# CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-386
21-223/S-003

## STATISTICAL REVIEW(S)

# STATISTICAL REVIEW AND EVALUATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

**Medical Division:** Oncology Drug Products (HFD-150)
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|---|---|
| NDA NUMBER: | **21-386** |
| DRUG NAME: | **Zometa® (zoledronic acid for injections)** |
| INDICATION: | **Treatment of Bone Metastases** |
| SPONSOR: | **Novartis** |
| DOCUMENTS REVIEWED: | 1, 67, 68, 92, 94, 97, 98, 100, 106, 107, 109, 112, 114, 115 |
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# STATISTICAL REVIEW AND EVALUATION

## 1 Executive Summary and Statistical Findings

### 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 ranomized 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 $\leq 2$ 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 (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 meyeloma 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 meatastatic 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.

**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

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: ≥ 27% in study 010 (at 12 months), ≥ 56% in study 011 (at 9 months), and ≥ 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.

**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.

**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

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 | | | | 0.82 |
| **Aredia** | 167 | 301(191, ---) | .97(.71, 1.31) | |
| Zol 4 mg | 183 | 372(225, 504) | | |
| Breast(CT) | | | | 0.81 |
| **Aredia** | 181 | 366(259, ---) | .96(.70, 1.32) | |
| Zol 4 mg | 178 | 364(249, ---) | | |
| Breast(HT) | | | | 0.22 |
| **Aredia** | 207 | 370(258, ---) | .83(.62, 1.12) | |
| Zol 4 mg | 200 | >380 (---, --) | | |
| **Total** | | | | **0.31** |
| **Aredia** | **555** | **363(273, 399)** | **.92(.77, 1.09)** | |
| **Zol 4 mg** | **561** | **373(350, 504)** | | |

**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).

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

| | | 95% C.I. and P-value for the difference | |
|---|---|---|---|
| | Proportion | 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

**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**

| | | 95% C.I. and P-value for the difference | |
|---|---|---|---|
| | Proportion | 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.

**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.

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-sidered 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

### 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.

## STATISTICAL REVIEW AND EVALUATION

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.

**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.

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

### 2.1.1 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.

### 2.1.2 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.

### 2.1.3 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.

### 2.1.4 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.

### 2.1.5 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.

### 2.1.6 Stratification

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

### 2.1.7 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.

### 2.1.8 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 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 $\Delta$ 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.

### 2.1.9 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.

#### 2.1.9.1 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 $\geq 2$. 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).

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

| | Zol 4 mg N=377 | Zol 8/4 mg N=384 | 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.

### 2.1.9.2 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.

**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 comparetor. 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):

**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

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

to bone were similar, indicating the consistent effect of Aredia inn 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.

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

| Treatment | N | 3 month | 6 month | 9 month | 12 month |
|---|---|---|---|---|---|
| **Myeoloma:** | | | | | |
| 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 |
|---|---|---|---|---|---|
| **Myeoloma:** | | | | | |
| Aredia 90 mg | 167 | 44.9% | | 47.3% | |
| Zometa 4 mg | 183 | 40.4% | 4.9% | 42.6% | 0.75 |
| **Breast (Chemo):** | | | | | |
| Aredia 90 mg | 181 | 39.2% | | 42.5% | |
| Zometa 4 mg | 178 | 38.7% | 1.5% | 42.1% | 0.68 |
| **Breaset(Hormonal)** | | | | | |
| Aredia 90 mg | 207 | 40.6% | | 43.5% | |
| Zometa 4 mg | 200 | 34.0% | 6.6% | 40.0% | 0.35 |
| **Overall:** | | | | | |
| Aredia 90 mg | 555 | 41.4% | | 44.3% | |
| Zometa 4 mg | 561 | 37.4% | 4.0% | 41.5% | 0.30 |

### 2.1.9.3 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.

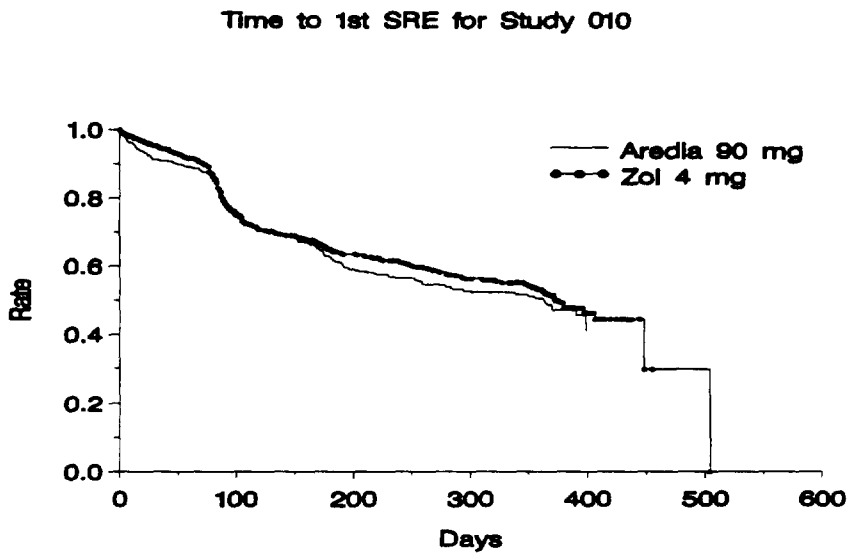
**Table 2.3.8: Time to first SRE by Stratum and Treatment Arm**

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

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

APPEARS THIS WAY
ON ORIGINAL

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.

### 2.1.9.4 Safety Analyses

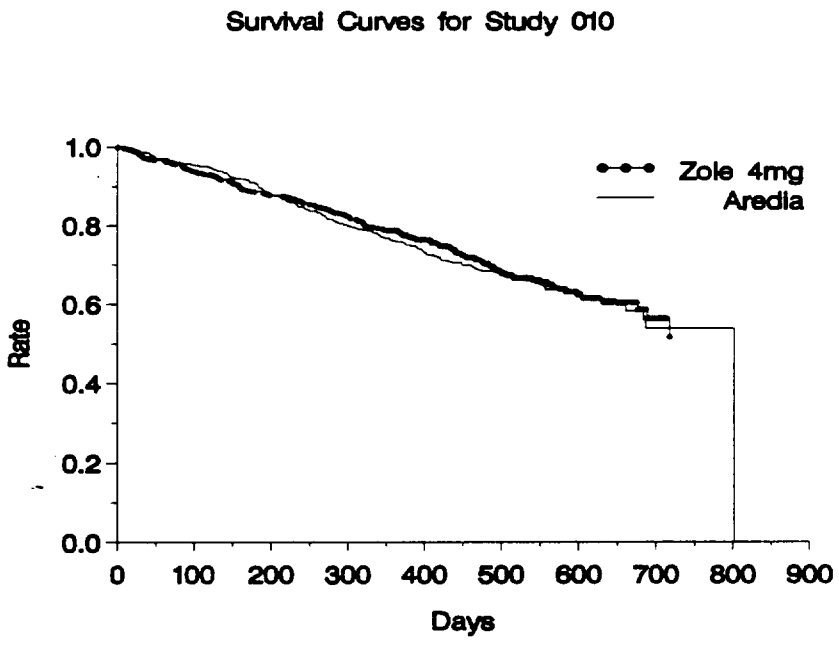
**(1) Overall Survival Time**

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.**



*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.

### 2.1.10 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.

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

### 2.1.11 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.

### 2.1.12 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\datatsets\011" in the EDR. The following volumes were reviewed: 1, 92, 94, 97, 98, and 100.

### 2.1.13 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 meyeloma or prostate cancer. Originally skeletal-related events (SREs) were defined as radiation therapy to bone, a change in antineoplastic therapy to treat bone pain,

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.

### 2.1.14 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.

### 2.1.15 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

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).

### 2.1.16 Stratification

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

### 2.1.17 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.

### 2.1.18 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

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 coavariance 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.

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.

### 2.1.19 Sponsor's Results and Reviewer's Findings/Comments

#### 2.1.19.1 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).

## 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%0 |
| 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%) |

| | 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 |

## 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 |

| | 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.

### 2.1.19.2 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**

| | | 95% C.I. and P-value for the difference | |
|---|---|---|---|
| | **Proportion** | **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%) | - | - |

*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

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

4. The $\alpha$ 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).

**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 |

5. 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.

### 2.1.19.3 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 hypercacemia of mailignancy (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)**

| | | | | | P-values* for the between treatment comparison | |
|---|---|---|---|---|---|---|
| | N | Event rate at day 252 | 25% Quartile (days) | Median (days) | 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).