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INDICATION: Treatment of Bone Metastases

SPONSOR: Novartis

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1 Executive Summary and Statistical Findings

1.1 Overview of the Studies Reviewed

Zometa® or zoledronate (zoledronic acid for injection) is proposed to be used for the treatment of osteolytic, osteoblastic, and mixed bone metastases of solid tumors and osteolytic lesions of multiple myeloma, in conjunction with standard antineoplastic therapy in cancer patients. Zometa® is a member of a class of compounds known as bisphosphonates and it is a third generation bisphosphonate. Bisphosphonates are effective inhibitors of osteoclastic bone resorption. Zometa® has been approved for the treatment of hypercalcemia of malignancy. The current NDA application describes three randomized clinical trials with Zometa® in the treatment of cancer patients with bone metastases.

Study 010 was a multicenter, double-blind, randomized, controlled, Phase III parallel comparative trial of i.v. zoledronic acid (Zometa, 4 mg or 8 mg) versus iv. Aredia (90 mg) (pamidronate) as an adjunct to standard therapies in patients with multiple myeloma and breast cancer with cancer related bone lesions. The active control agent, intravenous pamidronate (90 mg) is the current standard of care for the treatment of patients with predominantly osteolytic bone metastases from breast cancer and osteolytic lesions associated with multiple myeloma. Pamidronate (90 mg via 2- to 4-hour infusion every 3 to 4 weeks) has been shown to significantly prolong the time to first skeletal-related event (SRE) and to significantly reduce the incidence of SREs for up to 21 months in patients with multiple myeloma and up to 2 years in patients with breast cancer and osteolytic lesions compared with placebo. A total of one-thousand-six-hundred-and-forty-eight (1648) patients were randomized in this trial: 564 patients in the zoledronic acid 4 mg treatment group, 526 patients in the zoledronic acid 8/4 mg treatment group and 558 patients in the Aredia 90 mg treatment group. The study was stratified by three cancer patient groups: Myeloma, Breast cancer with chemotherapy and breast cancer with hormonal therapy. The primary objective of study 010 was to show “non-inferiority” of i.v. Zometa to Aredia in preventing skeletal-related events (SRE) in Stage III myeloma or Stage IV breast cancer patients with cancer related bone lesions. The primary efficacy endpoint was the proportion of patients experiencing at least one SRE up to 13 months, defined as, radiation therapy to bone, surgery to bone, pathologic bone fracture or spinal cord compression.

Study 011 was a randomized, double-blind, multicenter, parallel-group, placebo controlled Phase III study conducted in a total of 773 patients aged 18 years or over with ECOG performance status # 2 and bone metastases from solid tumors other than breast or prostate cancer. Patients were randomized in a double-blind fashion to receive either zoledronate 4 mg intravenously, or zoledronate 8 mg intravenously, or a placebo intravenous infusion every three weeks for 12 doses in

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addition to their antineoplastic therapy. The randomized treatment assignment ratio was to be 1:1:1 (257 patients were randomized to the 4 mg zoledronic acid group, 266 patients to the 8 mg zoledronic acid group, and 250 patients to the placebo group). The randomization was stratified by site of cancer 'lung cancer' versus 'other solid tumor'. Patients were to be treated for 36 weeks (9 months). In addition, all patients were to receive 500 mg of calcium orally and a multivitamin tablet (containing 500 I.U. of vitamin D) daily throughout the study. The primary study objective of this study was to assess the efficacy of zoledronate therapy (4 or 8 mg) in addition to antineoplastic therapy, compared to antineoplastic therapy alone, in preventing skeletal-related events in patients with any cancer with bone metastases other than breast cancer, multiple myeloma or prostate cancer. The primary efficacy variable was the proportion of patients with any SRE exclusive of tumor induced hypercalcemia (TIH or -HCM) at 9 months.

Study 039 was an international, multicenter, randomized, double-blind, placebo-controlled, parallel study conducted in prostate cancer patients with a history of metastatic bone disease who have a rising serum PSA concentration despite treatment with first-line hormonal therapy for metastatic disease. Patients were randomized in a double-blind fashion to receive either zoledronate 4 mg intravenously, or zoledronate 8 mg intravenously, or a placebo intravenous infusion every three weeks in addition to their antineoplastic therapy. The randomized treatment assignment ratio was to be 1:1:1 (214 patients were randomized to zoledronate 4 mg, 221 patients to the zoledronate 8 mg group, and 208 patients to the placebo group). The randomization was stratified by prostate cancer history (no metastatic disease present at the time of the initial diagnosis of prostate cancer versus metastatic disease present at the time of the initial diagnosis). In addition all patients were to receive 500 mg of calcium orally and multivitamin tablet (containing 400-500 I.U. of vitamin D) daily throughout the study. The primary objective of this study was to assess the efficacy of zoledronate treatments (4 or 8 mg) in addition to antineoplastic therapy, compared to antineoplastic therapy alone to prevent skeletal-related events (SREs) in prostate cancer patients with a history of metastatic bone disease who have developed biochemical progression of disease. SREs were defined as pathologic bone fracture events, spinal cord compression events, surgery to bone, and radiation therapy to bone (including the use of radioisotopes). The primary efficacy variable in this study was the proportion of patients having at least one skeletal-related event at 15 months.

1.2 Some Statistical and Technical Issues

- The protocol stated objective of showing “non-inferiority” of i.v. Zometa to Aredia in study 10 is not appropriate according to the current understanding of non-inferiority trials. The objective should have been stated as demonstrating

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- the *effectiveness* of i.v. Zometa through a non-inferiority trial with Aredia as the active comparator.
- The protocol defined primary efficacy parameter in all the three studies is proportion of skeletal related events. This proportion was computed in each treatment arm as the ratio of the number of first skeletal related events at 12, 9 and 15 months in studies 010, 011 and 039, respectively, to the number of patients randomized to the treatment arm. These estimates of the skeletal event rates may be biased as there is high dropout rate: $\geq 27\%$ in study 010 (at 12 months), $\geq 56\%$ in study 011 (at 9 months), and $\geq 46\%$ in study 039 (at 15 months).
 - Time to first occurrence of skeletal-related event is preferred to the protocol specified analysis of proportion of skeletal-related events and it was recommended by the agency (statistical reviews dated 6/18/98 and 8/20/98). Due to high dropout rate in all three studies, the analysis of proportion at a fixed time point is questionable. The time to skeletal-related event analysis should be considered as the primary analysis, which can take into account censoring of observations during the course of the study.
 - In all the three studies, the 8 mg Zometa® treated arm was not included in the efficacy evaluation because of the Amendment 4 of the protocols to decrease the dose to 4 mg of every patient in the 8 mg due to observed renal toxicity. This change occurred after all the patients were enrolled in each of the studies and the patients in the 8 mg arm had received substantial treatment. However, if the efficacy analysis for the 8 mg arm was also performed then type I error rate should be adjusted in the comparisons of 4 mg versus placebo treated arms.

1.3 Principal Findings

Study 010:

The primary efficacy endpoint was the proportion of patients experiencing at least one SRE, defined as radiation therapy to bone, surgery to bone, pathologic bone fracture or spinal cord compression. The sponsor's analysis result is summarized in Table 1.3.1.

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Table 1.3.1: Proportion of SRE to Month 13 by Stratum (Sponsor’s Analyses)

	Zometa (4mg)	Aredia	Difference Δ (95% CI)*	Log-rank p-value
Myeloma	47% (86/183)	49% (82/167)	-2% (-12.6%, 8.4%)	0.694
Breast (Chemo)	44% (79/178)	43% (78/181)	1% (-9%, 11.6%)	0.806
Breast (Hormonal)	42% (83/200)	47% (97/207)	-5% (-15%, 4.3%)	0.277
Total	44% (248/561)	46% (257/555)	-2% (-7.9%, 3.7%)	0.461 OR=0.919

* Δ =Zometa-Aredia

During design of the non-inferiority study, the sponsor defined a “non-inferiority” margin of 8% which is based on preserving 60% of the point estimate of the active control effect (Aredia vs. placebo). By reviewing the original protocol and the original studies comparing Aredia with placebo, the active control effect was determined based upon the following data (Table 1.3.2):

Table 1.3.2: Active Control (Aredia vs. Placebo) Effect by Studies (012, 018, 019)

	Placebo	Aredia	Difference Δ (95% CI)*	Log-rank p-value
Myeloma	44% (79/179)	28% (56/198)	16% (6.2%, 25.5%)	0.001
Breast (Chemo)	56% (110/195)	43% (79/185)	13.7% (3.8%, 23.7%)	0.007
Breast (Hormonal)	55% (104/189)	47% (85/182)	8% (-1.8%, 18.5 %)	0.108
Total	52.0% (293/563)	38.9% (220/565)	13.1% (7.3%, 18.9%)	<0.0001 OR**=1.702

* Δ =Placebo-Aredia; **OR= Odds Ratio

From current understanding of active control non-inferiority trial, margins defined in terms of point estimate of the control effect tends to be liberal [1, 2, 3]. Since there is only one active control non-inferiority trial and there are only a few historical randomized studies for the assessment of the control effect, the margin

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of the non-inferiority test should be defined based on an Aredia effect estimated by the lower limit of the 95% CI.

Table 1.3.3 summarizes the results of “Non-inferiority” analysis for study 010.

Table 1.3.3: Results of “Non-inferiority” Analysis

Method	Zole 4mg-Aredia Δ (95% CI)	Placebo- Aredia Δ (95% CI)	“Non-inferiority” Test**
8% Margin	-2% (-7.9%,3.7%)		Yes (Upper limit 3.7% <8%)
3.65%* Margin	-2% (-7.9%,3.7%)	13.1% (7.3%,18.9%)	No (Upper limit 3.7% >3.65%)

* 3.65% margin is calculated based on 50% of the lower limit of 95% CI of the estimator of the Aredia effect.

** Test result is significant at 0.05 level if the upper limit of 95% CI of Zometa effect (3.7%) is less than the given margin.

Table 1.3.4 summarizes the results of time to first SRE analysis for study 010.

Table 1.3.4: Time to First SRE by Stratum and Treatment Arm

	N	Median (95%CI)	Hazard Ratio (95% CI)	Log-rank p-value
Myeloma Aredia Zol 4 mg	167 183	301(191, ---) 372(225, 504)	.97(.71, 1.31)	0.82
Breast(CT) Aredia Zol 4 mg	181 178	366(259, ---) 364(249, ---)	.96(.70, 1.32)	0.81
Breast(HT) Aredia Zol 4 mg	207 200	370(258, ---) >380 (---, --)	.83(.62, 1.12)	0.22
Total Aredia Zol 4 mg	555 561	363(273, 399) 373(350, 504)	.92(.77, 1.09)	0.31

Study 011:

The primary efficacy variable was the proportion of patients experiencing at least one SRE (-HCM). Per sponsor analysis by month 9 both the zoledronic acid 4 mg and 8/4 mg groups had a lower proportion than the placebo group (Table 1.3.5).

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Table 1.3.5: Proportion of Patients Having SRE (-HCM) up to Month 9 by Stratum and Treatment Group (ITT Patients) – Sponsor’s Analysis

	Proportion	95% C.I. and P-value for the difference	
		Zol 4 mg	Zol 8/4 mg
Lung Cancer			
Placebo	59/130 (45%)	(-15.6%,8.4%), p=0.557	(-23.3%,0.1%), p=0.053
Zol 4 mg	56/134 (42%)	-	(-19.5%,3.5%), p=0.175
Zol 8/4 mg	47/139(34%)	-	-
Other Solid Tumors			
Placebo	52/120 (43%)	(22.2%,2.2%), p=0.110	(-20.1%,4.3%), p=0.205
Zol 4 mg	41/123 (33%)	-	(-9.7%,13.9%), p=0.727
Zol 8/4 mg	45/127 (35%)	-	-
Total			
Placebo	111/250 (44%)	(-15.2%,1.9%), p=0.127	(-18.2%,-1.4%), p=0.023
Zol 4 mg	97/257 (38%)	-	(-11.4%,5.1%), p=0.452
Zol 8/4 mg	92/266 (35%)	-	-

Table 1.3.6 summarizes the results of time to first SRE analysis for study 011.

Table 1.3.6: Analysis of Time to First Skeletal Related Event Truncated at 9 Months Using Kaplan-Meier Estimation Procedure (ITT Population FDA Analysis)

	Event Rate at 9 Months	N	Median Time to Event in days (95% C.I.)	Hazard Ratio (95% C.I.)	P-value (Comparison to Placebo using Log-rank test)
Lung Cancer					
Placebo	67.9%	130	151 (90, 202)		
Zol 4 mg	60.7%	133	168 (154, *)	0.785 (0.544, 1.132)	0.19
Zol 8/4 mg	53.6%	139	249 (175, *)	0.673 (0.459, 0.987)	0.04
Other Solid Tumors					
Placebo	58.2%	120	168 (106, *)		
Zol 4 mg	43.9%	123	* (174, *)	0.664 (0.438, 1.009)	0.05
Zol 8/4 mg	52.4%	127	198 (156, *)	0.826 (0.553, 1.234)	0.35
Total					
Placebo	63.2%	250	163 (106, 188)		
Zol 4 mg	52.8%	256	230 (168, *)	0.733 (0.557, 0.965)	0.026
Zol 8/4 mg	53.0%	266	219 (172, *)	0.743 (0.563, 0.980)	0.035

* = Not Reached

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Study 039:

The primary efficacy variable was the proportion of patients experiencing at least one SRE (-HCM). Per sponsor analysis by month 15 both the zoledronic acid 4 mg and 8/4 mg groups had a lower proportion than the placebo group (Table 1.3.7).

Table 1.3.7: Proportion of Patients Having SRE (-HCM) up to Month 15 by Stratum and Treatment Group (ITT Patients) – Sponsor’s Analysis

	Proportion	95% C.I. and P-value for the difference	
		Zol 4 mg	Zol 8/4 mg
No Initial Metastases			
Placebo	54/116 (47%)	(-24.4%,0.9%), p=0.069	(-21.5%,3.0%), p=0.140
Zol 4 mg	40/115 (35%)	-	(-9.4%,14.5%), p=0.679
Zol 8/4 mg	50/134 (37%)	-	-
With Initial Metastases			
Placebo	38/92 (41%)	(-23.6%,3.6%), p=0.152	(-15.5%,13.3%), p=0.884
Zol 4 mg	31/99 (31%)	-	(-4.9%,22.7%), p=0.206
Zol 8/4 mg	35/87 (40%)	-	-
Total			
Placebo	92/208 (44%)	(-20.3%,-1.8%), p=0.021	(-15.1%,3.6%), p=0.222
Zol 4 mg	71/214 (33%)	-	(-3.7%, 14.3%), p=0.255
Zol 8/4 mg	85/221 (38%)	-	-

Table 1.3.8 summarizes the results of time to first SRE analysis for study 039.

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Table 1.3.8: Analysis of Time to First Skeletal Related Event Truncated at 15 Months Using Kaplan-Meier Estimation Procedure (ITT Population FDA Analysis)

	Event Rate at 9 Months	N	Median Time to Event in days (95% C.I.)	Hazard Ratio (95% C.I.)	P-value (Comparison to Placebo using Log-rank test)
No Initial Metastases					
Placebo	59.6%	116	304 (198, *)		
Zol 4 mg	45.6%	115	* (291, *)	0.673 (0.446, 1.016)	0.058
Zol 8/4 mg	50.7%	134	419 (251, *)	0.805 (0.547, 1.185)	0.270
With Initial Metastases					
Placebo	54.0%	92	335 (244, *)		
Zol 4 mg	44.4%	99	* (364, *)	0.673 (0.446, 1.016)	0.085
Zol 8/4 mg	57.0%	87	346 (209, *)	1.091 (0.689, 1.728)	0.709
Total					
Placebo	57.2%	208	321 (252, *)		
Zol 4 mg	44.9%	214	* (383, *)	0.661 (0.484, 0.903)	0.009
Zol 8/4 mg	53.2%	221	363 (255, *)	0.912 (0.679, 1.226)	0.541

* = Not Reached

3.1 Conclusions

The “non-inferiority” test in Study 010 demonstrates marginal effectiveness ($p=0.052$) with respect to proportion of SREs at 12 months of zoledronate 4mg arm, using a margin of 3.65% which is defined as preserving 50% of the lower limit of the 95% CI of the point estimate of the Aredia effect. The original selection of 8% margin is not acceptable based on the current understanding because it tends to be liberal.

Study 011 has failed to demonstrate efficacy of 4 mg zoledronate over placebo treated group in reducing the proportion of SREs at 9 months per protocol specified analysis (P -value=0.127). The protocol specified estimates of the proportion of SREs may be biased estimates because of high dropout rate. The sponsor was advised by the agency during the protocol development stage to consider time to first SRE as the primary efficacy parameter, which can take into account censoring of observations during the course of the study. Therefore, in order to account for the early censoring of the observations, this reviewer conducted time to first SRE analysis using Kaplan-Meier estimation procedure, which was recommended by the agency as the primary analysis, truncating the maximum follow up time at 9 months. There appears to be a statistically significant difference between the Zoledronate 4 mg group and placebo group ($p=0.026$, 2-sided log-rank test) by this analysis.

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In study 039, there is a statistically significant difference between zoledronate 4 mg and placebo groups ($p=0.021$) with respect to the proportion of SREs at 15 months as defined in the protocol. However, the per protocol estimates of the proportion of SREs may be biased estimates because of high dropout rate. The sponsor was advised by the agency during the protocol development stage to consider time to first SRE as the primary efficacy parameter, which can take into account censoring of observations during the course of the study. Therefore, in order to account for the early censoring of the observations, this reviewer conducted time to first SRE analysis using Kaplan-Meier estimation procedure, truncating the maximum follow up time at 15 months. There is a statistically significant difference between the zoledronate 4 mg group and placebo group ($p=0.009$, 2-sided log-rank test).

In these reviewers' opinion the results of Studies 11 and 39 support efficacy of zoledronate 4 mg given intravenously versus placebo given intravenously in patients with bone metastases from solid tumors other than breast cancer, and the results of Study 10 suggest marginal effectiveness of zoledronate 4 mg given intravenously in patients with bone metastases from breast cancer and multiple myeloma based on a "non-inferiority" test using Aredia as the active control .

2 Statistical Review and Evaluation of Evidence

2.1 Introduction

Zometa® or zoledronate (zoledronic acid for injection) is proposed to be used for the treatment of osteolytic, osteoblastic, and mixed bone metastases of solid tumors and osteolytic lesions of multiple myeloma, in conjunction with standard antineoplastic therapy in cancer patients. Zometa® is a member of a class of compounds known as bisphosphonates and it is a third generation bisphosphonate. Bisphosphonates are effective inhibitors of osteoclastic bone resorption. Zometa® has been approved for the treatment of hypercalcemia of malignancy.

The current NDA application describes clinical trials with Zometa® in the treatment of cancer patients with bone metastases. Pivotal efficacy data in the treatment of bone metastases are provided by three double-blind studies (010, 011 and 039), two of which (011, 039) were placebo-controlled, and the other (010) active-controlled, the active control being pamidronate (Aredia®). Study 010 was conducted in patients with bone metastases breast cancer or multiple myeloma. Study 011 was conducted in patients with any cancer with bone metastases other than breast cancer, multiple myeloma or prostate cancer. Study 039 was conducted in prostate cancer patients with bone lesions.

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Statistical review and evaluation of evidence of each of the studies 010, 011 and 039 are presented, respectively, in sections 2.3, 2.4 and 2.5 of this review. An overall statistical evaluation of collective evidence and conclusions are presented in section 3 of this review.

2.2 Some Statistical Issues:

- The protocol stated objective of showing “non-inferiority” of i.v. Zometa to Aredia in study 10 is not appropriate according to the current understanding of non-inferiority trials. The objective should have been stated as demonstrating the *effectiveness* of i.v. Zometa through a non-inferiority trial with Aredia as the active comparator.
- The protocol defined primary efficacy parameter in all the three studies is proportion of skeletal related events. This proportion was computed in each treatment arm as the ratio of the number of first skeletal related events at 12, 9 and 15 months in studies 010, 011 and 039, respectively, to the number of patients randomized to the treatment arm. These estimates of the skeletal event rates may be biased as there is high dropout rate: $\geq 27\%$ in study 010 (at 12 months), $\geq 56\%$ in study 011 (at 9 months), and $\geq 46\%$ in study 039 (at 15 months).
- Time to first occurrence of skeletal-related event is preferred to the protocol specified analysis of proportion of skeletal-related events and it was recommended by the agency (statistical reviews dated 6/18/98 and 8/20/98). Due to high dropout rate in all three studies, the analysis of proportion at a time point is questionable. The time to skeletal-related event analysis should be considered as the primary analysis, which can take into account censoring of observations during the course of the study.
- In all the three studies, the 8 mg Zometa® treated arm was not included in the efficacy evaluation because of the Amendment 4 of the protocols to decrease the dose to 4 mg of every patient in the 8 mg due to observed renal toxicity. This change occurred after all the patients were enrolled in each of the studies and the patients in the 8 mg arm had received substantial treatment. However, if the efficacy analysis for the 8 mg arm was also performed then type I error rate should be adjusted in the comparisons of 4 mg versus placebo treated arms.

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2.3 Study 010 (Breast cancer or multiple myeloma patients with bone metastasis)

2.3.1 Background

Study 010 was a multicenter, double-blind, randomized, controlled, phase III parallel comparative trial of i.v. zoledronic acid (Zometa, 4 mg or 8 mg) versus iv. Aredia (90 mg) (pamidronate) as an adjunct to standard therapies in patients with multiple myeloma and breast cancer with cancer related bone lesions.

The active control agent, intravenous pamidronate (90 mg), is the current standard of care for the treatment of patients with predominantly osteolytic bone metastases from breast cancer and osteolytic lesions associated with multiple myeloma. Pamidronate (90 mg via 2- to 4-hour infusion every 3 to 4 weeks) has been shown to significantly prolong the time to first skeletal-related event (SRE) and to significantly reduce the incidence of SREs for up to 21 months in patients with multiple myeloma and up to 2 years in patients with breast cancer and osteolytic lesions compared with placebo.

Study 010 was conducted in 21 countries including United States, Europe, Canada, South Africa and Australia. A total of one-thousand-six-hundred-and-forty-eight (1648) patients were randomized in this trial: 564 patients in the zoledronic acid 4 mg treatment group, 526 patients in the zoledronic acid 8/4 mg treatment group and 558 patients in the Aredia 90 mg treatment group. One site did not meet the GCP standards and 8 patients from this site were excluded from the efficacy analysis. The resulting intention-to-treat population has 1640 patients.

2.3.2 Data Analyzed and Sources

Data used for review is from the electronic submission received on 9/28/01. The network path is "cdsesub1\N21386\N_000\2001-10-02\datasets\CRT\010" in the EDR. The following volumes were reviewed: 1, 67, and 68.

2.3.3 Study Objectives

The primary objective of study 010 was to show non-inferiority of i.v. Zometa to Aredia in preventing skeletal-related events (SRE) in Stage III myeloma or Stage IV breast cancer patients with cancer related bone lesions. The study was completed as planned in the protocol and its amendments. Due to reports of renal SAEs for zoledronic acid 8 mg, patients randomized to zoledronic acid 8 mg were later switched to zoledronic acid 4 mg (Amendment 5; dated 07-Jun-2000); and their data would not be used to support any efficacy claim.

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2.3.4 Efficacy Endpoints

The primary efficacy endpoint was the proportion of patients experiencing at least one SRE, defined as radiation therapy to bone, surgery to bone, pathologic bone fracture or spinal cord compression.

The secondary objectives were to compare the effects of i.v. zoledronic acid 4 mg and/or 8 mg to i.v. Aredia 90 mg with respect to safety and tolerability and the assessment of SRE with or without HCM; time to first SRE; time to progression of bone metastases; time to overall progression of disease; quality of life scores, and BMD.

2.3.5 Sample Size Considerations

For the purposes of sample size calculation, the non-inferiority margin was set at 8%, which is approximately 60% of the difference that was observed in the percentage of patients experiencing SREs during the trials with Aredia and placebo (active vs. placebo).

To power for maximal variance, the percentage of patients with SREs was assumed to be 50% for each treatment group. To test a 50% retention of Aredia effect with the type I error rate of 0.025 and 80% power using a two-group large-sample normal approximation, the required number of patients is 484 per arm. The actual number of patients was sufficient enough for the assumed effect size.

2.3.6 Stratification

The study was stratified by three cancer patient groups: Myeloma, Breast cancer with chemotherapy and breast cancer with hormonal therapy.

2.3.7 Interim Analysis

No interim analysis for efficacy was planned for this study. However, at an interim time point the 8 mg zoledronate arm was dropped due to renal toxicity concerns. The sponsor claimed there was no efficacy interim look.

2.3.8 Efficacy Analysis Methods

The analysis for the primary efficacy variable, the proportion of patients who experience at least one SRE, exclusive of tumor induced hypercalcemia (TIH), during the complete core phase participation up to Month 13, is based upon the 95% CI of the rate difference. Either zoledronate dose (4 or 8 mg) will be declared non-inferior to Aredia 90 mg if the upper limit of the 95% confidence interval (2-sided) for the difference in the percentage of patients having SREs

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after administration of zoledronate and Aredia is below 8%. In terms of testing, this means that the statistical null hypothesis to be tested is $\Delta \geq 8\%$ with the alternative hypothesis $\Delta < 8\%$, where Δ is the above mentioned difference in percentages. The confidence interval will be based on the large-sample normal approximation of the distribution of the difference in the proportions.

Time to event analysis was performed using log-rank test, Cox regression models and Anderson-Gill approach for multiple events.

2.3.9 Sponsor's Results and Statistical Reviewer's Findings/Comments

This section will summarize the results of intention to treat analysis for study 010. The intention to treat patient population includes all patients as randomized (but one site did not meet GCP and was excluded from the analysis). All tests used in this review are two-sided unless otherwise stated.

2.3.9.1 Baseline Characteristics

The baseline demographic characteristics including age, sex, races, weight, and performance status were balanced between the two treatment groups (Zometa 4 mg and Aredia 90 mg). The baseline disease characteristics for both myeloma and breast cancer, including primary site of mets, time to diagnoses, baseline serum creatinine, previous SRE, and baseline quality of life scale scores were examined (Table 2.3.1). A slightly greater proportion of patients in the Aredia 90 mg group had a performance status of ≥ 2 . Patients with multiple myeloma were slightly older and a greater proportion were male than in the overall population. ECOG status was also worse in this group compared with the overall population, although time since initial diagnosis of cancer was much shorter. Characteristics within this stratum were similar across treatment groups, except that abnormal renal function was present in a lower proportion of patients in the Aredia 90 mg group. Within each breast cancer stratum, characteristics were generally similar across treatment groups, except that in the stratum of patients with hormonal therapy, a lower proportion of patients in the zoledronic acid 4 mg group than in the Aredia group were on first line anti-neoplastic therapy or had brain metastases. (Table 2.3.1).

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Table 2.3.1: Baseline Characteristics of Study 010 (Sponsor's Analysis)

	Zol 4 mg N=377	Zol 8/4 mg N=364	Aredia 90 mg N=389
First-Line Anti-neoplastic Therapy			
Yes	161 (42.7%)	180 (49.5%)	182 (46.8%)
No	216 (57.3%)	184 (50.5%)	207 (53.2%)
Previous SRE			
Yes	232 (61.5%)	207 (56.9%)	244 (62.7%)
No	145 (38.5%)	157 (43.1%)	145 (37.3%)
Site of Mets:			
Bone	377 (100%)	364 (100%)	389 (100%)
Liver	82 (21.8%)	69 (19.0%)	97 (24.9%)
Lung	69 (18.3%)	81 (22.3%)	80 (20.6%)
Brain	6 (1.6%)	5 (1.4%)	9 (2.3%)
Other	82 (21.8%)	76 (20.9%)	97 (24.9%)
Time from Init Diag of Cancer to Visit 2 (months)*			
Mean ± SD	78.6 ± 67.19	79.1 ± 74.89	71.9 ± 63.69
Median	59.8	60.3	54.1
Time from Init Diag of Cancer to Bone Mets (months)**			
Mean ± SD	61.2 ± 60.63	65.1 ± 69.75	59.3 ± 59.42
Median	46.0	42.2	44.6
Time from Init Diag of Cancer to 1st Met Disease (months)**			
Mean ± SD	57.0 ± 57.40	60.4 ± 65.83	54.4 ± 57.73
Median	42.0	39.4	37.9
Time from 1st Bone Mets to Visit 2 (months)*			
Mean ± SD	17.5 ± 33.85	14.1 ± 22.87	12.6 ± 21.68
Median	4.0	4.4	3.6
Baseline serum creatinine			
Normal (<1.4 mg/dL)	364 (96.6%)	348 (95.6%)	369 (94.9%)
Abnormal (≥1.4 mg/dL)	11 (2.9%)	11 (3.0%)	15(3.9%)
Missing	2 (0.5%)	5 (1.4%)	5 (1.3%)

* 28 days in a month

** Time from initial diagnosis of cancer to bone metastases or 1st metastatic disease is assigned to 0 when metastatic disease occurred before initial cancer diagnosis.

Source: Post-text table 7.4-2A.

2.3.9.2 Primary Efficacy Analyses: Skeletal Related Event (SRE) Rate

The primary efficacy endpoint was the proportion of patients experiencing at least one SRE, defined as radiation therapy to bone, surgery to bone, pathologic bone fracture or spinal cord compression. The sponsor's analysis result is summarized in Table 2.3.2.

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Table 2.3.2: Proportion of SRE to Month 13 by Stratum (Sponsor’s Analyses)

	Zometa (4mg)	Aredia	Difference Δ (95% CI)*	p-value*
Myeloma	47% (86/183)	49% (82/167)	-2% (-12.6%, 8.4%)	0.694
Breast (Chemo)	44% (79/178)	43% (78/181)	1% (-9%, 11.6%)	0.806
Breast (Hormonal)	42% (83/200)	47% (97/207)	-5% (-15%, 4.3%)	0.277
Total	44% (248/561)	46% (257/555)	-2% (-7.9%, 3.7%)	0.461 OR=0.919

* Δ =Zometa-Aredia

Reviewer’s Comments:

1. The sponsor’s analysis shows that the proportions were 44% and 46% for the zoledronic acid 4 mg group and the Aredia 90 mg group, respectively. The upper limit of the 95% confidence interval of the difference was 3.7%, which was less than the non-inferiority margin of 8% specified in the protocol. In the stratum of breast cancer patients receiving hormonal therapy, the difference in the proportions between the zoledronic acid 4 mg group and the Aredia 90 mg group was -5%, which was the largest difference of the three strata in this study. While In the stratum of breast cancer patients receiving chemotherapy, the difference in the proportions between the zoledronic acid 4 mg group and the Aredia 90 mg group was +1% with an upper bound of 11.6%, implying 11.8% worse than Aredia.
2. The protocol stated objective of showing “non-inferiority” of i.v. Zometa to Aredia in study 10 is not appropriate according to the current understanding of non-inferiority trials. The objective should have been stated as demonstrating the effectiveness of i.v. Zometa through a non-inferiority trial with Aredia as the active comparator. During design of the non-inferiority study, the sponsor intended to preserve 60% of the point estimator of the active control effect (Aredia vs. placebo), which resulted in an 8% non-inferiority margin. By reviewing the original protocol and the original study comparing Aredia with placebo, the active control effect was determined based upon the following data (Table 2.3.3):

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Table 2.3.3: Active Control (Aredia vs. Placebo) Effect by Stratum

	Placebo	Aredia	Difference Δ (95% CI)*	Log-rank p-value
Myeloma	44% (79/179)	28% (56/198)	16% (6.2%, 25.5%)	0.001
Breast (Chemo)	56% (110/195)	43% (79/185)	13.7% (3.8%, 23.7%)	0.007
Breast (Hormonal)	55% (104/189)	47% (85/182)	8% (-1.8%, 18.5 %)	0.108
Total	52.0% (293/563)	38.9% (220/565)	13.1% (7.3%, 18.9%)	<0.0001 OR=1.702

* Δ =Placebo-Aredia

3. The overall SRE difference between placebo and Aredia was 13.1% with 95% CI lower bound of 7.3%, which means that the Aredia was at least **7.3%** better than a placebo in the Aredia trials for previous approval. Thus, we may conclude that the active control effect using these trials is 7.3% if we believe that the patient populations and other conditions and parameters are similar in the historical trial and the current trial (Constant Assumption).
4. Concerns about the constant assumption: To design and analyze a non-inferiority study such as Study 010, requires a determination that the active control drug (Aredia) would have shown efficacy in the new study or current setting, and it also requires an estimation of the size of the effect that Aredia would have shown relative to a placebo in the current setting. A comparison of the previous Aredia/Placebo studies with the current Zometa/Aredia study has been conducted. The comparison was performed as a comprehensive analysis on the issue and consider such factors as the nature and stage of disease/previous treatment; concomitant treatment; timing of events, duration of follow-up, dropout rate, etc. According to the FDA reviewer's request, the sponsor provided a report regarding the comparability of the historical and current studies. Detailed review of this issue can be found in Medical Officer's NDA review. The conclusion is summarized as follows. The comparison was made using current study 010, historical trials 012, 018 and 019.

In the multiple myeloma population, the protocol 010 (current study) patients had a higher proportion of SREs at three months than did the protocol 012 (historical study) patients (25% compared to 10%), but the increase from 3 to 6 months in the proportion of patients with any SRE was similar (15% and 10%). The major differences between the study 010 and study 012 are that

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time since diagnosis was longer and previous history of an SRE was much less in the Aredia/placebo trial. Medical reviewer reviewed the data showed in tables below. These data demonstrated that the Aredia effect would be numerically larger in subgroup of patients with short time to diagnosis (<6 mo) as in the current trial (Table 2.3.4), and the Aredia treatment effect for patient with previous SRE is also larger than in patients had no SRE history (Table 2.3.5).

Table 2.3.4: Proportion of Myeloma Patients with SRE versus Time Since Diagnosis in Study 012

	Time since diagnosis	
	> 6mo	<6mo
Aredia Proportion with SRE	36/150 (24%)	11/55 (20%)
Placebo Proportion with SRE	50/127 (39%)	26/60 (43%)
Placebo - Aredia	15%	23%

Table 2.3.5: Proportion of Myeloma Patients with SRE versus History of Previous SRE

	History of SRE in previous 3 months	
	Yes	No
Aredia Proportion with SRE	35% (23/65)	17% (24/240)
Placebo Proportion with SRE	58% (33/57)	33% (43/130)
Placebo - Aredia	23%	16%

In conclusion, to use the effect of Aredia in study 012 in the testing of non-inferiority is a reasonable approach. In the population of breast cancer patients receiving hormonal treatment the proportions of patients with any SRE at 3 months were similar for the historical controls and the current population (32% and 28%). The increases in pathological fractures were identical, 6%, and were similar for radiation to bone, 5% and 8%. In the population of breast cancer patients receiving chemotherapy the proportion of patients with any SRE at 3 months was identical, and the increases in proportion of patients having any SRE, a pathological fracture or radiotherapy

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to bone were similar, indicating the consistent effect of Aredia in the historical and current studies. In conclusion, when the known demographic and prognostic differences between the historical and current studies are taken into account the descriptive analyses reveal that Aredia had a similar effect in the previous and the current trials.

Preservation of active control effect: The preservation of active treatment effect using the SRE rates can be determined by $(7.3\% - 3.7\%) / 7.3\% = 49.3\%$. Hence, the current trial demonstrated an at least 49.3% retention of Aredia vs. a placebo effect if we believe that the constant assumption holds. This result demonstrates marginal effectiveness ($p=0.052$) with respect to proportion of SREs at 12 months of zoledronate 4mg arm using a margin defined based on 50% retention of the lower limit of 95% CI of the Aredia effect.

5. The SRE event rates over the study period (the longitudinal follow-up) are presented in Tables 2.3.6 (the protocol defined event rate analysis) and 2.3.7. (K-M estimated event rate). Numerically, the Zole 4mg arm shows similar effect pattern to the Aredia arm.

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Table 2.3.6: SRE Event Rate (Intent-to-Treat Patients) over study period

Treatment	N	3 month	6 month	9 month	12 month
Myeloma:					
Aredia 90 mg	167	42 (25%)	66 (40%)	75 (45%)	82 (49%)
Zometa 4 mg	183	56 (31%)	70 (38%)	74 (40%)	86 (47%)
Breast (Chemo):					
Aredia 90 mg	181	49 (27%)	64 (35%)	72 (40%)	78 (43%)
Zometa 4 mg	178	39 (22%)	60 (34%)	68 (38%)	79 (44%)
Breaset(Hormonal)					
Aredia 90 mg	207	58 (28%)	79 (38%)	86 (42%)	97 (47%)
Zometa 4 mg	200	50 (25%)	58 (29%)	70 (35%)	83 (42%)
Overall:					
Aredia 90 mg	555	149(27%)	209(38%)	233(42%)	257 (46%)
Zometa 4 mg	561	145(26%)	188(34%)	212(38%)	248 (44%)

Table 2.3.7: K-M Estimated Event Rate (Intent-to-Treat Patients) Over Study Period

Treatment	N	9 month	Difference in Event Rate	12 month	p-value
Myeloma:					
Aredia 90 mg	167	44.9%	4.9%	47.3%	0.75
Zometa 4 mg	183	40.4%		42.6%	
Breast (Chemo):					
Aredia 90 mg	181	39.2%	1.5%	42.5%	0.68
Zometa 4 mg	178	38.7%		42.1%	
Breaset(Hormonal)					
Aredia 90 mg	207	40.6%	6.6%	43.5%	0.35
Zometa 4 mg	200	34.0%		40.0%	
Overall:					
Aredia 90 mg	555	41.4%	4.0%	44.3%	0.30
Zometa 4 mg	561	37.4%		41.5%	

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2.3.9.3 Secondary Efficacy Analyses

The secondary efficacy endpoints for the study include time to first SRE, skeletal morbidity rate (SMR), and the overall survival. The time to event “Time” defined in the protocol is the time period from the date of randomization to the first date of event or censoring date.

(1) Time to first SRE

Time to first SRE is one of the secondary efficacy endpoints. Table 2.3.8 summarizes the results for study 010.

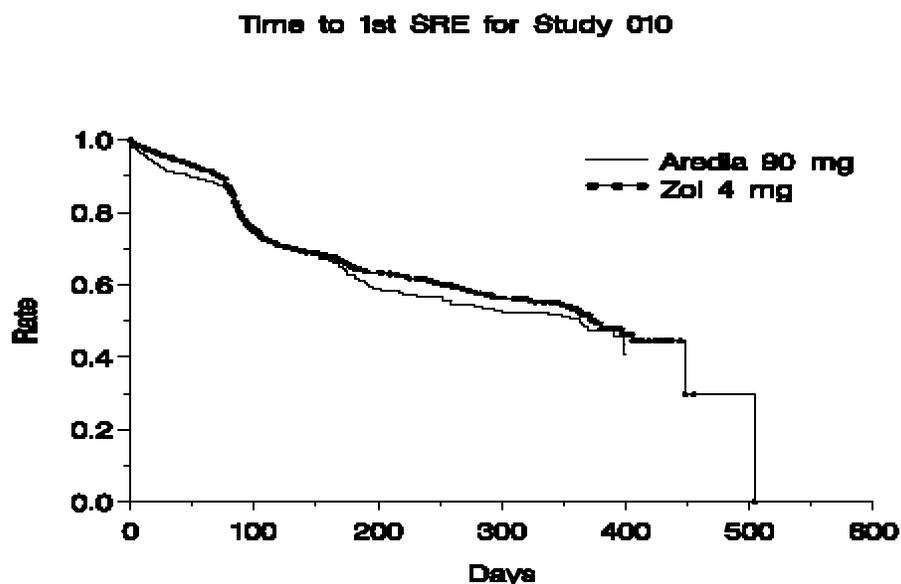
Table 2.3.8: Time to first SRE by Stratum and Treatment Arm

	N	Median (95%CI)	Hazard Ratio (95% CI)	Log-rank p-value
Myeloma				
Aredia	167	301(191, ---)	.97(.71, 1.31)	0.82
Zol 4 mg	183	372(225, 504)		
Breast(CT)				
Aredia	181	366(259, ---)	.96(.70, 1.32)	0.81
Zol 4 mg	178	364(249, ---)		
Breast(HT)				
Aredia	207	370(258, ---)	.83(.62, 1.12)	0.22
Zol 4 mg	200	>380 (---, --)		
Total				
Aredia	555	363(273, 399)	.92(.77, 1.09)	0.31
Zol 4 mg	561	373(350, 504)		

Figure 2.3.1 is the K-M curve for the time to first SRE comparing overall Aredia with Zol 4 mg arm.

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Figure 2.3.1



(2) Time to Multiple Events:

Because the patients could continue on the study after the occurrence of a skeletal-related-event, multiple events might be observed. Analysis for the time to multiple events (SRE) was conducted by the sponsor. The sponsor used the Anderson-Gill approaches for the analysis. The analysis results of multiple events analysis of all SRE (-HCM) showed that there was no difference between the two treatment arms ($p=0.076$), though favoring zoledronic acid 4 mg over Aredia 90 mg. Most of the contribution of this trend was derived from the breast cancer patients with hormonal therapy at study entry.

Reviewer's Comment:

The Anderson-Gill approach requires the assumption of independent events. This assumption may not hold in this study because skeletal related events for each patient might be highly correlated. The meaning of this analysis result should be cautiously interpreted.

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2.3.9.4 Safety Analyses

(1) Overall Survival Time

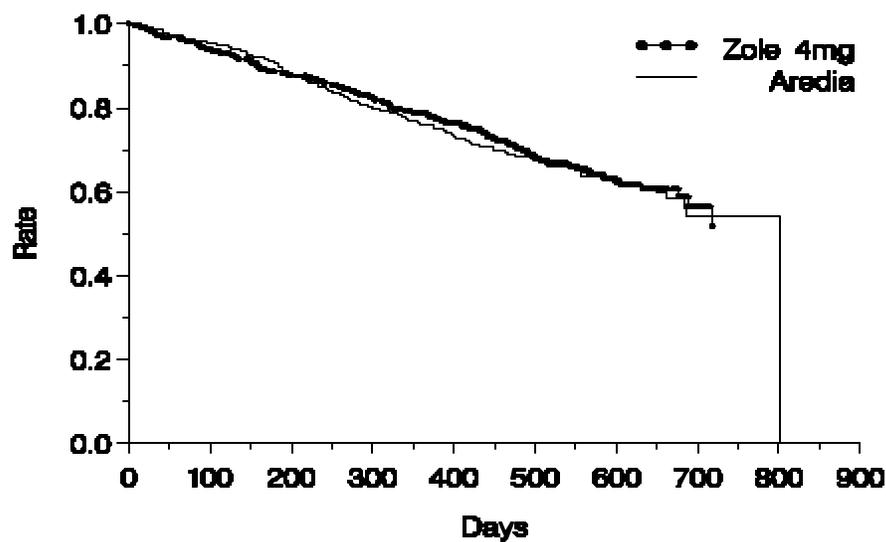
One of the safety endpoints in this study was overall survival. Table 2.3.9 summarizes the survival result using the most updated safety database.

Table 2.3.9: Sponsor’s Analysis for Overall Survival (Safety Population)

ITT Population N=1119	Median (95% CI) (Days)	Hazard Ratio	95% CI for Hazard Ratio	Log-rank P-value
Aredia (179/556)	802(684-802)			
Zole 4mg (171/563)	Not reached	0.958	0.776-1.182	0.55

Figure 2.3.2.

Survival Curves for Study 010



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Reviewer's Comments:

1. The survival curves are presented in Figure 2.3.2.
2. The median survival time for Aredia arm is 802 days, but the median was not reached for the Zole 4mg arm. There is no statistically significant difference between the two treatment arms.

2.3.10 Sponsor's Conclusion and Reviewer's Conclusion/Comments

The primary objective of study 010 was to show non-inferiority in SRE in patients with myeloma and breast cancer with cancer related bone lesions. SRE, the primary objective for study 010, was not statistically significant between the arm and the control arm. Regarding the non-inferiority test, the upper limit of 95% CI for the difference of SRE event rate between the two treatment arms was 3.7%. A 49% retention of Aredia effect can be demonstrated.

Study 010 demonstrated marginal efficacy with respect to proportion of SREs of zoledronate 4mg arm relative to the active control Aredia 30mg arm. The SRE rate in zoledronate 4mg retained at least 49% of the active control Aredia effect in the similar patient population as demonstrated in a previous registration trial under the condition that the current medical practice is similar to the historical trial.

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2.4 Study 011 (Cancer patients with bone metastasis, other than breast cancer, multiple myeloma or prostate cancer)

2.4.1 Background

Bone metastases are frequently one of the first signs of disseminated disease in cancer patients. Skeletal complications due to metastatic disease include bone pain, spinal cord compromise, and pathological fractures. The purpose of this clinical study was to determine if therapy with zoledronate is an effective treatment to decrease the occurrence of skeletal-related complications associated with metastatic bone disease in patients with cancer other than breast cancer, multiple myeloma or prostate cancer. Skeletal-related events included radiation therapy to bone (including the use of radioisotopes), surgery to bone, spinal cord compression, and pathological fracture events. In this study, zoledronate treatment in addition to antineoplastic therapy versus antineoplastic therapy alone was administered to the cancer patients with metastatic bone lesions.

Study 011 was a randomized, double-blind, multicenter, parallel-group, placebo controlled Phase III study conducted in a total of 773 patients aged 18 years or over with ECOG performance status # 2 and bone metastases from solid tumors other than breast or prostate cancer. Patients were randomized in a double-blind fashion to receive either zoledronate 4 mg intravenously, or zoledronate 8 mg intravenously, or a placebo intravenous infusion every three weeks for 12 doses in addition to their antineoplastic therapy. The randomized treatment assignment ratio was to be 1:1:1. Patients were to be treated for 36 weeks (9 months). In addition, all patients were to receive 500 mg of calcium orally and a multivitamin tablet (containing 500 I.U. of vitamin D) daily throughout the study.

2.4.2 Data Analyzed and Sources

Data used for this review was obtained from the electronic submission dated 8/21/2001. The network path is "\\Cdsesub1\n21386\N_000\2001_08_21\CRT\datatasets\011" in the EDR. The following volumes were reviewed: 1, 92, 94, 97, 98, and 100.

2.4.3 Study Objectives

The primary study objective of this study was to assess the efficacy of zoledronate therapy (4 or 8 mg) in addition to antineoplastic therapy, compared to antineoplastic therapy alone, in preventing skeletal-related events in patients with any cancer with bone metastases other than breast cancer, multiple myeloma or prostate cancer. Originally skeletal-related events (SREs) were defined as radiation therapy to bone, a change in antineoplastic therapy to treat bone pain,

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surgery to bone, spinal cord compression, and pathologic fracture events. This definition of SRE was amended in Amendment 2 (Volume 98 Page 8-18) and excluded the change in antineoplastic therapy to treat bone pain as a SRE.

2.4.4 Efficacy Endpoints

The primary efficacy variable was the proportion of patients with any SRE exclusive of tumor induced hypercalcemia (TIH or -HCM)).

The secondary efficacy variables were: (a) proportion of patients with any SRE inclusive of TIH; (b) time to first occurrence of a SRE; (c) skeletal morbidity rate, defined as the ratio of the number of occurrences of any SRE, allowing one event per assessing period (3 weeks), divided by the time at risk for each patient. Time at risk for each assessing period is defined as the duration from the start of the assessing period to the first SRE. If there is no SRE for an assessing period, the whole duration of the assessing period was considered at risk. Time at risk during the study was the sum of time at risk of each assessing period of the study. (d) Time to progression to bone metastases; (e) time to overall progression of disease; (f) quality of life index (FACT-G), performance status (ECOG), Pain (BPI pain composite score), and analgesic scores; (g) biochemical markers; and (h) objective bone lesion response.

Reviewer's Comments:

FDA reviewer of the IND protocol had conveyed to the sponsor that the if the drop-out rate is relatively high, then the primary endpoint, SRE proportion estimate may be biased and had also suggested that the time to the first SRE be used as the co-primary endpoint.

2.4.5 Sample Size Considerations

This trial was designed to have 80% power to detect a 16% difference in the proportion of patients reporting any SRE during the first 9 months of the trial between the two dose levels (4 mg and 8 mg) of zoledronate and placebo. Based on the Bonferroni's adjustment, the samples size was calculated, assuming a 48% incidence rate on placebo; a 32% incidence rate on either dose level of zoledronate, with an overall type I error rate of 0.05 (two-sided). The total sample size was determined to be 570 patients (190 on each arm). It was recommended that 600 patients be enrolled allowing for a 5% noise included in the intent-to-treat population. However, the sample size was increased (Amendment 4, Volume 98, Page 8-33) that at least 700 patients would be enrolled in order to obtain 663 patients (221 patients per treatment arm). It was stated that the amendment was based on the higher than expected overall drop-out rate of 40% and the lower than expected SRE rate of less than 30%. The sample size was

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modified assuming to have 80% power to detect a 14% difference in the proportion of SREs during the first 9 months of the trial between the two dose levels of zoledronate and placebo (Bonferroni adjustment for multiple comparisons, overall type I error rate=0.05).

Reviewer's Comments:

1. The sample size calculations were based on that zoledronate would be considered more efficacious than placebo if either of the two comparisons (4 mg versus placebo or 8 mg versus placebo) was statistically significant at a 2-sided p-value < 0.025 .
2. During the study, the design was amended (Amendment 5) to treat all patients on study in the 8 mg group at 4 mg dose level because of the observed renal toxicity with 8 mg group. In lieu of this, in the Amendment 6 (Volume 98, Page 8-54), it was stated that zoledronate 4 mg will be considered more efficacious than placebo if the comparison for the primary efficacy outcome is statistically significant at 0.05 level (2-sided) favoring zoledronate 4 mg. It should be noted that the original design and calculation of sample size was based on comparing 4 mg versus placebo group at 0.025 level. Dropping a treatment arm (in this case 8 mg group) could potentially inflate the overall type I error rate. (Reference: Tsong, Y, Hung HMJ, Wang SJ, et. al. Dropping a treatment arm in clinical trial with multiple arms, JSM Proceedings, 1997).

2.4.6 Stratification

The randomization was stratified by site of cancer 'lung cancer' versus 'other solid tumor' (Appendix 5, Volume 100, page 8-319).

2.4.7 Interim Analysis

There was no planned interim analysis for this study. However, at an interim time point the 8 mg zoledronate arm was dropped due to renal toxicity concerns. The sponsor claimed there was no efficacy analyses conducted at the interim look.

2.4.8 Efficacy Analyses Methods

The primary efficacy endpoint of proportion of patients with SREs per protocol would be compared between treatment groups using a Cochran-Mantel-Haenszel (CMH) test statistic. 95% confidence intervals by treatment group within each stratum for the proportion of patients reporting SRE exclusive of TIH would be presented. Zoledronate would be considered more efficacious than placebo if either of the two comparisons of the primary efficacy outcome is statistically superior at a two-sided p-value < 0.025 . In Amendment 2 (Volume 98, page 8-20) the primary analysis was modified to state that the analysis of the primary

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endpoint at 9 months would be the primary analysis and that the last observation of each patient before the time point would be carried forward to the respective time points.

The secondary efficacy endpoint of proportion of patients with any SRE inclusive of TIH would be compared between the treatment groups using CMH statistic and 95% confidence intervals by treatment group within each stratum for the proportion of patients reporting any SRE inclusive of TIH would be presented.

Time from randomization to the first occurrence of any SRE, inclusive and exclusive of TIH would be compared between the treatment groups, using stratified survival analysis methods, including Kaplan-Meier product-limit estimates of the survival functions, and the log-rank test. Death not related to SRE would be considered as censored observation. Multiple events analysis, allowing one event every assessing period would be explored using Anderson-Gill approach.

Skeletal morbidity rate (SMR) will be compared between the treatment groups using CMH test statistic with modified ridit scores.

Time to the progression of bone metastases would be compared between the treatment groups using log-rank test. Time to overall progression of disease would be compared between the treatment groups using stratified log-rank test statistic.

FACT-G-total score is defined as the sum of the 4 subscales (physical, functional, social, and emotional). Change from baseline FACT-G-total scores and the 4 subscales would be compared between the treatment groups using analysis of covariance with baseline value as covariate and treatment group and disease population as factors, at 3, 6, and 9 months. The mean of the two BPI pain composite scores and two analgesic use for each 3 month interval would be used for the analysis of BPI pain score and analgesic use, respectively. Change from baseline in mean BPI composite score would be compared between the treatment groups using analysis of covariance with baseline value as a covariate and treatment group and disease population as factors at 3, 6, and 9 months. Change from baseline in mean analgesic use and performance status would be compared between the treatment groups using CMH test statistic with the modified ridit scores at 3, 6, and 9 months.

Reviewer's Comments:

1. Early dropouts and missing assessments were not considered in the above planned analyses.

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2. The infusion time was amended (Amendment 3) from 5 minutes to 15 minutes during the study.
3. After the enrollment was completed in all the three treatment arms, the dose was reduced in the 8 mg arm to 4 mg (Amendment 5) because of renal toxicity. In this Amendment it was also stated that the 8/4 mg arm would not be evaluated for efficacy. However, it should be noted that by the time of this Amendment, majority of the patients had completed the study treatment phase (9 months) or had dropped out of the study.

2.4.9 Sponsor's Results and Reviewer's Findings/Comments

2.4.9.1 Baseline Characteristics

A total of 773 patients were randomized as follows: 257 patients were randomized to the 4 mg zoledronic acid group, 266 patients to the 8 mg zoledronic acid group, and 250 patients to the placebo group. Eligible patients were randomized into two groups: patients with non-small cell lung cancer (NSCLC) and patients with all other types of solid tumor cancers except breast and prostate. Several patients in each treatment group were randomized to the incorrect stratum as follows: 35 patients with small cell lung cancer were randomized into the NSCLC stratum, instead of other solid tumor stratum (12 in the 4 mg group, 10 in the 8/4 mg group, and 13 in the placebo group); 3 patients with NSCLC were randomized into the other solid tumors stratum (one patient in each treatment group). It is reported that 7 patients did not receive treatment with the study medication, one of these 7 patients died prior to receiving any study medication. One patient in the 4 mg group was found to have no evidence of skeletal metastases on the radiographic evaluations performed at study entry and the films for another patient on 8/4 mg group were lost in transit and therefore had no confirmed radiographic evidence of bone metastases. Ten patients, 2 in 4 mg group, 1 in 8/4 mg group, and 7 in the placebo group were unblinded at the study sites. All were discontinued from the study. The following Table 2.4.1a describes the baseline characteristics as presented by the sponsor in the per protocol or safety population (Sponsor's Table 7-3, page 8-52, Volume 92).

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Table 2.4.1a: Baseline Characteristics (Sponsor’s Analysis – Safety Population)

	Total		
	Zol 4 mg N=254	Zol 8/4 mg N=265	Placebo N=247
Age (years)			
N	254	265	247
Mean " SD	62.3" 10.60	60.8" 10.46	62.3" 10.87
Median	63.5	62.0	64.0
Age n (%)			
# 60	106 (41.7%)	124 (46.8%)	98 (39.7%)
> 60	148 (58.3%)	141 (53.2%)	149 (60.3%)
Sex n (%)			
Male	158 (62.2%)	186 (70.2%)	159 (64.4%)
Female	96 (37.8%)	79 (29.8%)	88 (35.6%)
Race n (%)			
Caucasian	226 (89.0%)	237 (89.4%)	223 (90.3%)
Black	15 (5.9%)	15 (5.7%)	12 (4.9%)
Other	13 (5.1%)	13 (4.9%)	12 (4.9%)
Weight (kg)			
N	252	262	245
Mean " SD	72.8" 15.23	74.3" 16.91	71.6" 16.04
Median	72.0	73.0	69.8
Primary site of cancer n (%)			
Lung	124 (48.8%)	134 (50.6%)	123 (49.8%)
Other			
Renal cell carcinoma	27 (10.6%)	28 (10.6%)	19 (7.7%)
Cancer unknown primary	15 (5.9%)	14 (5.3%)	14 (5.7%)
Thyroid	2 (0.8%)	5 (1.9%)	4 (1.6%)
Head and neck	6 (2.4%)	7 (2.6%)	4 (1.6%)
Other	80 (31.5%)	77 (29.1%)	83 (33.6%)
Prior type of therapy			
Chemotherapy	207 (81.5%)	212 (80.0%)	197 (79.8%)
Hormonal	3 (1.2%)	1 (0.4%)	2 (0.8%)
Missing	44 (17.3%)	52 (19.6%)	48 (19.4%)
Previous SRE n (%)			
Yes	166 (65.4%)	180 (67.9%)	179 (72.5%)
No	88 (34.6%)	85 (32.1%)	68 (27.5%)
Serum creatinine n (%)			
Normal (< 1.4 mg/dL)	233 (91.7%)	232 (87.5%)	220 (89.1%)
Abnormal (≥ 1.4 mg/dL)	18 (7.1%)	33 (12.5%)	25 (10.1%)
Missing	3 (1.2%)	0 (0.0%)	2 (0.8%)
Time from initial diagnosis of cancer to bone metastases (month)			
N	254	265	247
Mean " SD	20.3" 46.58	15.5" 39.50	17.2" 33.24
Median	3.8	2.4	2.5
Time from bone metastases to Visit 2 (month)			
N	254	265	247
Mean " SD	4.7" 7.69	4.9" 7.90	5.1" 9.52
Median	1.6	1.8	1.8
ECOG status n (%)			
ECOG 0-1	211 (83.1%)	218 (82.3%)	215 (87.0%)
ECOG ≥ 2	42 (16.5%)	45 (17.0%)	32 (13.0%)
Missing	1 (0.4%)	2 (0.8%)	0 (0.0%)
Analgesic score n (%)			
0	30 (11.8%)	27 (10.2%)	24 (9.7%)
1	39 (15.4%)	44 (16.6%)	38 (15.4%)
2	6 (2.4%)	8 (3.0%)	5 (2.0%)

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	Total		
	Zol 4 mg N=254	Zol 8/4 mg N=265	Placebo N=247
3	93 (36.6%)	86 (32.5%)	76 (30.8%)
4	86 (33.9%)	100 (37.7%)	103 (41.7%)
Missing	0 (0.0%)	0 (0.0%)	1 (0.4%)
BPI composite pain score			
N	234	245	227
Mean " SD	3.6" 2.20	3.3" 1.94	3.4" 1.99
Median	3.5	3.3	3.3
FACT-G total score			
N	230	241	227
Mean " SD	70.1" 15.21	69.3" 16.85	70.8" 17.73
Median	71.0	69.0	71.2

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Table 2.4.1b: Baseline Characteristics (FDA Analysis – ITT population)

	NSCLC			All Others Tumors			Total		
	Zol 4 mg N=134	Zol 8/4 mg N=139	Placebo N=130	Zol 4 mg N=123	Zol 8/4 mg N=127	Placebo N=120	Zol 4 mg N=257	Zol 8/4 mg N=266	Placebo N=250
Age (years)									
N	134	139	130	123	127	120	257	266	250
Mean " SD	63.2"0.8	61.9"0.9	62.5"0.9	61.0"1.1	59.6"0.9	62.5"1.1	62.0"0.7	60.8"0.6	62.3"0.7
Median	64.0	63.0	64.0	62.0	60.0	63.0	63.0	62.0	63.5
Age n (%)									
# 60	54 (40.3%)	60 (43.2%)	51 (39.2%)	55 (44.7%)	65 (51.1%)	48 (40.0%)	109 (42.4%)	125 (47.0%)	99 (39.6%)
> 60	80 (59.7%)	79 (56.8%)	79 (60.8%)	68 (55.3%)	62 (48.9%)	72 (60.0%)	148 (57.6%)	141 (53.0%)	151 (60.4%)
Sex n (%)									
Male	89 (66.4%)	99 (71.2%)	82 (63.1%)	71 (57.7%)	87 (68.5%)	80 (66.7%)	160 (62.3%)	186 (69.9%)	162 (64.8%)
Female	45 (33.6%)	40 (28.8%)	48 (36.9%)	52 (42.3%)	40 (31.5%)	40 (33.3%)	97 (37.7%)	80 (30.1%)	88 (35.2%)
Race n (%)									
Caucasian	121 (90.3%)	123 (88.5%)	119 (91.5%)	108 (87.8%)	115 (90.6%)	107 (89.2%)	229 (90.2%)	238 (89.5%)	226 (90.4%)
Black	3 (2.2%)	8 (5.8%)	5 (3.6%)	12 (9.8%)	7 (5.5%)	7 (5.8%)	12 (4.7%)	15 (5.6%)	12 (4.8%)
Other	10 (6.5%)	8 (5.8%)	6 (4.6%)	3 (2.4%)	5 (3.9%)	6 (5.0%)	13 (5.1%)	13 (4.9%)	12 (4.8%)
Weight (kg)									
N	133	137	128	121	125	119	254	262	247
Mean " SD	72.8"1.3	74.0"1.5	70.0"1.3	72.7"1.5	74.7"1.5	73.3"1.6	72.7"1.0	74.3"1.0	71.6"1.0
Median	72.2	73.0	68.8	71.4	73.0	72.0	72.0	73.0	69.8
Previous SRE									
Yes	44 (33.1)	47 (33.8)	32 (24.8)	44 (36.1)	38 (30.3)	36 (30.3)	88 (34.5)	85 (32.1)	68 (27.4)
No	89 (66.9)	92 (66.2)	97 (75.2)	78 (63.9)	88 (69.7)	83 (69.7)	167 (65.5)	180 (67.9)	180 (72.6)
Serum creatinine									
Normal (< 1.4 mg/dL)	129 (96.3%)	125 (89.9%)	125 (96.1%)	110 (89.4%)	108 (85.0%)	100 (83.3%)	239 (93.0%)	233 (87.6%)	225 (90.0%)
Abnormal (≥ 1.4 mg/dL)	5 (3.7%)	14 (10.1%)	5 (3.9%)	13 (10.6%)	19 (10.6%)	20 (16.7%)	18 (7.0%)	33 (12.4%)	25 (10.0%)
Time from initial diagnosis of cancer to bone metastases (month)									
N	134	139	130	123	127	120	257	266	250
Mean " SD	10.2"2.4	6.5"1.3	8.3"1.4	31.0"5.3	25.5"4.7	26.5"3.9	20.1"2.9	15.6"2.4	17.0"2.1
Median	1.1	0.6	0.6	12.3	4.9	11.3	3.8	2.4	2.6
Time from bone metastases to Visit 2 (month)									
N	134	139	130	123	127	120	257	266	250
Mean " SD	3.6"0.5	3.4"0.4	3.9"0.5	5.9"0.8	6.5"0.9	6.2"1.1	4.7"0.5	4.9"0.5	5.0"0.6
Median	1.3	1.5	1.8	1.9	2.1	2.0	1.6	1.8	1.8
ECOG status n (%)									
ECOG 0-1	110 (82.1%)	118 (85.5%)	116 (89.2%)	102 (84.2%)	100 (80.0%)	102 (90.0%)	212 (83.1%)	218 (82.9%)	218 (87.2%)
ECOG ≥ 2	24	20	14	19	25	18	43	45	32

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	NSCLC			All Others Tumors			Total		
	Zol 4 mg N=134	Zol 8/4 mg N=139	Placebo N=130	Zol 4 mg N=123	Zol 8/4 mg N=127	Placebo N=120	Zol 4 mg N=257	Zol 8/4 mg N=266	Placebo N=250
	(17.9%)	(14.5%)	(10.2%)	(15.7%)	(20.0%)	(10.0%)	(16.9%)	(17.1%)	(12.8%)
Analgesic score n (%)									
0	15 (11.4)	14 (10.1)	10 (7.8)	15 (12.3)	13 (10.2)	14 (11.9)	30 (11.8)	27 (10.2)	24 (9.8)
1	20 (15.2)	30 (21.6)	14 (10.9)	19 (15.6)	14 (11.0)	24 (20.3)	39 (15.4)	44 (16.5)	38 (15.5)
2	3 (2.3)	4 (2.9)	4 (3.1)	3 (2.5)	4 (3.2)	1 (0.9)	6 (2.4)	8 (3.0)	5 (2.0)
3	49 (37.1)	39 (28.1)	42 (32.8)	44 (36.1)	47 (37.0)	34 (28.8)	93 (36.6)	86 (32.3)	76 (30.9)
4	45 (34.1)	52 (37.4)	58 (45.3)	41 (33.6)	49 (38.6)	45 (38.1)	86 (33.9)	101 (38)	103 (41.9)
BPI composite pain score									
N	109	120	106	125	125	121	234	245	227
Mean " SD	3.6"0.2	3.5"0.2	3.4"0.2	3.6"0.2	3.2"0.2	3.4"0.2	3.6"0.1	3.3"0.1	3.4"0.1
Median	3.5	3.5	3.3	3.5	3.0	3.3	3.5	3.3	3.3
FACT-G total score									
N	108	120	106	122	121	121	230	241	227
Mean " SD	69.4"1.3	68.4"1.5	69.8"1.7	70.7"1.5	70.2"1.6	71.7"1.7	70.1"1.0	69.3"1.1	70.8"1.2
Median	70.0	67.1	70.0	71.1	69.0	74.0	71.0	69.0	71.2

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Reviewer's Comments:

1. Table 2.4.1b describes the baseline characteristics of the ITT population as analyzed by the reviewer.
2. Although there appears to be no imbalance between the treatment arms, there are significant differences between the two stratum (lung versus other solid tumors) with respect time from initial diagnosis of cancer to bone metastases, and time from first bone metastases to Visit 2 of the study (study start day). It is not clear as to how this difference in time between the two strata translates to differences or lack of differences with respect to skeletal related events. These patients were also receiving concomitantly anticancer therapy and this may be a confounding factor with the study drug in estimating the reduction in skeletal related events attributable to the study drug in each stratum and treatment group.

2.4.9.2 Primary Efficacy Analyses

The primary efficacy variable was the proportion of patients experiencing at least one SRE (-HCM). Per sponsor analysis by month 9 both the zoledronic acid 4 mg and 8/4 mg groups had a lower proportion than the placebo group. However, there was **no statistically significant difference between 4 mg and placebo groups (p=0.13)** as presented below in Table 2.4.2 (Sponsor Table 9-1, Volume 92, page 8-58).

Table 2.4.2: Proportion of Patients Having SRE (-HCM) up to Month 9 by Stratum and Treatment Group (ITT patients) – Sponsor's Analysis

	Proportion	95% C.I. and P-value for the difference	
		Zol 4 mg	Zol 8/4 mg
Lung Cancer			
Placebo	59/130 (45%)	(-15.6%,8.4%), p=0.557	(-23.3%,0.1%), p=0.053
Zol 4 mg	56/134 (42%)	-	(-19.5%,3.5%), p=0.175
Zol 8/4 mg	47/139(34%)	-	-
Other Solid Tumors			
Placebo	52/120 (43%)	(22.2%,2.2%), p=0.110	(-20.1%,4.3%), p=0.205
Zol 4 mg	41/123 (33%)	-	(-9.7%,13.9%), p=0.727
Zol 8/4 mg	45/127 (35%)	-	-
Total			
Placebo	111/250 (44%)	(-15.2%,1.9%), p=0.127	(-18.2%,-1.4%), p=0.023
Zol 4 mg	97/257 (38%)	-	(-11.4%,5.1%), p=0.452
Zol 8/4 mg	92/266 (35%)	-	-

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Reviewer's Comments:

1. The study has failed to demonstrate efficacy of 4 mg zoledronate over placebo treated group in reducing the proportion of SREs at 9 months. Since the decision of dropping 8/4 mg zoledronate arm for toxicity was made, the efficacy comparison between 8/4 mg arm and placebo arm is not appropriate and may result in type I error adjustment.
2. The estimates of the proportion of SREs presented in Table 2.4.2 may be biased estimates because of high dropout rate (approximately only 27% were treated at 9 months) as presented below in Table 2.4.3. In the least conservative approach, if the total number of events at 9 months in each of the treatment groups are subtracted from the total number of patients that were randomized, then 71/160 patients (44.3%) in zoledronate 4 mg group, 69/173 patients (39.9%) in zoledronate 8/4 mg group, and 69/133 patients (50.4%) in the placebo group received treatment at 9 months. Therefore the dropout rate was at least 56%.

Table 2.4.3: Number of Patients Treated up to 9 Months (FDA Analysis)

	Lung Cancer			Other Solid Tumors			Total		
	Zol 4 mg	Zol 8/4 mg	Placebo	Zol 4 mg	Zol 8/4 mg	Placebo	Zol 4 mg	Zol 8/4 mg	Placebo
Study Start (Visit 2)	134	139	130	123	127	120	257	266	250
3 months	98	96	84	89	80	84	187	176	168
6 months	59	50	48	53	56	48	112	106	96
9 months	38 (28.4%)	30 (21.6%)	35 (26.9%)	33 (26.8%)	39 (30.7%)	32 (26.7%)	71 (27.6%)	69 (25.9%)	67 (26.8%)

3. The sponsor was advised by the agency during the protocol development stage to consider time to first SRE as the primary efficacy parameter, which can take into account censoring of observations during the course of the study. Therefore, in order to account for the early censoring of the observations, this reviewer conducted time to first SRE analysis using Kaplan-Meier estimation procedure, truncating the maximum follow up time at 9 months (Table 2.4.4). Data beyond 9 months was confounded because of cross over of patients to zoledronate treatment group from placebo group. The Kaplan-Meier estimates of the proportion of skeletal event rate at 9 months are higher than those presented in Table 2.4.2 using simple proportion method. This is because the censoring information was incorporated in the Kaplan-Meier estimates. There appears to be a statistically significant difference between the Zoledronate 4 mg group and placebo group ($p=0.026$) by this analysis. In this analysis death before SRE was censored for SRE. Patient with subject ID 12452 the visit 2 date (start date) was after the date of death and therefore this patient was deleted from the analysis. Patients with subject IDs 12451, 12485, 13108, 21719 and 22515 was recorded with time to first SRE greater than survival time and therefore in these patients time to first SRE was replaced with survival time and censored for the SRE. Kaplan-Meier

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estimates of proportion of SREs at 3, 6, and 9 months respectively are presented in Table 2.4.4b.

Table 2.4.4a: Analysis of Time to First Skeletal Related Event Truncated at 9 Months Using Kaplan-Meier Estimation Procedure (ITT Population FDA Analysis)

	Event Rate at 9 Months	N	Median Time to Event in days (95% C.I.)	P-value (Comparison to Placebo using Log-rank test)
Lung Cancer				
Placebo	67.9%	130	151 (90, 202)	
Zol 4 mg	60.7%	133	168 (154, *)	0.19
Zol 8/4 mg	53.6%	139	249 (175, *)	0.04
Other Solid Tumors				
Placebo	58.2%	120	168 (106, *)	
Zol 4 mg	43.9%	123	* (174, *)	0.05
Zol 8/4 mg	52.4%	127	198 (156, *)	0.35
Total				
Placebo	63.2%	250	163 (106, 188)	
Zol 4 mg	52.8%	256	230 (168, *)	0.026
Zol 8/4 mg	53.0%	266	219 (172, *)	0.035

* = Not Reached

Table 2.4.4b: Analysis of Time to First Skeletal Related Event Truncated at 3, 6, and 9 Months Using Kaplan-Meier Estimation Procedure (ITT Population FDA Analysis)

Total	At 3 Months		At 6 Months		At 9 Months	
	Event Rate	*Event Rate difference	Event Rate	*Event Rate difference	Event Rate	*Event Rate difference
Placebo	33.2%		53.7%		63.2%	
Zol 4 mg	25.4%	7.8%	43.6%	10.1%	52.8%	10.4%
Zol 8/4 mg	26.7%	6.5%	42.1%	11.6%	53.0%	10.2%

* Difference between Placebo and Treatment, not for comparison

- The α penalty for dropping a treatment group (8/4 group) with respect to type I error rate is debatable because although the treatment group was dropped for safety reasons, the decision to drop the treatment arm from efficacy analysis was made after all the patients were enrolled into the 8 mg group and had received a significant amount of treatment. Table 2.4.5 lists the occurrence of events during the 9 months study period. More than 75% of the SREs had occurred by 3 months evaluation, at which time majority of the patients in the 8 mg treatment group had received the treatment per original protocol at 8 mg dose level (Table 2.4.6).

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Table 2.4.5: Number of SREs by Stratum, Treatment, and Evaluation Times (FDA Analysis)

	3 months	6 months	9 months	Total up to 9 months
Lung Cancer				
Placebo	48	9	5	62
Zol 4 mg	39	13	4	56
Zol 8/4 mg	36	8	4	48
Other Solid Tumors				
Placebo	43	10	2	55
Zol 4 mg	30	7	4	41
Zol 8/4 mg	35	8	2	45
Total				
Placebo	91	19	7	117
Zol 4 mg	69	20	8	97
Zol 8/4 mg	71	16	6	93

Table 2.4.6: Number of Patients in the Zoledronate 8 mg group Who Were Treated at Reduced Dose of Zoledronate 4 mg up to 3 Months

Visit #:	2 (start)	3	4	5	6 (3 months)
# of patients treated at Zol 4 mg	0/265	0/234	2/206	12/173	29/151

- It should also be noted that according to this reviewer's analysis (Table 2.4.5) there were 6 more events in the placebo group and one more event in the zoledronate 8/4 mg group than the number of events reported by the sponsor (Table 2.4.2). Furthermore, these events were based on evaluation of 239 patients (instead of 250 patients as randomized) in the placebo group, 247 patients (instead of 257 patients as randomized) in the zoledronate 4 mg group, and 253 patients (instead of 266 patients as randomized) in the zoledronate 4/8 mg group. The sponsor has clarified that 7 of the 34 patients on whom event data were not available, did not receive any treatment on the study and were not evaluable. The sponsor has also clarified that the remaining 27 patients had dropped out of the study before the 3 month radiological evaluation of skeletal related events. This furthermore indicates that the estimate of proportion as defined in the protocol would be biased because, 34 patients who were not even evaluated for the primary efficacy endpoint were in fact counted as having no events in the sponsor analysis.

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2.4.9.3 Secondary Efficacy Analyses

The sponsor evaluated several parameters as secondary efficacy variables. The results of the parameters: (1) the proportion of patients experiencing a SRE, including hypercalcemia of malignancy (HCM) or also known as tumor-induced hypercalcemia (TIH); (2) the proportion of patients experiencing individual SREs, including HCM; (3) change in ECOG performance status; (4) change in FACT-G score; (5) change in analgesic scores; and (6) change in pain scores, evaluated by the sponsor will not be further presented or discussed in this review (see comment 2 below).

Time to first occurrence of an SRE was evaluated by the sponsor as a secondary efficacy parameter as specified in the protocol (Table 2.4.7) (Sponsor's Table 9-3, page 8-61, Volume 92).

Table 2.4.7: Summary of Time to the First SRE (-HCM) up to Month 9, by Stratum and Treatment Group (Sponsor Analysis)

	N	Event rate at day 252	25% Quartile (days)	Median (days)	P-values* for the between treatment comparison	
					Zol 4 mg	Zol 8/4 mg
Lung Cancer						
Placebo	130	67.9%	74	151	0.188	0.041
Zol 4 mg	134	60.5%	84	171		0.406
Zol 8/4 mg	139	53.6%	82	249		
Other Solid Tumors						
Placebo	120	58.2%	69	168	0.051	0.342
Zol 4 mg	123	43.9%	89	314		0.328
Zol 8/4 mg	127	52.4%	83	198		
Total						
Placebo	250	63.2%	70	163	0.023	0.034
Zol 4 mg	257	52.7%	84	230		0.969
Zol 8/4 mg	266	52.9%	82	219		

* P-values from Cox-regression with factor treatment stratified by the strata

Skeletal morbidity rate defined as the number of SREs divided by the time at risk in years was analyzed by the sponsor as presented below in Table 2.4.8. (Sponsor's Table 9-5, page 8-62, Volume 92).

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Table 2.4.8: Summary of Skeletal Morbidity Rate (risk set definition) of any SRE (-HCM) up to Month 9, by Stratum and Treatment Group (Sponsor Analysis)

	N	Skeletal morbidity rate (no. of events per year)		P-values* for the between treatment comparison	
		Mean \pm SD	Median	Zol 4 mg	Zol 8/4 mg
Lung Cancer					
Placebo	130	2.37 \pm 4.102	0	0.307	0.012
Zol 4 mg	134	2.62 \pm 11.815	0		0.117
Zol 8/4 mg	139	1.36 \pm 3.279	0		
Other Solid Tumors					
Placebo	120	2.67 \pm 6.039	0	0.116	0.147
Zol 4 mg	123	1.82 \pm 4.707	0		0.849
Zol 8/4 mg	127	1.75 \pm 4.300	0		
Total					
Placebo	250	2.52 \pm 5.115	0	0.069	0.005
Zol 4 mg	257	2.24 \pm 9.124	0		0.309
Zol 8/4 mg	266	1.55 \pm 3.798	0		

The time to multiple occurrences of SREs was also analyzed by the sponsor using Anderson-Gill approach. In this analysis every counted occurrence of an SRE was followed by a 20-day period during which no other occurrence of an SRE was counted. Time to each counted occurrence of an SRE was counted from the 22nd day of the last counted occurrence of an SRE to the onset day. Per sponsor analysis the difference between placebo and zoledronate 4 mg group was statistically significant.

Reviewer's Comments:

1. All secondary efficacy analyses can only be considered as exploratory and supportive of a positive primary efficacy analysis. In this study per sponsor and protocol specified primary efficacy analysis the treatment (zoledronate 4 mg) is not statistically significantly different from placebo.
2. The agency had recommended that the time to first occurrence of an SRE to be evaluated as a primary efficacy variable. The results of this analysis have already been discussed in the previous section (section 2.3.8.2, Reviewer's comment 3).
3. As stated before (section 2.3.8.2, Reviewer's comments), the estimates of the treatment effect may be biased due to high drop out rate and less than optimum method used for evaluation of missing data (last observation carried forward).
4. Per sponsor analysis there is no statistically significant difference between the placebo and zoledronate 4 mg with respect to skeletal morbidity rate (Table 2.4.8).
5. The sponsor's multiple event analysis has not been verified by the reviewer at this time.

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6. This reviewer conducted exploratory multivariable Cox regression analyses of the time to first SRE data with treatment (placebo=0, zoledronate=1), prior history of skeletal events (no=0, yes=1), time from initial diagnosis of cancer to bone metastases (in months), and time from first bone metastases to Visit 2 of the study (in months). The results of these analyses are presented in Tables 2.4.9a - 2.4.9c. In all of the models treatment effect was statistically significant. The point estimate of hazard ratio for placebo versus treatment was consistent among all the models and the upper 95% confidence limit of the hazard ratio was less than 1. Exploratory models comparing placebo with zoledronate 8/4 mg groups are presented in Appendix (Appendix 4.2).

Table 2.4.9a: Cox Regression Model with Treatment (Placebo vs. Zol 4 mg) as Co-variate

Co-variate	Hazard Ratio (95% C.I.)	P-value
Treatment Overall	0.733 (0.557, 0.965)	0.027
Treatment Lung Cancer Group	0.785 (0.544, 1.132)	0.194
Treatment Other Solid Tumors Group	0.664 (0.438, 1.009)	0.055

Table 2.4.9b: Cox Regression Model with Treatment (Placebo vs. Zol 4 mg) and prior history of SRE (Yes or No) as Co-variables

Co-variate	Hazard Ratio (95% C.I.)	P-value
Treatment	0.741 (0.563, 0.976)	0.033
Prior SRE	1.437 (1.050, 1.965)	0.023

Table 2.4.9c: Cox Regression Model with Treatment (Placebo vs. Zol 4 mg) and Prior History of SRE (Yes or No), Time from Initial Diagnosis of Cancer to Bone Metastases, and Time from First Bone Metastases to Visit 2 of the Study as Co-variables

Co-variate	Hazard Ratio (95% C.I.)	P-value
Treatment	0.722 (0.548, 0.952)	0.021
Prior SRE	1.535 (1.116, 2.110)	0.008
Time from Initial Dx. of Ca. To Bone Met.	0.994 (0.989, 0.999)	0.015
Time from First Bone Met. to Study Entry	0.986 (0.969, 1.003)	0.102

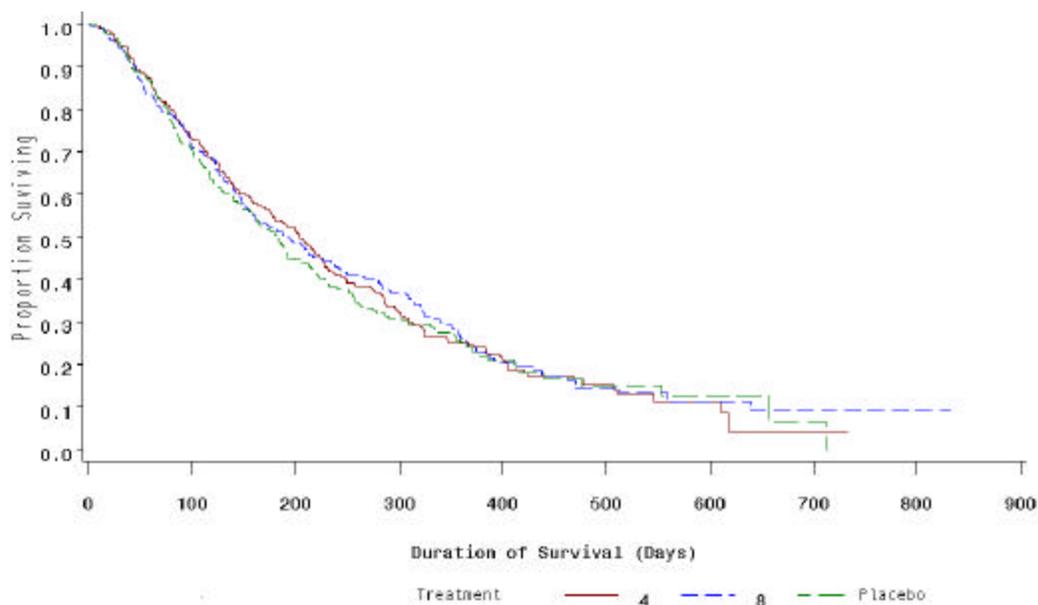
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2.4.9.4 Safety Analyses

2.4.9.4.1 Survival Analysis

Because the zoledronate treatment was not expected to improve survival, it was evaluated as part of safety analysis. The following is the survival analysis results of FDA analysis using the ITT population (instead of safety population used by sponsor). There were no statistically significant differences in survival between zoledronate 4 mg and placebo groups, or between zoledronate 8 mg and placebo groups as presented in Figures 2.4.1-2.4.3 and Table 2.4.10. All other safety analyses are presented in the clinical review of the application.

Figure 2.4.1: Kaplan-Meier Survival Analysis of Over All Survival in ITT Population (FDA Analysis)



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Figure 2.4.2: Kaplan-Meier Survival Analysis of Zoledronate 4 mg versus Placebo groups in ITT Population (FDA Analysis)

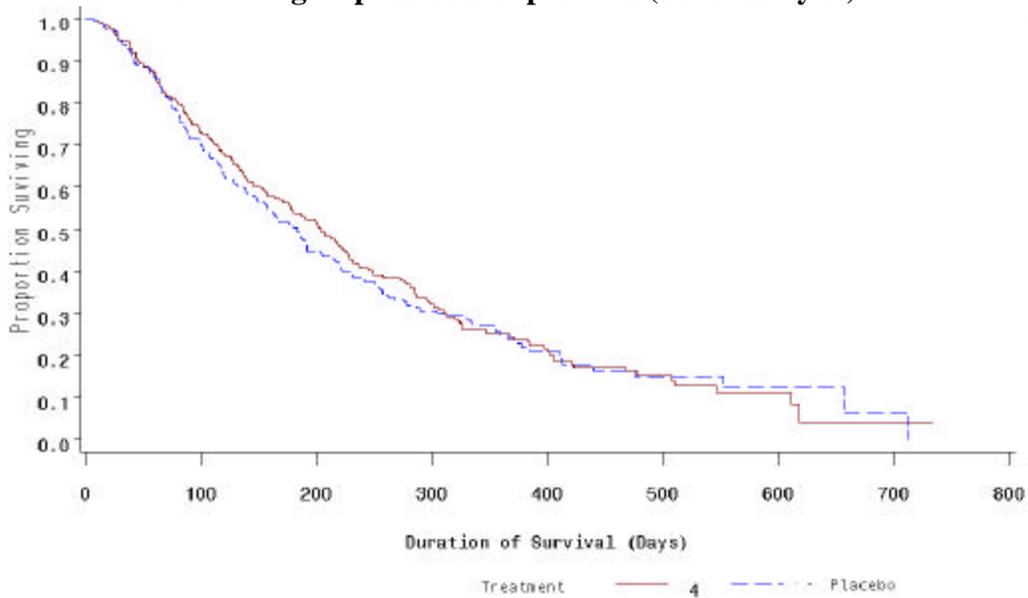
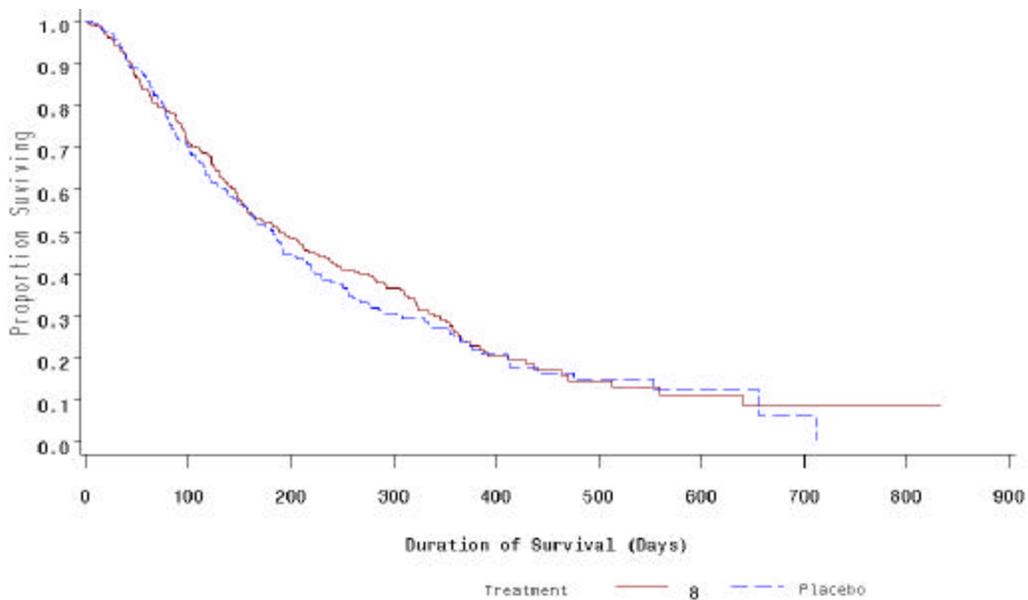


Figure 2.4.3: Kaplan-Meier Survival Analysis of Zoledronate 8/4 mg versus Placebo Groups in ITT Population (FDA Analysis)



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Table 2.4.10: Summary of Survival Analyses Results (FDA Analysis)

	N	Number of Events	Median (95% C.I.) in days	Hazard Ratio (95% C.I.)	P-values (Treatment versus Placebo, Log-rank test)
Placebo	250	188	183 (155, 205)		
Zol 4 mg	256	199	203 (175, 228)	0.632 (0.780, 1.163)	0.63
Zol 8/4 mg	266	191	189 (154, 237)	0.923 (0.755, 1.129)	0.44

2.4.10 Sponsor's Conclusions and Reviewer's Conclusions/Comments

Study 011 was a randomized, double-blind, multicenter, parallel-group, placebo controlled Phase III study conducted in a total of 773 patients aged 18 years or over with ECOG performance status # 2 and bone metastases from solid tumors other than breast or prostate cancer. The primary objective of this study was to assess the efficacy of zoledronate therapy (4 or 8 mg) in addition to antineoplastic therapy, compared to antineoplastic therapy alone, in preventing skeletal-related events in patients with any cancer with bone metastases other than breast cancer, multiple myeloma or prostate cancer. Skeletal-related events (SREs) were defined as radiation therapy to bone, surgery to bone, spinal cord compression, and pathologic fracture events. The primary efficacy endpoint was the proportion of patients with any SRE exclusive of tumor induced hypercalcemia by month 9.

1. The sample size calculations were based on that zoledronate would be considered more efficacious than placebo if either of the two comparisons (4 mg versus placebo or 8 mg versus placebo) was statistically significant at a 2-sided p-value < 0.025. During the study, the design was amended to treat all patients on study in the 8 mg group at 4 mg dose level because of the observed renal toxicity with 8 mg group. In lieu of this, the protocol was amended (Amendment 6) which stated that zoledronate 4 mg will be considered more efficacious than placebo if the comparison for the primary efficacy outcome is statistically significant at 0.05 level (2-sided) favoring zoledronate 4 mg. It should be noted that the original design and calculation of sample size was based on comparing 4 mg versus placebo group at 0.025 level. Dropping a treatment arm (in this case 8 mg group) could potentially inflate the overall type I error rate.
2. Although there appears to be no imbalance between the treatment arms there are significant differences between the two stratum (lung versus other solid tumors) with respect time from initial diagnosis of cancer to bone metastases, and time from first bone metastases to Visit 2 of the study (study start day). It is not clear as to how this difference in time between the two strata translates to differences or lack of differences with respect to skeletal related events. These patients were also receiving concomitantly anticancer therapy and this

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- is a confounding factor with the study drug in estimating the reduction in skeletal related events attributable to the study drug in each stratum and treatment group.
3. The study has failed to demonstrate efficacy of 4 mg zoledronate over placebo treated group in reducing the proportion of SREs at 9 months per protocol specified analysis (P-value=0.127). The protocol specified estimates of the proportion of SREs (Table 2.4.2) may be biased estimates because of high dropout rate. The sponsor was advised by the agency during the protocol development stage to consider time to first SRE as the primary efficacy parameter, which can take into account censoring of observations during the course of the study. Therefore, in order to account for the early censoring of the observations, this reviewer conducted time to first SRE analysis using Kaplan-Meier estimation procedure, truncating the maximum follow up time at 9 months (Table 2.4.4). There appears to be a statistically significant difference between the Zoledronate 4 mg group and placebo group ($p=0.026$, 2-sided log-rank test) by this analysis.
 4. Multivariate analyses of time to first occurrence suggest that the results are consistent and the zoledronate 4 mg treatment appears to have efficacy.
 5. Patients on the study were receiving varying anticancer therapy, which could potentially be confounding efficacy of the study drug in estimating the reduction in skeletal related events in each stratum and treatment group.

2.5 Study 039 (Prostate cancer patients with metastatic bone lesions)

2.5.1 Background

Prostate cancer is one of the most common cancers among men. The vast majority of patients with advanced prostate cancer have skeletal metastases. Skeletal complications due to metastatic disease include, bone pain, spinal cord compromise, and pathological fractures. The purpose of this clinical study was to determine if zoledronate would be an effective treatment to decrease the occurrence of skeletal-related complications associated with metastatic bone disease in prostate cancer patients. In this study, zoledronate treatment in addition to antineoplastic therapy versus antineoplastic therapy alone, was to be administered to prostate cancer patients who have developed biochemical progression of disease (a rising serum prostate-specific antigen (PSA) level) while on first-line hormonal therapy for metastatic bone disease. Skeletal-related events were to include pathologic bone fracture event, spinal cord compression events, surgery to bone, radiation therapy to bone (including the use of radioisotopes) and a change of antineoplastic therapy to treat bone pain.

Study 039 was a international, multicenter, randomized, double-blind, placebo-controlled, parallel study conducted in prostate cancer patients with a history of metastatic bone disease who have a rising serum PSA concentration despite treatment with first-line hormonal therapy for metastatic disease. Patients were randomized in a double-blind fashion to receive either zoledronate 4 mg intravenously, or zoledronate 8 mg intravenously, or a placebo intravenous infusion every three weeks in addition to their antineoplastic therapy. The randomized treatment assignment ratio was to be 1:1:1. In addition all patients were to receive 500 mg of calcium orally and multivitamin tablet (containing 400-500 I.U. of vitamin D) daily throughout the study.

2.5.2 Data Analyzed and Sources

Data used for this review was obtained from the electronic submission dated 8/21/2001. The network path is "\\Cdsub1\n21386\N_000\2001_08_21\CRT\datatsets\039" in the EDR. The following volumes were reviewed: 1, 106, 107, 109, 112, 114, and 115.

2.5.3 Study Objectives

The primary objective of this study was to assess the efficacy of zoledronate treatments (4 or 8 mg) in addition to antineoplastic therapy, compared to antineoplastic therapy alone to prevent skeletal-related events (SREs) in prostate cancer patients with a history of metastatic bone disease who have developed

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biochemical progression of disease. SREs were defined as pathologic bone fracture events, spinal cord compression events, surgery to bone, and radiation therapy to bone (including the use of radioisotopes).

2.5.4 Efficacy Endpoints

The primary efficacy variable in this study was the proportion of patients having at least one skeletal-related event.

The secondary efficacy variables included: (1) skeletal morbidity rate (SMR), (2) time to the first occurrence of a SRE, (3) time to disease progression in bone, (4) time to disease progression, (5) pain scores (BPI), (6) analgesic scores, (7) performance status (ECOG), (8) quality of life (FACT-G and EURO QOL EQ-5D), (9) objective bone lesion response from radiological studies, and (10) biochemical variables.

Reviewer's Comments:

FDA reviewer of the IND protocol had conveyed to the sponsor that the if the drop-out rate is relatively high, then the primary endpoint, SRE proportion estimate may be biased and had also suggested that the time to the first SRE be used as the co-primary endpoint.

2.5.5 Sample Size Considerations

This trial was designed to have 80% power to detect a 16% difference in the proportion of patients reporting any SRE during the first 15 months of the trial (Phase I) between the two dose level (4 mg and 8 mg) of zoledronate and placebo. Based on the bonferroni's adjustment, the sample size was calculated, assuming a 40% incidence rate on placebo; a 24% incidence rate on either dose level of zoledronate, with an overall Type I error rate of 0.05 (two-sided). The total sample size was determined to be 519 patients (173 on each arm). It was recommended that 550 patients be enrolled to account for the noise introduced by the use of intent-to-treat (ITT) population.

Reviewer's Comments:

1. A total of 643 patients were enrolled into the study (208 in placebo group, 214 in the zoledronate 4 mg group and 221 in the zoledronate 8/4 mg group) instead of the planned total of 550 patients.
2. The sample size calculations were based on that zoledronate would be considered more efficacious than placebo if either of the two comparisons (4 mg versus placebo or 8 mg versus placebo) was statistically significant at a 2-sided p-value < 0.025.

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3. During the study, the design was amended (Amendment 4) to treat all patients on study in the 8 mg group at 4 mg dose level because of the observed renal toxicity with 8 mg group. In lieu of this, in the Amendment 6 (Volume 112, Page 8-181), it was stated that zoledronate 4 mg will be considered more efficacious than placebo if the comparison for the primary efficacy outcome is statistically significant at 0.05 level (2-sided) favoring zoledronate 4 mg. It should be noted that the original design and calculation of sample size was based on comparing 4 mg versus placebo group at 0.025 level. Dropping a treatment arm (in this case 8 mg group) could potentially inflate the overall type I error rate. (Reference: Tsong, Y, Hung HMJ, Wang SJ, et. al. Dropping a treatment arm in clinical trial with multiple arms, JSM Proceedings, 1997).

2.5.6 Stratification

The randomization was stratified by prostate cancer history (no metastatic disease present at the time of the initial diagnosis of prostate cancer versus metastatic disease present at the time of the initial diagnosis), after Amendment 1 of the protocol (Volume 112, page 8-99).

2.5.7 Interim Analysis

No interim analysis was planned for this study. However, at an interim time point the 8 mg zoledronate arm was dropped due to renal toxicity concerns. The sponsor claimed there was no efficacy analyses conducted at the interim look.

2.5.8 Efficacy Analysis Methods

The primary efficacy endpoint of proportion of patients with any SRE during the first 15 months of the study, was originally planned to be compared between treatment and placebo groups using chi-squared test. This plan was amended after Amendment 1 of the protocol (Volume 112, page 8-119) to compare the treatment and placebo groups using the Cochran-Mantel-Haenzel test statistic. 95% CI for the proportion of patients reporting any SRE by treatment group was also to be presented. In the Amendment 1 the analysis also included evaluation of the influence of stratum and previous experience of SREs using logistic regression analyses.

One of the secondary efficacy variables, skeletal morbidity rate (SMR) defined as the ratio of the number of occurrences of any SRE, allowing one event per assessing period (3 weeks), divided by the time at risk, was originally planned to be compared between treatment groups using Wilcoxon rank sum test, which was later amended (Amendment 1, Volume 112, page 8-120) to analyze using Cochran-Mantel-Haenzel test statistic with modified ridit scores.

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Time to first occurrence of a SRE was planned to be compared between the treatment groups using survival analysis methods, including Kaplan-Meier product limit estimates and the log-rank test. Death not related to SRE would be considered as censored observation. Multiple events analysis, allowing one event every assessing period would be explored using Anderson-Gill approach.

For each particular type of SRE, the proportion of patients with the SRE, the SMR of the SRE, at month 3, 6, 9, 12 and 15 and the time to first occurrence of the SRE was planned to be similarly analyzed using the method for the respective variable with any SRE.

Change from baseline in BPI composite score was planned to be compared between the treatment groups using analysis of covariance with baseline value as a covariate and the treatment group as a factor at 3, 6, 9, 12, and 15 months. Change from baseline in mean analgesic use and performance status were planned to be compared between the treatment groups using the Cochran-Mantel-Haenzel (CMH) test statistic with modified ridit scores (originally planned to use Wilcoxon rank sum test) at 3, 6, 9, 12, and 15 months. Change from baseline in FACT-G total scores and the 4 subscales were planned to be compared between the treatment groups using analysis of covariance with baseline value as a covariate and treatment groups as a factor, at 3, 6, 9, 12, and 15 months. Change from baseline in EURO QOL-5D was planned to be analyzed similarly.

Time to progression of disease and time to progression of bone lesions were planned to be compared between treatment groups using Kaplan-Meier product limit estimates and log-rank test.

Percent change from baseline of biochemical variables were planned to be compared between the treatment groups using the CMH test statistics with modified ridit scores.

Reviewer's Comments:

1. Early dropouts and missing assessments were not considered in the above planned analyses.
2. The infusion time was amended (Amendment 3) from 5 minutes to 15 minutes during the study.
3. After the enrollment was completed in all the three treatment arms, the dose was reduced in the 8 mg arm to 4 mg (Amendment 4) because of renal toxicity. In this Amendment it was also stated that the 8/4 mg arm would not be evaluated for efficacy. However, it should be noted that by the time of this Amendment, majority of the patients had completed the phase I (15 months) or had dropped out of the study.

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4. The definition of ITT population was modified (Amendment 6) to include all randomized patients who had evidence of bone metastases at study entry.

2.5.9 Sponsor's Results and Reviewer's Findings/Comments

2.5.9.1 Baseline Characteristics

A total of 643 patients were randomized as follows: 214 patients were randomized to zoledronate 4 mg, 221 patients to the zoledronate 8 mg group, and 208 patients to the placebo group. At the time of randomization, patients were stratified by their history of prostate cancer (presence or absence of metastatic disease at the time of their initial diagnosis of prostate cancer). Several patients in each stratum were randomized to the incorrect stratum as follows: 30 patients were incorrectly assigned to the stratum of patients with no metastases at the time of initial diagnosis, and 27 patients were incorrectly assigned to the stratum of patients with metastases at the time of initial diagnosis. Thirty one patients were withdrawn from the study prematurely. One patient in the zoledronate 4 mg group was discovered to never have had bone lesions. Table 2.5.1a describes the baseline characteristics as presented by the sponsor in the safety population (Sponsor's Table 7-3, 7-4, 7-5, Volume 106, pages 8-56 to 8-58).

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Table 2.5.1a: Baseline Characteristics (Sponsor's Analysis – Safety Population)

	Total		
	Zol 4 mg N=214	Zol 8/4 mg N=218	Placebo N=208
Age (years)			
N	214	218	208
Mean " SD	71.8"7.91	71.2"8.04	72.2"7.89
Median	72.0	72.0	73.0
Age n (%)			
# 60	19 (8.9%)	19 (8.7%)	98 (7.2%)
> 60	195 (91.9%)	199 (91.3%)	149 (92.8%)
Race n (%)			
Caucasian	178 (83.2%)	184 (84.4%)	172 (82.7%)
Black	24 (11.2%)	18 (8.3%)	19 (9.1%)
Other	12 (5.6%)	16 (7.3%)	17 (8.2%)
Weight (kg)			
N	212	217	207
Mean " SD	82.7"14.15	82.2"14.50	83.4"16.08
Median	81.9	81.0	80.2
Metastases other than bone at initial diagnosis n (%)			
Lung	4 (.9%)	1 (0.5%)	1 (0.5%)
Liver, Brain, Skin, and Eye	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pleura	0 (0.0%)	1 (0.5%)	0 (0.0%)
Distant lymph nodes	19 (8.9%)	9 (4.1%)	9 (4.3%)
Other	2 (0.9%)	4 (1.8%)	4 (1.9%)
Serum creatinine n (%)			
Normal (< 1.4 mg/dL)	173 (80.8%)	168 (77.1%)	170 (81.7%)
Abnormal (≥ 1.4 mg/dL)	41 (19.2%)	47 (21.6%)	33 (15.9%)
Missing	0 (0.0%)	3 (1.4%)	5 (2.4%)
Previous SRE n (%)			
Yes	66 (30.8%)	70 (32.1%)	78 (37.5%)
No	148 (69.2%)	148 (67.9%)	130 (62.5%)
Prostate Specific Antigen			
Mean " SD	276.5 " 737.10	354.0 " 1156.54	211.1 " 464.89
Median	81.7	88.5	61.0
Time from initial diagnosis of cancer to bone metastases (month)			
N	214	217	207
Mean " SD	39.1"47.98	41.7"46.00	38.4"47.72
Median	19.6	26.6	19.6
Time from bone metastases to Visit 2 (month)			
N	214	217	207
Mean " SD	23.5"25.77	25.5"31.33	28.4"30.70
Median	16.1	15.5	17.8
ECOG status n (%)			
ECOG 0-1	197 (92.1%)	199 (91.3%)	190 (91.3%)
ECOG ≥ 2	17 (7.9%)	18 (8.3%)	18 (8.7%)
Analgesic score n (%)			
0	93 (43.5%)	73 (33.5%)	77 (37.0%)
1	70 (32.7%)	83 (38.1%)	77 (37.0%)
2	9 (4.2%)	11 (5.0%)	9 (4.3%)
3	40 (18.7%)	48 (22.0%)	41 (19.7%)
4	2 (0.9%)	3 (1.4%)	3 (1.4%)
BPI composite pain score			
N	193	198	191
Mean " SD	2.0"1.98	2.5"2.10	2.1"2.04
Median	1.8	2.3	1.8

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	Total		
	Zol 4 mg N=214	Zol 8/4 mg N=218	Placebo N=208
FACT-G total score			
N	193	192	187
Mean " SD	81.0" 15.36	81.2" 13.69	82.2" 14.57
Median	82.5	82.1	82.8

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Table 2.5.1b: Baseline Characteristics (FDA Analysis – ITT population)

	No Metastasis at Initial Diagnosis			Metastases at Initial Diagnosis			Total		
	Zol 4 mg N=115	Zol 8/4 mg N=134	Placebo N=116	Zol 4 mg N=99	Zol 8/4 mg N=87	Placebo N=92	Zol 4 mg N=214	Zol 8/4 mg N=221	Placebo N=208
Age (years)									
N	115	134	116	99	87	92	214	221	208
Mean " SD	72.6"0.8	70.8"0.7	73.0"0.7	70.9"0.8	71.7"0.9	71.3"0.9	71.8"0.5	71.2"0.5	72.2"0.5
Median	73	71	74	71	72	73	72	72	73
Age									
# 60	9 (7.8%)	11 (8.2%)	6 (5.2%)	10 (10.1%)	8 (9.2%)	9 (9.8%)	19 (8.9%)	19 (8.6%)	15 (7.2%)
> 60	106 (92.2%)	123 (91.8%)	110 (94.8%)	89 (89.9%)	79 (90.8%)	83 (90.2%)	195 (81.2%)	202 (91.4%)	193 (92.8%)
Race n (%)									
Caucasian	102 (88.7%)	116 (86.6%)	93 (80.2%)	76 (76.8%)	70 (80.5%)	79 (85.9%)	178 (83.2%)	186 (84.2%)	172 (82.7%)
Black	8 (7.0%)	10 (7.5%)	11 (9.5%)	16 (16.2%)	9 (10.3%)	8 (8.7%)	24 (11.2%)	19 (8.6%)	19 (9.1%)
Other	5 (4.3%)	8 (5.9%)	12 (10.3%)	8 (7.0%)	8 (9.2%)	5 (5.4%)	12 (5.6%)	16 (7.2%)	17 (8.2%)
Weight (kg)									
N	114	133	116	98	87	91	212	220	207
Mean " SD	83.8"1.3	82.3"1.3	83.9"1.5	81.5"1.5	81.9"1.6	82.8"1.7	82.8"1.0	82.1"1.0	83.4"1.1
Median	82.3	81.0	79.7	81.4	79.8	82.0	82.0	81.0	80.2
Serum creatinine									
Normal (< 1.4 mg/dL)	92 (80.0%)	101 (75.4%)	96 (82.8%)	81 (81.8%)	72 (82.8%)	79 (85.9%)	173 (80.8%)	173 (78.3%)	175 (84.1%)
Abnormal (≥ 1.4 mg/dL)	23 (20.0%)	33 (24.6%)	20 (17.2%)	18 (18.2%)	15 (17.2%)	13 (14.1%)	41 (19.2%)	48 (21.7%)	33 (15.9%)
Previous SRE									
Yes	30 (26.1%)	42 (31.6%)	44 (37.9%)	36 (36.7%)	29 (33.3%)	34 (37.0%)	66 (31.0%)	71 (32.3%)	78 (37.5%)
No	85 (73.9%)	91 (68.4%)	72 (62.1%)	62 (63.3%)	58 (66.7%)	58 (63.0%)	147 (69.0%)	149 (67.7%)	130 (62.5%)
Prostate Specific Antigen									
N	115	132	113	97	86	87	212	218	200
Mean " SD	261.2±63.4	382.3±109.4	164.1±38.8	294.7±82.6	302.8±104.1	272.2±55.9	276.5±50.6	350.9±77.8	211.1±32.9
Median	89.4	90.9	56.0	76.7	87.2	69.7	81.7	88.2	61.0
Time from initial diagnosis of cancer to bone metastases (month)									
N	115	133	115	99	87	92	214	220	207
Mean " SD	64.7"4.5	64.4"3.7	63.8"4.6	8.1"2.2	7.9"2.7	6.6"1.8	38.5"3.3	42.0"3.1	38.4"3.3
Median	60.8	58.3	53.0	0.2	0.3	0.2	19.2	28.6	19.6
Time from bone metastases to Visit 2 (month)									
N	115	133	115	99	87	92	214	220	207
Mean " SD	15.0"2.1	13.6"1.4	20.0"2.4	33.9"2.6	44.5"4.2	39.0"3.5	23.8"1.8	25.8"2.1	28.4"2.1
Median	6.5	6.5	12.3	26.2	31.3	32.3	16.1	16.1	17.8

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	No Metastasis at Initial Diagnosis			Metastases at Initial Diagnosis			Total		
	Zol 4 mg N=115	Zol 8/4 mg N=134	Placebo N=116	Zol 4 mg N=99	Zol 8/4 mg N=87	Placebo N=92	Zol 4 mg N=214	Zol 8/4 mg N=221	Placebo N=208
ECOG status n (%)									
ECOG 0-1	106 (92.2%)	124 (92.5%)	104 (89.7%)	91 (91.9%)	78 (90.7%)	86 (93.5%)	197 (92.1%)	202 (91.8%)	190 (91.3%)
ECOG ≥ 2	9 (7.8%)	10 (7.5%)	12 (10.3%)	8 (8.1%)	8 (9.3%)	6 (6.5%)	17 (7.9%)	18 (8.2%)	18 (8.7%)
Analgesic score n (%)									
0	56 (48.7%)	46 (34.6%)	44 (38.3%)	38 (38.4%)	27 (31.4%)	33 (35.9%)	94 (43.9%)	73 (33.3%)	77 (37.2%)
1	32 (27.8%)	49 (36.8%)	39 (33.9%)	37 (37.4%)	35 (40.7%)	38 (41.3%)	69 (32.2%)	84 (38.4%)	77 (37.2%)
2	4 (3.5%)	6 (4.5%)	6 (5.2%)	5 (5.0%)	5 (5.8%)	3 (3.3%)	9 (4.2%)	11 (5.0%)	9 (4.4%)
3	23 (20.0%)	31 (23.3%)	25 (21.7%)	17 (17.2%)	17 (19.8%)	16 (17.4%)	40 (18.7%)	48 (21.9%)	41 (19.8%)
4	0 (0.0%)	1 (0.8%)	1 (0.9%)	2 (2.0%)	2 (2.3%)	2 (2.2%)	2 (0.9%)	3 (1.4%)	3 (1.5%)
BPI composite pain score									
N	107	124	110	86	75	81	193	199	191
Mean " SD	2.2"0.2	2.3"0.2	2.2"0.2	1.9"0.2	2.8"0.3	2.0"0.2	2.0"0.1	2.5"0.1	2.1"0.1
Median	1.8	2.0	1.9	2.0	2.8	1.8	1.8	2.3	1.8
FACT-G total score									
N	107	120	107	86	73	80	193	193	187
Mean " SD	80.7"1.5	81.1"1.2	81.2"1.4	81.3"1.6	81.9"1.7	83.6"1.6	81.0"1.1	81.4"1.0	82.2"1.1
Median	80.2	80.0	82.0	83.0	83.0	83.4	82.5	82.2	82.8

Reviewer's Comments:

1. Table 2.5.1b above describes the baseline characteristics of the ITT population as analyzed by this reviewer.
2. Both by the Sponsor's description (Table 2.5.1a) and FDA description (Table 2.5.1b) there appears to be imbalance between treatment groups favoring zoledronate 4 mg group with respect to age group, serum creatinine, previous SRE, time from initial diagnosis of cancer to bone metastases, performance status, analgesic score and BPI composite pain score.
3. There are significant differences between the two stratum (no metastases at initial diagnosis of prostate cancer versus metastases at initial diagnosis of prostate cancer) with respect to time from initial diagnosis of cancer to bone metastases, and time from first bone metastases to Visit 2 of the study (study start day). As in Study 011, in this study also, it is not clear as to how this difference in time between the two strata translates to differences or lack of differences with respect to skeletal related events. These patients were also receiving concomitantly anticancer therapy and this is a confounding factor with the study drug in estimating the reduction in skeletal related events attributable to the study drug in each stratum and treatment group.

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2.5.9.2 Primary Efficacy Analyses

The primary efficacy variable was the proportion of patients experiencing at least one SRE (-HCM). Per sponsor analysis by month 15 both the zoledronic acid 4 mg and 8/4 mg groups had a lower proportion than the placebo group. There was statistically significant difference between 4 mg and placebo groups ($p=0.021$), where as there was no statistically significant difference between 8/4 mg and placebo groups ($p=0.222$), as presented below in Table 2.5.2 (Sponsor Table 9-1, Volume 106, page 8-61).

Table 2.5.2: Proportion of Patients Having SRE (-HCM) up to Month 15 by Stratum and Treatment Group (ITT patients) – Sponsor’s Analysis

	Proportion	95% C.I. and P-value for the difference	
		Zol 4 mg	Zol 8/4 mg
No Initial Metastases			
Placebo	54/116 (47%)	(-24.4%,0.9%), $p=0.069$	(-21.5%,3.0%), $p=0.140$
Zol 4 mg	40/115 (35%)	-	(-9.4%,14.5%), $p=0.679$
Zol 8/4 mg	50/134 (37%)	-	-
With Initial Metastases			
Placebo	38/92 (41%)	(-23.6%,3.6%), $p=0.152$	(-15.5%,13.3%), $p=0.884$
Zol 4 mg	31/99 (31%)	-	(-4.9%,22.7%), $p=0.206$
Zol 8/4 mg	35/87 (40%)	-	-
Total			
Placebo	92/208 (44%)	(-20.3%,-1.8%), $p=0.021$	(-15.1%,3.6%), $p=0.222$
Zol 4 mg	71/214 (33%)	-	(-3.7%, 14.3%), $p=0.255$
Zol 8/4 mg	85/221 (38%)	-	-

Reviewer’s Comments:

1. Since the decision was made to drop 8/4 mg zoledronate arm for toxicity, the efficacy comparison between 8/4 mg arm and placebo arm is not appropriate and may result in type I error adjustment.
2. The estimates of the proportion of SREs presented in Table 2.5.2 may be biased estimates because of high dropout rate (approximately only 35% were treated at 15 months) as presented below in Table 2.5.3. In the least conservative approach, if the total number of events at 15 months in each of the treatment groups are subtracted from the total number of patients that were randomized, then 84/143 patients (58.7%) in zoledronate 4 mg group, 63/136

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patients (46.3%) in zoledronate 8/4 mg group, and 66/116 patients (56.9%) in the placebo group received treatment at 15 months. Therefore the dropout rate was at least 46%.

Table 2.5.3: Number of Patients Treated up to 15 Months (FDA Analysis)

	No Initial Metastases			With Initial Metastases			Total		
	Zol 4 mg	Zol 8/4 mg	Placebo	Zol 4 mg	Zol 8/4 mg	Placebo	Zol 4 mg	Zol 8/4 mg	Placebo
Study Start (Visit 2)	115	134	116	99	87	92	214	221	208
3 months	99	117	108	80	69	79	179	186	187
6 months	75	94	84	67	57	64	142	151	148
9 months	65	69	62	54	51	48	119	120	110
12 months	54	50	43	50	36	41	104	86	84
15 months	42 (36.5%)	36 (26.9%)	35 (30.2%)	42 (42.4%)	27 (31.0%)	31 (33.7%)	84 (39.3%)	63 (28.5%)	66 (31.7%)

- The sponsor was advised by the agency during the protocol development stage to consider time to first SRE as the primary efficacy parameter, which can take into account censoring of observations during the course of the study. Therefore, in order to account for the early censoring of the observations, this reviewer conducted time to first SRE analysis using Kaplan-Meier estimation procedure, truncating the maximum follow up time at 15 months (Table 2.5.4). Data beyond 15 months was confounded because of cross over of patients to zoledronate treatment group from placebo group. The Kaplan-Meier estimates of the proportion of skeletal event rate at 15 months are larger than the estimates presented in Table 2.5.2 (protocol specified analysis). There is significant difference between the zoledronate 4 mg group and placebo group ($p=0.009$, 2-sided log rank test). Kaplan-Meier estimates of proportion of SREs at 3, 6, and 9 months respectively are presented in Table 2.5.4b.

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Table 2.5.4a: Analysis of Time to First Skeletal Related Event Truncated at 15 Months Using Kaplan-Meier Estimation Procedure (ITT Population FDA Analysis)

	Event Rate at 9 Months	N	Median Time to Event in days (95% C.I.)	P-value (Comparison to Placebo using Log-rank test)
No Initial Metastases				
Placebo	59.6%	116	304 (198, *)	
Zol 4 mg	45.6%	115	* (291, *)	0.058
Zol 8/4 mg	50.7%	134	419 (251, *)	0.270
With Initial Metastases				
Placebo	54.0%	92	335 (244, *)	
Zol 4 mg	44.4%	99	* (364, *)	0.085
Zol 8/4 mg	57.0%	87	346 (209, *)	0.709
Total				
Placebo	57.2%	208	321 (252, *)	
Zol 4 mg	44.9%	214	* (383, *)	0.009
Zol 8/4 mg	53.2%	221	363 (255, *)	0.541

* = Not Reached

Table 2.5.4b: Analysis of Time to First Skeletal Related Event Truncated at 3, 6, 9, 12 and 15 Months Using Kaplan-Meier Estimation Procedure (ITT population FDA Analysis)

Total	At 3 Months		At 6 Months		At 9 Months		At 12 Months		At 15 Months	
	Event Rate	*Diff. in Event Rate	Event Rate	*Diff. in Event Rate	Event Rate	*Diff. in Event Rate	Event Rate	*Diff. in Event Rate	Event Rate	*Diff. in Event Rate
Placebo	16.5%		31.6%		42.7%		52.8%		57.2%	
Zol 4 mg	9.1%	7.4%	21.8%	9.8%	30.0%	12.7%	36.9%	15.9%	43.7%	13.5%
Zol 8/4 mg	16.7%	-0.2%	29.6%	2.0%	42.0%	0.7%	46.5%	6.3%	53.2%	4.0%

* Difference in event rates between placebo and treatment groups - not for comparison.

4. The α penalty for dropping a treatment group (8/4 group) with respect to type I error rate is debatable because although the treatment group was dropped for safety reasons, the decision to drop the treatment arm from efficacy analysis was made after all the patients were enrolled into the 8 mg group and had received a significant amount of treatment. Table 2.5.5 lists the occurrence of events during the 15 months study period. More than 50% of the SREs had occurred by 3 months evaluation in the two zoledronate treatment groups, at which time majority (99%) of the patients in the 8 mg treatment group had received the treatment per original protocol at 8 mg dose level (Table 2.5.6).

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**Table 2.5.5: Number of SREs by Stratum, Treatment, and Evaluation Times
(FDA Analysis)**

	3 months	6 months	9 months	12 months	15 months	Total up to 15 months
No Initial Metastases						
Placebo	29	11	8	3	3	54
Zol 4 mg	15	13	6	5	1	40
Zol 8/4 mg	28	9	9	3	1	50
With Initial Metastases						
Placebo	18	7	7	5	1	38
Zol 4 mg	10	8	3	6	4	31
Zol 8/4 mg	20	6	3	5	1	35
Total						
Placebo	47	18	15	8	4	92
Zol 4 mg	25	21	9	11	5	71
Zol 8/4 mg	48	15	12	8	2	85

Table 2.5.6: Number of Patients in the Zoledronate 8 mg Group Who Were Treated at Reduced Dose of Zoledronate 4 mg up to 3 Months

Visit #:	2 (start)	3	4	5	6 (3 months)
# of patients treated at Zol 4 mg	1/219	1/208	1/199	2/188	1/178

2.5.9.3 Secondary Efficacy Analyses

The sponsor evaluated several parameters (as listed in section 2.5.3) as secondary efficacy variables. Here we will present analyses of only two of the secondary efficacy variables.

Time to first occurrence of an SRE was evaluated by the sponsor as a secondary efficacy parameter as specified in the protocol (Table 2.5.7) (Table 9-2, page 8-62, Volume 106). By this analysis zoledronate 4 mg group was significantly different from placebo group ($p=0.011$) and there was no difference between the zoledronate 8/4 mg and placebo groups ($p=0.491$). However, there appears to border line significant difference between zoledronate 4 mg and 8/4 mg groups ($p=0.059$).

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Table 2.5.7: Summary of Time to the First SRE (-HCM) up to Month 15, by Stratum and Treatment Group (Sponsor Analysis)

	N	Event rate at day 252	25% Quartile (days)	Median (days)	P-values* for the between treatment comparison	
					Zol 4 mg	Zol 8/4 mg
No Initial Metastases						
Placebo	116	59.6%	109	304	0.045	0.225
Zol 4 mg	115	45.6%	175	Not Reached	-	0.398
Zol 8/4 mg	134	50.7%	133	419	-	-
With Initial Metastases						
Placebo	92	54.0%	140	335	0.110	0.709
Zol 4 mg	99	44.4%	222	Not Reached	-	0.052
Zol 8/4 mg	87	57.0%	105	346	-	-
Total						
Placebo	208	57.2%	122	321	0.011	0.491
Zol 4 mg	214	44.9%	182	Not Reached	-	0.059
Zol 8/4 mg	221	53.2%	127	363	-	-

* P-values from Cox-regression with factor treatment stratified by the strata

Skeletal morbidity rate defined as the number of SREs divided by the time at risk in years was analyzed by the sponsor as presented below in Table 2.5.8. (Sponsor's Table 9-3, page 8-63, Volume 106).

Table 2.5.8: Summary of Skeletal Morbidity Rate (risk set definition) of any SRE (-HCM) up to Month 15, by Stratum and Treatment Group (Sponsor Analysis)

	N	Skeletal morbidity rate (no. of events per year)		P-values* for the between treatment comparison	
		Mean \pm SD	Median	Zol 4 mg	Zol 8/4 mg
No Initial Metastases					
Placebo	116	1.32 \pm 2.19	0.00	0.068	0.132
Zol 4 mg	115	0.91 \pm 1.70	0.00	-	0.730
Zol 8/4 mg	134	0.95 \pm 1.86	0.00	-	-
With Initial Metastases					
Placebo	92	1.70 \pm 4.38	0.00	0.040	0.627
Zol 4 mg	99	0.67 \pm 1.70	0.00	-	0.109
Zol 8/4 mg	87	1.23 \pm 2.62	0.00	-	-
Total					
Placebo	208	1.49 \pm 3.33	0.00	0.006	0.143
Zol 4 mg	214	0.80 \pm 1.70	0.00	-	0.191
Zol 8/4 mg	221	1.06 \pm 2.19	0.00	-	-

The time to multiple occurrences of SREs was also analyzed by the sponsor using Anderson-Gill approach. In this analysis every counted occurrence of an SRE was followed by a 20-day period during which no other occurrence of an SRE was counted. Time to each counted occurrence of an SRE was counted from the

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22nd day of the last counted occurrence of an SRE to the onset day. Per sponsor analysis the difference between placebo and zoledronate 4 mg group was statistically significant.

Reviewer's Comments:

1. The agency had recommended that the time to first occurrence of an SRE to be evaluated as a primary efficacy variable. The results of this analysis have already been discussed in the previous section (section 2.5.8.2, Reviewer's comment 1).
2. Per sponsor analysis there is statistically significant difference between the placebo and zoledronate 4 mg groups with respect to skeletal morbidity rate (Table 2.5.8). However these estimates of the treatment effect may be biased because of high drop out rate.
3. The sponsor's multiple event analysis has not been verified by the reviewer at this time. It should be noted that the Anderson-Gill approach assumes the multiple events are independent of each other. However the skeletal related events being considered here are likely to be highly correlated.
4. This reviewer conducted exploratory multivariable Cox regression analyses of the time to first SRE data with treatment (placebo=0, zoledronate=1), prior history of skeletal events (no=0, yes=1), time from initial diagnosis of cancer to bone metastases (in months), time from first bone metastases to Visit 2 of the study (in months), log_e of baseline PSA and baseline analgesic scores. The results of these analyses are presented in Tables 2.5.9a - 2.5.9c. Although in all of the models considered here zoledronate 4 mg treatment effect was statistically significant, when the factors identified with imbalance in section 2.5.8.1, Reviewer comment, the p-value increased. The point estimate of hazard ratio for placebo versus zoledronate 4 mg treatment was consistent among all the models and the upper 95% confidence limit of the hazard ratio was less than 1. Exploratory models comparing placebo with zoledronate 8/4 mg groups are presented in Appendix (Appendix 4.3).

Table 2.5.9a: Cox Regression Model with Treatment (Placebo vs. Zol 4 mg) as Co-variate

Co-variate	Hazard Ratio (95% C.I.)	P-value
Treatment Overall	0.661 (0.484, 0.903)	0.009
Treatment No Metastases at Initial Dx.	0.673 (0.446, 1.016)	0.06
Treatment With Metastases at Initial Dx.	0.658 (0.408, 1.063)	0.088

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Table 2.5.9b: Cox Regression Model with Treatment (Placebo vs. Zol 4 mg) and prior history of SRE (Yes or No) as Co-variates

Co-variate	Hazard Ratio (95% C.I.)	P-value
Treatment	0.670 (0.490, 0.916)	0.012
Prior SRE	1.450 (1.055, 1.992)	0.022

Table 2.5.9c: Cox Regression Model with Treatment (Placebo vs. Zol 4 mg) and prior history of SRE (Yes or No), time from initial diagnosis of cancer to bone metastases, and time from first bone metastases to Visit 2 of the study as Co-variates

Co-variate	Hazard Ratio (95% C.I.)	P-value
Treatment	0.680 (0.491, 0.941)	0.020
Prior SRE	1.374 (0.984, 1.919)	0.063
Time from Initial Dx. of Ca. To Bone Met.	0.999 (0.996, 1.003)	0.725
Time from First Bone Met. to Study Entry	0.993 (0.986, 1.000)	0.042
Log _e (baseline PSA)	1.154 (1.047, 1.272)	0.004
Baseline Analgesic Score	1.214 (1.056, 1.396)	0.007

2.5.9.4 Safety Analyses

2.5.9.4.1 Survival Analyses

Because the zoledronate treatment was not expected to improve survival, it was evaluated as part of safety analysis. The following is the survival analysis results of FDA analysis using the ITT population (instead of safety population used by sponsor). There were no statistically significant differences in survival between zoledronate 4 mg and placebo groups, or between zoledronate 8 mg and placebo groups as presented in Figures 2.5.1-2.5.3 and Table 2.5.10. All other safety analyses are presented in the clinical review of the application.

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Figure 2.5.1: Kaplan-Meier Survival Analysis of Over All Survival in ITT Population (FDA Analysis)

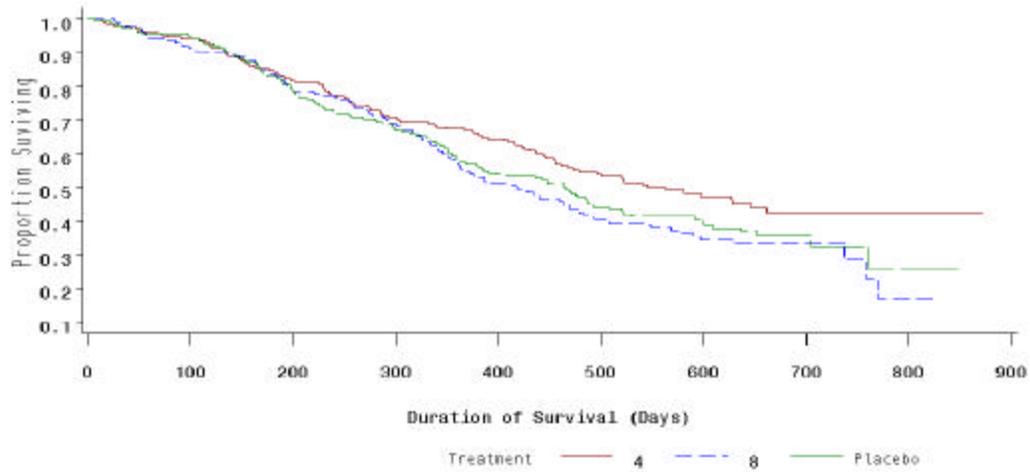
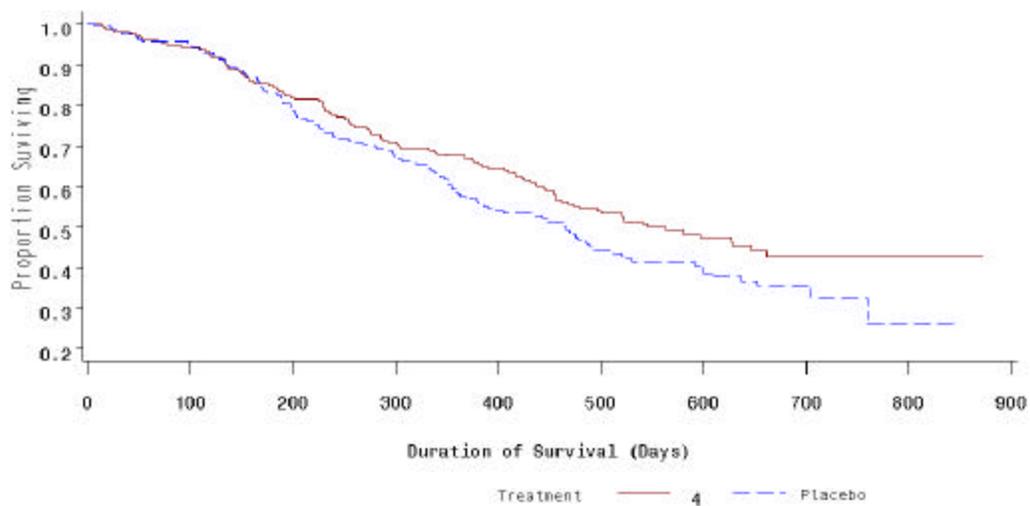


Figure 2.5.2: Kaplan-Meier Survival Analysis of Zoledronate 4 mg versus Placebo in ITT Population (FDA Analysis)



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Figure 2.5.3: Kaplan-Meier Survival Analysis of Zoledronate 8/4 mg versus Placebo in ITT Population (FDA Analysis)

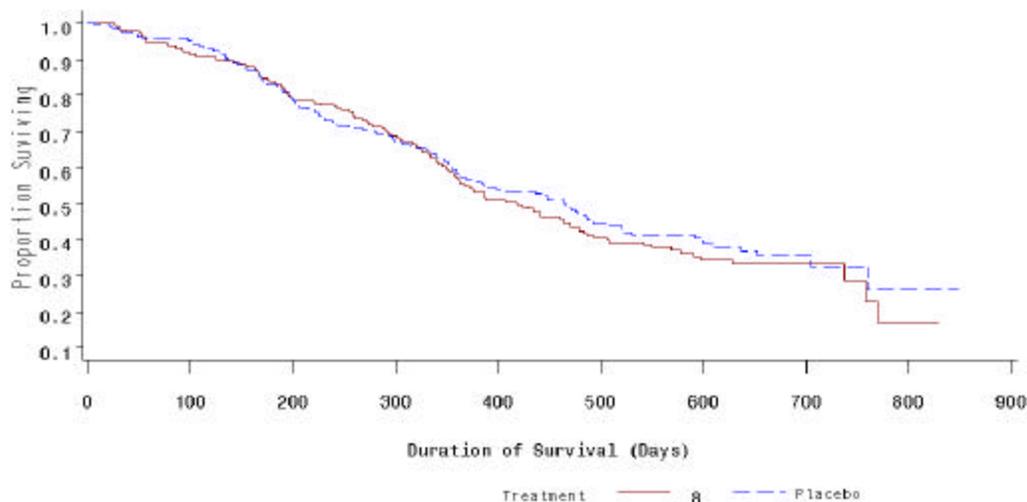


Table 2.5.10: Summary of Survival Analyses Results (FDA Analysis)

	N	Number of Events	Median (95% C.I.) in days	Hazard Ratio (95% C.I.)	P-values (Treatment versus Placebo, Log-rank test)
Placebo	208	122	464 (379, 521)		
Zol 4 mg	214	107	546 (461, *)	0.792 (0.611, 1.027)	0.078
Zol 8/4 mg	221	138	419 (363, 478)	1.083 (0.849, 1.382)	0.521

Reviewer's Comments:

It appears from the survival analysis of the time to death that the zoledronate 8/4 mg was slightly worse than the placebo group. It is not clear if this is because of inherent not apparent differences in baseline prognostic factors, or because of chance mechanism.

2.5.10 Sponsor's Conclusions and Reviewer's Conclusions/Comments

Study 039 was a international, multicenter, randomized, double-blind, placebo-controlled, parallel study conducted in prostate cancer patients with a history of metastatic bone disease who have a rising serum PSA concentration despite treatment with first-line hormonal therapy for meatastatic disease. A total of 643 patients were enrolled into the study (208 in placebo group, 214 in the zoledronate

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4 mg group and 221 in the zoledronate 8/4 mg group). The primary objective of this study was to assess the efficacy of zoledronate treatments (4 or 8 mg) in addition to antineoplastic therapy, compared to antineoplastic therapy alone to prevent skeletal-related events (SREs) in prostate cancer patients with a history of metastatic bone disease who have developed biochemical progression of disease. SREs were defined as pathologic bone fracture events, spinal cord compression events, surgery to bone, and radiation therapy to bone (including the use of radioisotopes). The primary efficacy endpoint of this study was the proportion of patients having at least one skeletal-related event by month 15.

1. A total of 643 patients were enrolled into the study instead of the planned total of 550 patients. No explanation is provided for the increase in sample size.
2. The sample size calculations were based on that zoledronate would be considered more efficacious than placebo if either of the two comparisons (4 mg versus placebo or 8 mg versus placebo) was statistically significant at a 2-sided p -value < 0.025 . During the study, the design was amended (Amendment 4) to treat all patients on study in the 8 mg group at 4 mg dose level because of the observed renal toxicity with 8 mg group. In lieu of this, it was stated that zoledronate 4 mg will be considered more efficacious than placebo if the comparison for the primary efficacy outcome is statistically significant at 0.05 level (2-sided) favoring zoledronate 4 mg (Amendment 6). It should be noted that the original design and calculation of sample size was based on comparing 4 mg versus placebo group at 0.025 level. Dropping a treatment arm (in this case 8 mg group) could potentially inflate the overall type I error rate. It should also be noted that by the time of this Amendment, majority of the patients had completed the phase I (15 months) or had dropped out of the study.
3. There appears to be imbalance between treatment groups favoring zoledronate 4 mg group with respect to age group, serum creatinine, previous SRE, time from initial diagnosis of cancer to bone metastases, performance status, analgesic score and BPI composite pain score.
4. There are significant differences between the two stratum (no metastases at initial diagnosis of prostate cancer versus metastases at initial diagnosis of prostate cancer) with respect to time from initial diagnosis of cancer to bone metastases, and time from first bone metastases to Visit 2 of the study (study start day).
5. There is statistically significant difference between zoledronate 4 mg and placebo groups ($p=0.021$). The per protocol estimates of the proportion of SREs may be biased estimates because of high dropout rate. The sponsor was advised by the agency during the protocol development stage to consider time to first SRE as the primary efficacy parameter, which can take into account censoring of observations during the course of the study. Therefore, in order to account for the early censoring of the observations, this reviewer conducted time to first SRE analysis using Kaplan-Meier estimation procedure,

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- truncating the maximum follow up time at 15 months. There is statistically significant difference between the zoledronate 4 mg group and placebo group ($p=0.009$, 2-sided log-rank test).
6. Multivariate analyses of time to first occurrence adjusting for some of the covariates which appear to be imbalanced among the treatment groups suggest that the results are consistent and the zoledronate 4 mg treatment appears to have efficacy, although the strength of evidence is not as significant.
 7. It appears from the survival analysis of the time to death that the zoledronate 8/4 mg was slightly worse than the placebo group. It is not clear if this is because of inherent differences in baseline prognostic factors, or because of chance mechanism.

3 Statistical Evaluation of Collective Evidence

Zometa® or zoledronate (zoledronic acid for injection) is proposed to be used for the treatment of osteolytic, osteoblastic, and mixed bone metastases of solid tumors and osteolytic lesions of multiple myeloma, in conjunction with standard antineoplastic therapy in cancer patients. Sponsor has submitted efficacy data and results from three double-blind studies (Studies 010, 011, and 039). In all the three studies patients were randomized in a double-blind fashion to receive either zoledronate 4 mg intravenously, or zoledronate 8 mg intravenously, or an active control/placebo intravenous infusion every three weeks in addition to their antineoplastic therapy. The randomized treatment assignment ratio was to be 1:1:1. The primary efficacy endpoint in all the three studies was the proportion of patients experiencing at least one SRE, defined as radiation therapy to bone, surgery to bone, pathologic bone fracture or spinal cord compression.

Study 010 was a multicenter, double-blind, randomized, controlled, Phase III parallel comparative trial of i.v. zoledronic acid (Zometa, 4 mg or 8 mg) versus iv. Aredia (90 mg) (pamidronate) as an adjunct to standard therapies in a total of 1640 patients with multiple myeloma and breast cancer with cancer related bone lesions. The “non-inferiority” test in Study 010 demonstrates marginal effectiveness ($p=0.052$) with respect to proportion of SREs at 12 months of zoledronate 4mg arm, using a margin of 3.65% which is defined as preserving 50% of the lower limit of the 95% CI of the point estimate of the Aredia effect. The original selection of 8% margin is not acceptable based on the current understanding because it tends to be liberal.

Study 011 was a randomized, double-blind, multicenter, parallel-group, placebo controlled Phase III study conducted in a total of 773 patients with bone metastases from solid tumors other than breast or prostate cancer. The study has failed to demonstrate efficacy of 4 mg zoledronate over placebo treated group in reducing the proportion of SREs at 9 months per protocol specified analysis ($p=0.127$). The protocol specified estimates of the proportion of SREs (Table 2.4.2) may be biased estimates because of high dropout rate. The sponsor was advised by the agency during the protocol development stage to consider time to first SRE as the primary efficacy parameter, which can take into account censoring of observations during the course of the study. Therefore, in order to account for the early censoring of the observations, this reviewer conducted time to first SRE analysis using Kaplan-Meier estimation procedure, truncating the maximum follow up time at 9 months (Table 2.4.4). There appears to be a statistically significant difference between the Zoledronate 4 mg group and placebo group ($p=0.026$, 2-sided log-rank test) by this analysis.

Study 039 was an international, multicenter, randomized, double-blind, placebo-controlled, parallel study conducted in 643 prostate cancer patients with a history

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of metastatic bone disease who have a rising serum PSA concentration despite treatment with first-line hormonal therapy for metastatic disease. There was statistically significant difference between zoledronate 4 mg and placebo groups ($p=0.021$) with respect to the proportion of SREs at 15 months as defined in the protocol. However, the per protocol estimates of the proportion of SREs may be biased estimates because of high dropout rate. The sponsor was advised by the agency during the protocol development stage to consider time to first SRE as the primary efficacy parameter, which can take into account censoring of observations during the course of the study. Therefore, in order to account for the early censoring of the observations, this reviewer conducted time to first SRE analysis using Kaplan-Meier estimation procedure, truncating the maximum follow up time at 15 months. There is statistically significant difference between the zoledronate 4 mg group and placebo group ($p=0.009$, 2-sided log-rank test).

In these reviewers' opinion the results of Studies 11 and 39 support efficacy of zoledronate 4 mg given intravenously versus placebo given intravenously in patients with bone metastases from solid tumors other than breast cancer, and the study results of Study 10 suggest marginal effectiveness of zoledronate 4 mg given intravenously in patients with bone metastases from breast cancer and multiple myeloma based on a "non-inferiority" test using Aredia as the active control .

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References:

1. Gang Chen, George Chi, Mark Rothmann, Ning Li (2001), Active Control Trials - Hypotheses and Issues. ASA Proceedings.
2. Mark Rothmann, Ning Li, Gang Chen, George Chi and Hsiao-Hui Tsou (2001), Non-inferiority Methods for Mortality Trials, ASA Proceedings.
3. Ning Li, Mark Rothmann, Gang Chen, George Chi, (2001), Application of non-inferiority analysis methods in oncology NDA, ASA Proceedings.

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HFD-710/ Dr. Sridhara
HFD-710/ Dr. Li
HFD-710/ Dr. Chen
HFD-710/ Dr. Mahjoob
HFD-710/ Dr. Chi
HFD-700/ Dr. Anello

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4 APPENDICES

4.1 APPENDIX 1 - STUDY 010 - Zol. 8/4 mg versus Aredia

Skeletal related Event (SRE) rate

The sponsor provided data for SRE for Zole 8/4 mg arm. The Zole 8/4 mg arm was the original 8 mg arm but changed the dosage due to renal toxicity. The exploratory analysis result is summarized in Table 4.1.1.

Table 4.1.1: Proportion of SRE to Month 13 by Stratum

	Zometa (8/4mg)	Aredia	Difference Δ (95% CI)*	p-value*
Myeloma	49% (79/160)	49% (82/167)	0% (-10.6%,11.1%)	0.961
Breast (Chemo)	47% (80/172)	43% (78/181)	4% (-7%, 13.8%)	0.519
Breast (Hormonal)	43% (83/192)	47% (97/207)	-4% (-13.4%, 6.1%)	0.467
Total	46% (242/524)	46% (257/555)	0% (-6.1%, 5.8%)	0.963

* Δ =Zometa-Aredia

Reviewer's Comments:

- The analysis shows that the proportions were 46% and 46% for the zoledronic acid 8/4 mg group and the Aredia 90 mg group, respectively. The upper limit of the 95% confidence interval of the difference was 5.8%, which was less than the non-inferiority margin of 8% specified in the protocol before dose amendment. In the stratum of breast cancer patients receiving hormonal therapy, the difference in the proportions between the zoledronic acid 8/4 mg group and the Aredia 90 mg group was -4%, while in the stratum of breast cancer patients receiving chemotherapy, the difference in the proportions between the zoledronic acid 8/4 mg group and the Aredia 90 mg group was +4% with an upper bound of 13.8%, implying 13.8% worse than Aredia is possible.

Preservation of active control effect: The preservation of active treatment effect using the SRE rates can be determined by $(7.3\% - 5.8\%) / 7.3\% = 20.5\%$. Hence, the current trial arm 8/4 mg arm demonstrated a 20.5% retention of Aredia vs. a placebo effect if we believe that the constant assumption holds.

STATISTICAL REVIEW AND EVALUATION

Time to First SRE

Table 4.1.2 summarizes the results for study 010 by comparing Zole 8/4 mg with Aredia.

Table 4.2.2.: Time to First SRE by Stratum and Treatment Arm

	N	Median (95%CI)	Hazard Ratio (95% CI)	p-value*
Myeloma				0.58
Aredia	167	301(191, ---)	1.09(.80, 1.49)	
Zol 8/4 mg	160	283(196, ---)		
Breast(CT)				0.87
Aredia	181	366(259, ---)	1.03(0.75, 1.4)	
Zol 8/4 mg	172	351(262, ---)		
Breast(HT)				0.44
Aredia	207	370(258, ---)	.89(.67, 1.20)	
Zol 8/4 mg	192	381 (275, --)		
Total				0.90
Aredia	555	363(273, 399)	.99(.83, 1.18)	
Zol 8/4 mg	524	353(283, ---)		

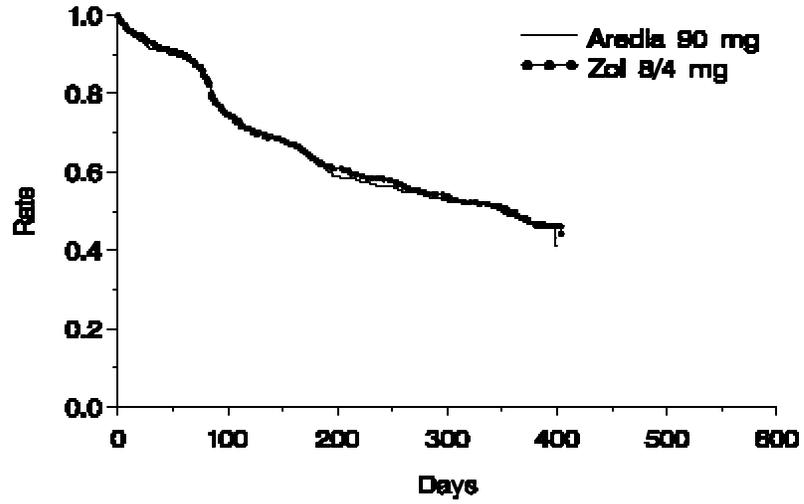
*Log-rank test

Figure 4.1.1 is the K-M curve for the time to first SRE comparing overall Aredia with Zol 8/4 mg arm.

STATISTICAL REVIEW AND EVALUATION

Figure 4.1.1

Time to 1st SRE for Study 010



STATISTICAL REVIEW AND EVALUATION

4.2 APPENDIX 2 - STUDY 011 - Zol. 8/4 mg versus Placebo

Table 4.2.1: Cox Regression Model with Treatment (Placebo vs. Zol 8/4 mg) as Co-variate

Co-variate	Hazard Ratio (95% C.I.)	P-value
Treatment Overall	0.743 (0.563, 0.980)	0.036
Treatment Lung Cancer Group	0.673 (0.459, 0.987)	0.043
Treatment Other Solid Tumors Group	0.826 (0.553, 1.234)	0.351

Table 4.2.2: Cox Regression Model with Treatment (Placebo vs. Zol 8/4 mg) and prior history of SRE (Yes or No) as Co-variables

Co-variate	Hazard Ratio (95% C.I.)	P-value
Treatment	0.745 (0.565, 0.983)	0.038
Prior SRE	1.359 (0.991, 1.864)	0.057

Table 4.2.3: Cox Regression Model with Treatment (Placebo vs. Zol 8/4 mg) and prior history of SRE (Yes or No), time from initial diagnosis of cancer to bone metastases, and time from first bone metastases to Visit 2 of the study as Co-variables

Co-variate	Hazard Ratio (95% C.I.)	P-value
Treatment	0.722 (0.547, 0.954)	0.022
Prior SRE	1.486 (1.077, 2.051)	0.016
Time from Initial Dx. of Ca. To Bone Met.	0.996 (0.991, 1.000)	0.062
Time from First Bone Met. to Study Entry	0.981 (0.963, 1.000)	0.047

STATISTICAL REVIEW AND EVALUATION

4.3 APPENDIX 3 - STUDY 039 - Zol. 8/4 mg versus Placebo

Table 4.3.1: Cox Regression Model with Treatment (Placebo vs. Zol 8/4 mg) as Co-variate

Co-variate	Hazard Ratio (95% C.I.)	P-value
Treatment Overall	0.912 (0.679, 1.226)	0.541
Treatment No Metastases at Initial Dx.	0.805 (0.547, 1.185)	0.272
Treatment With Metastases at Initial Dx.	1.091 (0.689, 1.728)	0.709

Table 4.3.2: Cox Regression Model with Treatment (Placebo vs. Zol 8/4 mg) and prior history of SRE (Yes or No) as Co-variables

Co-variate	Hazard Ratio (95% C.I.)	P-value
Treatment	0.926 (0.689, 1.245)	0.611
Prior SRE	1.534 (1.135, 2.073)	0.005

Table 4.3.3: Cox Regression Model with Treatment (Placebo vs. Zol 8/4 mg) and prior history of SRE (Yes or No), time from initial diagnosis of cancer to bone metastases, and time from first bone metastases to Visit 2 of the study as Co-variables

Co-variate	Hazard Ratio (95% C.I.)	P-value
Treatment	0.868 (0.638, 1.182)	0.368
Prior SRE	1.468 (1.059, 2.036)	0.021
Time from Initial Dx. of Ca. To Bone Met.	1.000 (0.996, 1.003)	0.901
Time from First Bone Met. to Study Entry	0.995 (0.989, 1.000)	0.073
Log_e (baseline PSA)	1.175 (1.070, 1.290)	0.0007
Baseline Analgesic Score	1.020 (0.888, 1.172)	0.777