potassium, bicarbonate, BUN, creatinine, glucose, phosphate, magnesium, alkaline phosphatase, total bilirubin, total protein, AST, ALT, and LDH.

#### **Bone markers**

Bone markers will include serum bone specific alkaline phosphatase and urine N-telopeptide corrected for creatinine. Urine and serum samples will be frozen and stored for possible future analysis of other bone markers.

### **3.5.3.8 Vital signs**

Vital sign measurement will include:

- Resting (sitting at least five minutes) blood pressure
- Resting (sitting at least five minutes) pulse
- Oral or ear body temperature
- Weight
- Height (at Visit 1 only)

### **3.5.3.9 Physical examination**

A physical examination, including neurologic assessment, will be performed at Visit 1 (screening), Visit 8 (treatment week 24) and end of study visits. Information about the physical examination must be present in the source documentation at the study site. Significant findings that are present prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions Case Report Form. Significant changes in physical condition after the start of study drug which meet the definition of an AE must be recorded on the Adverse Events CRF.

### **3.5.4 Data Safety Monitoring Board (Data Monitoring Committee)**

A Data Safety Monitoring Board (DSMB), also known as Data Monitoring Committee (DMC), consisting of experts in the fields of oncology, nephrology, oral surgery, and statistics, will be established to monitor both safety (renal and oral cavity safety) and efficacy (SRE rate). The DMC will consist of an odd number of members (e.g., five). Data will be provided to the DMC every six months. The trial will remain double-blinded, and treatment group assignment will be known only to DMC members and a designated Novartis statistician and programmer.

The DMC will receive patient listings consisting of the following:

- All patients whose study medication dose must be delayed because of serum creatinine increases as defined in [Section 3.5.3.2 \(Serum creatinine monitoring\)](#).
- All patients who are diagnosed with osteonecrosis of the jaw (ONJ)
- All patients who experience skeletal related events
- All patients who experience Serious Adverse Events

DMC activities will be specified in the charter for their meetings and decisions.

### **3.5.5 Drug levels and pharmacokinetic assessments**

Patients enrolled in the overall study will be invited to participate in the pharmacokinetic (sparse sampling) sub-study. Participation requires written informed consent specifically for the PK sub-study. Zoledronic acid concentrations will be determined using a validated radio-immunoassay.

Concentrations will be determined in:

- Urine
  - second-voided morning specimen (timed)
  - 0 - 2 hours collection
  - 2 - 6 hours collection
- Serum
  - Prior to infusion
  - At the end of infusion
  - 2 hours post start of infusion
  - 6 hours post start of infusion

Time of first urine void and time of second urine void should also be recorded. PK sampling will take place during the first (Visit 2) and tenth (Visit 11) infusions.

## **4 Protocol amendments, other changes in study conduct**

### **4.1 Protocol amendments**

Any change or addition to this protocol requires a written protocol amendment that must be approved by Novartis and the investigator before implementation. Amendments significantly

affecting the safety of subjects, the scope of the investigation or the scientific quality of the study, require additional approval by the IRB at all centers, and by the regulatory authority. A copy of the written approval of the IRB, which becomes part of the protocol, must be given to the Novartis monitor.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Novartis in the interests of preserving the safety of all subjects included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented by him/her for safety reasons, Novartis should be notified and the IRB at the center should be informed within 10 working days.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB of each center must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB approval that can be treated as administrative amendments include:

1. changes in the staff used to monitor trials (i.e. Novartis staff versus a CRO)
2. minor changes in the packaging or labeling of Zometa

#### **4.2 Other changes in study conduct**

Changes in study conduct from this written protocol and any approved amendments are not permitted. Any unforeseen changes in study conduct will be recorded in the clinical study report.

### **5 Data management**

#### **5.1 Data collection**

Designated investigator staff must enter the information required by the protocol onto the study Case Report Forms (CRFs) that are printed on 3-part, non carbon required paper. Field monitors will review the CRFs for completeness and accuracy, and instruct site personnel to make any required corrections or additions. The CRFs are forwarded to the Contract Research Organization (CRO) by the investigational site, one copy being retained at the investigational site. Once the CRFs are received by the CRO, their receipt is recorded, the original copy is placed in the CRO Central Files and the non-carbon required copy is forwarded to the CRO medical data management staff for processing. All CRFs sent to the CRO by investigational sites are reviewed upon receipt for any serious adverse events. At the end of the study, the CRFs are sent to Novartis for archiving purposes.

Data obtained by central analyses of laboratory values, will not be captured on the CRF form but will be recorded by the central laboratory using a suitable format and will be sent to the CRO (as an ASCII file) for loading into the clinical database. Nevertheless, the collection of the corresponding samples as well as the performance of bone surveys and bone scans according to the protocol will be documented in the CRF.

#### **5.2 Database management and quality control**

Data items from the Case Report Forms are entered centrally into the study database by CRO staff using double data entry with verification upon second entry. Text items (e.g. comments)



are entered once and checked manually against the CRFs. Screening failure data will not be entered into the clinical database, only the Screening Log will be entered.

Subsequently, the entered data are systematically checked by the CRO Data Management staff, using error messages printed from validation programs and database listings. Obvious errors are corrected by CRO personnel. Other errors or omissions are entered on Data Query Forms, which are returned to the investigational site for resolution. The signed original and resolved Data Query Forms are kept with the Case Report Forms at the investigational site, and a copy is sent to the CRO, so the resolutions can be entered centrally into the database. Quality control audits of all key safety and efficacy data in the database are made after entering data from each visit.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List which employs the Anatomical Therapeutic Chemical classification system. Coexistent diseases and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Laboratory samples will be processed through a central laboratory and the results will be sent electronically to the designated CRO for data management.

When the database has been declared to be complete and accurate, the database will be locked and unblinded. Any changes to the database after that time can only be made by joint written agreement between the Global Head of Biostatistics and Statistical Reporting and Global Therapeutic Area Head.

## **6 Statistical methods**

### **6.1 Statistical methods**

The primary objective of the study is to determine whether Zometa every 12 weeks is non-inferior to Zometa every 4 weeks. The clinical margin of non-inferiority is 10%. If the non-inferiority is met, then the treatment difference will be evaluated with a two-sided significance level of 0.05.

All patients randomized to the placebo arm prior to Amendment 2 will be switched to Zometa every 4 weeks, will be analyzed separately and will not be included in the efficacy analysis. Summary statistics will be provided.

It is planned that data from all centers participating in the trial will be combined, so that an adequate number of patients will be available for analysis.

Data will be summarized with respect to demographic and baseline characteristics, efficacy measurements, safety measurements and other assessments. Unless otherwise specified, all statistical tests will be performed against a two-sided alternative hypothesis, employing a significance level of 0.05.

#### **6.1.1 Populations**

The intent to treat (ITT) population will include all randomized patients. The ITT population is the Full Analysis Set (FAS) and it will be considered as the primary analysis population.



The Per Protocol Set (PPS) will include all randomized patients who meet the entry criteria and have an evaluation at Visit 5 (at 3 months from the date of randomization), and who do not deviate in a major way from the protocol procedures. For the purposes of determining the PPS, a major protocol deviation is defined as follows:

1. The use of any of the following inhibitors of osteoclastic bone resorption during the study:  
a bisphosphonate other than the study treatment (zoledronic acid), calcitonin, mithramycin, gallium nitrate, denosumab, and commercial zoledronic acid.
2. Missing 50% or more of the scheduled study treatments while on the study.

The Safety Set will include all randomized patients who receive at least one dose of study medication and who have at least one valid post baseline assessment. The Safety Set will be used for safety analysis.

The Full Analysis Set is the primary analysis population. The Per Protocol Set is the secondary analysis population. The claim of non-inferiority requires a statistically significant result for both the FAS and the PPS. If non-inferiority is established, then the superiority of efficacy between treatment arms will be evaluated in both analysis sets.

### **6.1.2 Background and demographic characteristics**

Background and demographic characteristics such as age, gender, race, history of prior SRE, and disease characteristics will be summarized by treatment groups by descriptive statistics (mean, standard deviation, median and range for continuous variables, and frequencies and percentages for categorical variables). Appropriate tests will be used to test the comparability between the treatment groups with respect to these variables. If treatment groups are not comparable in any of these variables, additional analyses may be performed to adjust for the influence, if any, of the variable on the efficacy outcome.

### **6.1.3 Study medication**

Study medication data will be summarized by the number of treatment days on the trial and the cumulative doses of study medication received.

### **6.1.4 Concomitant therapy**

Descriptive statistics such as frequency counts and percentages of patients who use concomitant therapies will be provided by therapy and also by treatment group.

### **6.1.5 Efficacy evaluation**

#### **6.1.5.1 Primary efficacy variable**

The primary efficacy variable is the proportion of patients who experience at least one SRE during the study period (SRE rate) up to week 52.

The proportion of patients who experience at least one SRE will be compared among the treatment groups using stratified Cochran-Mantel-Haenszel test. The stratification factors are the duration of IV bisphosphonates (10-15 months and >15 months) prior to entering the study and the level of urinary N-Tx/Cr N-Tx/Cr (>100 nmol bone collagen equivalent (BCE)/mmol creatinine or ≤ 100 nmol BCE/mmol creatinine) prior to the study.

The primary objective of the study is to determine whether Zometa every 12 weeks is non-inferior to Zometa every 4 weeks. This means that if the upper limit of the 95% confidence interval of the treatment difference (Zometa every 12 weeks vs. Zometa every 4 weeks) in the SRE rate is less than or equal to 10%, then Zometa every 12 weeks is non-inferior to Zometa every 4 weeks. If the non-inferiority criteria are met, then the treatment difference will be evaluated with a two-sided significance level of 0.05.

Primary efficacy analysis will also be done using the ITT and per-protocol population. In addition, sub-group analyses will be performed (e.g., based on type of antineoplastic therapy).

In order to evaluate the impact of the missing values (i.e., patients who discontinue early without SRE events) on the non-inferiority analysis, a sensitivity analysis will be performed on the FAS using the Tipping-point analysis method (Yan et al 2009).

The sub-group analysis will also be performed based on the duration of IV bisphosphonates (10-15 months and >15 months) prior to entering the study.

As supportive analysis, the proportion of patients who experience at least one SRE will also be compared among the treatment groups using stratified Cochran-Mantel-Haenszel test adjusting for the use of IV bisphosphonates (zoledronic acid vs. pamidronate vs. both zoledronic acid and pamidronate) prior to entering the study.

#### **6.1.5.2 Secondary efficacy variables**

Secondary efficacy variables are:

- Time to the first SRE during the study
- SRE free survival
- Time to first individual type of SRE up to week 52
- Skeletal morbidity rate
- Proportion of patients experiencing each individual type of SRE
- Bone pain score, assessed by numerical rating scale and the brief pain inventory (BPI)
- Analgesic consumption as assessed by analgesic score
- Urinary N-Tx /creatinine ratio and serum bone alkaline phosphatase

#### **Time to the 1<sup>st</sup> SRE during the study**

The time to the first SRE is defined as the time from randomization to the date of first occurrence of any SRE which includes at least one of the following: pathologic bone fracture, radiation therapy to bone, surgery to bone, and spinal cord compression. Patients who do not have evidence of any SRE within 52 weeks of study entry, who died or who are lost to follow-up without evidence of any SRE will be considered censored at the last date patients are known to be without any SRE.

The time to first SRE will be compared among the treatment groups using the stratified log-rank test for the ITT and per protocol population. The stratification factor is the duration of IV bisphosphonate therapy prior to enter the study and N-Tx/Cr N-Tx/Cr level prior to the study.

As supportive analysis of this efficacy endpoint, Cox's proportional hazard model, stratified by the randomization strata (Section 3.1), with treatment as the factor will be used to compare the treatments. Time to first SRE will also be summarized and plotted using Kaplan-Meier (K-M) method. If applicable, estimates of 25th percentile, median and 75th percentile of time to first SRE along with corresponding confidence intervals will be provided for each treatment group within each stratum. In addition, the hazard ratio (relative risk) and the corresponding confidence interval will be estimated based on Cox's model with only treatment as a factor within each stratum.

### **SRE free survival**

SRE free survival is defined as the time from randomization to the date of death or first occurrence of any SRE, whichever occurs first. Patients who completed the study without any SRE or who were lost to follow-up without any SRE will be considered censored at the last date they are known to be alive and without any SRE. SRE free survival will be analyzed using similar methods described for the time to first SRE during the study.

### **Time to first individual type of SRE up to week 52**

Time to first individual type of SRE up to week 52 will be compared among the treatment groups using similar methods described for the time to first SRE.

### **Skeletal morbidity rate (SMR)**

The ratio of the number of occurrences of any (or a particular) SRE allowing one event in any 3 week interval, divided by the "time at risk" for each patient will be compared between the treatment groups using Cochran-Mantel-Haenszel test statistic with modified riddit score. Time at risk is defined as the total number of days in the study minus the number of days which fall within a 21 day window of the previous SRE.

SREs will be assigned according to the start date of the SREs. For example, if a course of radiation to bone starts and continues into 21 days and beyond, only the start date of the radiation will be counted for the analysis.

### **Proportion of patients experiencing each individual type of SRE**

Proportion of patients experiencing each individual type of SRE will be summarized and compared among the treatment groups using the stratified Cochran-Mantel-Haenszel test.

### **Bone pain score and analgesic consumption**

The bone pain score assessed by the numerical rating scale and the brief pain inventory (BPI), and analgesic consumption assessed by analgesic score will be summarized over time by treatment group. The change from baseline in BPI pain composite score will be compared among the treatment groups using analysis of covariance (ANCOVA) with baseline value as a covariate and treatment and stratum as factors at 12, 24, 36, and 52 weeks. The change from baseline in numerical rating for pain (and analgesic consumption) will be compared among the treatment groups using Cochran-Mantel-Haenszel test with modified riddit scores at 4, 8

and 12 weeks (at 12, 24, 36, and 52 weeks for analgesic consumption). Within-treatment difference from baseline for these variables will be analyzed by Wilcoxon signed-rank test.

### **Urinary N-Tx/Cr ratio and serum bone specific alkaline phosphatase**

Urinary N-Tx/Cr ratio and serum bone specific alkaline phosphatase will be summarized and compared among the treatment groups using analysis of variance (ANOVA) model with treatment and stratum as factors at each time point. Change from baseline in these parameters will be compared among the treatment groups using analysis of covariance (ANCOVA) with baseline value as a covariate and treatment and stratum as factors at each post-baseline time point.

All secondary efficacy analyses will also be done using the ITT and per-protocol populations. In addition, sub-group analyses will be performed (e.g., based on type of antineoplastic therapy). Also the subgroup analysis will be performed based on the duration of IV bisphosphonates (10-15 months and >15 months) prior to entering the study.

Potential risk factors for SRE would be tested prospectively. Urine N-Tx/Cr > 100 nmolBCE/mg, abnormal creatinine levels and history of prior SRE will be tested, and supported by the baseline stratification procedure at randomization. Additional potential risk factors for SRE would be ascertained at baseline and end of the study; these include: urine N-Tx/Cr > 50 nmolBCE/mg cr, serum bone alkaline phosphatase > 146 U/L, history of prior SRE, 4 or more metastatic bone lesions, ECOG performance status  $\geq 2$ , time since diagnosis of bone metastasis, and moderate to severe pain. These criteria have been identified in retrospective analyses of the registration trials for Zometa to correlate with SREs.

Exploratory analysis will be performed to evaluate the effects of the patient baseline characteristics on primary efficacy endpoints (e.g., prior SRE, entry urine N-Tx).

Multiple events analysis, allowing one event in any 3 week interval, will be explored using Anderson-Gill approach. The same time at risk definition as defined in skeletal morbidity rate (SMR) will be used in this analysis

#### **6.1.6 Safety evaluation**

All safety data analyses will be performed using the Safety Set.

The assessment of safety will be based mainly on the type and frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges including calculated creatinine clearance. Other safety data (e.g., vital signs, physical examination, and special tests) will be considered as appropriate.

Subgroup analyses of safety will also be performed by the type (zoledronic acid, pamidronate, or a sequence of both) and duration (10-15 months vs. > 15 months) of pre-treatment with intravenous bisphosphonates before entering the study. Adverse events will be summarized by presenting, for each treatment group, the number and percentage of patients having any adverse event, having an adverse event in each body system and having each individual adverse event. Any other information collected (e.g. severity or relatedness to study medication) will be listed as appropriate.

Laboratory data including serum creatinine will be summarized by presenting shift tables using extended normal ranges (baseline to most extreme post-baseline value), by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges) and by the flagging of notable values in data listings.

The following adverse events of special interest will be analyzed: renal function deterioration, osteonecrosis of the jaw (ONJ), atrial fibrillation, and cardiac ischemic events. Of note, this study was not designed to capture the newly recognized safety risk of atypical femoral fractures (AFF). However, data on potential cases of AFF will be collected retrospectively and adjudicated [Section 3.5.3.3](#).

The proportion of patients with a diagnosis of osteonecrosis of the jaw (ONJ) will be summarized and compared among treatment groups using Cochran-Mantel-Haenszel test statistics. If possible, time from randomization to the diagnosis of ONJ will be presented as Kaplan-Meier curves and will be compared among the treatment groups by stratified log-rank test. Patients who die, are lost to follow-up, or complete the study without a diagnosis of ONJ will be censored at the last date that patients are known to be without a diagnosis of ONJ.

Serum creatinine will be summarized by treatment group at each time point. Change from baseline in serum creatinine values will also be summarized. The proportion of patients who require delaying of the dose of Zometa due to increase in serum creatinine from baseline will be presented. The proportion of patients who have renal function deterioration will be compared among the treatment groups using a Cochran-Mantel Haenszel test statistic at the end of study. Time from randomization to the first occurrence of renal function deterioration will be compared among the treatment groups using similar methods described above for time to ONJ.

Cardiac ischemic events and atrial fibrillation events will also be summarized by treatment group. Potential atypical subtrochanteric femoral fracture events will be adjudicated ([Section 3.5.3.3](#)). The adjudicated results will also be summarized by treatment group in an exploratory analysis.

Survival data will be presented as a Kaplan-Meier plot by treatment group and will be compared among treatment groups by stratified log-rank test.

### **6.1.7 Interim analyses**

Except for the blinded sample size reassessment, there is no plan for an unblinded interim efficacy analysis. Safety data listings will be provided to the DMC every 6 months. The DMC will monitor safety for the study. See [Section 3.5.4](#).

### **6.1.8 Other topics**

#### **6.1.8.1 Pharmacokinetics (sparse sampling method)**

From the urine samples collected at 0-2h and 2-6h, the amount of drug delivered to the skeleton at 6h after start of infusion will be estimated ([Cremers 2002](#), [Cremers 2003](#), [Cremers 2004](#), [Cremers 2005](#)). This Whole Body Retention at 6h (WBR6h) is calculated by subtracting the amount excreted in urine within 6 hours after start of infusion from the intravenous dose. WBR6h is the only non-compartmental pharmacokinetic parameter that will be calculated.

For each occasion, mean, median, range and standard deviation will be described. Intra-patient variability in WBR6h will be described by Coefficient of Variation. Potential change in WBR6h will be investigated by paired t-test and paired Wilcoxon Ranking test.

Compartmental analysis will be based on the combination of all sparse sampling zoledronic acid data, with data on file from Novartis, and from clinical study [CZOL446E2105], using non-linear mixed effect modeling (NOMEM). The result of compartmental analysis will be reported separately.

#### **6.1.8.2 Pharmacokinetic/pharmacodynamic relationships**

Relationships between the non-compartmental PK parameter WBR6h (Dose-Ae0-6h) (corrected for the dose regimen) and (change in) bone markers will be investigated using exploratory correlation analysis (Pearson, Spearman, log-transformation of data if needed). Pharmacodynamic data (urine N-Tx/Cr) will be expressed as absolute value and percent change from pre-study (baseline) and pre-infusion value. Relationships with PK parameters at each occasion will be explored for pre-infusion and before next infusion level of parameter of bone turnover.

Compartmental analysis will be based on the combination of all sparse sampling zoledronic acid data, and all urine N-Tx/Cr data, with data on file from Novartis and from clinical study [CZOL446E2105], using nonlinear mixed effect modeling (NONMEM). The result of compartmental analysis will be reported separately.

#### **6.1.8.3 Pharmacodynamic - efficacy relationships evaluation**

It will be investigated if those patients with rate of bone resorption (urine N-Tx/Cr) higher than the upper normal limit (both for healthy volunteers and women with postmenopausal osteoporosis) have a higher likelihood of developing SREs. The values of the biochemical markers of bone resorption will be the average pre-infusion level during one year, the pre-infusion levels at 0, 12, 24, 36, and 52 weeks, and the latest pre-infusion level determined prior to the first SRE. The likelihood to develop SREs will be expressed as time to first SRE as well as SMR. The analyses will be performed separately for both Zometa treatment groups, as well as for the combined Zometa treatment groups.

### **6.2 Sample size and power considerations**

Zometa [Study 0010] evaluated the efficacy and safety of Zometa in multiple myeloma and breast cancer patients. In the breast cancer sub-group taking Zometa every 3-4 weeks, who entered the extension phase after completion of the 13 month core phase, the SRE rate on day 360 was estimated to be 24.1% (using K-M estimate). This rate was calculated counting from the entry date of the extension phase to the end of the extension phase. Since no bone surveys or bone scans were performed at specific time points during the extension phase, this SRE rate is assumed to be the symptomatic SRE rate. Furthermore, based on the core phase data in same study, the estimated total SRE rate and symptomatic SRE rate on day 364 (counted from date of randomization to end of core phase) are 47.9% and 25.6% respectively for the Zometa 4 mg every 3-4 weeks group. It is, therefore, estimated in present study that the Zometa every 4 weeks group will have a 48% total SRE rate after one year (365 days) in the study.



Zometa [Study 1501] was a randomized, placebo controlled study of Zometa in Japanese women with bone metastases from breast cancer. This is the only placebo-controlled trial of Zometa in women with bone metastases from breast cancer that measures SRE rates. In [Study 1501], the SRE rates at month 13 were estimated to be 32% and 55% (using K-M estimate), respectively, for the Zometa 4 mg every 4 weeks group and the placebo group. These rates yield a hazard ratio of 2.07 (placebo over Zometa). Based on data from [Study 1501], it was estimated that the treatment difference in SRE rates between Zometa every 4 weeks and placebo was approximately 20%. The 50% of this observed treatment difference is 10%. Therefore the clinical margin for non-inferiority of 10% is derived.

Based on above derivation, it will be assumed that the SRE rate at one year is 58% for Zometa every 12 weeks and 48% for Zometa every 4 weeks. The clinical margin for non-inferiority of 10% is used. Assuming that the dropout rate is 5%, with a one-sided alpha level of 0.05 and 80% power, a total of 650 patients will be randomized (for 1:1 randomization; 325 in each treatment group). The sample calculation is agreed by FDA on July 10, 2007. Prior to Amendment 2, 55 patients were randomized into study (including placebo arm). We will have a total of 705 patients in the study. All patients randomized to the placebo arm prior to Amendment 2 will be switched to Zometa every 4 weeks and will be analyzed separately and will not be included in the efficacy analysis.

The ZOOM study provided important new data on the incidence of SREs during the second year of Zometa therapy in this patient population. The overall pooled SRE incidence (rate) was 15% in ZOOM; this was much lower than anticipated from the assumptions made in the protocol. Because of the similarity in patient populations between ZOOM and OPTIMIZE-2, there may be an overestimation of the assumed SRE rate in OPTIMIZE-2. A decision was made to evaluate the pooled, blinded SRE rate observed in OPIMIZE-2. Pooled, blinded data with a cutoff date of December 10, 2010 had been prepared for an OPTIMIZE-2 DMC meeting. This data included 209 patients randomized post-Amendment 2 who either completed the study or discontinued prematurely. In this patient sub-population, the overall pooled, blinded SRE rate as of the cutoff date was 21%. In contrast, the assumptions for the SRE rates used for the Optimize-2 sample size calculation in the protocol were 58% and 48% for the every 12-week and the every 4-week treatment arms, respectively. With the newly acquired overall blinded, pooled data on the SRE rate in OPTIMIZE-2, the sample size was re-estimated with the statistical requirements (type I error, type II error and the non-inferiority margin) remaining as they were in Amendment 2. A newly estimated standard deviation replaces the assumed standard deviation in Amendment 2. The newly estimated sample size per treatment arm was calculated by the following equation:

$$n_{new} = \frac{n_{amd\ 2} \times \sigma_{newj}^2}{\sigma_{amd\ 2}^2} = \frac{309 \times 0.21 \times 0.79}{0.48 \times 0.52} \approx 206$$

Where  $n_{new}$  and  $\sigma_{new}$  are the newly estimated sample size and standard deviation, respectively, and  $n_{Amend\ 2}$  and  $\sigma_{Amend\ 2}$  are similarly defined for these two estimates in Amendment 2.

The newly estimated sample size will maintain the same probability of detecting the non-inferiority if the SRE rates of the two treatment regimens are truly identical. In consideration





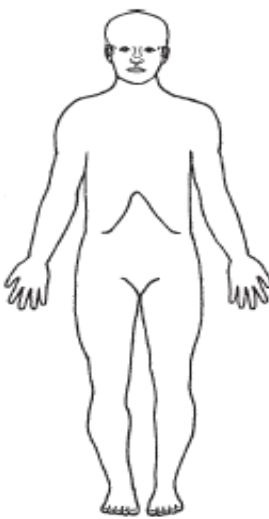
### 7.2.2 Brief pain inventory (BPI)

**Brief Pain Inventory (Short Form)**

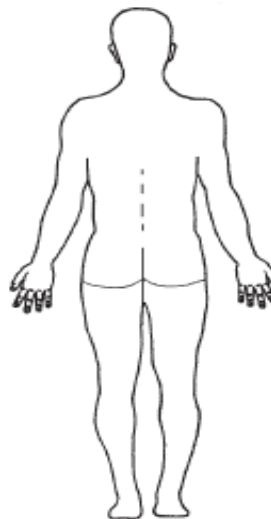
1. *Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?*  1. Yes  2. No

2. *On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.*

Right Front Left



Back Left Right



The form contains two diagrams of a human figure. The left diagram is a front view with labels 'Right', 'Front', and 'Left' above it. The right diagram is a back view with labels 'Left', 'Back', and 'Right' above it. Both diagrams are simple line drawings of a person's torso and limbs, intended for shading or marking areas of pain.

<p>3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours:</p>
0    1    2    3    4    5    6    7    8    9    10
No Pain <span style="float: right;">Pain as bad as you can imagine</span>
4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours:
0    1    2    3    4    5    6    7    8    9    10
No Pain <span style="float: right;">Pain as bad as you can imagine</span>
5. Please rate your pain by circling the one number that best describes your pain on the average:
0    1    2    3    4    5    6    7    8    9    10
No Pain <span style="float: right;">Pain as bad as you can imagine</span>
6. Please rate your pain by circling the one number that tells how much pain you have right now:
0    1    2    3    4    5    6    7    8    9    10
No Pain <span style="float: right;">Pain as bad as you can imagine</span>
7. In the last 24 hours, how much relief have pain treatments or medications provided? (Please circle the one percentage that most shows how much relief you have received.)
0%    10%    20%    30%    40%    50%    60%    70%    80%    90%    100%
No Relief <span style="float: right;">Complete relief</span>

### 7.2.3 Analgesic score

**Type of pain medication administered:**

0 = None

1 = Minor analgesics (aspirin, NSAID, acetaminophen, propoxyphene, etc.)

2 = Tranquilizers, antidepressants, muscle relaxants, and steroids

3 = Mild narcotics (oxycodone, meperidine, codeine, etc.)

4 = Strong narcotics (morphine, hydromorphone, etc.)

### 7.2.4 ECOG score

Criteria for evaluation of performance status:

<b>Grade</b>	<b>Scale</b>
0	Fully active, able to carry out all predisease performance without restriction, (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work. (Karnofsky 70-80)
2	Ambulatory and capable of all self-care but unable to carry out work activities. Up and about more than 50% of waking hours. (Karnofsky 50-60)
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40)
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. (Karnofsky 10-20)

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## **9 Procedures and instructions**

### **9.1 Special safety-related procedures**

#### **9.1.1 Instructions for rapid notification of serious adverse events**

##### **Reporting responsibility**

Each serious adverse event must be reported by the investigator to Novartis within 24 hours of learning of its occurrence, even if it is not felt to be treatment-related. Follow-up information about a previously reported serious adverse event must also be reported within 24 hours of the investigator receiving it. If the serious adverse event is not previously documented (new occurrence) and is thought to be related to the Novartis study drug (or therapy), an Integrated Medical Safety associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an investigator notification, to inform all investigators involved in any study with the same drug (or therapy) that this serious adverse event has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

All diagnosed cases of ONJ should be considered as “medically significant,” irrespective of whether the event meets the definition of “serious adverse event (SAE)” under current health authority guidelines. These cases are therefore to be reported to Novartis CS&E as well as local health authorities under the guideline of SAE reporting (see [Section 3.5.3.4](#))

##### **Reporting procedures**

The investigator must complete the Serious Adverse Event Report Form in English, assess the relationship to study treatment and send the completed, signed form by fax within 24 hours to the local Novartis Integrated Medical Safety. The original copy of the Serious Adverse Event Form and the fax confirmation sheet must be kept with the case report form documentation at the study site

Follow-up information is sent to the same person sent the original Serious Adverse Event Form. A new serious adverse event form is sent, stating that this is a follow-up to the previously reported serious adverse event and giving the date of the original report. Each re-occurrence, complication or

progression of the original event should be reported as a follow-up to that event. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or discontinued study participation. The form and fax confirmation sheet must be retained. Refer to the Novartis guidelines as needed for instructions for completing the Serious Adverse Event Form.

## **Contact persons and numbers**

The telephone and telefax numbers of the contact persons in the local Clinical Research department, at the Clinical Research Organization and in the local department of Clinical Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site.

### **9.1.2 Instructions for rapid notification of pregnancies**

Each pregnancy that started during the study must be reported by the investigator to Novartis within 24 hours of learning of its occurrence. Pregnancies and pregnancy follow-up should be reported on the Clinical Trial Pregnancy Form but any serious adverse event experienced during pregnancy must be reported on the Serious Adverse Event Report Form. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, the presence or absence of any congenital abnormalities, birth defects, maternal or newborn complications and their relation to the Novartis study drug (or therapy). Refer to the Novartis guidelines as needed for instructions for completing the Clinical Trial Pregnancy Form.

### **9.1.3 Emergency procedure for unblinding**

Emergency unblinding should only be done when necessary in order to treat the patient. Emergency code breaks are performed using the IVRS. When the investigator telephones the system to unblind a patient, he/she must provide the requested patient identifying information and confirm the medical necessity for the code break. The investigator will then receive details of the drug treatment for the specified patient and a fax confirming this information. The system will automatically inform the Novartis monitor for the site and the Clinical Trial Leader that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IVRS in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The protocol number, study drug name if available, patient number, and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) will be provided to the patient in case emergency unblinding is required at a time when the investigator and backup are unavailable.

### **9.1.4 Instructions for completing adverse event case report forms**

Each adverse event is to be reported on the Adverse Event Case Report Form provided. Refer to the Case Report Form or to the Case Report Form Completion Guideline for details.

## **9.2 Administrative procedures**

### **9.2.1 Changes to the protocol**

Any change or addition to this protocol requires a written protocol amendment that must be approved by Novartis and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study, require additional approval by the IRB/IEC/REB of all centers, and, in some countries, by the regulatory authority. A copy of the written approval of the IRB/IEC/REB, which becomes part of the protocol, must be given to the Novartis monitor. Examples of amendments requiring such approval are:

1. an increase in drug dosage or duration of exposure of subjects
2. a significant change in the study design (e.g. addition or deletion of a control group)



3. an increase in the number of invasive procedures to which subjects are exposed
4. addition or deletion of a test procedure for safety monitoring.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Novartis in the interests of preserving the safety of all subjects included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented by him/her for safety reasons Novartis should be notified and the IRB/IEC/REB at the center should be informed within 10 working days.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC/REB approval but the IRB/IEC/REB of each center must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB/IEC/REB approval that can be treated as administrative amendments include:

1. changes in the staff used to monitor trials (e.g. Novartis staff versus a CRO)
2. minor changes in the packaging or labeling of study drug.

### **9.2.2 Monitoring procedures**

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and case report forms with the investigators and their staff. During the study the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the case report forms, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and also to ensure that study medication is being stored, dispensed and accounted for according to specifications. Key trial personnel must be available to assist the field monitor during these visits.

The investigator must give the monitor access to relevant hospital or clinical records, to confirm their consistency with the case report form entries. No information in these records about the identity of the subjects will leave the study center. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of serious adverse events and the recording of primary efficacy and safety variables. Additional checks of the consistency of the source data with the case report forms are performed according to the study-specific monitoring plan.

### **9.2.3 Recording of data and retention of documents**

The investigator must complete the case report forms provided, transmit the data as instructed by Novartis at study initiation and must store copies of the case report forms or the Novartis computer that contains them with other study documents (e.g. the protocol, the investigators' brochure and any protocol amendments) in a secure place. All entries to the case report forms must be made as described in the Case Report Form Completion Guideline or as instructed by Novartis at study initiation.

Data on subjects collected on case report forms during the trial will be documented in an anonymous fashion and the subject will only be identified by the subject number, and by his/her initials if also required. If, as an exception, it is necessary for safety or regulatory reasons to identify the subject, both Novartis and the investigator are bound to keep this information confidential.

The investigator must maintain source documents for each patient in the study, consisting of all demographic and medical information, including laboratory data, electrocardiograms, etc, and keep a copy of the signed informed consent form. All information on case report forms must be traceable to these source documents in the patient's file. Data without a written or electronic record will be defined before trial start and will be recorded directly on the case report forms, which will be documented as being the source data.

Essential documents, as listed below, must be retained by the investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). Novartis will notify the investigator(s)/institution(s)

when the study-related records are no longer required. The investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

1. IRB/IEC/REB approvals for the study protocol and all amendments
2. all source documents and laboratory records
3. CRF copies (paper copies or electronic copies on a CDROM, depending on the trial)
4. patients' informed consent forms (with study number and title of trial)
5. FDA form 1572 (as required)
6. any other pertinent study document.

#### **9.2.4 Auditing procedures**

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance Unit exists within Novartis. This unit conducts audits of clinical research activities in accordance with internal Standard Operating Procedures to evaluate compliance with the principles of Good Clinical Practice. A regulatory authority may also wish to conduct an inspection (during the study or even after its completion). If an inspection is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

#### **9.2.5 Handling of study medication**

All study medication will be supplied to the principal investigator by Novartis. Drug supplies must be kept in an appropriate, secure area (e.g. locked cabinet) and stored according to the conditions specified on the drug labels. The investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger, a copy of which must be given to Novartis at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time.

All drug supplies are to be used only for this protocol and not for any other purpose. The investigator must not destroy any partly-used or unused drug supply. At the conclusion of the study, and, as appropriate during the course of the study, the investigator will return all partly-used and unused drug containers, and a copy of the completed drug disposition form to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

#### **9.2.6 Publication of results**

Any formal presentation or publication of data from this trial will be considered as a joint publication by the investigator(s) and appropriate Novartis personnel. Authorship will be determined by mutual agreement. For multicenter studies it is mandatory that the first publication is based on data from all centers, analyzed as stipulated in the protocol by Novartis statisticians, and not by the investigators. Investigators participating in multicenter studies agree not to present data gathered from one center or a small group of centers before the full publication, unless formally agreed to by all other investigators and Novartis.

Novartis must receive copies of any intended communication in advance of publication (at least 15 working days for an abstract or oral presentation and 45 working days for a journal submission). Novartis will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that confidential information is not being inadvertently divulged and provide any relevant supplementary information.

The investigator may be required to sign the clinical study report, if it is to be used in a registration submission to the health authorities of some countries. For multicenter studies only the coordinating (principle) investigator nominated by Novartis at the start of the trial would provide any needed signature.

### **9.2.7 Disclosure and confidentiality**

By signing the protocol, the investigator agrees to keep all information provided by Novartis in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by Novartis (protocols, investigators' brochures, case report forms and other material) will be stored appropriately to ensure their confidentiality. The information provided by Novartis to the investigator may not be disclosed to others without direct written authorization from Novartis, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

### **9.2.8 Discontinuation of study**

Novartis reserves the right to discontinue any study under the conditions specified in the clinical trial agreement.

## **9.3 Ethics and Good Clinical Practice**

This study must be carried out in compliance with the protocol and the principles of Good Clinical Practice, as described in Novartis standard operating procedures and:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects).

The investigator agrees when signing the protocol to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

### **9.3.1 Institutional Review Board/Independent Ethics Committee**

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. The name and occupation of the chairman and the members of the IRB/IEC/REB must be supplied to Novartis. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

### **9.3.2 Informed consent**

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB/IEC/REB approval. Novartis supplies a proposed informed consent form, which complies with regulatory requirements and is considered appropriate for the study. Any changes

to the proposed consent form suggested by the Investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB approval.

### **9.3.3 Declaration of Helsinki**

The investigator must conduct the trial in accordance with the principles of the Declaration of Helsinki. Copies of the Declaration of Helsinki and amendments will be provided upon request or can be accessed via the website of the World Medical Association at [http://www.wma.net/e/policy/17-c\\_e.html](http://www.wma.net/e/policy/17-c_e.html).

## **10 Protocol adherence**

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.