Treatment arm	Placebo	Zol. 4 mg	Zol. 8/4 mg
2	18	17	18
Baseline PSA			
Range	0.25-8410	0.15-5963	0.2-9124
Median	57.8	79.8	88.5
Analgesic score (per sponsor)			
0	77	93	73
1	77	70	83
2	9	9	11
3	41	40	48
4	3	2	3
BPI composite Pain score (per sponsor)			
N	187	193	192
Median	1.8	1.8	2.3
Fact-G score (per sponsor)			
N	187	193	192
Median	82.8	82.5	82.1

Reviewer's Comments:
The primary reason for examining baseline factors is to consider whether factors which are prognostic for efficacy outcome are balanced among the study arms. Because there have been no previous studies using SRE-based endpoints in prostate cancer, it is difficult to be certain which factors are predictive for future SREs. In previous studies of biphosphonates in breast cancer and myeloma, a patient history of a prior SRE was a strong predictor for future SREs. Other suggested prognostic factors are based on theoretical considerations or their prognostic value for other prostate cancer endpoints such as survival. Factors that seem reasonable to consider also include performance status and black race. The number of potential SREs could also be expected to correlate with tumor load. It is unclear whether serum PSA would be useful in this setting. PSA might not identify more aggressive disease, since some patients with aggressive disease may have a low PSA. However, there is a suggestion in a retrospective analysis, that pretreatment PSA is a predictor of biochemical failure and death due to prostate cancer. Gleason scores were not collected in this study.

Performance status, age and number of bone metastases per patient were equally balanced among the arms. However, there was a slightly increased number of blacks, and patients with a higher number (2-4) of organs involved in the 4 mg arm compared to other arms. Baseline serum PSA was highest in the 8/4 mg arm and lowest for placebo. Baseline pain scores were highest for 8/4 mg arm and lowest for the 4 mg arm.

Reviewer's comments:
As discussed later in this review, the discordant outcomes for the Zol 4 mg and Zol 8mg arms were perplexing. The difference in outcomes was not changed by the FDA statistical reviewer's Cox regression model which included prior SREs, time from initial diagnosis of cancer to bone

metastases, baseline PSA and baseline analgesic scores. The treatment effect of 8/4 mg remained not significant although the p value decreased.

The baseline metastatic sites were recorded by the investigator only as number of organs involved and not as number of metastases. The recorded sites were classified as bone, liver, lymph nodes, lung, pleura, skin, eye, brain and other. A comparison of extraskeletal sites of metastases is given in Table 4. Extraskeletal metastases other than distant lymph nodes were highest in number in the 8/4 mg group (20 in Zol 8/4 mg, 10 in Zol 4mg, and 13 in placebo).

Table 14: Distribution of the metastases according to treatment arm

Site of metastases	Placebo	Zol. 4 mg	Zol. 8/4 mg
Lung	5	6	4
Liver, brain, skin, eye	1	1	5
Pleura	0	0	1
Distant lymph nodes	15	29	19
Other	7	3	10

Protocol Violations

The Applicant identified only one major protocol violation. This patient on the Zol 4mg arm had no history of bone metastases (CAN/2006/15191). He was removed from the trial after 9 visits and was not followed. Other violations which occurred frequently (at least in 4 patients) are as given in Table below.

Table 15: Violations in at least 4 patients

Violation	4 mg (# of pts.)	Placebo (# of pts.)	4/8 mg (# of pts.)
Unblinding	11	12	14
No histological diagnosis	10	14	11
PSA did not comply with Inclusion criteria of protocol	53	40	43
Randomized by incorrect strata	19	20	18
Chemotherapy less than 2 weeks from randomization	1	2	1
Violation involving hormonal treatment history or required castration testosterone levels	3	7	5

The most serious violations were unblinding and lack of histological diagnosis. Unblinding occurred mostly at two study sites – 3123 and 2044. The following table shows the efficacy results of these study sites (proportions of patients with at least one SRE).

Table 16: Proportion of patients with SRE at Study Site 3123 and 2044

Study Site	4 mg (# of pts.)	8/4 mg (# of pts.)	Placebo (# of pts.)	N at study site (# of pts.)
2044 (USA)	1/10	2/8	1/9	27
3123 (Argentina)	0/2	2/2	2/3	7
Total (proportion)	1/12 (8.3%)	4/10 (40%)	3/12 (25%)	34

Reviewer's comment regarding study violations:
Out of the 37 patients that were unblinded, 34 were from study sites 3123 and 2044. The number of patients in these two studies constitute 5.3 % of the total number of patients. The results of these studies are similar to the overall results of the study. Due to the relatively small number of patients involved, it is doubtful that unblinding at these sites would significantly alter the results of the study.

Lack of histological diagnosis is reason for concern. However, the likelihood that these patients did not have prostate cancer is low. Patients were required to have documentation of three increasing values of PSA at least 2 weeks apart from each other. There were three patients who had protocol violations involving inclusion criteria for PSA as well as lack of histological documentation of Prostate cancer (pt ID 11038, 11232, 11246). These patients were included in the FDA efficacy analyses.

Pt ID 11038 and 11232 were in the placebo arm and did not suffer from any SRE. Pt ID 11246 was in the 4 mg arm and had SREs. The PSA measurements of these patients prior to the study were less than 2 weeks apart. However, prior to these measurement, there is a record of elevated PSA. In larger numbers, this could alter the target population. The results of efficacy of Zoledronate would not be altered.

Discontinuation of Study Drug

As summarized in the following table, most patients either discontinued study drug or died prior to completing the study.

Table 17: Early discontinuations and deaths

Arm	N	Deaths	Other Early Discontinuations	Total D/D
Zol. 4 mg	214	25	108	133
Placebo	208	32	111	143
Zol. 8/4 mg	221	40	119	159

Table below from the Applicant's submission summarizes the reasons for study discontinuation. Adverse events (AE), unsatisfactory therapeutic effect and patient withdrawal of consent were the most common reasons for discontinuation. As would be expected if a drug was effective,

discontinuation due to unsatisfactory therapeutic effect was more common in the placebo arm compared to the Zol 4 mg and Zol 8 mg arm. There were more deaths and adverse events in the Zol 8 mg arm.

Reviewer's comment:
The increased discontinuation for AEs might have been due to the increased incidence of renal toxicity found in this arm.

Table 18: Reasons for discontinuation

Reason for discontinuation	Placebo	Zol. 4 mg	Zol. 8/4 mg
Withdrawal of consent	35	40	48
Adverse Events	29	38	44
Death	32	25	40
Unsatisfactory therapeutic effect	34	19	17
Lost to follow-up	5	4	0
Abnormal lab values	2	3	5
Abnormal test procedures results	0	1	0
Condition no longer requires study drug	3	1	3
Protocol violation	0	1	0
Administrative problems	3	0	0
Total	143	132	157

Primary Efficacy Analysis:

Proportion of patients with at least one SRE

The protocol specified primary endpoint was the proportion of patients with at least one SRE. In reviews prior to NDA analysis, however, FDA statisticians noted that this analysis could produce biased estimates because of high dropout rates and recommended using time to first SRE as a coprimary endpoint. Time to event analyses factor in the time when dropouts occur and minimize associated bias. The proportion and time to event analyses were truncated at 15 months, since that was the pre-specified duration of the study.

According to the Applicant's analysis, the proportion of patients experiencing at least one SRE during the first 15 months was significantly less in the 4 mg arm compared to placebo (33% vs. 44%; p= 0.021). However, there was no significant difference between the proportion in the 8 mg arm and placebo (38% vs. 44%, p=0.222). FDA results were similar.

Table 19: Proportion of patients with at least one SREs during the first 15 months

	Proportion	95% C.I. and P-value for the difference	
		Zol 4 mg	Zol 8/4 mg
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%	-	-

Proportion = (no. of patients with the event)/total no. in the group) up to month 15.
C.I. for the difference (treatment labeled in the column minus row) of percent of patients with events.
P-values are based on stratified Cochran-Mantel-Haenzel test for the proportion

Reviewer's comment:
Two hundred and fifty patients (38.8%) had at least 1 SRE. Since the 8/4 mg arm was too toxic, it is excluded from efficacy analysis as specified in amendment # 4. The 4 mg arm is statistically better in terms of proportions of events over the placebo arm by a difference of 10%. There is no statistically significant difference in the efficacy of the 8 mg arm over the placebo, although a trend towards improvement is observed. It is counter intuitive that a lower dose (4 mg) would be efficacious but not a higher dose (8/4 mg).

Analyses to evaluate lack of concordance of Zoledronate 4 mg & 8/4 mg arms

a) Early discontinuations
Early discontinuations could cause spurious results leading to the lack of concordance of results seen above. As seen in table 20, the number of patients treated were equal across arms at three months. At this time, a divergence in results could already be seen.

Table 20: Infusions and SREs by 3 months

	Placebo	4 mg	8/4 mg
Total # of patients	208	213	219
Infusions at 3 mos.	173 83%	174 82%	178 81%
SREs by 3 mos.	47 23%	25 12%	48 22%

b) Baseline imbalances
No baseline imbalances were found. Prior SRE, time from initial diagnosis of cancer to bone metastasis, time from first bone metastasis to study entry, Log_e (baseline PSA), and baseline analgesic score were individually strong prognostic factors for both treatment groups. Overall

treatment effect remained essentially unchanged when evaluated in a multivariate Cox regression analysis (see tables 21 and 22)

Table 21: Cox Regression Model (Placebo vs. Zol 4 mg)

(From FDA Statistical Review)

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

Table 22: Cox Regression Model (Placebo vs. Zol 8/4 mg)

(From FDA Statistical Review)

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

Secondary Efficacy Analysis

Time to first SRE:

The median time to first SRE had not been reached for 4 mg arm, but the 25% quartile was about 60 days longer for the 4mg arm than placebo or the 8/4 mg arm (p value compared to placebo = 0.009). For 8/4 mg arm and placebo, the median time to first event are 363 and 321 days (p = 0.541).

Table 23: Analysis of Time to First Skeletal Related Event Truncated at 15 Months Using Kaplan-Meier Estimation Procedure (ITT population FDA Statistical Reviewer's Analysis)

	N	Median Time to Event in days (95% C.I.)	P-value (Log-rank test)
Placebo	208	321 (252, NR)	
Zol 4 mg	214	NR (383, NR)	0.009
Zol 8/4 mg	221	363 (255, NR)	0.541

NR = Not Reached

Reviewer's Comment:
Time to first SRE in the 4mg group is statistically longer than in the placebo group. There is again no difference between the placebo and 8/4 mg groups, and this fails to support the efficacy observed in the 4 mg arm. A chance imbalance in prognostic factors might explain this finding. As previously discussed, however, although we know many factors in prostate cancer that are prognostic for endpoints such survival, we do not know which factors are prognostic for the occurrence of SREs in prostate cancer. FDA reviewers evaluated known factors for balance among treatment arms. As noted above, performance status, age and number of bone metastases per patient were equally balanced in different arms. However, there was a slightly increased number of blacks, and patients with a higher number (2-4) of extraskeletal metastases in the 4 mg arm as opposed to other arms. Baseline serum PSA was highest in the 8/4 mg arm and lowest for placebo. Baseline pain scores were highest for 8/4 mg arm and lowest for the 4 mg arm. When prior SREs, time from initial diagnosis of cancer to bone metastases, baseline PSA and baseline analgesic scores were analyzed in a Cox Regression model by the FDA statistics reviewer, the treatment effect of 8/4 mg remained not significant..

Skeletal Morbidity Rate (SMR)

SMR attempts to capture efficacy in additional SREs occurring after the first SRE, as FDA has noted in review of prior biphosphonate NDAs. However, clinical significance of some of these additional events may be questioned. For instance, some events may be highly correlated or may occur at the same time. In analyses by the applicant, the SMR for the 4 mg, 8/4 mg and placebo arms are 57%, 44%, and 53% respectively with the difference between 4 mg and placebo being significant (p=0.011). P value for the difference between 8/4 mg arm and placebo is 0.059.

BPI pain score, analgesic scores, QoL and performance status change:

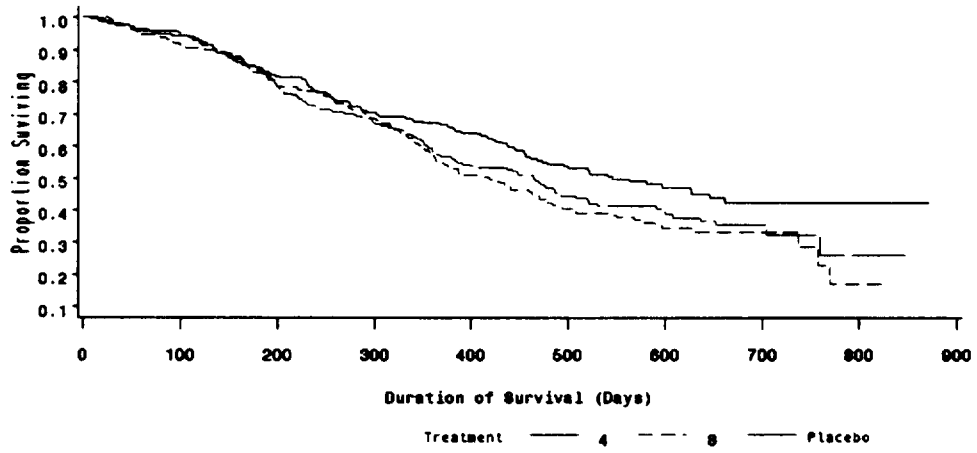
In analyses by the Applicant, the BPI pain score increased from baseline to Month 15 for all treatment groups (p = 0.134). There was no statistical difference in quality of life scores, analgesic scores, performance status change from baseline among the treatment arms at month 15.

Time to progression of bone metastases and overall disease progression:

There was no difference between treatment groups in the distribution of time to progression of bone metastases or overall disease progression.

Survival:
As shown in the following table and figure from the FDA statistical review, although there was a trend in favor of the 4mg arm, there was no statistical difference survival difference among the three treatment groups.

Figure 1: Kaplan Meier Curve for analysis of overall survival - 039



Reviewer Exploratory analyses

Some SREs are of questionable clinical benefit such as asymptomatic vertebral fractures and change of chemotherapy due to increased pain. Chemotherapy is changed in USA due to progression of disease and not due to increased intensity of pain. In the following table, various exploratory analyses performed with the assistance of the statistical reviewer are illustrated. The trends remain the same. Hazard ratios (upper 95% C.I. greater than 1) of the 4 mg arm vs placebo are probably due to the small sample size.

Exploratory Analyses	N	Comparison	Hazard ratios and 95% C.I.
Symptomatic patients only	114	4 mg vs placebo	0.784 (0.539, 1.142)
	115	8/4 mg vs placebo	1.268 (0.871, 1.846)
Excluding TIH and chemotherapy change	422	4 mg vs placebo	0.682 (0.496,0.939)
	429	8/4 mg vs placebo	0.839 (0.613, 1.147)
Excluding unblinded sites	397	4 mg vs placebo	0.657 (0.80, 0.899)
	402	8/4 mg vs placebo	0.906(0.672, 1.221)

Administration of radiation:

The reason for administration of radiation for each event was not given by the sponsor in the raw datasets. Due to blinding and randomization, bias in changing therapy is not expected. However, to evaluate the quality of the data, the reviewer evaluated the anatomical sites treated by radiation in asymptomatic patients. This analysis showed that most patients appropriately received radiation weight-bearing sites. Three patients on the Zoledronate arm, listed in table 23, had radiation for lesions that may not have been clinically significant. It is not known if the skull lesions could mean impending injury to the brain

Table 24: Asymptomatic patients who received XRT

Pt ID	Site of Radiation	Treatment arm
15051	Skull - bony framework of head	8/4 mg
25022	Base of skull	8/4 mg
26027	Left scapula	4 mg

XRT and vertebral fracture were counted as separate SREs, although the primary bony lesion may have been the same. The next table lists this occurrence on the treatment arms.

Table 25: Patients with vertebral fractures who received XRT

Treatment arm	Number of patients with vertebral # and XRT
4	4
8	6
Placebo	10

Change in PSA

The change in PSA of the 8/4 mg arm was the greatest, and that for placebo arm was the lowest.

Table 26: Median change in serum PSA

Treatment arms	Total	Median change in PSA
4	214	88
8	221	107
Placebo	208	78

Pooled Analysis of Zoledronate arms

When pooled together, the Zoledronate arms had a borderline efficacy, as can be noted from table 27.

Table 27: Pooled Analysis of Zol. 4 mg amd 8/4 mg arm

	p-value	H.R. and 95% C.I
Time to first SRE	0.06	0.78 (0.60, 1.01)
Proportion of Patients with SRE	0.04	-0.08(-0.161, -0.001)

The p-value should be interpreted with caution due to exploratory nature of the analysis. α is not adjusted for multiple testing

Efficacy Conclusions of Study 039

Study 039 was well-conducted and well-controlled. Patients treated on the Zol 4 arm demonstrated significantly less morbidity than patients on the placebo arm both by the protocol-specified primary analysis of proportions of patients with at least one SRE (33% vs. 44%, respectively, p = 0.021) and by the FDA-preferred analysis of time to first SRE (p = 0.011). By both analyses, however, the Zol 8/4 arm failed to demonstrate a statistically significant difference from placebo (Proportions: 38% vs. 44%, respectively, p = 0.222; Time to SRE: p = 0.491). After multivariate analyses that included potential prognostic factors (treatment, prior history of skeletal events, time from initial diagnosis of cancer to bone metastases, time from first bone metastases to randomization, $\log_e$ of baseline PSA, and baseline analgesic scores), the results of the Zol 8/4 arm remained unchanged although the p value decreased.

The major problem with this study is the unsupportive evidence provided by efficacy analyses of the Zol 8/4 arm.

Several minor problems were discussed in this review:
Asymptomatic vertebral compression fractures and changes in chemotherapy, events of questionable clinical meaning, were included as elements of the SRE endpoint. Because there were few such events on the study, this was not a signficant problem.
Unblinding of patients to treatment arm was noted in about 5% of patients. These were equally distributed among study arms.

Placebo Controlled Trial #011 in Other Solid Tumors

6.3.2 Placebo Controlled Trial #011 in all solids tumors, other than Breast Cancer and Prostate Cancer

The Applicant proposes that Study 011 supports the use of zoledronate 4 mg administered intravenously as an adjuvant to anticancer therapy to patient with any cancer metastatic to bone other than breast cancer, multiple myeloma, or prostate cancer.

Reviewer's Comment:
Although patients in Study 011 were not required to receive antineoplastic treatment in this study, over two thirds did so.

Protocol Title:

"A randomized, double-blind, placebo-controlled, multicenter trial to evaluate the safety and efficacy of zoledronate (4 and 8 mg) administered intravenously as an adjuvant to anticancer therapy to patients with any cancer with bone metastases other than breast cancer, multiple myeloma or prostate cancer."

First patient accrued:	27 August 1998
Last Patient's 1st visit:	20 April 2000
Last patient completed:	30 January 2001
Date of Unblinding:	30 March 2001

FDA communications regarding protocol design:

- *FDA questioned including worsening of an existing vertebral compression fracture as an SRE.*
- *FDA questioned including a change in antineoplastic therapy to treat bone pain as an SRE. Chemotherapy is usually changed because of progressive disease, and distinguishing between a change in therapy because of progression versus pain would be difficult.*

Background

The following excerpts from the protocol summarize the background and the study rationale:

"Biphosphonates have been approved for the treatment of humoral hypercalcemia of malignancy (HHM); Aredia (pamidronate) has been approved to prevent skeletal-related complications of lytic bone lesions in patients with multiple myeloma and breast cancer. Zoledronate is a third-generation biphosphonate with greater potency to inhibit osteoclastic bone resorption, less renal effects, and a wider therapeutic window (i.e., less inhibition of bone formation). In addition, zoledronate can be given as a rapid IV infusion over 5 minutes, compared to a 1-2 hour administration of pamidronate".

"Bone metastases frequently occur in patients with advanced cancer. Although they are rarely directly responsible for mortality, they frequently cause morbidity with fractures, spinal cord

compression, and pain. The use of daily radiation therapy and/or surgery to alleviate these problems may decrease quality of life or add to patient morbidity. Thus, a trial evaluating the effectiveness of zoledronate for these patients is justified".

Reviewer's Comments:
A major weakness of this study is its unproven assumption that morbidity of all cancer metastatic to bone is affected in a similar manner by biphosphonates. This study is designed for all solid tumors metastatic to bone, except for prostate cancer and breast cancer which were evaluated in trials 011 and 010. There is no evidence to date that any biphosphonate is effective in decreasing skeletal related events for these tumors. The design of this study is based on the hypothesis that even though tumor cells vary greatly in their natural history and in their response to antineoplastic agents, once they metastasize to bone, a bisphosphonate will have the same impact on the bone morbidity from each tumor. The current study is not designed to rigorously evaluate zoledronate efficacy in any of the individual tumor types included. Perhaps a better design would have powered the study to fully evaluate efficacy in at least the largest subgroup, i.e., patients with NSCLC.

Study Design:

The following excerpt from the protocol summarizes the study design:

"The trial will be an international multicenter randomized double-blind placebo-controlled study. Patients Information on prior skeletal-related events will be collected".

"Patients are to be 18 years or older, with a histologically or cytologically confirmed diagnosis of cancer, and objective evidence of at least one site of metastatic disease to bone., diagnosed no longer than 6 weeks prior to visit 1. Patients with cancer other than breast cancer, prostate cancer, and multiple myeloma, and must have at least one site of metastatic bone disease that was detected within 6 weeks of study entry. Patients must have > 3 foci of uptake on bone scan consistent with metastatic disease. If there are < 3 foci, there must be either additional radiographic or biopsy confirmation of the presence of metastases. Patients must enter the trial with a normal calcium and may not have received prior biphosphonate therapy".

"Treatment of SRE present prior to visit 1 is permitted as long as therapy did not include the use of a biphosphonate. Likewise TIH may be treated with agents other than biphosphonates. Patients must have a corrected serum calcium between 8 and 12 mg/dl at visit 1. Prior therapy with a biphosphonate will exclude a patient from the study. The patient will be discontinued if hypercalcemia occurs".

"Patients will be stratified by type of cancer: lung cancer or other cancer. Patients will then be randomized in a double-blind fashion to receive zoledronate 4 mg, zoledronate 8 mg, or placebo in a 1:1:1 ratio. All drug assignments will be given as a rapid 5 minute IV infusion every 3 weeks for 12 doses in addition to antineoplastic therapy. Patients will receive treatment for 9 months. They will also receive 500 mg of oral calcium supplementation and a multivitamin containing 400-500 IU of vitamin D daily in order to blunt the compensatory rise in serum PTH

levels caused by the administration of biphosphonates. Supplementation may also help prevent SRE because PTH is an osteoclast activating factor".

"Data on the occurrence of SRE, inclusive and exclusive of TIH, will be collected for each patient. The proportion of patients experiencing at least one SRE, the time to the first SRE, and the skeletal morbidity rate will be calculated. Time to progression of bone metastases and objective bone lesion response will be assessed by a central radiologist. Time to overall progression of disease will be determined in several ways: by the treating physician, by the central radiologic assessments of bony sites of involvement, by central review of appropriate serial radiographic studies of non-skeletal sites. Quality of life, performance status, pain, and analgesic scores will be determined serially throughout the study. Survival data will be collected on each patient. Adverse event information and serial biochemical marker data will be collected".

"Patients will not be taken off study solely for the occurrence of a SRE or progressive disease, because the study is designed to evaluate the total number of skeletal events that occur over the entire duration of the study. A change in antineoplastic therapy will not cause the patient to be discontinued from the study. The development of TIH will be an off-study criteria. The need for use of other drugs that affect osteoclast function, such as gallium nitrate, calcitonin, mithramycin, or other biphosphonate, will also cause patients to be removed from study. Other reasons for withdrawal from study are listed in the protocol and are standard factors. Patients who are removed from study for any reason should still be followed".

"The sample size is planned to be 600 in order to obtain 570 patients (190 patients per arm) who meet entry criteria. No interim analyses will be performed".

Reviewer's Comment:
This protocol required histological confirmation for every patient, as opposed to study 039, where patients could have be enrolled on the basis of serially escalating serum PSA. Another difference is that all patients must have documents bone metastases within 6 weeks of randomization.

Planned Study Duration
Time permitted for patient enrollment: 12 months
Duration of individual participation: 9 months (36 weeks)
Total duration of treatment : 9 months (36 weeks)
Total duration of study: 21 months

Drug Administration and Formulation

The following are details of drug adminiatration for the study arms:
Zoledronate 4 mg in 50 ml normal saline IV infusion over 5 minutes q 3 weeks plus calcium 500 mg taken by mouth with food (daily) and one MVI tablet by mouth daily.
Zoledronate 8 mg in 50 ml normal saline IV infusion over 5 minutes q 3 weeks plus calcium 500 mg taken by mouth with food (daily) and one MVI tablet by mouth daily.

Placebo in 50 ml normal saline IV infusion over 5 minutes q 3 weeks plus calcium 500 mg taken by mouth with food (daily) and one MVI tablet by mouth daily .

As zoledronate may bind to glass, the solution was to be prepared in plastic syringes, bags, and tubes. If not used immediately, the solution was to be stored at temperatures between 36-46° F and can be used for up to 8 hours.

Reviewer's comment:
With Amendment #3, infusion duration was increased to 15 minutes and infusion volume to 100 ml of normal saline.

Inclusion Criteria:
-Signed Informed Consent
-Age 18 years or older
-A histologically or cytologically confirmed diagnosis of cancer other than breast cancer, multiple myeloma or prostate cancer.
-Objective evidence (at least 3 foci of increased activity on bone scan) of disease to bone within 6 weeks of study entry. If there are less than 3 foci, other radiologic or biopsy studies are required to confirm the presence of osteoblastic or osteolytic malignant lesions.
-Performance status of 0, 1 or 2 at Visit 1.

Exclusion Criteria:
-Previous treatment with a biphosphonate.
-Other investigational agent.
-History of non-compliance.
-Liver metastases with bilirubin higher than 2.5 mg/dl at visit 1.
-Abnormal corrected serum calcium.
-Severe cardiovascular disease.
-Pregnancy or lactation.

Objectives:

Primary Objective
The primary efficacy variable was the proportion of patients having at least one skeletal-related event (SRE).

Events were the same as those defined in study 039 (see FDA review of Study 039 for detailed description):
They are:

- Radiation therapy to bone
- Change of antineoplastic therapy to treat bone pain includes any change in anticancer agents to palliate pain. This was later excluded in an amendment.
- Surgery to bone
- Spinal cord compression

- Pathologic fractures

Secondary Objectives

- Time to First Event
- Skeletal-related event rate inclusive of tumor induced hypercalcemia
- Time to first skeletal-related event or TIH
- Skeletal morbidity rate
- Time to progression of bone metastases
- Time to overall progression of disease
- Quality of life (FACT-G)
- Performance status
- Pain scores
- Analgesic scores
- Biochemical markers
- Objective bone lesion response

Reviewer's Comments

After FDA reviewed the protocol and analysis plans, the Applicant was informed that:

- *The FDA would not consider hypercalcemia as an SRE in the primary analysis of efficacy. FDA maintained that zoledronate effects on bone should be separate from its calcium-lowering effects*
- *Events in separate radiation ports could be considered separate skeletal-related events if separated in time.*
- *Multiple events occurring in as the result of a single local problem should not be counted as multiple events, e.g., a spinal cord compression occurring because of vertebral collapse in 2 adjacent vertebral bodies should not count as 3 events*

Note:

- In amendment 2, *change in antineoplastic therapy* was removed from the definition of SRE.
- *Inclusion of worsening of a compression fracture* as an SRE had minimal impact. According to the Applicant, there was only one patient (randomized to the 4 mg arm) who had a worsening compression fracture counted as a new SRE.

Follow-up:

The schedule for follow-up is reproduced from the protocol:

Table 28: Schematic Design diagram

Period	Screening	Randomized treatment and evaluation												Final Evaluation
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Week	-2 weeks	0	3	6	9	12	15	18	21	24	27	30	33	36
Treatment	none	Zoledronate 4 mg q 3 weeks Zoledronate 8 mg q 3 weeks Placebo q 3 weeks												

A radionuclide bone scan was performed at visit 1. Follow-up bone scans and bone surveys were to be performed every three months at visit 6, 10, and 14. Supplement radiographs of areas not covered by a routine survey were to be performed in the following circumstances if clinically indicated. All films are to be reviewed by the central radiologist.

FACT-G and performance status scores were assessed initially and then at visits 6, 10, and 14 Analgesic and pain scores were assessed at visits 2, 3, 4, 6, 8, 10, 12 and 14.

Removal from the study:
Patients were not to be discontinued from study due to progression of disease. If a patient discontinued therapy, every effort was to be made to continue visits on an every 3 month schedule through 9 months from date of randomization. Survival data will be collected for all randomized patients. The following were reasons listed for removing a patient from study:

- Adverse events
- Abnormal laboratory values
- Abnormal test procedure results
- Unsatisfactory therapeutic results
- Patients condition no longer requires study drug
- Protocol violation
- Lost to follow up
- Administrative problems
- Death

Statistical considerations and sample size:

General

The following are important excerpts from the protocol's statistical plan:

"An intent-to-treat analysis of all randomized patients who receive trial medication and from whom at least one measurement is obtained will be performed for all efficacy analyses. For patients who withdraw from the study and begin treatment with a biphosphonate, all data after the new treatment point will be excluded".

"Background and demographic data will be evaluated by summary statistics. If the treatment groups are not comparable, additional analyses will be performed to adjust for the influence, if any, of the variable on the efficacy outcome. Concomitant therapy will be summarized".

"All evaluations will be performed using stratified analysis for the two cancer populations, lung cancer versus other. Two comparisons will be performed: 4 mg zoledronate versus placebo and 8 mg zoledronate versus placebo, and 4 mg zoledronate versus 8 mg zoledronate. The Bonferroni criteria will be used to adjust for multiple comparisons, and will use a significance level of 0.05".

Primary efficacy evaluation

"The primary efficacy variable is the *proportion of patients with any SRE exclusive of tumor-induced hypercalcemia.* Treatment groups will be compared using a Cochran-Mantel-Haenszel test statistic. The 95% CI by treatment group within each stratum will be presented".

"A comparison of the proportion of patients reporting any SRE exclusive of TIH during the first 3, 6, and 9 months of the study will be presented. Summary statistics for the primary efficacy variables will be tabulated by country. Effects of country or treatment-by-country interactions will not be examined unless enrollment in each country is sufficient".

"The primary efficacy variable will be summarized by the baseline prognostic factors of PS (0-1 versus > 1), renal function (creatinine < 2.0 mg/dl versus ≥ 2.0 mg/dl) and age (≤ 60 versus >60). Zoledronate will 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 of < 0.025".

Reviewer's comments:

Amendment 7 changed the primary efficacy analysis. Due to safety concerns, all patients in the 8 mg arm received 4 mg. According to the amended analysis plan, 8 mg would not be evaluated for efficacy, and that zoledronic acid 4 mg would be considered more efficacious than placebo if the comparison for the primary efficacy outcome was statistically significant at 0.05 level (2-sided).

At the time of the amendment discontinuing the 8 mg dose, all patients had already been enrolled in the study and had completed at least visit #3.

Table 29: Patient enrollment at the time of amendment 7

Treatment arm	No of patients	Range of visit numbers at time of amendment change
4	68	4 -14
8	67	4 -14
60	65	4 -14

Secondary efficacy variables

- Statistical plans were also provided for secondary endpoints (See FDA statistical review for details) :
- Proportion of patients with any SRE inclusive of TIH
- Time to the first occurrence of a SRE
- Multiple events analysis
- Skeletal morbidity rate
- Time to progression of bone metastases.
- Time to overall progression of disease.
- QoL, PS, pain, and analgesic scores.
- The FACT-G score is defined as the sum of 4 subscales (physical, functional, social, and emotional). Change from baseline of the total score will be the primary end point.
- The BPI pain composite score will be the primary efficacy variable for QoL, including pain, analgesic use, PS, and QoL index. The mean of the two BPI composite scores and two analgesic use scores for each 3 month interval will be used for the analysis of BPI pain composite score and analgesic use respectively.
- Biochemical markers
- Objective bone lesion response.

Sample size and power calculations

"The trial is 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 of zoledronate and placebo. Bonferroni's adjustment was used, and it was assumed that the SRE incidence rate will be 48% on placebo and 32% on either dose of zoledronate. An alpha of 0.05 (two-sided) was used. With these assumptions, the sample size was determined to be 570 patients, 190 per arm. Six hundred patients will be enrolled in order to allow 5% for an intent-to-treat analysis".

Reviewer's comment:

The study was probably underpowered due to an overly optimist estimate of the zoledronate effect. Results from this trial for the 8mg versus placebo comparison showed a difference between arms of only 7%.

Protocol Amendments:

There were 6 amendments to the protocol, with two addressing renal safety issues.

Date of Protocol: March 5, 1998

Amendment 1 June 26, 1998:

Modification to match the Tumor Response Criteria to match other Zoledronic acid bone metastases trials.Amendment 2 November 24, 1998

- Change in antineoplastic therapy was removed from the definition of SRE.
- Patients with asymptomatic brain metastases could be included.

- In patients with an ECOG PS of 2, the bone metastases should have been diagnosed within 6 weeks of visit 1.
- There were no restrictions concerning diagnosis of bone metastases for patients with a PS of 0 or 1 at visit 1.

Amendment 3 June 24, 1999:

- Zoledronate for all study patients was to be diluted in 100 ml. of normal saline and administered intravenously as a 15 minute infusion. This amendment was due to 3 SAE reports of renal failure. All 3 patients were receiving 8 mg of Zoledronate. One of these patients died because of sepsis, and creatinine returned to base for another. The outcome for the third patient was not known at that time because of inadequate follow up.

Amendment 4 February 16, 2000

- Target sample size was increased to 700 patients to procure 663 evaluable patients.
- This amendment indicated that the modified Bonferroni criteria would be used in efficacy analysis.

Reviewer's note:
773 patients were enrolled in to this study.

Amendment 5 June 7, 2000:

- All Patients receiving Zoledronate 8 mg had their dose reduced to 4 mg, effective immediately. This was based on the suggestions by the Data Safety Monitoring Board (DSMB) and the Renal Advisory Board (RAB). The blind was to continue.
- Serum creatinine was to be measured prior to each dose of study drug. Drug administration will be delayed as outlined in the next table.

Table 30: Dose modification according to serum creatinine

Baseline creatinine (mg/dl)	Creatinine elevation above baseline prior to drug administration (mg/dl)	Action
<1.4	0.5	Delay in drug administration until the serum creatinine returns to less than 10% of baseline.
> 1.4	1.0	
Any	doubling	

Reviewer's note:
Due to first part of amendment 5, 70 of 266 patients received 8 and then 4 mg doses in the 8mg arm. The change in dosage occurred some time after visit # 3. No patient in this arm received 4 mg dosage from the first treatment visit. Approximately 27% of infusions in the 8/4 mg arm were administered at a 4 mg dosage.

Table 31: No. of infusions per actual dose administered

Dose administered	# of infusions administering actual dose	4 mg	8/4 mg	Placebo
Placebo	1600	0	0	1600
Zol. 4mg	2083	1755	328	0
Zol. 8/4mg	1384	0	1384	0

Table 32: No. of patients per actual dose administered

Dose administered	# of patients receiving actual dose	4 mg N=257	8/4 mg N=266	Placebo N=250
Placebo	247	0	0	247
Zol. 4mg	321	254	67	0
Zol. 8/4mg	265	0	265	0

There is a lack of concordance between the total number of patients randomized to an arm and the number of patients receiving drug because seven randomized patients did not receive study drug.

Amendment 6 Oct 13, 2000

- The ITT population was defined as all randomized patients who had evidence of bone metastases at study entry.
- The efficacy evaluation section was modified to explain the efficacy analyses as follows:
  -- For all efficacy variables analyzed, zoledronic acid 4 mg vs. placebo would be used to assess the effectiveness of the zoledronic acid treatment. Comparisons between zoledronic acid 8/4 mg and 4 mg acid would be available to assess whether an initial treatment of Zoledronic acid 8 mg would prove greater efficacy than the initial treatment with 4 mg.
  – Explained that zoledronic acid 4 mg would be considered more efficacious than placebo if the comparison for the primary efficacy outcome was statistically significant at 0.05 level (2-sided), favoring the zoledronic acid 4 mg group.

Reviewer's comments on the original protocol and amendments:

- *The study was based on an assumption that all osteolytic tumors in bone behave in a similar fashion to Zoledronate or by bone osteoclast. Generally cells from breast cancer, small cell lung cancer, or pancreatic cancer behave quite differently from each other in the human body. This study assumes that these cells would behave similar to each other when acted upon by Zoledronate once inside bone. This hypothesis has not been proven for any biphosphonate.*

- *Amendment 6 made changes to the way statistical plan after all patients had already been enrolled in to the study. The alpha value in the original protocol would have been 0.025 because of the two planned comparisons to avoid obtaining significance by chance. Amendment 6 was made after enrollment was completed. In it, alpha was increased to 0.05. Since all patients had*

been enrolled by the time the amendment was submitted, it is this reviewer's opinion that the level of significance should remain at 0.025.

- *Patients with any number of prior chemotherapeutic regimens could have been enrolled and they could receive more chemotherapy during the study. Response to chemotherapy administered could affect progression of bone metastases and consequent occurrence of SREs. Data documenting the number of prior chemotherapy regimens and response prior to prior chemotherapy should have been noted and perhaps served as stratification factor since it would be expected to impact the study results.*

- *According to the protocol, the randomization was stratified lung cancer vs. other. However, it is not specified whether both Non Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC) patients would be included in this category. This apparently led to confusion so that many patients with small cell cancer were incorrectly stratified with the NSCLC group.*

- *Inclusion or exclusion criteria did not specify whether a patient should have been on treatment for the cancer or not, although the proposed zoledronate indication is for use in conjunction with antineoplastic therapy.*

- *Clinical relevance of asymptomatic SREs is not clear. For example if there are asymptomatic vertebral fractures, delay in these events is of no obvious clinical benefit.*

- *The reason for administration of radiation is not captured well in the protocol, or the electronic dataset.*

- *The protocol was improved by an FDA-suggested amendment that change of chemotherapy secondary to pain as SRE not be included in this protocol. In US, chemotherapy is usually not changed prior to disease progression.*

- *The secondary endpoint skeletal morbidity rate (SMR) is based on a value calculated using arbitrary time points, its utility is questionable. Several major events in a time period in one patient would have the same significance as a single event in another patient. This endpoint is an attempt to capture efficacy beyond the first event.*

- *Specific criteria for removal from study for based on "abnormal" lab values and test results are not given.*

- *According to the protocol, the central radiologist was to assess the time to progression of bone metastasis and objective lesions. It is expected that the radiologist will determine only the presence rather than time to progression of bone metastasis.*

Efficacy Results of Study 011:

Patient Disposition:
Seven hundred and seventy three patients were randomized, but seven did not receive the study drug (10410, 10816, 12452, 12811, 20642, 22707, and 22708). The seven patients were included in the efficacy analysis, but were excluded from the safety analysis.

According to the sponsor, 35 patients with small cell lung cancer were randomized in the incorrect group, with the NSCLC patients. Three patients were randomized with the 'other solid tumor' stratum. The sponsor analyzed the patients in the incorrect stratum.

Reviewer's Comment:
Although the randomization to the incorrect stratum may affect the individual strata's results, it does not change the overall result of the study.

Discontinuation of Study Drug
Only about a quarter of patients completed the study. According to the Applicant, percentage of patients who did not complete the study was similar for all treatment groups: 73.2% in the 4 mg arm, 75.5% in the 8/4 mg arm, and 74.4% in the placebo arm. (The reviewer obtained similar results using the electronic data).

Reviewer's Comments:
Table below shows dropouts in study 039 and 011. Whereas dropout rates varied among study arm in study 039, in study 011 the rates were higher, and were more similar among study arms.

Table 33: Patients discontinuing Zoledronate for protocols 039 and 011.

Protocol	Placebo	4 mg	8/4 mg
039	68.7%	61.7%	71%
011	73.2%	73.2%	75.5%

The number of deaths (counted from study phase completion or within 28 days of study drug discontinuation) were similar across treatment arms. (35%, 33.6% and 33.6% in the 4 mg, 8/4 mg and placebo arms respectively).

Reviewer's Comments:
Death was the primary reason for discontinuation from study. Reasons for withdrawal were similar between the 4 mg arm and Placebo. The top three reasons are the same as in study 039, although the order is different. Withdrawal of consent followed by adverse events, and then deaths were the primary reasons for discontinuation from protocol. Deaths are less in study 039 probably due to the often prolonged course of prostate cancer.

Death and adverse events were more in the 8/4 mg arm. Interestingly, unsatisfactory therapeutic result as a reason was similar across 4 mg and placebo arm for study 011.

Table 34: Reason for discontinuation from protocol

Reason for discontinuation from protocol	Protocol 011			Protocol 039		
	4 mg	Placebo	8/4 mg	4 mg	Placebo	8/4 mg
Death	72	74	81	25	32	40
Adverse events	50	53	66	38	29	44
Consent withdrawal	46	44	36	40	35	48
Unsatisfactory therapeutic result	17	19	13	19	34	17
Abnormal labs	1	2	4	3	2	5
Condition does not require study drug	2	3	2	1	3	3
Lost to follow up	2	1	4	4	5	0
Administrative problem	2	1	1	0	3	0
Protocol violation	3	0	0	1	0	0
Abnormal Test Results	1	0	1	1	0	0

Population

The study population is described in the following table:

Table 35: Demography

Treatment arm	4 mg	Placebo	8 mg
No of patients per FDA	257	250	266
No. of patients per sponsor	257	250	266
Age range	25-88	25-86	28-84
Median	63	63.5	62
Age ≤ 60 years	109	99	125
Age > 60 years	148	151	141
Race (per sponsor)			
Caucasian	226 89%	223 90.3%	237 89.4%
Black	15 5.9%	12 4.0%	15 5.7%
Other	13 5.1%	12 4.9%	13 4.9%
Time from initial diagnosis to randomization (per sponsor) N	120	117	130
Median (months)	4.1	5.6	4.6
Range (months)	0-282	0-97	0-124
Time from initial diagnosis to diagnosis of bone mets N	254	247	265
Median (months)	3.8	2.5	2.4

Treatment arm	4 mg	Placebo	8 mg
Range (months)	0-520	0-211	0-371
Time from first bone mets to randomization (per sponsor) N	254	247	265
Median (months)	1.6	1.8	1.8
Range (months)	0-46	0-102	0-63
Prior history of bone metastasis (per sponsor)			
No prior history of bone metastasis (per sponsor)			
No of bone metastasis per patient	247	235	250
median	2	3	2
range	1-10	1-9	1-12
Previous SRE			
Yes	80 66.7%	88 75.2%	89 68.5%
No	40 33.3%	29 24.8%	41 31.5%
Performance status			
0	50	50	60
1	162	168	158
2	42	30	44
3	1	1	1
4	0	1	0
Analgesic score (per sponsor)			
0	13 10.8%	8 6.8%	13 10%
1	17 14.2%	15 12.8%	27 20.8%
2	3 2.5%	3 2.6%	4 3.1%
3	44 36.7%	41 35%	38 29.2%
4	43 35.8%	50 42.7%	48 36.9%
BPI composite Pain score (per sponsor)			
N	234	227	245
Median	3.5	3.3	3.3
Fact-G score (per sponsor)			
N	230	227	241
Median	71	71.2	69

Reviewer's comments:

The Applicant analyzed 'time from initial diagnosis to diagnosis of bone metastases' and 'time from first bone metastases to randomization' according to the safety evaluation groups. The

results would likely be similar if the same calculations were performed according to the 'efficacy' group of patients. Note that the ranges of these evaluations are quite broad, indicating extensive variability from patient to patient. This is expected with such a diverse study population.

The patients are fairly well matched across treatment arms for the prognostic factors listed in the table above, except for whether the patient had any SRE prior to entering the study. This imbalance favors the 4 mg treatment arm (67% on 4mg versus 75% on placebo). Presence or absence of prior SREs has emerged as the strongest prognostic factor for study 011 as well as the study 039. The FDA statistician included this factor in a multivariate analysis (see discussion of results).

The distribution of patients by tumor type according to the Applicant and according to FDA analysis of the data are given in tables below. The number of patients in this table is different from that provided by the sponsor. The reason for this is given in the section on protocol violations.

Table 36: Distribution of patients by cancer type and treatment arm per Applicant

Cancer type	Number of patients	4 mg	Placebo	8/4 mg
NSCLC	386	126	126	134
Thyroid	11	2	4	5
Head and Neck	17	6	4	7
Renal	74	27	19	28
Unknown primary	43	15	14	14
Other	242	81	83	78

Table 37: Distribution of patients by cancer type and treatment arm per FDA Review

Cancer type	Number of patients	4 mg	placebo	8/4 mg
NSCLC	375	124	121	130
Renal	73	26	19	28
Small cell lung cancer	66	19	22	21
Colorectal	52	19	16	17
Unknown	47	17	14	16
Bladder	33	11	16	6
GI (other)	29	10	12	7
Head and neck	16	6	4	6
Genitourinary	15	6	6	3
Malignant melanoma	15	5	4	6
Hepatobiliary	11	3	4	4
Thyroid	11	2	4	5
Other	9	3	2	4
Sarcoma	9	3	3	3
Neuroendocrine/carcinoid	7	2	3	2
NHL	3	0	0	3
Mesothelioma	2	1	0	1

There was a difference of 10% between the 4 mg and the placebo group for the renal cancer patients. This difference was less for the rest of the cancer types in the non-NSCLC stratum. All NHL patients (they should not have been included per inclusion criteria) were in the 8 mg arm.

Study Treatment

The number of infusions delivered on each study arm is given in the following table. The highest number of infusions were administered in the 4 mg followed by 8/4 mg and placebo. Patients in the placebo arm received 91% of the number infusions as those in the 4 mg arm. Sixteen per cent of infusions in the 8/4 mg arm were 4 mg infusions.

Table 38: Doses and Infusions administered

Actual Dose Administered mg	Total Infusions	Treatment arms		
		Zol. 4 mg	Zol. 8/4 mg	Placebo
0	1600	0	0	1600
4	2083	1755	328	0
8	1384	0	1384	0

Protocol Violations

The most common protocol violations are listed in the next table. This table was prepared from the electronic dataset provided by the sponsor

Table 39: Protocol Violations per sponsor in at least 5 patients

Protocol Violations	Placebo (# of pts.)	Zol. 4 mg (# of pts.)	Zol. 8/4 mg (# of pts.)
Patient randomized to incorrect stratum	18	18	15
Treatment with bisphosphonate during the 12 months prior to visit1	4	1	12
Patients ECOG status of 2 not diagnosed within 6 weeks of visit 1	2	4	8
No objective evidence of metastatic bone disease	1	3	7
No bone metastases on bone lesion survey at visit1	2	3	4
Consent form not signed prior to study procedure	5	1	1
Corrected serum calcium out of range at visit 1	1	2	1
Unblinding	5	2	1
Treatment with bisphosphonate 12 months after start of study drug	3	1	1
treatment with other investigational drugs	0	3	0

Reviewer's comments:

According to the sponsor, there are 403 patients with NSCLC, whereas on FDA review, there were 375 patients with NSLC in the study. The discrepancy is partly due to the incorrect stratification, in which 51 patients with SCLC were assigned to the NSCLC stratum.

There were also discrepancies in the diagnosis. Of 773 patients, only 262 (34%) patients had a brief histology report submitted, allowing FDA to verify the diagnosis. By FDA review of these reports, eleven patients who were classified by the Applicant as having NSCLC had either SCLC (n=10) or mesothelioma (n=1). Other patients incorrectly labeled as having NSCLC are listed in the following table. Although these discrepancies may effect the relative numbers in the two strata, they should not affect the overall comparison of the study arms.

Table 40: Patients stratified as NSCLC per Applicant, not consistent with documented histology

Patient no.	Histology	Treatment arm
10459	Mesothelioma	Zol.4 mg
12705	Carcinoid typical	Zol.4 mg
20699	Carcinoid (atypical)	Zol. 4 mg
10601	Neuroendocrine carcinoma	Zol. 8/4 mg
11573	Neuro endocrine	Zol. 8/4 mg
21081	Carcinoid	Zol. 8/4 mg
10181	Neuroendrocrine carcinoma	Placebo
10783	Carcinoid with neuroendocrine diff.	Placebo
20810	Carcinoid tumor of lung	Placebo
22413	Small cell lung cancer	Placebo
22714	Microutoma (SCLC)	Placebo

Another serious protocol violation would be lack of evidence of bone metastases. According to the Applicant, all but two patients had documented bone metastases. Several patients did not have the specific protocol-required evidence on bone scans or survey. For these patients, however, a CT scan, MRI, or pathological evidence was available.

There were 3 patients with a hematological malignancy included (NHL), though only patients with solid tumors were to be included in this study. All 3 patients were in the 8/4 mg arm.

Administration in conjunction with antineoplastic therapy

As shown in the following table, five hundred and fifty seven patients out of the 773 (72%) received concurrent antineoplastic therapy. The distribution of patients was similar across treatment arms.

Table 41: Patients receiving concurrent antineoplastic therapy

Treatment Arm	Placebo	Zol. 4 mg	Zol. 8/4 mg
No. of patients	181	192	184
% of total number	72	75	70

Results of Primary Efficacy Analysis

The primary efficacy endpoint was the proportion of patients experiencing at least one SRE. Hypercalcemia is excluded from this analysis. The cut-off for all analyses except for survival is end of phase 1, at visit 14 (9 months). Table 42 provides the results from analyisis of the electronic data sets. By both the FDA and Applicant analyses the proportion of patients with an SRE is about 9% less on the 8/4 mg arm than placebo, a statistically significant difference.

However, the proportion is only 5-6% less on the 4 mg arm than placebo, and this difference is not statistically significant.

Table 42: Proportion of patients having any SRE up to Month 9 by Treatment group (ITT)

	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%)	-	-

The following table lists the proportion of patients having at least one SRE by the FDA analyzed strata vs. the Applicant's ITT strata up to 9 months.

Table 43: Comparison of proportion of patients in each stratum having any SRE up to 9 months according to treatment group

	Treatment Arm	Proportion	
		FDA	Applicant
Lung Cancer	Placebo	54/121 45%	59/130 45%
	Zol. 4 mg	51/124 41%	56/134 42%
	Zol. 8/4 mg	43/130 33%	47/139 34%
Other	Placebo	56/145 39%	52/120 43%
	Zol. 4 mg	43/133 32%	41/123 33%
	Zol. 8/4 mg	50/136 37%	45/127 35%

Reviewer's comment:

There were some differences in numbers of patients included for individual tumor types due to reasons noted earlier in the review. However, the proportions with SREs in FDA and Sponsor analyses are similar for the NSCLC strata.

Proportions of patients by tumor type are shown in the next table. Note that the percentages shown in this table are based on number of patients in arm/ total number of patients in tumor type. This is not the proportion percentage. These are given in table on the previous page.

Table 44: Proportion of patients with at least one SRE, by tumor type, FDA analysis

Cancer type Per FDA	Pts. with SRE/Total # of patients in Ca type %	Patients with SRE in treatment arm/ total # of patient in treatment arm of Cancer type		
		4 mg % of total tumor type	Placebo % of total tumor type	8/4 mg % of total tumor type
NSCLS	148/375 39.47%	51/124 13.60%	54/121 14.40%	43/130 11.47%
Renal	36/73 49.32%	8/26 10.96%	14/19 19.18%	14/28 19.18%
SCLC	25/66 37.88%	7/19 10.61%	9/22 13.64	9/25 13.64%
Colorectal	17/52 32.69%	7/19 13.46%	5/16 9.62%	5/17 9.62%
Unknown	16/47 34.04%	3/17 6.38%	7/14% 14.89	6/16 12.77%
Bladder	9/33 27.27%	4/11 12.12%	5/16 15.15%	0/6 0%
GI other	12/29 41.38%	3/10 10.34%	6/12 20.69%	3/7 10.34%
Head and neck	9/16 56.25%	4/6 25.00%	2/4 12.50%	3/6 18.75%
GU	4/15 26.67%	1/6 6.67%	1/6 6.67%	2/3 13.33%
Malignant melanoma	3/15 20%	3/5 20%	0/4 0%	0/6 0%
Hepatobiliary	3/11 27.27%	0/3 0%	2/4 18.18%	¼ 9.09%
Thyroid	4/11 36.36%	0/2 0%	2/4 18.18%	2/5 18.18%
Other	4/9 44.44%	0/3 0%	1/2 11.11%	3/4 33.33%
Sarcoma	4/9 44.44%	1/3 22.22%	1/3 11.11%	1/3 11.11%
Neuroendocrine/carcinoid	2/7 28.57%	0/2 0%	1/3 14.29%	1/2 14.29%
NHL	0/3 0%	0/0 0%	0/0 0%	0/3 0%
Mesothelioma	½ 50%	1/1 50%	0/0 0%	0/1 0%

Reviewer's comments:
The improvement in proportions of patients suffering from at least one SRE in the 4 mg arm does not reach statistical significance over placebo in the analysis for the primary objective.
(p= 0.127)

Analyses of Secondary Objectives

Time to First SRE

Time to first SRE was a secondary end point. Time to first SRE was 67 days longer in the 4mg arm than placebo (230 days versus 163 days, p = 0.026 by log rank test).

Table 45: Time to First SRE up to 9 months (-HCM)

	Treatment arm	Median	p value compared to placebo and 95% confidence limits
Per Sponsor	4 mg	230	0.023
	Placebo	163	
	8/4 mg	219	0.034
Per FDA	4 mg	230	0.026 168-* days
	Placebo	163	106-188 days
	8/4 mg	219	0.035 172-* days

* not reached
P values were calculated using Cox-regression by the sponsor
P values were calculated using Log-rank method by the FDA

The relative efficacy of the subgroups was also addressed in the FDA statistical reviewer's Cox regression analysis:

Table 46: 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

The overall hazard is 0.73 while the estimated hazard in the subgroups are 0.79 and 0.66 for *NSCLC* and *other tumors*, respectively.

Reviewer's Comments:

'Time to First Event' although a secondary endpoint, is more sensitive than 'proportions of patients'. This is because it accounts and adjusts for the timing of dropouts. Median time to first event was increased by a median of 67 days in the 4 mg arm over placebo. Although the difference in time to first event is statistically significant for all patients, this difference is lost when evaluating each stratum separately

Proportion of patients with each type of SRE

According to Applicant analyses (Volume 1.92), the proportion of patients having each type of SRE (fracture, radiation, etc.) was lower in the zoledronic acid groups than in placebo except surgery to bone. However, statistical significance was not reached.

Time to first SRE for each type of SRE

According to Applicant analyses (volume 1.92), the median time to the first event was generally not reached due to low event rates. The distribution of time to first event was statistically significant in favor of the 4 mg arm versus placebo in the case of fractures.

Reviewer's comment:
Pathologic vertebral fractures are of questionable clinical significance if they include asymptomatic events. An exploratory analysis of symptomatic events only is given in the next section on Exploratory Analysis.

Skeletal Morbidity Rate (SMR):

Skeletal morbidity rate captures all events as one in an evaluation period of 28 days. It sums all occurrences and divides by time on study. It attempts to capture events occurring beyond the first event. However, it does not distinguish between the severity or number of events in one evaluation period. The Applicant analysis of the skeletal morbidity rates for the 4, 8/4mg arms and placebo for all patients together is not given in the study report (p 56). Compared to placebo, SMR was significantly lower on the 8/4 arm ($p = 0.005$) but not the 4 mg arm ($p = 0.069$) and not in subgroups of the 4 mg arm.

Brief Pain Inventory (BPI) composite pain score:

A higher composite pain score indicates more pain. In the Applicant analysis, the mean BPI score increased slightly from baseline to Month 9 for all 3 treatment groups. There was no statistically significant difference between any of the treatment groups. This lack of significance was also observed in protocol 039.

Analgesic scores:

In this analysis, analgesic scores ranged from 0 to 4, higher scores indicating stronger analgesic used. In Applicant analyses, there were no statistical differences in analgesic score changes from baseline among the treatment arms at Month 9.

Performance Status:

In Applicant analyses, there were no statistical differences in the ECOG performance status from baseline among the treatment arms at Month 9.

Quality of Life (FACT-G)

In applicant analyses, there were no statistical differences in change from baseline among the treatment arms at Month 9.

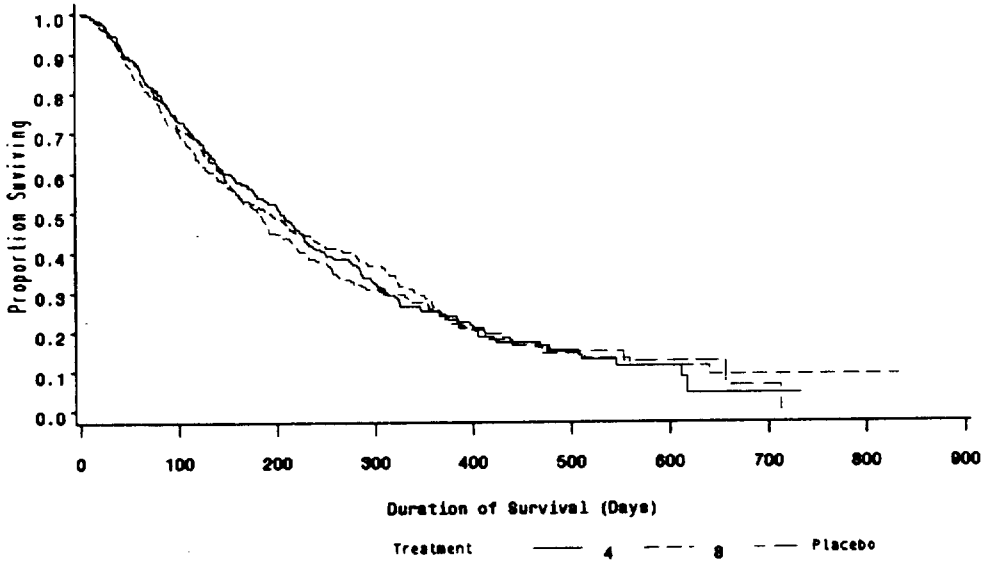
Progression of bone metastases and disease

There was no difference between treatment groups in the distribution of time to progression of bone metastases or overall disease progression.

Survival

The median survival of patients was similar in the three treatment arms. The Kaplan-Meier curve is shown in the next Figure.

Figure 2: Kaplan-Meier Curve for survival



Survival according to subgroups is described in the following tables. The first presents survival according to subgroups reclassified by the medical reviewer, and the second provides subgroups as analyzed by the Applicant.

Table 47: FDA's analysis of median survival by stratum

Tumor type	Median survival Days		
	4 mg	Placebo	8 mg
NSCLC	202	157	174
Other	208	192	214
Total	203	183	189

Table 48: Applicant's analysis of median survival by stratum

Tumor type	Median survival days		
	4 mg	Placebo	8 mg
NSCLC	199	155	181
Other	215	192	213
Total	203	183	189

Reviewer's Comment:
The purpose of analyzing overall survival is to provide assurance that Zoledronate does not affect survival adversely. It is not expected to improve survival.

Exploratory Analyses

Evaluation of symptomatic events

Using the electronic data, the reviewer evaluated whether SREs were listed as symptomatic. These data are given below in the table. As indicated, about half (20/41) of vertebral fractures were asymptomatic.

Table 49: First events, whether symptomatic or otherwise by treatment arm

Event	Symptomatic	Total	4 mg	8 mg	Placebo
Radiation	Unknown	3	1	2	0
Radiation	No	26	5	12	9
Radiation	Yes	155	53	45	57
Nonvertebral Fracture	Unknown	7	3	1	3

Event	Symptomatic	Total	4 mg	8 mg	Placebo
Nonvertebral Fracture	No	19	7	7	5
Nonvertebral Fracture	Yes	22	7	5	10
Vertebral Fracture	Unknown	4	2	0	2
Vertebral Fracture	No	20	5	6	9
Vertebral Fracture	Yes	17	4	3	10
Surgery	No	2	1	1	0
Ssurgery	Yes	13	3	7	3
Cord Compression	Unknown	1	1	0	0
Cord Compression	Yes	13	5	5	3

The reviewer performed an exploratory analysis evaluating the proportion of patients with SREs excluding asymptomatic vertebral fractures. As shown in the table below, the relative differences between study arms are little affected by exclusion of these data.

Table 50: Proportions of patients with any SRE excluding patients with asymptomatic vertebral fractures.

Treatment arm	Number of patients with at least 1 SRE
4	90/257 35%
8	90/266 34%
Placebo	103/250 41%

Analyses of time to first event excluding SCLC

Small cell lung cancer is characterized by a rapid rate of growth, unlike that of most other solid tumor. An exploratory analysis was performed with the assistance of the statistical reviewer. The hazard ratios and C.I. suggest activity in both Zoledronate arms in patients excluding those with SCLC. The results are as in table N.

Table 51: Time to event excluding SCLC

Treatment arm comparison	N	Hazard Ratios and 95% C.I.
Zol 4 mg vs. placebo	465	0.695 (0.522, 0.925)
Zol 8/4 mg vs. placebo	469	0.707 (0,529, 0.945)

Analysis of Chemotherapy on study

The chemotherapy received by the patients could have impacted the SRE by its effect on bone metastases. An expoloratory analysis of antineoplastic therapy was performed by the reviewer to evaluate potential imbalances. In the data set, any change in treatment, such as addition or deletion of an agent,was recorded as a new regimen by the sponsor. No data was available on the number of regimens prior to coming on study and can not be analyzed. One might assume that randomization would provide balance for this baseline factor. The following table describes the number of regimens given while on study.

Table 52:Number of on-study antineoplastic regimens

Number of regimens	Total	Placebo	Zol. 4 mg	Zol. 8/4 mg
0	213	67	64	82
1-2	495	166	166	166
3-6 regimens	61	15	25	21

Table 53: Number of on-study antineoplastic regimens in NSCLC patients

Number of regimens	Total	Placebo	Zol. 4 mg	Zol. 8/4 mg
0	79	27	23	29
1-2	255	84	84	87
3-6	83	8	16	14

The number of patients receiving chemotherapy on study was similar across arms.

Best tumor Response

The next table shows results of the Applicant's analysis of the best tumor from the study report.

Table 54: Best bone tumor response/patient /arm (from Applicant table)

Best bone lesion response	Zol 4mg N=257	Zol 8/4mg N=266	Placebo N=250
Complete response	0 (0%)	0 (0%)	0 (0%)
Partial response	21 (8%)	27 (10%)	11 (4%)
Stable disease	55 (21%)	51 (19%)	49 (20%)
Progression	86 (33%)	75 (28%)	90 (36%)
Unknown	95 (37%)	113 (42%)	100 (40%)

Reviewer's Comments:

The responses across the arms are similar. However, a third of patients had no response outcome recorded. Furthermore, the study was not designed to evaluate the impact of chemotherapy and prior history of treatment with chemotherapy was not known. For these

reasons, it is difficult to draw any conclusions regarding the effect of chemotherapy on bone metastases and its impact on results obtained for Zoledronate.

Administration of radiation:

The reason for administration of radiation was not given by the sponsor in the raw datasets. Using the electronic data, the reviewer determined the anatomical sites treated by radiation therapy in asymptomatic patients. This analysis showed that most of these patients received radiation to weight bearing sites that seemed to justify radiation therapy in the absence of symptoms. There were four patients who were exceptions. The number of these patients who received radiation for unclear reasons is small and similar across treatment arms.

Efficacy Summary and Conclusions of Study 011

Study design

In this study, 773 patients with a variety of solid cancers metastatic to bone were randomized 1:1:1 to treatment with zoledronate 4 mg, zoledronate 8/4 mg, or placebo to evaluate zoledronate's effect on SREs. Randomization was stratified according to cancer type as either *NSCLC* or *other tumors*. Stratification was imperfect, with a number other tumor types incorrectly included in the *NSCLC* stratum. However, there was no evidence that the randomization process itself was compromised. The primary objective was to compare *the proportion of patients with at least one SRE* on the zoledronate 4 mg arm versus placebo, although FDA statisticians, because of design concerns, had suggested making *time to first SRE* a co-primary endpoint.

Design Problems

The reviewer noted some deficiencies in the study. First, prior chemotherapy regimens were not documented, so FDA could not determine whether extent of prior therapy was balanced among the study arms. Instead, FDA examined data on changes in chemotherapy regimens and reported tumor response rates during the study, but these data were not complete. Therefore, response to chemotherapy, which likely would have affected the incidence of SREs, could not be fully assessed. Second, there was no central review of the pathology specimens. In the one third of patients where pathology reports were provided, some of the tumors were incorrectly classified. Change in this classification could change the results of the subgroup analyses.

Efficacy Results

The proportion of patients with an SRE was lower on the 4 mg arm than placebo, but the difference was not statistically significant (37% versus 44%, respectively, $p = 0.106$). The comparison of the 8/4 mg group to placebo showed a significant difference (35% versus 44% respectively, $p = 0.044$).

Time to first SRE was 67 days longer in the 4mg arm than placebo (230 days versus 163 days respectively, $p = 0.026$) and was also significantly longer for the 8/4 mg arm. For the 4mg versus placebo comparison, subgroup analysis demonstrated a marginally statistically significant difference for the *other tumors* group, but the difference for the *NSCLC* group was not

statistically different. FDA Cox regression analysis provided estimates for the relative contribution of each stratum in the overall analysis: the overall hazard ratio for 4 mg versus placebo was 0.73 while the estimated hazard in the subgroups were 0.79 and 0.66 for *NSCLC* and *other tumors*, respectively.

Table 55: Cox Regression Model with Treatment (Placebo vs. Zol 4 mg) as Co-variate

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

Conclusions from Study 011 (other solid tumors)

This study provides some evidence that zoledronate 4 mg provides clinical benefit to the overall population studied. Although the primary endpoint was not statistically significantly improved, the FDA-preferred secondary endpoint was. Positive results from the 8/4 mg arm were supportive.

However, the study design was based on an assumption that zoledronate will have a similar effect on bone morbidity, regardless of the tumor type. Generally cells from breast cancer, small cell lung cancer, or pancreatic cancer behave quite differently from each other in the body. This study assumes that these cells would behave similar to each other when acted upon by once inside bone. This hypothesis has not been proven for any biphosphonate. Although an efficacy trend is suggested for both subgroups in this study, the stronger evidence for efficacy comes from the subgroup of patients having a variety of types of cancer.

In Study 011, 773 patients with a variety of solid cancers metastatic to bone were randomized 1:1:1 to treatment with zoledronate 4 mg (Zol 4), zoledronate 8/4 mg (Zol 8/4), or placebo to evaluate zoledronate's effect on SREs. Randomization was stratified according to cancer type as either *NSCLC* or *other tumors*. Stratification was imperfect, with a number of other tumor types incorrectly included in the *NSCLC* stratum. However, there was no evidence that the randomization process itself was compromised.

The main issues for this indication were:

- Lack of statistical significance for the Zol. 4 mg arm for the protocol-specified endpoint.
- Heterogenous populations that including a variable tumor type.
- To what extent the zoledronate NDA trials for prostate cancer, breast cancer, and myeloma provide support for efficacy in this setting
- Whether a positive study of this design indicates that efficacy is established for all tumor types evaluated

Design Flaws

The reviewer noted some deficiencies in the study. First, prior chemotherapy regimens were not documented, so FDA could not determine whether extent of prior therapy was balanced among

the study arms. Instead, FDA examined data on changes in chemotherapy regimens and reported tumor response rates during the study, but these data were not complete. Therefore, response to chemotherapy, which likely would have affected the incidence of SREs, could not be fully assessed. Second, there was no central review of the pathology specimens. In the one third of patients where pathology reports were provided, some of the tumors were incorrectly classified and patients were incorrectly stratified into subgroups. Change in this classification could change the results of the subgroup analyses. However, there appeared to be no serious design flaws that biased the comparison of the two study arms or the overall conclusions.

Efficacy Results

The proportion of patients with an SRE was lower on Zol 4 than placebo, but the difference was not statistically significant (37% versus 44%, respectively, p = 0.106). The comparison of the Zol 8/4 to placebo showed a significant difference (35% versus 44% respectively, p = 0.044). Time to first SRE was 67 days longer in the 4mg arm than placebo (230 days versus 163 days respectively, p = 0.026) and was also significantly longer for Zol 8/4.

The subgroup analyses of Zol 4 versus placebo demonstrated a marginally statistically significant difference for the *other tumors* group, but the difference for the *NSCLC* group was not statistically different. As noted above, conclusions based on subset analyses are unreliable because of incorrect stratification and insufficient power. While it is tempting to fault the design of this study design for insufficient power to evaluate efficacy in individual tumor subgroups, it would be difficult to conduct a trial of Zoledronate separately in each cancer type.

This study provides substantial evidence that Zol 4 mg provides clinical benefit to the overall population studied. Although Zol 4 was not statistically better than placebo for the primary analysis (the proportions analysis), Zol 4 was significantly better than placebo for the the FDA-preferred secondary endpoint, time to first SRE. Furthermore, the Zol 8/4 was significantly better than placebo for both of these analyses. The ODAC was asked "Do you agree with FDA that these results provide substantial evidence of Zometa (4 mg) efficacy in the population studied?" The response was YES-10, NO-0, and A-1.

A major question FDA presented for discussion before the ODAC was whether the major underlying assumption of this trial design is valid. The design assumes zoledronate will have similar effects on bone morbidity from metastases, regardless of the primary tumor type. This is an important assumption because cells from various cancers, for example, cells from breast cancer, small cell lung cancer, or pancreatic cancer, behave quite differently from each other in different body organs. This hypothesis has not been proven for any bisphosphonate. To date, pamidronate is the only bisphosphonate with proven efficacy in bone metastases, and proof is limited to osteolytic breast cancer metastases and multiple myeloma. After viewing all of the data from these trials, ODAC strongly supported this design assumption, and voted unanimously that zoledronate is indicated for patients with bone metastases from all solid tumors irrespective of the primary tumor.

6.3.3 Active Controlled Trial #010 in Breast Cancer and Myeloma

Protocol Title:
"A randomized, double-blind multicenter, comparative trial of i.v. zoledronate (4 or 8 mg) versus i.v. Aredia (90 mg), as an adjunct to standard therapies, in the treatment of multiple myeloma and breast cancer patients with cancer-related bone lesions"

First patient randomized:	October 16, 1998
Last patient randomized:	December 13, 1999
Last data for Phase 1 analysis:	December 20, 2000
Data cutoff:	July 3, 2001

Background

By comparing zoledronate 4 mg to pamidronate 90 mg in Study 10, the Applicant claims that zoledronate 4 mg is effective for treating myeloma and breast cancer metastatic to bone. This conclusion is from demonstrating not *superiority* but rather *non-inferiority* of zoledronate compared to pamidronate and involves not only direct evidence from the trial, but also inference and assumptions about the historical pamidronate placebo-controlled trial. To reach the conclusion that zoledronate is effective, one must examine the historical evidence that pamidronate is effective compared to placebo, estimate the size of that pamidronate effect versus placebo, assume that that same effect is manifest in the conditions of the new study of zoledronate versus pamidronate, and, using statistical methods, estimate what fraction of that pamidronate effect must have been retained by zoledronate if the trial assumptions are valid.

The critical historical information describing the results of the pamidronate trials is discussed in section 1.2 of this review.

Study design

The following is a brief overview of protocol 010 emphasizing important differences from the other pivotal studies in this NDA.

Protocol Amendments

Below are important protocol amendments with the dates and number of patients accrued at the time of the amendment. The two most critical amendments were because of renal toxicity. Amendment #2, which occurred after about half of the patients had been randomized, increased the infusion time to 15 minutes, and amendment #5, which occurred after all patients had been randomized, decreased the dose of zoledronate from 8mg to 4mg for patients randomized to the 8mg arm. The following are details of the amendments:

#1 February 19, 1999

This early amendment affected virtually all patients entering the study:

- Clarified that breast cancer patients should be receiving first or second line treatment and that all myeloma patients should be receiving anti-cancer therapy at the time of study entry.
- Specified that patients should be followed for SRE's even after study medication was discontinued.
- Specified that skeletal surveys would be performed in both breast cancer and myeloma patients every 3 months but that bone scans would only be done in breast cancer patients (every 6 months).
- The statistical section clarified that the time to event secondary endpoints will use the Cox regression model with creatinine (<2 vs >=2), ECOG PS (0-1 vs >1), age (<=60 vs >60), previous SRE experience (yes/no), and treatment group, with stratum as the stratified variable.
- Sample size calculations adjust goal to 1509 patients (503 per arm)

#2 June 25, 1999
This amendment was activated when about half (815) of the patients had been entered.

- Because of renal toxicity, the infusion volume was increased from 50 ml to 100 ml and the infusion time was increased from 5 minutes to 15 minutes.

#3 September 30, 1999
This amendment was activated after 83% (1374) of the patients had been accrued. Less than 10% (158) patients had reached their last visit in Phase I.

- An interim analysis plan was provided for a single analysis when 40% of patients had been evaluated for 13 months. A Lans-Demets plan was specified.

#4 February 21, 2000 This was a minor amendment.

#5 June 7, 2000
This amendment was activated about 6 months after the last patient was randomized (December 13, 1999).

- Because of renal toxicity noted with 8 mg zoledronate, patients on the 8mg arm were to receive 4mg. This amendment occurred when about 60% (304) of the patients on the 8mg arm had already reached their last visit in Phase I.

#6 October 13, 2000
This amendment presented statistical amendments to the protocol. Most patients (1446) had reached their last efficacy visit for phase I prior to this amendment.

- 4 mg is specified as the primary arm for analysis.
- Two logistic regression analyses are proposed analysis of SRE's: (1) stratum, previous SREs, treatment, and interaction terms, and (2) stratum, previous SREs.
- The previous interim analysis plan is deleted.

Protocol #010 Design

The primary objective was to demonstrate non-inferiority of i.v. zoledronate 4mg and/or 8 mg to Aredia in preventing SREs in myeloma or breast cancer. If non-inferiority was demonstrated, the possibility of superiority would be tested. (The definition of SRE is the same as that in the prostate cancer Protocol 039). Secondary objectives were also similar to those stated in Protocol 039.

This was in international, multicenter, stratified, double-blind, study that randomized patients 1:1:1 to zoledronate 4 mg, zoledronate 8mg, or pamidronate 90 mg i.v. every 3-4 weeks for 12 months. Randomization was stratified by center and 3 disease strata: myeloma, breast cancer treated with hormones, and breast cancer treated with chemotherapy. The primary analysis was to be a non-inferiority analysis of the proportion of patients with at least one SRE, performed after 13 months (12 months of treatment and one month of followup), comparing each of the zoledronate arms to the active pamidronate active control arm with confidence intervals of the difference excluding a 8% difference. However, with Amendment #5 on June 7, 2000, the 8mg zoledronate arm was dropped from the primary analysis because of nephrotoxicity.

All patients received treatment in the same volume of normal saline over the same time, initially in 50 ml over 5 minutes, and after amendment #2, in 100 ml over 15 minutes. Only the local pharmacist was unblinded to treatment. Drugs were given every 3-4 weeks, depending upon the chemotherapy administration schedule.

Inclusion and exclusion criteria:

Entry criteria were similar to those in Trial 039, with the following exceptions:

- Patients with myeloma were to have Durie-Salmon Stage III disease, at least one lytic lesion, and were to be receiving chemotherapy (per amendment 1).
- Breast cancer patients were to have at least one bone lesion visible on conventional radiographs. According to amendment #1, all patients were required to be receiving first or second line chemotherapy.
- Includes ECOG PS 0-2.

Reviewer's comment.
These entry criteria select patients reasonably similar to those entered in the pamidronate breast cancer and myeloma trials. One difference, however, is the inclusion of patients with osteoblastic disease in the breast cancer patients.

Treatment interruption or discontinuation

Patients were to remain on study for efficacy and safety evaluations despite progression of disease, change in antineoplastic therapy, or the occurrence of an SRE.

Reviewer's comment:
As discussed later in this review, few data were actually captured after discontinuation of study drug.

Treatment:

A double dummy system was used. The initial infusion was either Zoledronate or placebo, and this was followed by a 2-hour infusion of placebo or pamidronate. 500 mg calcium tables were taken daily to suppress parathyroid hormone response to biphosphonate treatment. Most concomitant antineoplastic medications were allowed, except for drugs known to affect calcium metabolism, such as biphosphonates.

Randomization

Lists of numbers randomized numbers in blocks of 3 were provided to the centers for each of the 3 treatment strata leading to stratification by the 3 disease groups and center. In an emergency, the investigator could determine the blinded treatment assignment by removing a scratch-off cover on a "code break card."

Study Schedule

Randomization occurred on visit 2, day 0. Skeletal related events and blood work were evaluated at every visit, every 3-4 weeks. Skeletal surveys were done every 3 months in all patients and bone scans every 6 months in only the breast cancer patients. Other details are outlined in the attached excerpts from the protocol schedule. Visits were planned for every 3 weeks. Patients receiving treatments every 4 weeks would not have visits at V5, 9, 13, and 17. If patients went off study medication, they were to be followed for SREs every 3 months.

Reviewer's comments

The Applicant notes that data were collected differently in these Zoledronate trials than in the pamidronate trials because data were to be collected even after patients discontinued study medication (albeit only at 3-month intervals). One might expect that the quality of these data collected after stopping study medication would be poor because of less frequent and potentially erratic follow-up in these patients. FDA asked Novartis to evaluate the effect of these data on efficacy. Review of the Novartis 12/10/01 submission showed that only 9 additional patients had an SRE affecting the primary analysis when these data were included, six patients on Zom 4, two on Zom 8, and four on placebo. Therefore, efficacy results differed little whether they were included or excluded.

Excerpts from the Protocol Schedule of Assessments:

Month				12	13
Week	39-40	42-44	45	48-49	51-52
Day ranges	269-289	290-310	311-331	332-352	353-373
Visit	V15	V16	(V17) *	V18	V19
Calcium supplements and multi-vitamin tablets dispensed/administered [a]	X	X	X	X	
Medication Administered	X	X	X	X	
Physical Exam, complete or partial [b]	X	X	X	X	X
Adverse Events	X	X	X	X	X
Concomitant Medications/ Non-Drug Therapy	X	X	X	X	X
Anti-neoplastic Therapy *	X	X	X	X	X
Tumor Assessment *					X
Tumor Response * [c]					X
Bone Scan * [d]					X
Bone Survey * [e]					X
Bone Mineral Density [f]					X
Pain Score (BPI) * [g]		X		X	X
Analgesic Score * [h]		X		X	X
ECOG Performance Status * [i]					X
Fact-G Quality of Life * [j]					X
Hospitalization and out-patient care *	X	X	X	X	X
Home care, long-term care, employment status*					X
Serum Chemistry	X	X	X	X	X
Hematology					X
Urinalysis					X
BAP [k]					X
Urine Chemistries [l]					X
Serum PTH [m]					X
SPEP * [n]					X
SIEP * [o]					X
UPEP * [p]					X
Skeletal-Related Events *	X	X	X	X	X
Termination					X

* In patients who discontinued study medication, these follow-up procedures were to be performed according to a three month schedule.

Planned Efficacy Assessments

Primary Endpoint

The proportion of patients with SRE (-HCM) at 13 months was the primary endpoint. As noted earlier, these events included pathologic bone fractures, vertebral compression fractures (a 25% decrease in anterioror or posterior vertebral height), spinal cord compression, surgery to bone, and radiation therapy to bone (including strontium-89). Fractures were determined by a central radiologist who had access to serial films.

Secondary Endpoints

Tumor assessment was to be done every 3 months according to SWOG criteria. The definitions of tumor progression according to these criteria were:

- In myeloma, a 50% increase of M protein on two occasions constituted progression.
- In breast cancer, a new bone lesion or a 25% increase in the product of bidimensionally measurable tumor measurements

Pain and analgesic data were collected every two visits. Pain scores used the Brief Pain Inventory (BPI). This consists of questions rating each specific pain (1-10) and how pain interfers with activity, mood, walking, normal work, relationships, sleep, and enjoyment of life. A composite score was specified as the main variable, but derivation of the composite was not explained in the protocol or study report. Analgesic use was scored as none, 1 = minor analgesics, 2 = tranquilizers, 3 = mild narcotics (oxycodone, meperidine, codeine) and 4 = strong narcotics (morphine, hydromorphone).

Planned Statistical Analysis

The original protocol specified that the analysis of the proportion of patients with at least one SRE would be a non-inferiority test between 8mg zoledronate arm and placebo. If the 8 mg arm was non-inferior to placebo, then the 4mg arm would also be compared to placebo. If a Zoledronate arm was non-inferior to placebo, then tests for superiority were allowed. Originally, the protocol specified one-sided confidence intervals of the difference in proportions between study arms were to show that Z arms were no more than 8% inferior to placebo. After amendment 5, the 8mg arm was dropped from the analysis plan. Furthermore, the final study report uses two-sided 95% confidence intervals upon advice of the FDA at Pre-NDA meetings.

The target "delta" of 8% for the non-inferiority analysis was derived from the pamidronate registration studies for myeloma and breast cancer. The Applicant calculated that a difference of 8% represented 60% of the treatment effect that would be expected in +this study. The expected effect of 13% was averaged from the results from the 3 registration studies listed below:

Disease	Study duration	Placebo SRE	Pamid. SRE	Placebo - Pam
Myeloma	9 mos	40.9%	24.0%	16.9%
Breast-chemo.	12 mos	56.4%	42.7%	13.7%
Breast-horm.	12 mos	55.0%	46.7%	8.3%

The original protocol designated a sample size of 1470 (490 per arm) to have 80% power to determine the non-inferiority boudary of 8% using 2-sided 95% confidence intervals with alpha of 0.05. The final sample size of 1648 exceeded this goal due to rapid accrual.

Results of Study #010

Patient Disposition and Grouping for Analysis

Novartis randomized 1648 patients to the 3 study arms. The following table summarizes patient randomization and grouping for Novartis analyses:

Number (%) of patients in analysis populations by treatment group (All randomized patients)

Populations	Zol 4 mg	Zol 8/4 mg	Aredia 90 mg	Total
All Randomized pts.	564	526	558	1648
Safety evaluable population	563 (99.8%)	524 (99.6%)	556 (99.6%)	1643
ITT population	561 (99.5%)	524 (99.6%)	555 (99.5%)	1640
Per Protocol population	453 (80.3%)	435 (82.7%)	446 (79.9%)	1334

For the safety population the Applicant included all patients that received study drug, excluding 5 patients. The eight patients accrued from one center (2711) were excluded from the Applicant's efficacy analyses because the center did not meet Good Clinical Practices (GCP) standards. Problems included inadequate reporting of trial related issues to the ethics committee, improper informed consent process, and inadequate procedures to maintain the blind. Efficacy was also analyzed in a per protocol analysis that included all patients that met entry criteria and had a 3-month evaluation and did not have a major protocol deviation (use of bone-active agent, missed cycle of study drug during first three months, or missed more than 50% of cycles after the first three months). This excluded about 100 patients per arm.

Reviewer's comment:
The 8 patients excluded in the ITT analysis included only 1 patient with an event on the Zom 4 arm and only one patient with an event on the Pam arm. Excluding these 8 patients is unlikely to alter the outcome.FDA efficacy assessment usually emphasizes the ITT analysis. However, for non-inferiority assessments, the per protocol (PP) analysis is also important. Missing data from patients in the ITT analysis may obscure differences in non-inferiority trials, and PP analyses

may help to lessen the "noise" caused by the incomplete data. This secondary PP analysis is more credible in Study 010 because the criteria for inclusion in the PP analysis were carefully specified in the protocol. As noted in the table above, 20% of the patients in each arm are not included in the PP analysis.

The following Applicant table describes patient disposition during the study:

Patient disposition for each treatment group (Safety evaluable patients)

	Zol 4 mg n (%)	**Zol 8/4 mg n (%)**	**Aredia 90 mg n (%)**
Total no. of patients - n(%)			
randomized	564	526	558
safety evaluable	563	524	556
completed	353 (62.7)	313 (59.7)	338 (60.8)
Discontinuations of study medication			
total	210 (37.3)	211 (40.3)	218 (39.2)
adverse event(s)	57 (10.1)	71 (13.5)	51 (9.2)
abnormal lab value(s)	6 (1.1)	3 (0.6)	4 (0.7)
abnormal procedure	0 (0.0)	2 (0.4)	2 (0.4)
unsat. therap. effect	18 (3.2)	18 (3.4)	22 (4.0)
cond. no longer required study drug	6 (1.1)	7 (1.3)	8 (1.4)
protocol violation	6 (1.1)	4 (0.8)	4 (0.7)
patient withdrew consent	46 (8.2)	44 (8.4)	54 (9.7)
lost to follow-up	3 (0.5)	4 (0.8)	3 (0.5)
administrative problems	7 (1.2)	2 (0.4)	6 (1.1)
death	61 (10.8)	56 (10.7)	64 (11.5)

Source: Post-text tables 7.1-1 and 7.1-3.

Reasons for discontinuation were balanced among the study arms, with three categories (adverse events, patient withdrawal of consent, and death) each accounting for about 10% of the discontinuations in each arm. Further reviewer examination of distribution of these reasons by study arm and according to stratum (mylema, breast-chemo, breast-hormone) did not find marked imbalances between study arms (NDA volume 69, p 723). The Zol 8 arm showed a higher rate of discontinuation for adverse events in the myeloma stratum (12.5% for Zol8 versus about 5% in the other arms).

Protocol Violations

Assessment of study conduct is especially important for a non-inferiority trial. The following presents the reviewer analysis of electronic data on protocol violations. 825 protocol violations are listed, with about the same number of violations for the zoledronate 4mg and placebo arms (298 and 287 respectively).

Table 56: Protocol Violations

	Zol 4 mg	Zol 8 mg	Pam
Breast Chemo	96	86	95
Breast Hormonal	122	94	109
Myeloma	80	60	83

The median number of violations per study site was 0.44 per patient entered and the median number of patients with a violation per site was 0.5 per patient entered.

In the breast cancer chemotherapy stratum, about 30 patients in each arm were not receiving chemotherapy at the time of study entry. About 30 patients in each arm missed one dose of biphosphonate during the first 3 months. About 10 patients in each arm were randomized in the wrong stratum. There were a variety of other infrequent deviations from protocol.

In the breast cancer hormone treatment stratum, about 35 patients on the Zom 4 arm and 21 patients on the placebo arm were not receiving hormone therapy at study entry. The other frequent violation, missing a dose in the first 3 months, was noted in 23 patients on Zom 4 and 22 on placebo.

In the myeloma stratum 31 patients were not on chemotherapy in the Zom 4 arm compared to 28 patients on placebo. 23 patients missed a biphosphonate dose in the first 3 months in the Zom 4 arm compared to 23 on placebo.

Reviewer's comments:
The nature and frequency of these protocol violations seem unlikely to significantly affect analyses of efficacy or safety.

Baseline Demographic and Disease Factors

When evaluating the validity of any randomized trial, one should compare baseline prognostic factors among study arms. An equally important question in non-inferiority studies is whether the current study population is sufficiently similar to the historical population in whom the efficacy of the active control (pamidronate) was established. This latter issue will be addressed in later sections of the review.

The following tables from the study report describe the demographic factors common to all three strata: