



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

**FDA CLINICAL BRIEFING DOCUMENT FOR THE ONCOLOGIC
DRUGS ADVISORY COMMITTEE**

NDA NUMBER: 21-386

DRUG NAME: Zometa® (zoledronic acid for injection)

INDICATION: Treatment of Bone Metastases

SPONSOR: Novartis

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1 Executive Summary

This briefing document provides the Oncologic Drugs Advisory Committee (ODAC) with findings from the FDA clinical review of three zoledronate studies. At the 1/31/02 meeting of ODAC, FDA will seek advice on the zoledronate efficacy supplement for "treatment of osteolytic, osteoblastic, and mixed bone metastases of solid tumors and osteolytic lesions of multiple myeloma, in conjunction with standard antineoplastic therapy." Because the review process is ongoing (this document was prepared one month prior to the meeting and four months into a six-month review cycle), FDA may need to communicate additional findings during the 1/31/02 meeting.

1.1 Recommendations

At this point, the clinical team makes no firm recommendations whether zoledronate should be approved for treatment of patients with bone metastases. Some issues for the ODAC to consider are listed below.

- Efficacy in breast cancer and myeloma seems reasonably well established by the Applicant's large randomized trial (010) that compared zoledronate and pamidronate. However, the ODAC should discuss whether the zoledronate breast cancer indication should be limited to patients with lytic bone metastases. The efficacy of the active control, pamidronate, has only been established in patients with lytic disease.
- In Study 039, the statistically significant difference between zoledronate 4 mg and placebo in both the primary and secondary efficacy analyses suggests that zoledronate is efficacious in prostate cancer. However, these same analyses comparing the 8/4 mg arm to placebo showed no statistically significant differences. ODAC should advise FDA how to reconcile these findings.
- The *other solid tumors* indication evaluated in Study 011 seems problematic. Although the difference between zoledronate 4mg and placebo in the primary efficacy analysis was not statistically significant, the difference was statistically significant for a closely related secondary endpoint (time to first SRE). ODAC should consider whether this is sufficient evidence of efficacy. A second issue is whether to accept the trial hypothesis that all solid tumors metastatic to bone behave in a similar manner when treated with a bisphosphonate. About half of the population in Study 011 had Non Small Cell Lung Cancer, but the rest had a variety of other solid tumors. ODAC should advise FDA whether to approve zoledronate for the proposed indication of *other solid tumors*, for a subgroup of these tumors, or for none of these tumors.

1.2 Overview of Studies

This document discusses the FDA safety and efficacy findings for three randomized studies of zoledronate for patients with cancer bone metastases. In each of the studies the primary endpoint was the proportion of patients with skeletal-related events (SREs). SRE is an aggregate endpoint: pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression. Change in chemotherapy due to increased pain was an SRE in the prostate cancer study only.

Two placebo-controlled randomized studies compared zoledronate 4 mg (zol 4) to zoledronate 8 mg (zol 8) to placebo in patients with prostate cancer (Study 039) or patients with solid tumors other than breast cancer and prostate cancer (Study 011). The third trial was an active control trial comparing zol 4 to zol 8 to pamidronate 90 mg in patients with breast cancer and myeloma. Early in the studies, because of renal toxicity, the zoledronate infusion duration was increased from 5 to 15 minutes. After accrual was complete for all studies, but while many patients were still on study, the 8mg dose was discontinued from the Zol 8 arm of each study because of continued renal toxicity. Patients on the zol 8 arms were given 4 mg doses of zoledronate. (This arm is hence designated as zol 8/4).

Study duration was 15 months for Study 039, 9 months for Study 011, and 13 months for Study 010. When the toxicity of 8 mg zoledronate dose was established (after accrual was complete), the statistical plan was amended so that the primary comparisons were between the zol 4 arms and the control arms (with two-sided testing and alpha of 0.05)

1.3 Efficacy

Prostate cancer

The patients entering Study 039 had prostate cancer with PSA progression while on first-line hormonal therapy for metastatic disease. 643 patients were randomized to the three arms. Efficacy analyses showed significantly less skeletal morbidity on the zol 4 arm than 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: $p = 0.491$). The proportions analysis and a reviewer exploratory analysis of symptomatic SREs trended in favor of the zol 8/4 mg arm. 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 of baseline PSA, and baseline analgesic scores), the results overall remained unchanged, although the p value decreased.

The study was a well-conducted, well controlled trial. 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 significant problem.
- Unblinding of patients to treatment arm was noted in about 5% of patients, but was equally distributed among study arms.

The major problem with this study is the unsupportive evidence provided by efficacy analyses of the 8/4 mg arm. The FDA and ODAC must consider the nature of analytical framework for evaluating this dilemma. Do we consider that the 4 mg/placebo comparison as a positive trial and the 4/8 mg/placebo comparison like a negative (i.e., not positive) trial? Do the positive and negative results cancel each other out? Since beta error is 20% when a trial has 80% power, do we attribute the negative results to beta error? (The latter finding is somewhat credible given trends in favor of the 8 mg arms in some efficacy analyses.) Do data from trials of Zometa in other cancers metastatic to bone provide any support for efficacy in prostate cancer? We look forward to discussing these issues with ODAC on January 31.

Other Solid Tumors

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, 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 of other tumor types incorrectly included in the *NSCLC* stratum. However, there was no evidence that the randomization process itself was compromised.

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.

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

Conclusions

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. For example, cells from breast cancer, small cell lung cancer, or pancreatic cancer behave quite differently from each other in various body organs. 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. 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.

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 Zometa separately in each cancer type. Given the prognosis and survival of patients in Study 011, the estimated zoledronate benefit, an increase of 67 days in time to first skeletal event, seems clinically meaningful. At the time of preparing this briefing document, the FDA review team is uncertain whether this trial supports a separate zoledronate treatment indication. The advice of the Oncologic Drugs Advisory Committee will be helpful to the FDA in making this determination. Issues that should be considered include:

- To what extent do the zoledronate NDA trials for prostate cancer, breast cancer, and myeloma provide support for efficacy in this setting?
- Would a positive study of this design indicate that efficacy is established for all tumor types evaluated?
- Or, should one evaluate the study population to determine which tumor-types were sufficiently represented?
- Are some tumors sufficiently different that they should be excluded from consideration, e.g., small cell lung cancer?

- Approval of this drug for *all tumors metastatic to bone* would mean exposure of a large number of cancer patients to zoledronate along with its toxicity and its expense. Is there adequate evidence for such a blanket approval?

Myeloma and Breast Cancer

Study 010 was an 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)

The Applicant randomized 1648 patients to the three study arms. Results suggest that zoledronate 4 mg is effective in decreasing the skeletal morbidity of myeloma and breast cancer metastatic to bone. As outline below, conservative non-inferiority methodology using the *two 95% confidence interval method of estimation* demonstrate that zoledronate retains at least 49.3% of the pamidronate-versus-placebo effect:

- The first step in this method is to estimate the size of the pamidronate effect based on historical data. The combined data from the three pamidronate trials show that 52.0% (293/563) on placebo compared to 38.9% (220/565) on pamidronate had an SRE. The treatment effect is thus 13.1% (95% ci: 7.3%,18.9%). This method uses the conservative limit of the confidence interval to estimate effect size (7.3%).
- The next step is to estimate how much of that pamidronate effect is retained (with 95% confidence) by zoledronate. On the zoledronate arm of this non-inferiority trial 44% (248/561) of patients had at least one SRE compared to 46% (257/555) on the pamidronate arm (95% ci: -7.9%, 3.7%). Although the estimate from these data favors zoledronate by 2%, again this method uses the conservative limit of the confidence interval to estimate the zoledronate effect. The confidence interval excludes zoledronate being 3.7% worse than pamidronate. The following are the calculations estimating that at least 49.3% of the pamidronate-versus-placebo effect has been retained: $(7.3\% - 3.7\%) / 7.3\% = 49.3\%$.

A critical aspect of making conclusions from non-inferiority trials is the *constant assumption*. This aspect of trial design, discussed in more depth in the FDA statistical review, requires a determination that the active control drug (pamidronate) would have shown efficacy in the new study or current setting, and it also requires an estimation of the size of the effect that pamidronate would have shown in the current setting. The FDA reviewers carefully evaluated the historical pamidronate studies with this assumption in mind. Important differences were found between the current and historical studies. Compared to the pamidronate-versus-placebo studies, more patients on Study 010 had:

- a short time since diagnosis of bone metastases
- history of a previous SRE
- no lytic bone lesion

Retrospective analysis of the pamidronate-versus-placebo data showed that the pamidronate effect appeared even greater in patients with a short time since diagnosis of bone metastasis and

in patients with a history of a previous SRE. Therefore, enrichment of the study population with these patients should, if anything, increase the sensitivity of the study.

The question of whether the active control (pamidronate) is effective in breast cancer patients with non-lytic lesions, however, cannot be directly examined in the pamidronate-versus-placebo study because only patients with lytic lesions were entered. One can examine whether zoledronate appears to be effective in Study 010 in the subgroup corresponding to the historical pamidronate study population (patients with lytic disease). Such a subgroup analysis of Study 010, comparing zoledronate versus pamidronate in breast cancer patients with lytic bone lesions, did not suggest a lack of zoledronate efficacy. In fact, the trend was in favor of zoledronate versus pamidronate.

Whether zoledronate approval in breast cancer should extend to patients without lytic bone lesions needs further consideration. The results of Study 039, a study of zoledronate for treating the predominantly blastic metastases of prostate cancer, may be relevant in making this judgement.

1.4 Safety

Zoledronate 4 mg i.v. over 15 minutes every 3-4 weeks has an acceptable safety profile, and is comparable in toxicity to Aredia 90 mg i.v. over 2 hours every 3-4 weeks as an adjuvant to standard anticancer therapy in patients with bone metastases from breast cancer and lesions of multiple myeloma. Zoledronate 4 mg i.v. over 15 minutes every 3 weeks has an acceptable safety profile, but is more toxic than placebo when used as an adjuvant to standard anticancer therapy in patients with prostate cancer and other solid tumors.

The major safety concern identified in the randomized trials is increased risk of renal function deterioration, which is dose-related and increases with duration of therapy. In the NDA studies, most incidences were mild and reversible, with rare incidences of acute renal failure. During the course of the studies, the renal safety of zoledronate was improved by prolonging the infusion time to 15 minutes (instead of 5 minutes) and eliminating the 8 mg dose. The safety of the 4 mg dose was improved by requiring assessment of serum creatinine before each dose and holding zoledronate for renal deterioration, until the return of creatinine to within 10% of the baseline. When Aredia 90 mg i.v. over 2 hours was compared to zoledronate 4 mg i.v. over 15 minutes every 3-4 weeks in patients with metastatic breast cancer to bone and multiple myeloma (study #010), the incidence of renal deterioration was similar (8.8% and 8.2%, respectively). In patients with prostate cancer (Study #039) and in patients with other solid tumors (Study #011), the incidence of renal deterioration was increased relative to placebo, but the differences were not statistically significant.

Symptoms possibly associated with bisphosphonates as a class, such as arthralgias, pyrexia, as well as electrolyte disturbances, were noted for zoledronate and pamidronate, but were not a major concern.

Anemia was slightly more common with zoledronate 4 mg, compared with placebo. In the Aredia-controlled study, more patients in the zoledronate 4 mg group had a decrease of > 25% from baseline hemoglobin. This is of uncertain significance.

2 Introduction and Background

2.1 Drug Information

Established Name: zoledronic acid for injection

Proposed Trade Name: Zometa®

Drug Class: bisphosphonate

Sponsor's Proposed Indication(s):

The following is the wording of the proposed indication:

"ZOMETA is indicated for the treatment of osteolytic, osteoblastic, and mixed bone *metastases* of solid tumors and osteolytic lesions of multiple myeloma, in conjunction with standard antineoplastic therapy."

Reviewer's comment

A more precise description of proven zoledronate benefit should be considered for labeling. This wording suggests that zoledronate decreases the morbidity of existing bone lesions. In zoledronate clinical studies, patients with bone metastases were treated, but analyses did not establish whether benefit was from effects on baseline metastases or effects on subclinical disease. Aredia labeling contains similar imprecise wording.

Dose, Regimens

The proposed regimen is zoledronate 4 mg diluted in 100 mL of saline given intravenously over 15 minutes . The following section in dosage and administration emphasizes a safety concern:

" *Method of Administration* DUE TO THE RISK OF CLINICALLY SIGNIFICANT DETERIORATION IN RENAL FUNCTION, WHICH MAY PROGRESS TO RENAL FAILURE, SINGLE DOSES OF ZOMETA SHOULD NOT EXCEED 4 MG AND THE DURATION OF INFUSION SHOULD BE NO LESS THAN 15 MINUTES. (SEE WARNINGS)"

Reviewer's Comment

The proposed labeling should be amended to provide a recommended frequency of treatment.

2.2 Regulatory Background on Approval of Bisphosphonates for Treatment of Patients with Cancer Metastatic to Bone

Before approaching the review of the zoledonate NDA, we must understand the historical basis for pamidronate NDA approvals for several reasons: first, the pamidronate studies provide strong rationale that bisphosphonates can be associated with clinical benefit; second, the NDA approvals set a regulatory precedent for drugs of this class; and third, the design, details, and results of the pamidronate trials provide critical support for Study 010, the Applicant's "non-inferiority" trial in breast cancer and myeloma. This latter issue is discussed in detail in the FDA medical and statistical reviews of Study 010.

Pamidronate (Aredia R) is the only bisphosphonate approved to decrease morbidity in patients with bone metastases. The following is the current approved indication:

"Aredia is indicated, in conjunction with standard antineoplastic therapy, for the treatment of osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma. The Aredia treatment effect appeared to be smaller in the study of breast cancer patients receiving hormonal therapy than in the study of those receiving chemotherapy, however, overall evidence of clinical benefit has been demonstrated."

FDA involvement in the design and review of these trials established the regulatory precedent that an aggregate endpoint, coined a "skeletal related event" (SRE), represented an adequate efficacy measure for new drug approval and that decreasing the number of SREs would represent clinical benefit. It was the FDA's judgement that each of the elements composing the endpoint (pathologic fractures, radiation to bone lesions, surgery to bone, spinal cord compression) represented an adequate measure of morbidity. The FDA refused to allow episodes of hypercalcemia to be included as SREs because such events were not local, irreversible events as were other elements of the endpoint and because physicians could treat hypercalcemia with bisphosphonates if it occurred.

Historically, the first NDA approval for pamidronate was based on a single nine-month study in multiple myeloma. The second pamidronate approval was for breast cancer and was based on two twelve-month studies, one in patients receiving chemotherapy and one in patients receiving hormonal therapy. Subsequent pamidronate approvals increased the labeled duration of treatment to two years decreased the infusion duration from four hours to two hours. The following excerpt from the drug labeling describes the myeloma study:

"In a double-blind, randomized, placebo-controlled trial, 392 patients with advanced multiple myeloma were enrolled to receive Aredia or placebo in addition to their underlying antimyeloma therapy to determine the effect of Aredia on the occurrence of skeletal-related events (SREs). SREs were defined as episodes of pathologic fractures, radiation therapy to bone, surgery to bone, and spinal cord compression. Patients received either 90 mg of Aredia or placebo as a monthly 4-hour intravenous infusion for 9 months. Of the 392 patients, 377 were evaluable for efficacy (196 Aredia, 181 placebo). The proportion of patients developing any SRE was significantly smaller in the Aredia group (24% vs 41%, $P < 0.001$), and the mean skeletal morbidity rate (#SRE/year) was significantly smaller for Aredia patients than for placebo patients (mean: 1.1 vs 2.1, $P < .02$). The times to the first SRE occurrence, pathologic fracture, and radiation to bone were significantly

longer in the Aredia group (P=.001, .006, and .046, respectively). Moreover, fewer Aredia patients suffered any pathologic fracture (17% vs 30%, P=.004) or needed radiation to bone (14% vs 22%, P=.049)."

The following excerpt describes the data on treatment beyond 9 months:

"After 21 months, the proportion of patients experiencing any skeletal event remained significantly smaller in the Aredia group than the placebo group (P=.015). In addition, the mean skeletal morbidity rate (#SRE/year) was 1.3 vs 2.2 for Aredia patients vs placebo patients (P=.008), and time to first SRE was significantly longer in the Aredia group compared to placebo (P=.016). Fewer Aredia patients suffered vertebral pathologic fractures (16% vs 27%, P=.005)."

Reviewer's comments:

These data show that efficacy of pamidronate is established at two years in patients taking the drug for two years, however, they do not establish how long treatment is needed. It is conceivable that the pamidronate bone-protecting effect is imparted early and that later benefit is an ongoing manifestation of that early change. Only a study which randomizes patients to continue or discontinue treatment is likely to determine the required duration of treatment. Another possible approach to this questions would to evaluate reliable pharmacodynamic correlates of bone protection.

The submission in patients with breast cancer is described in the following excerpt from labeling:

"Two double-blind, randomized, placebo-controlled trials compared the safety and efficacy of 90 mg of Aredia infused over 2 hours every 3 to 4 weeks for 24 months to that of placebo in preventing SREs in breast cancer patients with osteolytic bone metastases who had one or more predominantly lytic metastases of at least 1 cm in diameter: one in patients being treated with antineoplastic chemotherapy and the second in patients being treated with hormonal antineoplastic therapy at trial entry.

382 patients receiving chemotherapy were randomized, 185 to Aredia and 197 to placebo. 372 patients receiving hormonal therapy were randomized, 182 to Aredia and 190 to placebo. All but three patients were evaluable for efficacy. Patients were followed for 24 months of therapy or until they went off study. Median duration of follow-up was 13 months in patients receiving chemotherapy and 17 months in patients receiving hormone therapy. Twenty-five percent of the patients in the chemotherapy study and 37% of the patients in the hormone therapy study received Aredia for 24 months. The efficacy results are shown in the table below:"

	Breast Cancer Patients Receiving Chemotherapy						Breast Cancer Patients Receiving Hormonal Therapy					
	Any SRE		Radiation		Fractures		Any SRE		Radiation		Fractures	
N	A	P	A	P	A	P	A	P	A	P	A	P
Skeletal Morbidity Rate (#SRE/year) Mean	2.5	3.7	0.8	1.3	1.6	2.2	2.4	3.6	0.6	1.2	1.6	2.2
P-Value	<.001		<.001 *		.018 *		.021		.013 *		.040 *	
Proportion of patients having an SRE	46%	65%	28%	45%	36%	49%	55%	63%	31%	40%	45%	55%
P-Value	<.001		<.001 *		.014 *		.094		.058 *		.054 *	
Median Time to SRE (months)	13.9	7.0	NR **	14.2	25.8	13.3	10.9	7.4	NR **	23.4	20.6	12.8
P-Value	<.001		<.001 *		.009 *		.118		.016 *		.113 *	
* Fractures and radiation to bone were two of several secondary endpoints. The statistical significance of these analyses may be overestimated since numerous analyses were performed.												
** NR = Not Reached.												

Although FDA accepted the concept that decreasing the number of SREs represented clinical benefit, there have been many discussions between sponsors and the FDA regarding the best SRE endpoint for comparing efficacy in randomized studies. In the pamidronate protocols, the primary endpoint was skeletal morbidity rate (SMR). This measure used all events in the denominator and time on study in the numerator to provide a rate, events per month. After reviewing the pamidronate data, FDA found SMR not to be an unacceptable measure for primary comparison of efficacy. Criticisms of the endpoint were that many events within the same patient were highly correlated and that including time in the denominator suggested that event rates were constant over time, and the data suggested otherwise.

Subsequently, FDA has emphasized the more conservative endpoints of *proportions of patients having an SRE on study* and *time to first SRE event*. These endpoints are discussed in greater detail in the FDA statistical review. The two endpoints are closely related: both utilize only the first SRE in a patient, ignoring the morbidity of additional events. FDA statisticians have suggested that the time to first SRE may provide a more precise estimate because data from patient dropouts are censored whereas in the proportions analysis these data are effectively "carried forward" to the end of the study. Even the time to SRE analysis, however, may underestimate morbidity if censoring is not random but, rather, is "informative censoring." A potential example of this phenomenon is when more patients drop out on the placebo arm because of "inadequate therapeutic response." It seems possible that such patients are having bone pain and are more likely to have a subsequent SRE, thus violating the assumption of "informative censoring." So, there seems to be no perfect endpoint. The *proportions analysis* and *the time to first SRE* are the endpoints emphasized in FDA reviews.

As the pamidronate labeling excerpts show, the pamidronate treatment effect was in myeloma and in those breast cancer patients who were receiving chemotherapy. In breast cancer patients receiving hormones, the benefit was less, and there were only trends in favor of pamidronate in the overall analyses. Statistical significance was seen only in the radiation therapy SRE analysis and only with the time to SRE analysis. Nevertheless, the FDA approved this indication because of the supporting data from breast cancer patients receiving chemotherapy. As noted above, a special notation regarding the lesser apparent benefit in breast cancer patients receiving hormones was placed in the indication section of the labeling.

2.3 Important Milestones in Product Development

The Applicant undertook parallel zoledronate clinical development programs for treatment of hypercalcemia of malignancy (HCM) and for treatment of bone metastases. IND 43,240 was submitted to the Division of Metabolic and Endocrinology Drug Products (DMEDP) for treatment of HCM while IND 55831 was submitted to the Division of Oncology Drug Products (DODP) for treatment of bone metastases. An NDA was submitted to DMEDP for treatment of HCM in December of 1999. Concerns were raised by DMEDP about renal toxicity. FDA issued an approvable letter in September 2000, and FDA approval was granted in August 2001 for this indication.

The current submission to DODP is for a zoledronate efficacy supplement for treatment of bone metastases. Three phase III studies evaluate skeletal-related complications in patients with bone metastases in three classes of tumor types. They are (i) prostate cancer, (ii) breast cancer and myeloma, and (iii) solid tumors other than breast cancer and prostate cancer.

The Phase III protocols were submitted in April, May, and September of 1998. After reports of increased incidence of renal failure, all protocols were amended in June of 1999 to increase the volume of normal saline infused with zoledronate from 50 to 100 ml to increase infusion duration from 5 to 15 minutes. Another amendment in June of 2000 eliminated the 8 mg dose of zoledronate from all protocols because of an increased incidence of renal failure. The studies of zoledronate given in the adjuvant setting were placed on clinical hold. Trials in metastatic disease continued at the 4mg dose.

During conduct of the studies, the Applicant informed DODP of violations of good clinical conduct at a Netherlands site in Study 010 and of unblinding of an investigator at a site in Study 039. FDA instructed the Applicant to analyze the trials both including and excluding data from the involved sites. After review of the data, FDA would decide whether to include or exclude the data.

FDA met with the Applicant several times during development and conduct of the studies. The following are selected points discussed with the Applicant:

Nov 14, 00:

- The intent-to-treat analysis should include all randomized patients.
- Given the toxicity of the 8 mg dose, it is unlikely that the 8 mg dose will be approved in any context.

2-13-01: (Pre-NDA meeting)

- FDA did not agree with the sponsor that patients without baseline radiographs should be excluded from analysis.
- FDA recommended analyzing efficacy according to the randomized treatment group and safety according to treatment actually received.

7-26-01: (Pre-NDA meeting)

- FDA suggested analyzing adverse events separately according to disease type as well as pooled.

3 Efficacy Review

This section presents FDA clinical efficacy review findings from the Applicant's placebo controlled trials in prostate cancer (Study 039) and in other solid tumors (Study 011) and an active controlled trial in breast cancer and myeloma (Study 010).

Placebo Controlled Trial #039 in Prostate Cancer

3.1 Placebo Controlled Trial #039 in Prostate Cancer

Protocol Title:

"A randomized, double-blind, placebo-controlled, multicenter, comparative, safety and efficacy study of intravenous zoledronate (4 and 8 mg) in prostate cancer patients with metastatic bone lesions receiving antineoplastic therapy"

First patient enrolled: June 22, 1998

Last patient completed: Jan 26, 2001

Unblinding: April 10, 2001

Background

Trial 039 evaluated Zometa's effect on Skeletal Related Events (SREs) in prostate cancer. Ideally, the focus of a literature review would be to determine prognostic factors associated with such events. With no literature available on this topic, however, the following paragraphs provide a general background on prostate cancer and describe prognostic factors associated with progression and survival.

Prostate cancer is a major U.S. public health problem. In 1999, more than 179,000 new cases were diagnosed leading to an estimated 37,000 deaths. Adenocarcinoma is the predominant, found in 95% of patients. Diagnosed at a median age of 72 years, it is the most common male malignancy and the second leading cause of cancer-related death in the US. Prostate cancer is 1.5 times higher in blacks than in whites. A higher testosterone level in American blacks than in their caucasian counterparts is hypothesized to contribute to the increased incidence of prostate cancer in the former. Asian men have a lower risk related to reduced 5 α -reductase activity.

Prostate cancer can be cured by surgery or radiation when it is truly confined to the prostate gland. According to some estimates, 75% of patients with apparently localized disease develop metastasis within 10 years. Hormonal manipulation by surgical (bilateral orchiectomy) or medical means is offered as adjuvant therapy or as first line treatment for advanced prostate cancer but no response is observed in 15-20% of patients. Even in those who do respond, the tumor becomes refractory to the hormonal agents in 18 to 36 months. Subsequently, radiation, radiopharmaceuticals (strontium and samarium), chemotherapy, corticosteroids and analgesics become mainstays of palliative therapy. It is in this palliative setting where trial 039 tests the palliative efficacy of Zometa.

Risk factors for cancer progression are tumor burden, poor performance status, visceral spread of disease, elevated serum level of alkaline phosphatase, non-axial bone disease and anemia. Aneuploid primary tumor, erb and p53 mutation may be risk factors for disease progression.

At the time of diagnosis, the survival is linked to the extent of tumor. Table 1 demonstrates the according to extent of disease. Other prognostic factors are histologic grade of tumor (Gleason's score), patient's age, concurrent illnesses, and level of PSA.

Survival according to extent of Prostate Cancer

Extent of Disease	Years
Confined to prostate gland	+5
Locally advanced	5
Metastatic disease	1-3

Prostate cancer metastasizes to the well-vascularized areas of skeleton such as the vertebral column, ribs, skull and the proximal ends of long bones, and bone metastases are a leading cause of morbidity for prostate cancer patients. Up to 62% of patients have bone metastases at the time of diagnosis. Prostate cancer presents with bone pain in 10-20% of patients. About 80-100% of patients who die of prostate cancer have bone metastases. Clinical stage and Gleason's score correlate with the long-term development of bone metastases. Patients with T1/T2 disease and T3/T4 disease develop metastasis at 10 years in 3-41% and 12-55% of cases respectively. Patients with well-, moderately-, and poorly-differentiated tumors develop metastases at 10 years in 2.7-10%, 13-57% and 42-80% of the cases respectively.

After prostate cancer metastasizes, survival correlates with tumor burden. In patients with a solitary metastasis, the median survival is approximately 50 months, while the median survival for all patients with bone metastases who receive hormonal therapy is 30-35 months. Severe bone pain, pathologic fractures and spinal cord compression are the major 'events' arising from bone metastases.

Study Design

Study 039 was a double-blind, multi-centered, placebo-controlled randomized trial in patients with prostate cancer. Patients were randomized in a ratio of 1:1:1 to treatment with zoledronate 4mg (Zol 4), zoledronate 8mg (Zol 8), or placebo. Zometa or placebo was administered intravenously once three weeks. After an early amendment, the randomization was stratified by prostate cancer bone metastases history (no metastatic disease present at the time of the initial diagnosis of prostate cancer versus metastatic disease present at the time of the initial diagnosis). The study duration was to be 15 months. Patients were not to be removed from the trial for disease progression.

The protocol-specified primary objective was to assess the efficacy of zoledronate at 4 mg or 8 mg in preventing skeletal-related events (SRE) in prostate cancer patients with rising PSAs after first-line hormonal therapy.

The secondary objectives were to evaluate Zoledronate's effect on time to first SRE, pain scores, analgesic use, performance status, QoL scores, and survival. Zoledronate's safety and tolerability were also secondary objectives. Tertiary objectives were evaluation of patient health care utilization, and productivity loss.

Reviewer's comment:

The primary objective as specified in the statistical section was proportions of patients with at least one SRE and time to first SRE was a secondary objective along with other secondary objectives noted above. Although the indication for use in the Applicant's proposed drug label states Zometa should be used in combination with antineoplastic therapy, the inclusion criteria for Study 039 did not require continuation of antineoplastic therapy and was not analyzed in the Applicant's study report.

Planned Study Duration:

Time for enrollment : 12 months

Duration of individual patient participation:

15 months (60 weeks) Phase 1

9 months (36 weeks) Phase 2 (to obtain long-term safety and survival data).

Total duration of treatment; 24 months (96 weeks)

Drug administration and formulation:

Per Protocol:

“Zolendronate 4 mg or 8 mg or placebo given as a 5 minute infusion every 3 weeks x 24 months. The drug was to be supplied in 4 mg lyophilized vials; reconstitute in 5 ml of sterile water for injection, then mixed with NS to a total infusion volume of 50 ml. Solutions must have been prepared in plastic, as the drug will bind to glass.”

Study Population:

The planned population for Study 039 was prostate cancer patients with a history of metastatic bone disease who have demonstrated biochemical progression of disease (e.g. a rising PSA) while on first-line hormonal therapy for metastatic disease which has resulted during an adequate state of androgen deprivation (serum testosterone < 50 ng/ml).

Inclusion Criteria:

- Aged 18 or older
- Signed informed consent
- Histologically confirmed diagnosis of prostate carcinoma
- Objective evidence of metastatic disease to bone: multiple foci (>3) on bone scan; if ≤ 3 , additional radiographic or biopsy studies are required to confirm metastatic disease. Patients with a complete response to first-line hormonal therapy were eligible, provided they had prior documentation of disease. Hormonal therapy administered in the adjuvant or neoadjuvant setting was not be considered to be first-line hormonal therapy.

- Must have had biochemical progression of disease despite therapy with first-line hormonal therapy; defined as 3 consecutively rising PSAs, each separated by at least 2 weeks; the 3rd measurement must be ≥ 0.4 ng/ml.
- ECOG PS 0, 1, 2

Exclusion criteria

- Bone pain due to metastatic bone disease that had developed since the best response to first-line hormonal therapy
- Previous or current treatment with cytotoxic chemotherapy (i.e., before Visit 2)
- Alteration of the first-line hormonal therapy prior to Visit 1
- Serum testosterone level at Visit 1 elevated above the castrate range
- Radiation therapy to bone (including radioisotopes) within 3 months prior to Visit 2
- Prior therapy with a biphosphonate
- Treatment with calcitonin, mithramycin, or gallium nitrate within 2 weeks prior to randomization
- Use of other investigational drugs within 30 days prior to randomization
- History of noncompliance, unreliability, inability to give informed consent
- Serum creatinine > 3.0 mg/dL
- Corrected serum calcium < 8.0 mg/dL or ≥ 11.6 mg/dL
- History of other neoplasm within 5 years except non-melanomatous skin cancer
- Patients with evidence in the 6 months prior to randomization of severe cardiovascular disease, refractory hypertension, or symptomatic coronary artery disease

Objectives

Primary Objective:

The protocol-specified primary endpoint was the proportion of patients having at least one SRE. SRE are defined in the next section of this review.

Secondary Objectives:

- time to first SRE
- Skeletal Morbidity rate
- safety
- Time to disease progression in bone
- Time to overall disease progression
- Pain scores
- Analgesic scores
- QoL
- Bone mineral density
- Bone lesion response from radiological studies
- Biochemical variables
 - Urinary N-telopeptide/creatinine ratio

Urinary pyridinoline/creatinine ratio
Urinary deoxy pyridinoline/creatinine ratio
Serum bone alkaline phosphatase

- Overall safety
- Survival

Reviewer's comment:

The applicant was advised by the agency to make time to first SRE a co-primary endpoint, since it is more sensitive and takes into account the drop outs from the study.

Definition of SRE:

Per protocol:

- “Pathologic bone fractures: those bone fractures which occur spontaneously or which result from trivial trauma. A new compression fracture is defined as a decrease in total vertebral height, or anterior vertebral height, or posterior height of $\geq 25\%$ from baseline. A further reduction in the vertebral fracture by $\geq 25\%$ during the study is classified as a new fracture. Each pathological fracture (vertebral and non-vertebral) is to be documented by x-ray and is to be counted separately. A central radiologist determine vertebral SRE”.
- “Spinal cord compression: These will be confirmed by an MRI. If spinal cord compression occurs in conjunction with a vertebral compression fracture, each will be counted as a separate SRE”.
- “Surgery to bone: This includes the procedures that are performed to set or stabilize pathologic fractures or areas of spinal cord compression, and surgical procedures which are performed to treat or prevent a fracture or a spinal cord compression”.
- “Radiation therapy to bone: this includes radiation administered to bone to palliate painful lesions or to prevent or treat fractures or spinal cord compressions. Each port of radiation will be considered a separate event. Administration of a radioisotope such as Strontium will be included as radiation to bone”.
- “Change of antineoplastic therapy to treat bone pain includes any change of anticancer therapy including hormonal therapy. Alteration of pain medications will count as an analgesic score and will not be recorded as a skeletal event.”

Reviewer's comment:

At FDA's request, hypercalcemia was not counted as an SRE. As explained in the introduction to this review, exclusion of hypercalcemia from the SRE endpoints has been the standard regulatory approach since the design and analysis of the trials leading to approval of Aredia.

Follow-up:

Schematic representation of the study follow-up is reproduced below from the original protocol. The following was the planned schedule of assessment:

- Radionuclide bone scans/Radiographic plain films by central radiologist: visits 6, 10, 14, 18, 22, 26, 30 and 34.
- SRE: visit 3 through visit 34.
- TTP in bone: visits 6, 10, 14, 18, 22, 26, 30 and 34 by the central radiologist.
- TTP: 6, 10, 14, 18, 22, 26, 30 and 34.

-Analgesic scores: at visits 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32 and 34 according to the analgesic score in appendix 7.

-Pain scores: visits 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32 and 34 according to brief Pain Inventory Short form.

-ECOG performance status and QoL: visits 1 (2 for QoL), 6, 10, 14, 18, 22, 26, 30 and 34

Schematic representation of the study follow-up

Phase 1 (Safety and Efficacy)

Period	Screening	Randomized treatment and evaluation																			Final Evaluation Phase 1 and First Randomized Treatment Phase 2	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Week	-2	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60
Treatment	none	Zoledronate 4 mg q 3 weeks Zoledronate 8 mg q 3 weeks Placebo q 3 weeks																			Zoledronate 4 mg q 3 weeks Zoledronate 8 mg q 3 weeks Placebo q 3 weeks	

Phase 2 (Extension)

Period	Randomized treatment and evaluation											Evaluation
Visit	23	24	25	26	27	28	29	31	31	32	33	34
Week	63	66	69	72	75	78	81	84	87	90	93	96
Treatment	Zoledronate 4 mg q 3 weeks Zoledronate 8 mg q 3 weeks Placebo q 3 weeks											Zoledronate 4 mg q 3 weeks Zoledronate 8 mg q 3 weeks Placebo q 3 weeks

Following visit 2, study visits are to be made on the designated study day with an error of not more than -3 to +7 days.

Removal from Study

Patients were NOT to be removed from study for the occurrence of a skeletal-related event; the study was designed to assess the total number of events that occur throughout the time period. Patients were NOT to be removed from study for changes in antineoplastic therapy.

Patients were to be removed from study for the following reasons:

- Adverse events
- Abnormal laboratory values
- Abnormal test procedure results
- Unsatisfactory therapeutic effect
- Patient's condition no longer requires study drug
- Protocol violation
- Patient withdrew consent
- Lost to follow-up
- Administrative problems
- Death

Patients who were removed from study were to be followed every 3 months for a total of 24 months from the date of randomization.

Reviewer's comment:

Some of the reasons for removal from the study are ill-defined, such as abnormal of laboratory values and abnormal test procedures.

Statistical considerations and sample size

After an early amendment, the randomization was stratified by prostate cancer history (no metastatic disease present at the time of the initial diagnosis of prostate cancer versus metastatic disease present at the time of the initial diagnosis).

The study was designed to have 80% power to detect a 16% difference in the proportion of patients reporting any SRE during the first 15 months of the trial between the two dose levels of zoledronate and placebo.). Bonferroni's adjustment was used to calculate the sample size, assuming a 40% incidence rate on placebo and a 24% incidence rate on zoledronate, with an overall Type I error rate of 0.05. Although the calculated sample size was 519 patients (173 on each arm), and the planned sample size was 550 patients to account for the noise introduced by the use of intent-to-treat (ITT) population, 643 patients were actually enrolled. After the Zol 8 mg arm was dropped from the analysis plan by Amendment #5, the plan for Bonferroni adjustment of alpha was dropped, and the primary analysis was specified to compare only the zoledronate 4mg and placebo study arms. There was no planned interim analysis.

The Applicant's defined the ITT population for efficacy evaluations was all randomized patients who received trial medication and had at least one follow-up measurement. Patients receiving a biphosphonate other than Zometa were to be excluded from analysis.

The primary efficacy analysis was planned for the end of Phase I, 15 months after patient entry, although other analyses were also to be performed when patients had been on study for 3, 6, 9, and 12 months. The last observation of each patient was carried forward. According to the original plan, the test statistic for the primary endpoint was a Chi-square test, but this was replaced by the Cochran-Mantel-Haenzel test with amendment 1. Baseline prognostic factors were specified as PS, renal function, and age.

Additional information about the statistical plan is detailed in the FDA statistical review.

Protocol Amendments:

Date of Protocol:

March 5, 1998

Amendment 1:

August 13th, 1998:

- Patients were to be stratified by their prostate cancer history according to whether they had
 - 1) No metastatic disease (M0 or Mx) or
 - 2) metastatic disease present at the time of initial diagnosis (Stage D2 or M1)
- Required last PSA measurement to be obtained within 8 weeks of visit 1.
- Specified 2 logistic regression analyses to determine the influence of stratum and previous experience of SREs.

Amendment 2:

April 27, 1999

Prior or current use of estramustine is permitted prior to visit 2.

Amendment 3

June 24, 1999:

Specified that Zoledronate would be diluted in 100 ml instead of 50 ml normal saline and was to be administered intravenously over 15 minutes rather than 5 minutes. This amendment was due to 3 reports of renal failure in 3 patients receiving 8 mg of Zoledronate. One of these patients died because of sepsis.

Amendment 4

June 7, 2000:

- All Patients receiving Zoledronate 8 mg had their dose reduced to 4 mg based on the suggestions by the Data Safety Monitoring Board (DSMB) and the Renal Advisory Board (RAB).
- As a precaution, serum creatinine was now measured prior to each dose of study drug. Drug administration will be delayed as outlined in Table

Dose modification according to serum creatinine

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

Amendment 5

June 7, 2000:

Patients who completed the two-year protocol, and who in the opinion of Principal Investigator might benefit from continuation of therapy, could receive open-label zoledronate.

Reviewer's comments:

Out of a total of 8033 infusions, 1688 infusions (21%) were administered prior to amendment 2 over 5 minutes. Six thousand three hundred and forty-five infusions (79%) were administered over 10 minutes.

Number of infusions affected by amendment 2

	Total infusions	4 mg	Placebo	8/4 mg
Prior to amendment 2	1688 (21%)	552	588	548
After amendment 2	6345 (79%)	2201	2024	2120

Amendment #4, which changed the Zol 8 dose from 4 mg to 8 mg, occurred after all patients had been accrued and less than six months before the last patient finished Phase I. Therefore, almost all patients in the 8/4 mg arm received only the 4 mg dose early in their course. Up until the 13th visit only 2 patients in the 8/4 mg arm received 4 mg infusions. For patients remained on study until the 21st visit, approximately half the patients were received 4 mg infusions in the 8/4 mg arm.

Efficacy Results of Study 039

Populations treated and analyzed

There were 136 study sites, in 17 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, France, Great Britain, Italy, New Zealand, Peru, Sweden, Switzerland, United Kingdom, Uruguay and USA). Some of the study sites listed had sub-sites that actually enrolled and treated patients listed under that site.

643 patients were randomized, but 3 did not receive the study drug. These three patients were not included in the evaluation for safety. There was one patient who received the incorrect study drug for the entire study period. Patient 11002 received 4 mg at all study visits although he was randomized to the 8/4 mg arm. This patient was included in the 8/4 mg arm for efficacy analysis. According to the Applicant, thirty one patients were withdrawn from the study prematurely because their blind was broken: 9 patients in the 4

mg group, 10 in the 8/4 mg group, 12 in the placebo group. The number of patients involved in unblinding according to FDA analysis of the electronic data was slightly larger the number of patients removed from the study. The violations in at least 4 patients per FDA review (based on Applicant's e-dataset) are compiled in the table listed on page 29.

Although patients could be entered into the study without detectable metastases (i.e., disease in CR), according to the reviewer's analysis, only seven such patients were entered.

Baseline demographic factors analyzed by the Applicant and selectively verified by FDA reviewers are listed in the table below.

Demography

Treatment arm	4 mg	Placebo	8/4 mg
No of patients	214	208	221
Age range	45-90	37-90	43-90
Median	72	73	72
Age ≤ 60 years	19	15	19
Age > 60 years	196	193	201
Time from initial diagnosis to randomization N	214	208	218
Median (months)	51.8	56.9	60.6
Range (months)	3 - 283	1 - 250	8 - 280
Time from initial diagnosis to diagnosis of bone mets N	214	207	217
Median (months)	19.6	19.6	26.6
Range (months)	0 - 228	0 - 216	0 - 215
Time from first bone mets to randomization N	114	115	132
Median (months)	5.8	12.3	5.4
Range (months)	0 - 121	0 - 111	0 - 87
Prior history of bone metastasis	99	92	87
No prior history of bone metastasis	115	116	134
No. of bone metastasis per patient			
median	4	4	4
range	1-13	1-11	1-12
Previous SRE N	214	208	218
Yes	66 30%	78 37.5%	70 32%
No	148 69%	130 62%	148 68%
Number of extraskkeletal organs involved			
0	2	3	2
1	176	182	188
2	33	18	24
3	3	5	6
4	0	0	1
Race			
Caucasian	178	172	186

Treatment arm	4 mg	Placebo	8/4 mg
Black	24	19	19
Oriental	3	2	1
Other	9	15	15
Performance status			
0	86	93	98
1	112	97	103
2	17	18	18
Baseline PSA			
Range	0.15-5963	0.25-8410	0.2-9124
Median	79.8	57.8	88.5
Analgesic score (per sponsor)			
0	93	77	73
1	70	77	83
2	9	9	11
3	40	41	48
4	2	3	3
BPI composite Pain score (per sponsor)			
N	193	187	192
Median	1.8	1.8	2.3
Fact-G score (per sponsor)			
N	193	187	192
Median	82.5	82.8	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 bisphosphonates 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 arm 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 extraskelatal sites of metastases is given in Table 4. Extraskelatal 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).

Distribution of the metastases according to treatment arm

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

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).

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 Zometa 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.

Early discontinuations and deaths

Arm	N	Deaths	Other Early Discontinuations	Total D/D
4 mg	214	25	108	133
Placebo	208	32	111	143
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.

Reasons for discontinuation

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

Primary Efficacy Endpoint:

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.

Proportion of patients with at least one SREs during the first 15 months of the study

	Proportion	95% C.I. and P-value for the difference	
		Zol 4 mg	Zol 8/4 mg
Zol 4 mg	71/214 (33%)	-	(-3.7%, 14.3%), p=0.255
Placebo	92/208 (44%)	(-20.3%,-1.8%), p=0.021	(-15.1%,3.6%), p=0.222
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).

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 value not significant).

Time to first Event per Applicant

Treatment Arm	N	25% quartile	Median Time to Event in days	P-values for between Rx comparisons	
				4 mg	8/4 mg
4 mg	214	182	Not reached		0.059
Placebo	208	122	321	0.011	0.491
8/4 mg	221	127	363		

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 (Comparison to Placebo using Log-rank test)
Zol 4 mg	214	*(383, *)	0.009
Placebo	208	321 (252, *)	
Zol 8/4 mg	221	363 (255, *)	0.541

* = Not Reached

As shown in table above, FDA analysis was almost identical, with p = 0.009.

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 extraskelatal 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 although the.

Secondary Efficacy Endpoints

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.

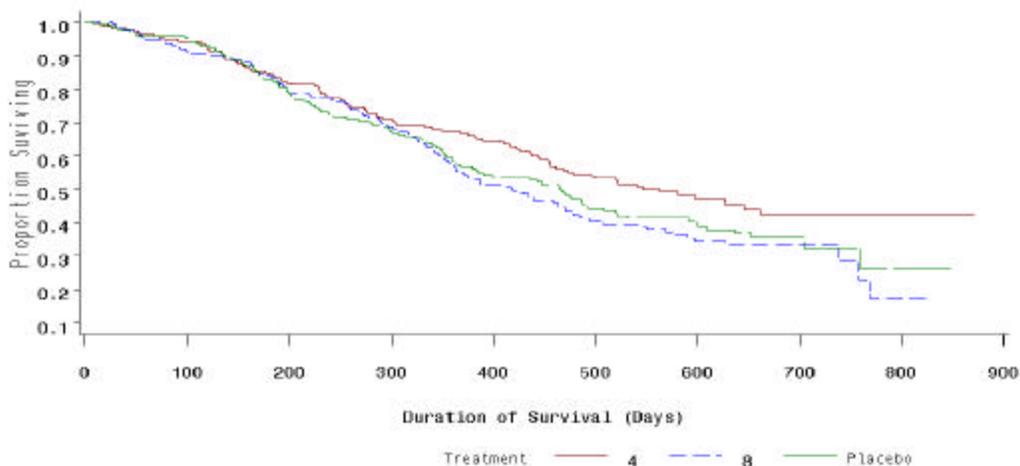
Time to progression of bone metastases and overall disease progression:

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.

Kaplan Meier Curve for analysis of overall survival



Reviewer exploratory analyses of SREs

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. The next table illustrates the first SREs by presence or absence of symptoms.

The numbers of patients who had asymptomatic vertebral fractures, or had change in chemotherapy due to pain are small and favor the 4 mg arm. There are more patients on the 8/4 mg arm who received chemotherapy due to pain, than on 4 mg or placebo group.

First SREs by presence of symptoms:

Event		4 mg	Placebo	8/4 mg
Pathological vertebral fracture	Unknown	2	2	0
	Asymptomatic	3	6	7
	Symptomatic	1	2	0
Pathological non-vertebral fracture	Unknown	1	1	4
	Asymptomatic	12	14	11
	Symptomatic	4	6	0
Spinal cord compression	Asymptomatic	0	0	1
	Symptomatic	3	6	2
Radiation	Unknown	0	2	4
	Asymptomatic	5	6	5
	Symptomatic	34	33	34
Surgery	Asymptomatic	0	1	0
	Symptomatic	1	2	0
Chemotherapy	Symptomatic	5	9	15

Proportion of patients with at least 1 *symptomatic* SRE

The reviewer performed an exploratory analysis of proportions of patients with at least 1 *symptomatic* SREs during the first 15 months. As shown in Table 12, results on the whole were unchanged, with the proportion of symptomatic SRE in the 4 mg arm significantly better than placebo (24.7% vs. 35.6%, $p = 0.21$). Again the comparison between 8/4 mg and placebo shows only a trend towards improvement.

Proportion of patients with at least 1 *symptomatic* SRE during the first 15 months

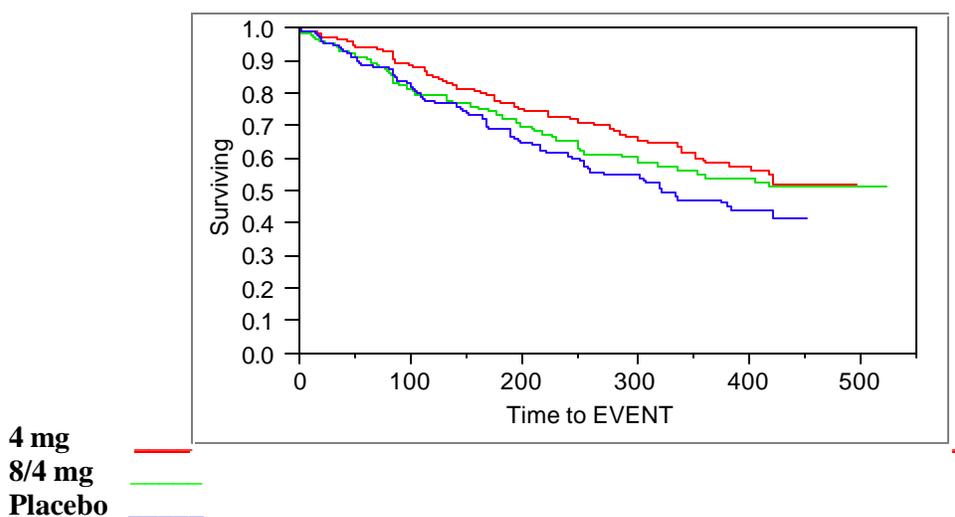
Treatment arm	Proportion	p value	
		4 mg	8 mg
4 mg	53/214 (24.7%)		
Placebo	74/208 (35.6%)	0.021	0.173
8/4 mg	64/221 (28.9%)		

P value is 2-sided using Chi square.

The inclusion of change in chemotherapy due to pain and of some asymptomatic events is of questionable clinical benefit as noted earlier. Time to SRE excluding chemotherapy was evaluated. The Kaplan Meier Curve and results are given below. The results in the three arms were similar and the 4 mg arm remained statistically more effective.

(Note, patient 51129 had a change of antineoplastic treatment that was listed as due to painful lesions, however he was also noted to be ‘asymptomatic’. This was not a first event for this patient.)

Time to first SRE excluding chemotherapy change as first event for all patients



Time to first SRE excluding change in chemotherapy

Treatment arm	Median Time
4	not reached
8	not reached
Placebo	324

Log rank p value of 4 mg vs. placebo is 0.02

Log rank p value of 8 mg vs. placebo is 0.25

Administration of radiation:

The reason for administration of radiation 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 Zometa arm, listed in table 19, had radiation for lesions that may not have been clinically significant.

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.

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.

Median change in serum PSA

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

Efficacy Conclusions of Study 039

Patients treated on the 4 mg 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 8/4 mg arm failed to demonstrate a statistically significant difference from placebo (Proportions: 38% vs. 44%, respectively, $p = 0.222$. Time to SRE: $p = 0.491$). The proportions analysis and a reviewer exploratory analysis of symptomatic SREs trended in favor of the 8/4/ mg arm. 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 overall remained unchanged although the p value decreased.

Reviewer's comments

The study was a well-conducted, well controlled trial. 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 significant problem.*
- Unblinding of patients to treatment arm was noted in about 5% of patients, but was equally distributed among study arms.*

The major problem with this study is the unsupportive evidence provided by efficacy analyses of the 8/4 mg arm. The FDA and ODAC must consider the nature of analytical framework for evaluating this dilemma. Do we consider that the 4 mg/placebo comparison as a positive trial and the 4/8 mg/placebo comparison like a negative (i.e., not positive) trial? Do the positive and negative results cancel each other out? Since beta error is 20% when a trial has 80% power, do we attribute the negative results to beta error? Do data from trials of Zometa in other cancers

metastatic to bone provide any support for efficacy in prostate cancer? We look forward to discussing these issues with ODAC on January 31.

Placebo Controlled Trial #011 in Other Solid Tumors

3.2 Placebo Controlled Trial #011 in Other Solid Tumors

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 1 st visit:	20 April 2000
Last patient completed:	30 January 2001
Date of Unblinding:	30 March 2001

Study Design

Rationale

The following excerpts from the protocol summarize 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 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, they all react in a similar manner to a biphosphonate. 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 Description:

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.

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 administration 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 efficacy endpoint

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):

- 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 efficacy parameters

- 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.*
- *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.*

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:

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.

- 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:

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 bisphosphonate, 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.*

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 optimistic 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.
- 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 is to be diluted in 100 ml. of normal saline and is to be 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

- Sample size increased to 700 patients to procure 663 evaluable patients.
- 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 should have 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 should be measured prior to each dose of study drug. Drug administration will be delayed as outlined in the next table.

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.

No. of infusions per actual dose administered

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

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
0	247	0	0	247
4	321	254	67	0
8	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 7 randomized patients did not receive study drug.

The dose modification for serum creatinine abnormalities as amended is in the table below.

Amendment 6

Oct 13, 2000

- ITT population will be all randomized patients who had evidence of bone metastases at study entry.
- Modified all efficacy evaluation section 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 Zometa 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 Zometa 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.*

Results:

Patient Disposition:

Seven hundred and seventy three patients were randomized, but 7 did not receive the study drug (10410, 10816, 12452, 12811, 20642, 22707, and 22708). All 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 protocol.

Patients discontinuing the study drug prior to study completion:

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.

Number of patients discontinuing Zometa prior to end of study for protocols 039 and 011.

Protocol	4 mg	Placebo	8/4 mg
039	61.7%	68.7%	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.

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 table titled Demography.

Table 3: 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
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)			

Treatment arm	4 mg	Placebo	8 mg
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, therefore, there will be extensive variability from patient to patient. This is expected with such a diverse treatment group.

The patients are fairly well matched across treatment arms for the prognostic factors listed in the table above, except whether the patient had any SRE prior to entering the study. This 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.

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

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.

Doses and Infusions administered

Actual Dose Administered mg	Total Infusions	Treatment arms		
		4 mg	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

Protocol Violations per sponsor in at least 5 patients

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

Reviewer's comments:

According to the sponsor, there are 403 patients with NSCLC, whereas on FDA review, there were 375 patients with NSCLC 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.

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

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

Another serious violation could 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.

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 14 visits (9 months). Table 26 provides results by the Applicant and FDA (based on evaluation 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 6-5% less on the 4 mg arm than placebo, and this difference is not statistically significant.

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.

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	4	51/124 41%	56/134 42%
	Placebo	54/121 45%	59/130 45%
	8/4	43/130 33%	47/139 34%
Other	4	43/133 32%	41/123 33%
	Placebo	56/145 39%	52/120 43%
	8/4	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. Please 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.

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%

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
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%	1/4 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	1/2 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)*

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).

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:

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 SREs

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.

Evaluation of symptomatic events

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

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
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
surgery	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.

Proportions of patients with at least 1 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%

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.

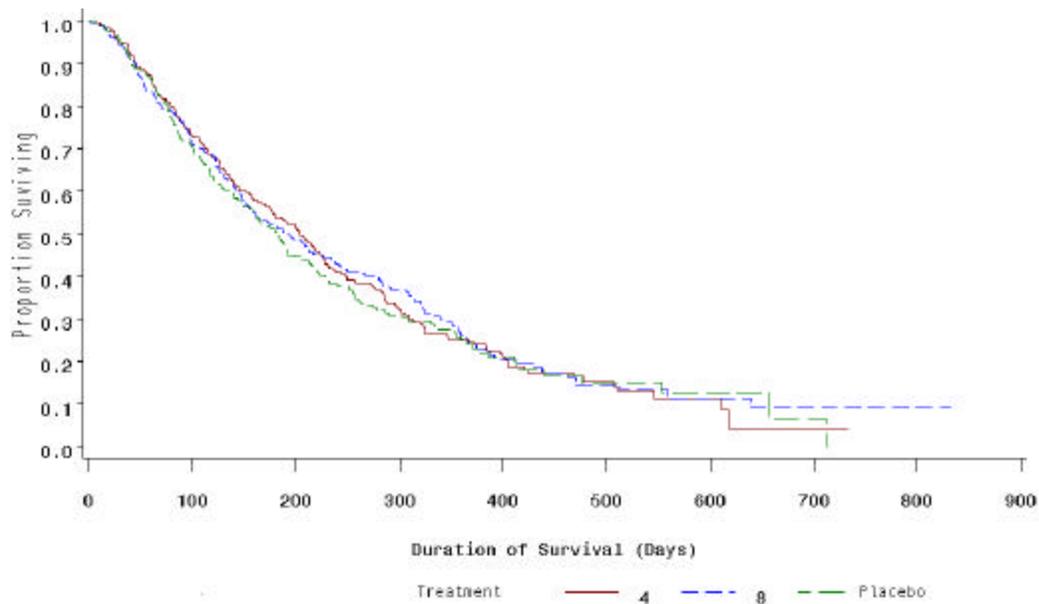
Progression of bone metastases and disease:

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.

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.

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

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 Zometa does not affect survival adversely. It is not expected to improve survival.

Reviewer's Exploratory Analysis of Chemotherapy on study

The chemotherapy received by the patients could have impacted the SRE by its effect on bone metastases. An exploratory 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.

Number of on-study antineoplastic regimens

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

Number of on-study antineoplastic regimens in NSCLC patients

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

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

Best tumor Response

The next table shows results of the reviewer's analysis of the best tumor responses (created from the electronic dataset 'tumoresp'). Only 607 patients were listed in the dataset. For 99 patients, the best tumor response was listed as unknown. Response was given for 513 of 773 (66%) patients in the electric dataset provided by the Applicant, and are given below:

Best tumor response/patient /arm

Maximum response	Total # of patients	4 mg	Placebo	8/4 mg
CR	4	1	2	1
PR	55	12	15	28
SD	170	66	51	53
PD	278	95	92	91

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 Zometa.

Distribution of First Events by Treatment Arm

The frequency of the individual types of SREs occurring first in patients (and hence composing events in the SRE proportions analysis and time to first SRE analysis) are given in the following table.

Distribution of first events for patients according to treatment arm

Event	Total	4 mg	Placebo	8/4 mg
Radiation	177	57	63	57
Non-vertebral fracture	46	16	16	14
Vertebral fracture	41	11	21	9
Surgery	16	4	4	8
Cord compression	16	6	5	5

Radiation treatment to bone was the most common SRE, followed by non-vertebral and vertebral fractures. There were relatively few surgeries to bone or spinal cord compressions. More vertebral fractures occurred on the placebo arm. Consequently, there are more symptomatic and asymptomatic patients with vertebral fractures in the placebo arm. Otherwise, the first events were similar across the treatment arms.

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.

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

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 Zometa 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.

At the time of preparing this briefing document, the FDA review team is uncertain to what extent this trial supports a separate zoledronate treatment indication. The advice of the Oncologic Drugs Advisory Committee will be helpful to the FDA in making this determination. Issues that should be considered include:

- To what extent do the zoledronate NDA trials for prostate cancer, breast cancer, and myeloma provide support for efficacy in this setting?
- Would a positive study of this design indicate that efficacy is established for all tumor types evaluated?
- Or, should one evaluate the study population to determine which tumor-types were sufficiently represented?
- Are some tumors sufficiently different that they should be excluded from consideration, e.g., small cell lung cancer? Approval of this drug for *all tumors metastatic to bone* would mean exposure of a large number of cancer patients to zoledronate along with its toxicity and its expense. Is there adequate evidence for such a blanket approval?
- On the other hand, it would be difficult to conduct a trial of Zometa in each type of cancer individually. If overall prognosis and survival for the cancer types included are considered, should one consider an increase of 67 days in time to first skeletal event, marked enough to reach overall statistical significance, as meaningful clinical benefit?

Active Controlled Trial #010 in Breast Cancer and Myeloma

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 2.2 of this review and is summarized again in section 4.3.4 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 Summary

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 an 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 tablets 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 Zometa 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 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 anterior 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 interferes 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:

<u>Disease</u>	<u>Study duration</u>	<u>Placebo SRE</u>	<u>Pamid. SRE</u>	<u>Placebo - Pam</u>
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 boundary 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, Baseline Factors

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)				
	Zol 4 mg	Zol 8/4 mg	Aredia 90 mg	Total
Populations				
Randomized	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 (myeloma, 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).

	<u>Zol 4 mg</u>	<u>Zol 8 mg</u>	<u>Pam</u>
Breast Chemo	96	86	95
Breast Hormonal	122	94	109
Myelma	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:

Table 7-3. Demographic summary by treatment group (Safety evaluable patients)

	Zol 4 mg	Zol 8/4 mg	Aredia 90 mg
Age (years)			
n	563	524	556
mean ± SD	59.7 ± 12.00	58.9 ± 12.33	58.8 ± 12.65
median	60.0	59.0	58.5
Age - n (%)			
≤ 60	301 (53.5)	290 (55.3)	307 (55.2)
> 60	262 (46.5)	234 (44.7)	249 (44.8)
Sex - n (%)			
male	104 (18.5)	96 (18.3)	92 (16.5)
female	459 (81.5)	428 (81.7)	464 (83.5)
Race - n (%)			
Caucasian	495 (87.9)	442 (84.4)	484 (87.1)
black	34 (6.0)	43 (8.2)	44 (7.9)
other	34 (6.0)	39 (7.4)	28 (5.0)
Weight (kg)			
n	538	504	539
mean ± SD	72.7 ± 16.41	72.8 ± 16.16	73.5 ± 16.43
median	70.2	70.7	72.0

Source: Post-text table 7.4-1.

Additional tables in the NDA submission evaluated these factors by stratum. The median age in each stratum was 54 y for Breast-Chemo, 59 y for Breast -Horm, and 62 y for Myeloma.

Baseline disease characteristics for the myeloma patients are outlined in the following table from the application:

Baseline Disease Characteristics in Myeloma

Disease characteristic	Zol 4 mg N=186	Zol 8/4 mg N=160	Aredia 90 mg N=167
Previous SRE			
Yes	150 (80.6%)	130 (81.3%)	136 (81.4%)
No	36 (19.4%)	30 (18.8%)	31 (18.6%)
Time from Init Diag of Cancer to Visit 2 (months)*			
Mean ± SD	18.3 ± 32.28	13.6 ± 22.30	17.3 ± 28.54
Median	2.9	2.5	2.7
Baseline serum creatinine			
Normal (<1.4 mg/dL)	147 (79.0%)	127 (79.4%)	145 (86.8%)
Abnormal (≥1.4 mg/dL)	36 (19.4%)	32 (20.0%)	22 (13.2%)
Missing	3 (1.6%)	1 (0.6%)	0 (0.0%)

As noted above, most patients were recently diagnosed; the median time from diagnosis to randomization was less than 3 months.

The following table summarizes the Applicant's evaluation of baseline disease characteristics of patients in the two breast cancer strata combined:

The Applicant evaluated together the disease characteristics of patients in the two breast cancer strata as documented in the following table from the submission:

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

* 28 days in a month

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

Source: Post-text table 7.4-2A.

In addition to these Applicant analyses of baseline factors according to the combined breast cancer strata, the following are reviewer analyses of important factors by stratum:

Percent patients with a prior SRE:

<u>STRATUM</u>	<u>Zol 4</u>	<u>Pam</u>
Breast-Chemo	85%	81%
Breast-Horm	61%	64%

Percent patients receiving first-line chemotherapy:

<u>STRATUM</u>	<u>Zol 4</u>	<u>Pam</u>
Breast-Chemo	50%	47%
Breast-Horm	37%	47%

Time since initial diagnosis of breast cancer:

<u>STRATUM</u>	<u>Zol 4</u>	<u>Pam</u>
Breast-Chemo	51 mo	51 mo
Breast-Horm	64 mo	62 mo

Finally, symptom findings combined from all three strata (breast-chemotherapy, breast-hormonal, myeloma) at baseline are summarized in the following table from the application:

Baseline quality of life variables by treatment group

	Zol 4 mg N=563	Zol 8/4 mg N=524	Aredia 90 mg N=556
ECOG status - n (%)			
ECOG 0-1	476 (84.5)	429 (81.9)	437 (78.6)
ECOG 2	86 (15.3)	94 (17.9)	116 (20.9)
Missing	1 (0.2)	1 (0.2)	3 (0.5)
Analgesic score – n (%)			
0	133 (23.6)	107 (20.4)	133 (23.9)
1	125 (22.2)	124 (23.7)	120 (21.6)
2	31 (5.5)	29 (5.5)	31 (5.6)
3	161 (28.6)	159 (30.3)	146 (26.3)
4	113 (20.1)	105 (20.0)	125 (22.5)
Missing	0 (0.0)	0 (0.0)	1 (0.2)
BPI composite pain score			
n	506	479	506
Median	3.0	3.0	2.8
FACT-G total score			
n	496	467	499
Median	76.0	75.0	77.2

Source: Post-text table 7.4-1.

The reviewer evaluated several factors by disease (stratum):

Percent patients with ECOG >=2:

<u>Zol 4</u>	<u>Pam</u>
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Myeloma Stratum	20%	27%
Breast-Chemo Stratum	14%	19%
Breast-Horm Stratum	11%	17%

Median Analgesia Score:

<u>STRATUM</u>	<u>Zol 4</u>	<u>Pam</u>
Myeloma	25	29
Breast-Chemo	20	21
Breast-Horm	25	22

Median BPI composite pain score:

<u>STRATUM</u>	<u>Zol 4</u>	<u>Pam</u>
Myeloma	3	2.8
Breast-Chemo	2.9	3.1
Breast-Horm	3.0	3.0

Reviewer's comments:

In each of the strata, there 3 to 7% more poor performance status patients in the Pam arm than in the Zol 4 mg arm. Other than this, the sponsor's evaluation of a large number of potential prognostic factors according to arm and stratum did not reveal any major imbalance of apparent relevance to efficacy analysis.

Novartis did not present an analysis of the extent of bone disease at baseline, a potential prognostic factor for the occurrence of an SRE. The following tables present results from reviewer analyses of bone scan and skeletal survey data. Again, the factors appear balanced in the most relevant study arms (Pam and Zom 4) for each stratum.

Lesions on bone scan per patient (median, mean)

Stratum	Zol 4	Pam
Breast-Chemo	5, 5.36	5, 5.24
Breast-Hormone	5., 5.08	5, 5.04

Lesions on plain film per patient

Stratum	Zom 4	Pam
Breast-Chemo	4, 4.31	4, 4.39
Breast-Hormones Median	4, 4.10	4, 4.26
Myeloma	5, 4.92	4, 4.75

% Patients with 1 or less lesions on skeletal survey

Stratum	Zom 4	Pam
Breast cancer with chemotherapy	13% (23/179)	12% (30/183)
Breast cancer with hormonal therapy	11% (22/201)	14% (30/208)
Multiple myeloma	11% (20/184)	7% (12/167)

% Patients with 2 or less lesions on skeletal survey

STRATUM	Zom 4	Pam
Breast cancer with chemotherapy	27% (49/179)	27% (49/183)
Breast cancer with hormonal therapy	30% (60/201)	28% (58/208)
Multiple myeloma	20% (36/184)	20% (33/167)

A potentially important factor not evaluated in the Novartis study report was whether patients had lytic bone lesions at baseline. Entry criteria for the historical Aredia breast cancer studies (which established the efficacy of Aredia versus placebo) required at least one lytic bone lesion. The following table presents the results of the reviewer analysis how many patients in each stratum had at least one baseline lytic lesion in Study #010

Number of patients with at least one lytic lesion at baseline

Stratum	Patients with lytic lesions (N,%)	
	Zometa 4mg	Aredia
Treatment Arm		
Breast Cancer (Chemo)	89/179 (50%)	74/183 (40%)
Breast Cancer (Hormone)	101/201 (50%)	90/208 (43%)
Myeloma	174/184 (95%)	149/167 (89%)

* Analysis used dataset BONE2, element TYPCODE where 1= lytic

There does seem to be a slight imbalance with 7 to 10% more patients with at least one baseline lytic bone lesion on Zom 4 than on Aredia. The presence of a baseline lytic lesion also appears to be an adverse prognostic factor in this trial, as the following analysis shows that 52% of patients with a lytic lesion subsequently had an SRE compared to 37% without.

Proportion of Patients with SRE according to presence or absence of baseline lytic bone lesion

Baseline Lytic event?	Proportion of Breast Cancer Patients with SRE During Study
NO	226/605 (37%)
YES	275/531 (52%)

Another potential prognostic factor is antineoplastic treatment received. FDA asked Novartis to evaluate the starting therapy on the two arms. The following are the most common baseline antineoplastic agents on each arm at baseline:

STRATUM	ANTINEOPLASTIC AGENT	Zol 4 (%)	Pam (%)
Multiple myeloma	MELPHALAN	34	40
	DEXAMETHASONE	33	23
	DOXORUBICIN	29	26
	PREDNISON	28	37
	VINCRIStINE	24	23
Breast cancer with chemotherapy	PACLITAXEL	37	35
	DOCETAXEL	31	39
	CYCLOPHOSPHAMIDE	30	31
	DOXORUBICIN	28	27
	FLUOROURACIL	25	25
	TRASTUZUMAB	22	17
Breast cancer with hormonal therapy	ANASTROZOLE	37	27
	TAMOXIFEN	30	36
	LETROZOLE	10	14

Medication Received

The mean duration of treatment was about 10 months for patients in all three strata and was similar in the study arms.

Reviewer's Comments

Multiple comparisons of the study arms for baseline demographic and disease factors demonstrate no critical imbalances. A few more patients with poor performance status and a few more breast cancer patients with lytic lesions were entered on the Zol 4mg arm than on pamidronate.

Results of Study #010, Primary Efficacy Analysis: Non-inferiority Comparison of Proportions of Patients with an SRE, Zoledronate 4mg versus Pamidronate

The goal of Study 010 was to demonstrate that Zoledronate is effective by comparing the proportion of zoledronate-treated patients to the proportion of pamidronate-treated patients suffering an SRE during the study. This non-inferiority comparison depends upon historical knowledge of the treatment effect of pamidronate, i.e., the historical value of the event rate of placebo minus pamidronate. One must show that conditions and study populations of the historical trial, which demonstrated pamidronate efficacy, are similar to the current trial, which is comparing efficacy outcomes of zoledronate and pamidronate. Statistical tests are then performed to assure us that the new drug, zoledronate, retains, with confidence, an acceptable amount of the pamidronate treatment effect.

The ideal methodology for performing non-inferiority analyses is a topic of statistical research and is widely discussed in academic and regulatory settings. The Applicant and FDA present different analyses, but they both conclude that the zoledronate 4mg arm is effective in decreasing the proportion of patients suffering an SRE. The Applicant's prospective analysis uses methodology that is no longer accepted by FDA. In that analysis, the historical pamidronate effect size is calculated using "point estimates." Current FDA thinking considers also the probability that the effect size is correctly estimated, and the FDA analysis uses 95% confidence intervals to estimate the original effect size.

The review sections below present the Applicant's results, the FDA results, and a comprehensive comparison of the historical pamidronate-versus-placebo study and the current zoledronate-versus-pamidronate study.

Applicant's Primary Analysis of Efficacy

The following table displays the Applicant's findings for the proportion of patients having at least one SRE, the primary endpoint of the study:

	Proportion	95% C.I. and P-value for the difference	
		Zol 4 mg	Zol 8/4 mg
Multiple myeloma			
Aredia 90 mg	82/167 (49%)	(-12.6%, 8.4%), p=0.694	(-10.6%, 11.1%), p=0.961
Zol 4 mg	86/183 (47%)	-	(-8.2%, 13.0%), p=0.660
Zol 8/4 mg	79/160 (49%)	-	-
Breast cancer with chemotherapy			
Aredia 90 mg	78/181 (43%)	(-9.0%, 11.6%), p=0.806	(-7.0%, 13.8%), p=0.519
Zol 4 mg	79/178 (44%)	-	(-8.3%, 12.6%), p=0.690
Zol 8/4 mg	80/172 (47%)	-	-
Breast cancer with hormonal therapy			
Aredia 90 mg	97/207 (47%)	(-15.0%, 4.3%), p=0.277	(-13.4%, 6.1%), p=0.467
Zol 4 mg	83/200 (42%)	-	(-8.1%, 11.5%), p=0.729
Zol 8/4 mg	83/192 (43%)	-	-
Total			
Aredia 90 mg	257/555 (46%)	(-7.9%, 3.7%), p=0.461	(-6.1%, 5.8%), p=0.963
Zol 4 mg	248/561 (44%)	-	(-3.9%, 7.9%), p=0.495
Zol 8/4 mg	242/524 (46%)	-	-

Proportion = (no. of patients with the event)/(total no. in the group) up to Month 13;

Confidence interval for the difference (treatment labeled in the column minus row) of percent of patients with events.

P-values are based on stratified Cochran-Mantel-Haenszel test for the proportion.

Source: Post-text tables 9.1-1 and 9.1-2.

The Applicant notes that in the overall analysis comparing Zol 4 to Aredia, 46% of the Aredia patients had an SRE compared to 44% on Zol 4, and that the 95% confidence interval of the difference excluded Zol 4 being 3.7% worse (more patients with events) than Aredia. Because the goal was to exclude being 8% worse, the Applicant claims that non-inferiority of Zol 4 with respect to Aredia has been demonstrated. Further, the Applicant notes that results were similar in the per protocol (PP) analysis (48% on Aredia, 47% on Zol 4, with upper 95% ci = 5%).

The Applicant also performed an analysis stratified by performance status (ECOG = 0-1 vs. >1) which gave upper 95% ci = 5%. By all analyses, the Applicant notes that the non-inferiority goal of 8% was met.

FDA's Primary Analysis of Efficacy

FDA analyses also demonstrate non-inferiority of Zometa to Aredia in the proportion of patients with an SRE during Study 010 and are described in more detail in the FDA statistical review. The following table describes the treatment effect estimated from the historical trials of pamidronate versus placebo.

Active Control (Aredia vs. Placebo) Effect by Stratum

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

Combining the data from the historical trials, the point estimate of effect is 13.1%, but the 95% confidence intervals allow us to determine with confidence that the effect size is at least **7.3%**.

Recall the results of the proportions analysis of the combined strata of Study 010 comparing zoledronate 4mg and pamidronate:

	Zoledronate (4mg)	Aredia	Difference D (95% CI)	p-value
Total	44% (248/561)	46% (257/555)	-2% (-7.9%, 3.7%)	0.461

95% confidence intervals of the difference of the difference between the zoledronate and pamidronate exclude a difference of **3.7%** or greater. The preservation of active treatment effect using the SRE rates can be determined by $(7.3\% - 3.7\%) / 7.3\% = 49.3\%$. Hence, using conservative methodology (the "two-95% confidence limit method") the current trial demonstrated a 49.3% retention of Aredia vs. placebo effect .

Results of Study #010, Primary Efficacy Analysis: FDA Evaluation of Design Assumptions for Analysis of the Primary Efficacy Endpoint

When designing a non-inferiority study, we make a critical assumption, *the constant assumption*, a determination that the active control drug (pamidronate) would have shown efficacy in the new study or current setting. While we cannot directly test this assumption, we can compare the historical and current study populations, study design, and study conduct. The Applicant's initial submission did not provide sufficient information or analyses to support the *constant assumption*. During the course of the NDA review, at the reviewer's request, the Applicant submitted a thorough analysis that compared the designs and populations of the historical Aredia trials and the Zometa trials (submission dated November 27, 2001) and provided electronic data sets from the Aredia trials. This section describes results from analyses requested or performed by the reviewer to evaluate the constant assumption.

Reviewer Approach to Comparing Historical and NDA Trials:

The reviewer's goal was to determine that the NDA Zometa clinical trial setting was sufficiently similar to the historical pamidronate clinical trial setting so that, were placebo substituted for Zometa, the pamidronate treatment effect versus placebo would be fully apparent. Considerations include:

- Evaluating whether historical and NDA populations were similarly responsive to pamidronate.
- Determining whether trial design and conduct would allow detection of the pamidronate effect. One difference between a "superiority trial" and a "non-inferiority trial" are the potential ramifications of poor study conduct. Sloppiness, which hides differences between treatment arms, generally makes superiority more difficult to detect, but sloppiness assist a claim of non-inferiority. Evaluation of the design and conduct of the study is one approach to addressing this issue. A second is to perform a per protocol (PP) analysis as the Applicant has done. The PP analysis excludes data of questionable utility which could obscure differences between study arms.

Comparison of baseline factors in historical trials of Aredia versus placebo and NDA trials of Zometa versus Aredia

The following are three Applicant tables comparing baseline factors in historical Aredia trials with the corresponding strata of the Zometa NDA trials (from the submission of 11/27/01). "Protocol 12" was the Aredia myeloma trial, "Protocol 18" was the Aredia breast cancer trial in patients receiving hormonal therapy, and "Protocol 19" was the Aredia breast cancer trial in patients receiving chemotherapy. I have added bold type to factors showing a major difference between the Aredia NDA trials and the Zometa NDA trials.

Summary of demographic and prognostic variables for multiple myeloma patients from Aredia 12 and Zometa 010

	Aredia study 12		Zometa study 010		
Demographic/ Prog.variables	Aredia 90 mg	Placebo	Aredia 90 mg	Zometa 4 mg	Zometa 8/4 mg
Number of patients	198 (100%)	179 (100%)	167 (100%)	183 (100%)	160 (100%)
Sex					
Male	110 (55.6%)	107 (59.8%)	91 (54.5%)	103 (56.3%)	92 (57.5%)
Female	88 (44.4%)	72 (40.2%)	76 (45.5%)	80 (43.7%)	68 (42.5%)
Age (yrs)					
Mean \pm s.d.	64.1 \pm 9.4	62.7 \pm 10.1	62.6 \pm 11.41	63.1 \pm 10.52	62.2 \pm 11.37
Median	66.0	63.0	62.0	62.0	63.0
ECOG					
0 - 1	141 (71.2%)	126 (70.4%)	120 (71.9%)	146 (79.8%)	117 (73.1%)
\geq 2	57 (28.8%)	53 (29.6%)	46 (27.5%)	37 (20.2%)	43 (26.9%)
Missing	N/C	N/C	1 (0.6%)	0 (0.0%)	0 (0.0%)
Myeloma Subtype					
IgA	28 (14.1%)	43 (24.0%)	31 (18.6%)	25 (13.7%)	41 (25.6%)
IgG	113 (57.1%)	83 (46.4%)	100 (59.9%)	115 (62.8%)	83 (51.9%)
Light Chain	42 (21.2%)	46 (25.7%)	28 (16.7%)	32 (17.5%)	27 (16.9%)
Other	15 (7.6%)	7 (3.9%)	7 (4.2%)	10 (5.5%)	5 (3.1%)
Time from Init Diag of Cancer to Visit 2					
Mean \pm s.d.	30.5 \pm 32.2	27.7 \pm 33.5	17.3 \pm 28.62	18.0 \pm 32.24	13.5 \pm 21.75
Median (mo.)	19.3	14.4	2.7	2.8	2.6
Prior type of therapy					
Chemo	152 (76.8%)	139 (77.7%)	156 (93.4%)	169 (92.3%)	147 (91.9%)
Other	46 (23.2%)	40 (22.4%)	11 (6.6%)	14 (7.7%)	13 (8.1%)
Previous SRE*					
Yes	63 (31.8%)	54 (30.2%)	135 (80.8%)	149 (81.4%)	128 (80.0%)
No	135 (68.2%)	125 (69.8%)	31 (18.6%)	34 (18.6%)	31 (19.4%)
Missing	N/C	N/C	1 (0.6%)	0 (0.0%)	1 (0.6%)

N/C: Not collected

Summary of demographic and prognostic variables for breast cancer patients with hormonal therapy from Aredia 18 and Zometa 010

Demographic/ Prog. variables	Aredia study 18		Zometa study 010		
	Aredia 90 mg	Placebo	Aredia 90 mg	Zometa 4 mg	Zometa 8/4 mg
Number of patients	182 (100%)	189 (100%)	207 (100%)	200 (100%)	192 (100%)
Sex					
Male	N/C	N/C	0 (0.0%)	0 (0.0%)	0 (0.0%)
Female	N/C	N/C	207 (100%)	200 (100%)	192 (100%)
Age (yrs)					
Mean ± s.d.	60 ± 12.0	62 ± 11.0	58.9 ± 13.11	59.9 ± 12.63	59.0 ± 12.96
Median	62	64	60.0	59.0	59.0
ECOG					
0 – 1	144 (79.1%)	139 (73.5%)	169 (81.6%)	177 (88.5%)	171 (89.1%)
≥ 2	38 (20.9%)	50 (26.5%)	36 (17.4%)	23 (11.5%)	21 (10.9%)
Missing	N/C	N/C	2 (1.0%)	0 (0.0%)	0 (0.0%)
Time from Init Diag of Cancer to Visit 2					
Mean ± s.d.	90.6 ± 73.1	82.1 ± 61.4	75.5 ± 65.14	82.3 ± 64.62	82.6 ± 81.16
Median (mo.)	75.3	71.9	62.6	63.5	62.6
Time from bone mets to Visit 2					
Mean ± s.d.	25.6 ± 34.2	24.2 ± 26.7	11.2 ± 22.3	16.1 ± 26.3	13.7 ± 25.0
Median (mo.)	13.0	14.9	3.2	4.4	4.1
Prior type of therapy					
Chemo	93 (51.1%)	95 (50.3%)	127 (61.4%)	115 (57.5%)	100 (52.1%)
Other	89 (48.9%)	94 (49.7%)	80 (38.6%)	85 (42.5%)	92 (47.9%)
Previous SRE*					
Yes	46 (25.3%)	57 (30.2%)	132 (63.8%)	123 (61.5%)	110 (57.3%)
No	136 (74.7%)	132 (69.8%)	75 (36.2%)	77 (38.5%)	81 (42.2%)
Missing	N/C	N/C	0 (0.0%)	0 (0.0%)	1 (0.5%)

N/C: Not collected

Summary of demographic and prognostic variables for breast cancer patients with chemotherapy therapy from Aredia 19 and Zometa 010

Demographic/ Prog. variables	Aredia study 19		Zometa study 010		
	Aredia 90 mg	Placebo	Aredia 90 mg	Zometa 4 mg	Zometa 8/4 mg
Number of patients	185 (100%)	195 (100%)	181 (100%)	178 (100%)	172 (100%)
Sex					
Male	N/C	N/C	1 (0.6%)	1 (0.6%)	4 (2.3%)
Female	N/C	N/C	180 (99.4%)	177 (99.4%)	168 (97.7%)
Age (yrs)					
Mean ± s.d.	57 ± 12	56 ± 12	54.9 ± 12.15	56.0 ± 11.68	55.8 ± 11.70
Median	58	56	54.0	54.5	57.0
ECOG					
0 - 1	121 (65.4%)	128 (65.6%)	147 (81.2%)	151 (84.8%)	140 (81.4%)
≥ 2	64 (34.6%)	67 (34.4%)	34 (18.8%)	26 (14.6%)	31 (18.0%)
Missing	N/C	N/C	0 (0.0%)	1 (0.6%)	1 (0.6%)
Time from Init Diag of Cancer to Visit 2					
Mean ± s.d.	80.9 ± 71.6	71.0 ± 66.3	65.9 ± 57.73	73.8 ± 69.72	73.7 ± 67.31
Median (mo.)	60.6	53.0	49.7	51.3	51.0
Time from bone mets to Visit 2					
Mean ± s.d.	24.8 ± 32.6	21.1 ± 22.4	13.8 ± 20.0	18.8 ± 40.7	14.4 ± 20.5
Median (mo.)	12.3	14.6	4.2	3.6	4.5
Prior type of therapy					
Chemo	175 (94.6%)	189 (96.9%)	174 (96.1%)	173 (97.2%)	166 (96.5%)
Hormonal	10 (5.4%)	6 (3.1%)	7 (3.9%)	5 (2.8%)	6 (3.5%)
Previous SRE*					
Yes	61 (32.9%)	80 (41.0%)	112 (61.9%)	109 (61.2%)	96 (55.8%)
No	124 (67.0%)	115 (58.9%)	68 (37.6%)	68 (38.2%)	76 (44.2%)
Missing	N/C	N/C	1 (0.6%)	1 (0.6%)	0 (0.0%)

N/C: Not collected

The reviewer notes three major differences between the populations in the historical Aredia trials and the Zometa NDA trials. These are listed below and then discussed in subsequent sections:

- Time since diagnosis of bone metastases (or time since diagnosis of myeloma which usually would include a bone lesion) was shorter for the Zometa NDA trial.
- More patients gave a history of a previous SRE in the Zometa NDA trial.
- Lytic bone lesions were present in all breast cancer patients in the Aredia trials compared to only about half of the breast cancer patients in Zometa trial.

The concern raised by these differences is whether biphosphonates have demonstrable efficacy in the subpopulations over-represented in the Zometa NDA trial. If the

Applicant demonstrates that Zometa is no different from Aredia in a setting where Aredia does not work, this proves nothing about the efficacy of Zometa. To evaluate the appropriateness of including these subpopulations in the Zometa trials, the reviewer performed the following exploratory subgroup analyses of efficacy with data from Aredia NDA. The purpose was to evaluate whether the Aredia effect (versus placebo) in these subgroups was at least similar to that in the overall study population where Aredia efficacy was established.

Time Since Diagnosis of Bone Metastases

The striking difference between the Aredia trials and the Zometa trial in time since diagnosis of myeloma (and hence time since diagnosis of bone metastasis) was evaluated in the following subgroup analysis of patients diagnosed within 6 months of study entry (similar to the Zometa trial population). Although numbers were small, benefit of Aredia is suggested in this subgroup with 23% more placebo patients than Aredia patients having an SRE.

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

History of Previous SRE

The number of patients with a history of a previous SRE at baseline was also different between the Aredia and Zometa NDA studies. However, as the Applicant notes, the findings were counterintuitive...time since diagnosis was longer in the Aredia trials yet history of an SRE was much less common. This apparent difference may stem from differences in the way data was collected. In the Aredia trials as history of SREs was solicited only for the three months prior to entry whereas in the Zometa trial a history of SRE was solicited for the prior year. Nevertheless, the Aredia data were evaluated to determine whether patients with a prior history of an SRE appeared to derive benefit from Aredia.

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

This analysis suggests that patients in the Aredia myeloma trial with a history of a recent SRE were more likely to have a subsequent SRE and were also at least as likely to derive benefit from Aredia.

Lytic bone lesions at baseline

In the studies comparing Aredia to placebo, inclusion criteria required at least one lytic bone lesion whereas the Zometa 010 trial allowed lytic or blastic lesions. As noted in a prior section of this review, about half of the breast cancer patient in Study 010 had no baseline lytic bone lesions. Is it possible that biphosphonates are effective only in patients with lytic lesions? If so, the breast cancer strata of Study 010 are grossly underpowered for comparing Zometa 4 mg and Aredia.

Two lines of evidence suggest that inclusion of breast cancer patients with non-lytic (blastic and "mixed") lesions is appropriate.

First, in subsets of Study 010 patients with baseline lytic bone lesions, the Zom 4 event rate is similar to the Aredia event rate:

- As discussed above, in the myeloma stratum of Study 010, where 95% of patients had lytic lesions, 49% of the Aredia arm had an event compared to 47% in the Zom 4 arm.
- The following reviewer exploratory subset analysis of the breast cancer strata of Study 010 shows no trend toward more SRE events occurring with Zom 4 relative to Aredia in patients with baseline lytic lesions; in fact, a trend in the opposite direction is suggested. (bolded):

Proportion of Patients in Zometa study 010 with an event, according to whether lytic bone lesion was present at baseline*

Stratum	Lytic Lesion at baseline?	# pts	#(%) of Patients with SRE		
			Aredia	Zom 4	Zom 8
Breast cancer with chemotherapy	No	284	37/109 (34%)	35/90 (39%)	34/85 (40%)
	Yes	251	42/74 (57%)	44/89 (49%)	46/88 (52%)
Breast cancer with hormonal therapy	No	321	44/118 (37%)	36/100 (36%)	40/103 (39%)
	Yes	280	53/90 (59%)	47/101 (47%)	43/89 (48%)

*(Analysis used dataset BONE2, element TYP CODE where 1= lytic)

Other data supports the claim that Zometa can be effective in blastic cancer metastases. Zometa Study 039 in prostate cancer, a different disease setting where essentially all patients have blastic disease, demonstrates that Zometa can be effective in decreasing SREs in patients with blastic metastases.

Comparison of type of SREs Between Aredia Trials and the Zometa Trial

Because the primary endpoint of the 010 trial is a composite endpoint (SRE), thorough comparison of the Zometa NDA Study 010 and the Aredia NDA studies includes comparison of the specific events observed. The reviewer's concern may be expressed by the following worst-case theoretical scenario:

Imagine that a composite endpoint (EP) consists of elements A and B. An event consists of an occurrence of either A or B. Aredia efficacy is shown by a decrease of EP on Aredia relative to placebo, and this is predominantly due to an advantage in decreasing type A events. Zometa is then compared to Aredia, and shows non-inferiority for the EP composite endpoint. However, in the Zometa trial, there are mostly B events. With this scenario, although the Zometa EP rate is identical to that of Aredia, Zometa has not been proven to be effective... without inclusion of "A" events, we cannot assume that the efficacy of Zometa with respect to Aredia has been tested.

In the Aredia NDA trials and the Zometa Study 010, the most frequent SRE events were *radiotherapy to bone* and *pathological fractures*. The following displays the effect of Aredia on these events and compares the frequency of these events in the corresponding trials/strata.

Type of SRE in Trials of Aredia versus Placebo and Zometa versus Aredia*					
Cancer Type	Type of Event	Proportion with Event in Aredia Arm of study		Difference in Proportions Compared to Control Arm	
		Aredia NDA Study	Zometa Study 010	Aredia NDA Study**	Zometa Study 010***
Myeloma	Any SRE	28%	49%	16%	2%
	- Fractures	22%	42%	10%	2%
	- RT to bone	16%	14%	12%	-1%
Breast Cancer (Hormone)	Any SRE	47%	47%	8%	5%
	- Fractures	36%	34%	8%	3%
	- RT to bone	21%	25%	12%	9%
Breast Cancer (Chemo)	Any SRE	43%	43%	13%	-1%
	- Fractures	34%	34%	5%	-3%
	- RT to bone	19%	20%	14%	5%
* Derived primarily from tables in the 11/27/01 submission					
** Placebo minus Aredia					
*** Aredia minus Zol 4					

Examination of this table demonstrates that reviewer worst-case scenario described above does not apply to these trials. The Aredia benefit versus placebo was apparent in both major types of SREs (RT to bone and fractures) and both types of events were well represented in the Zometa NDA Study 010.

Results of Study #010, Secondary Efficacy Analyses

Time to occurrence of an SRE

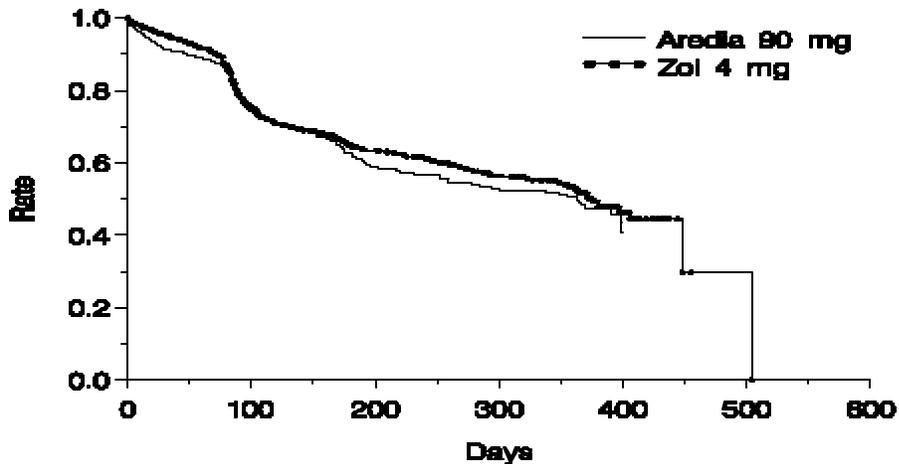
Time to first SRE was similar on Zom 4 and Aredia arms by both the Applicant's analysis and the FDA's analysis. Results from the FDA statistical review are displayed in the following table and Figure.

Time to first SRE by stratum and treatment arm

	N	Median (95%CI)	Hazard Ratio (95% CI)	p-value*
Myeloma				0.82
Aredia	167	301(191, ---)	.97(.71, 1.31)	
Zol 4 mg	183	372(225, 504)		
Breast(CT)				0.81
Aredia	181	366(259, ---)	.96(0.70, 1.32)	
Zol 4 mg	178	364(249, ---)		
Breast(HT)				0.22
Aredia	207	370(258, ---)	.83(.62, 1.12)	
Zol 4 mg	200	>380 (---, --)		
Total				0.31
Aredia	555	363(273, 399)	.92(.77, 1.09)	
Zol 4 mg	561	373(350, 504)		

*Log-rank test

Time to 1st SRE for Study 010



Other Secondary Efficacy Analyses

In any trial, secondary analyses and exploratory analyses are usually of marginal value for making a firm conclusion about efficacy. In a non-inferiority trial such as Study 010, one also must consider whether a non-inferiority conclusion is even remotely possible for that secondary or exploratory analysis. Since non-inferiority conclusions depend on careful documentation of historical evidence that control (Aredia) produces the effect of interest, these secondary analyses must also have been done with the historical data. It seems unlikely that historical data on the effect of the active control will be sufficient to serve as the basis for a non-inferiority analysis. Secondary analyses will be useful only if:

- They demonstrate superiority.
- Strong evidence of benefit is substantiated by evidence from other trials or strata.
- The findings are sufficiently robust to overcome the doubt (inflation of type one error) associated with performing multiple analyses.

Skeletal Morbidity Rate(SMR)

The SMR is the # events divided by time onstudy. The Applicant found no statistical difference between the study arms.

Proportion of Events by Type of Event

The following Applicant displays the proportion of events according to the event type:

**Proportion of patients having a SRE, for each type of SRE, up to Month 13
by treatment group**

	Zol 4 mg N=561	Zol 8/4 mg N=524	Aredia 90 mg N=555
Proportion of pathological fracture	200/561 (36%)	179/524 (34%)	203/555 (37%)
Proportion of vertebral fracture	109/561 (19%)	84/524 (16%)	108/555 (19%)
Proportion of non-vertebral fracture	145/561 (26%)	135/524 (26%)	148/555 (27%)
Proportion of spinal cord compression	11/561 (2%)	12/524 (2%)	16/555 (3%)
Proportion of radiation therapy to bone	85/561 (15%)	112/524 (21%)	112/555 (20%)
Proportion of surgery to bone	21/561 (4%)	15/524 (3%)	31/555 (6%)
Proportion of hypercalcemia	7/561 (1%)	5/524 (1%)	12/555 (2%)

P-values are based on stratified Cochran-Mantel-Haenszel test for the proportion.

Source: Post-text tables 9.2-9, 9.2-12, 9.2-15, and 9.2-18.

The proportions are similar between Zol 4mg and Aredia for each of the major event subtypes.

Brief Pain Inventory (BPI) composite endpoint

A higher composite score was meant to indicate more pain. According to the Applicant's analysis, the mean change from baseline was similar in each arm (-.5 on Zol 4 and -.4 on Aredia).

Analgesic score

Analgesic scores ranged from 0-4 with higher score indicating stronger analgesics. According to Applicant analyses, mean scores changes from baseline were similar for the Zol 4 and Aredia arms (-0.1 for each 3 month visit for each arm).

Performance status (PS)

In Applicant analyses, mean changes from baseline in ECOG PS were similar on the Zol 4 mg and Aredia arms at each 3-month comparison. Within each arm, mean PS increased from 0.1 at 3 months to 0.3 at 13 months.

Quality of Life (QoL)

QoL was evaluated by FACT-G. As shown in the following table from the Applicant's submission, results were statistically inferior in the Zol 4mg arm than Aredia, but also were worse on Zol 4mg than Zol 8mg. These results cannot be easily explained, and are probably due to chance and the inflation of alpha due the large number of secondary efficacy analyses.

Table 9-13. Mean/Median changes from baseline in quality of life scores at Month 13 by treatment group

	Zol 4 mg N=561	Zol 8/4 mg N=524	Aredia 90 mg N=555
Change in FACT-G total score			
Total no. of patients *	446	418	445
Mean ± SD	0.5 ± 14.9	3.1 ± 14.9	2.1 ± 15.6
Median	0.3	3.0	2.0
P-value: vs Aredia 90 mg	0.031	0.839	-
P-value: vs Zol 4 mg	-	0.020	-
Change in physical subscale			
Total no. of patients *	456	425	452
Mean ± SD	0.8 ± 6.0	1.2 ± 6.1	0.8 ± 6.2
Median	1.0	1.0	0.0
Change in functional subscale			
Total no. of patients *	457	422	453
Mean ± SD	0.0 ± 6.2	0.7 ± 6.4	0.9 ± 6.3
Median	0.0	0.0	1.0
Change in social subscale			
Total no. of patients *	454	424	450
Mean ± SD	-0.6 ± 5.0	-0.1 ± 4.5	-0.1 ± 4.5
Median	0.0	0.0	0.0
Change in emotional subscale			
Total no. of patients *	455	423	454
Mean ± SD	0.3 ± 4.3	1.2 ± 4.3	0.5 ± 4.3
Median	0.0	1.0	0.0

* Number of patients who had a non-missing score at both baseline and Month 13 with last observation carried forward.

P-values are from GLM model for the between treatment comparisons of least square means using Analysis of Covariance with baseline value as a covariate and treatment group as a factor at Month 13.

Source: Post-text tables 9.2-45, 9.2-46, 9.2-47, 9.2-49, 9.2-51, and 9.2-53.

Time to Progression (TTP)

In the Applicant's analysis of overall time to progression (Volume 69, post text table 9.2-56), median TTP was 134 days on Zol 4mg (p = 0.174 versus placebo) 125 days on Zol 8mg, and 111 days on placebo. Examination of the KM curves (post text figures 9.2-25) within each stratum shows the study arms to be nearly identical for myeloma and breast cancer treated with chemotherapy. In the stratum of patients with hormone-treated breast cancer, placebo appeared worse, with a median of 94 days compared to 104 days on Zol 4 mg (p = 0.063) and 107 days on Zol 8 mg (p = 0.035). (The low p values reflect differences in the curves beyond the median.) These TTP trends are not supported by Applicant analyses of time to bone event (NDA post text table 9.2-55 and figure 9.2-24).

Reviewer's Comments

Collection of data on tumor progression was not a primary goal of this study. Again, isolated subgroup findings which are of marginal statistical significance are questionable, especially when they represent only one of many secondary analyses performed.

Bone resorption markers

As documented in the Applicant's study report, markers of bone resorption (N-telopeptide, Pyridinoline, and Deoxypyridinoline) were decreased in all study arms relative to baseline and parathyroid hormone was increased 10 to 23%.

Survival

Median survival had not been reached in the study at the time of NDA submission. The following table presents the Applicant's analysis of survival. There were no significant differences or trends between the study arms.

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

Efficacy Summary and Conclusions from Study #010

This well-designed well-controlled clinical study demonstrates that zoledronate 4 mg is effective in decreasing the skeletal morbidity of myeloma and breast cancer metastatic to bone. As outline below, conservative non-inferiority methodology using the *two 95% confidence interval method of estimation* demonstrate that zoledronate retains at least 49.3% of the pamidronate-versus-placebo effect:

- The combined data from the three pamidronate trials show that 52.0% (293/563) on placebo compared to 38.9% (220/565) on pamidronate. The treatment effect is thus 13.1% (95% ci: 7.3%,18.9%). This method uses the conservative limit of the confidence interval to estimate effect size (7.3%).
- On the zoledronate arm of this non-inferiority trial 44%(248/561) of patients had at least one SRE compared to 46% (257/555) on the pamidronate arm (95% ci: -7.9%, 3.7%). Although the estimate from these data favors zoledronate by 2%, again this method uses the conservative limit of the confidence interval to estimate the zoledronate effect which exclude zoledronate being 3.7% worse than pamidronate. The following are the calculations estimating that at least 49.3% of the pamidronate-versus-placebo effect have been retained: $(7.3\%-3.7\%)/7.3\% = 49.3\%$.

A critical aspect of making conclusions from non-inferiority trials is the *constant assumption*. This aspect of trial design, discussed in more depth in the FDA statistical review, requires a determination that the active control drug (pamidronate) would have shown efficacy in the new study or current setting, and it also requires an estimation of the size of the effect that Aredia would have shown relative to a placebo in the current setting. The FDA reviewers carefully compared the historical pamidronate study with this assumption in mind. Important differences were found between the studies.

Compared to the pamidronate-versus-placebo studies, more patients on Study 010 had:

- a short time since diagnosis of bone metastases

- history of a previous SRE
- no lytic bone lesion

Retrospective analysis of the pamidronate-versus-placebo data showed that the pamidronate effect appeared even greater in patients with a short time since diagnosis of bone metastasis and in patients with a history of a previous SRE. Therefore, enrichment of the study population with these patients should, if anything, increase the sensitivity of the study.

The question of whether the active control (pamidronate) is effective in breast cancer patients with non-lytic lesions, however, cannot be directly examined in the pamidronate-versus-placebo study because only patients with lytic lesions were entered. One can examine whether zoledronate appears to be effective in Study 010 in the subgroup corresponding to the pamidronate study. Such a subgroup analysis of Study 010, comparing zoledronate versus pamidronate in breast cancer patients with lytic bone lesions, did not suggest a lack of zoledronate efficacy. In fact, the trend was in favor of zoledronate.

Whether zoledronate approval in breast cancer should extend to patients without lytic bone lesions needs further consideration. The results of Study 039, a study of zoledronate for treating the predominantly blastic metastases of prostate cancer, should also be considered in making this determination.

4 Integrated Safety Review

This integrated safety review discusses safety findings from all submitted zoledronate studies. Detailed FDA safety reviews of the studies in breast cancer and myeloma (010), prostate cancer (039), and other solid tumors (011) can be found in the appendices to this briefing document.

4.1 Brief Statement of Reviewer's Conclusions

Zoledronate 4 mg i.v. over 15 minutes every 3-4 weeks has an acceptable safety profile, and is comparable in toxicity to Aredia 90 mg i.v. over 2 hours every 3-4 weeks as an adjuvant to standard anticancer therapy in patients with bone metastases from breast cancer and lesions of multiple myeloma. Zoledronate 4 mg i.v. over 15 minutes every 3 weeks has an acceptable safety profile, but is more toxic than placebo when used as an adjuvant to standard anticancer therapy in patients with prostate cancer and other solid tumors.

The major safety concern identified in the randomized trials is increased risk of renal function deterioration, which is dose-related and increases with duration of therapy. Most incidences were mild and reversible, with rare incidences of acute renal failure. During the course of the studies, the renal safety of zoledronate was improved by prolonging the infusion time to 15 minutes (instead of 5 minutes) and eliminating the 8 mg dose. The safety of the 4 mg dose was improved by requiring assessment of serum creatinine before each dose and holding zoledronate for renal deterioration, until the return of creatinine to within 10% of the baseline. When compared with Aredia 90 mg i.v. over 2 hours, zoledronate 4 mg i.v. over 15 minutes every 3-4 weeks in patients with metastatic breast cancer to bone and multiple myeloma (study #010), the incidence of renal deterioration was similar (8.8% and 8.2%, respectively). The incidence of renal deterioration for patients with prostate cancer (study #039) and solid tumor malignancies other than prostate and breast (#011) was higher than placebo, but the difference was not statistically significant.

Symptoms felt possibly to be associated with bisphosphonates as a class, such as arthralgias, pyrexia, as well as electrolyte disturbances, were noted for zoledronate and Aredia, but were not a major concern.

Anemia was slightly more common with zoledronate 4 mg, compared with placebo. In the Aredia-controlled study, more patients in the zoledronate 4 mg group had a decrease of > 25% from baseline hemoglobin. This is of uncertain significance.

4.2 Description of patient exposure

Zoledronate was approved in August 2001 for treatment of hypercalcemia of malignancy. This was based on 2 identical randomized trials in which a total of 86 patients received

zoledronate 4 mg i.v. over 5 minutes, with Aredia 90 mg i.v. infusion over 2 hours as the control. The approved dose of zoledronate was 4 mg by 15-minute i.v. infusion. The infusion duration was prolonged because of the increased risk of renal deterioration associated with shorter infusions.

The primary safety population for the current NDA includes 3,337 safety evaluable patients (2,251 treated with zoledronate) in phase 2 and phase 3 randomized trials for cancer patients with metastatic disease to bone. Zoledronate was given i.v. every 3 or 4 weeks, usually to correspond with the schedule of concomitant anti-cancer therapy. The planned treatment duration for these studies was 9 months for protocol 011, 10 months for protocol 007, 12 months for protocol 10 and 15 months for protocol 039. Applicant table 1-1 provides a summary of the studies.

Applicant table 1-1

Table 1-1. Primary safety population: Summary of studies

Study no.	Tumor type	Zol < 4 mg	Zol 4 mg	Zol 8/4 mg	Aredia 90 mg	Placebo	Total No. of Patients
007	breast, multiple myeloma	145	68	-	75	-	288
010	breast, multiple myeloma	-	563	524	556	-	1643
011	solid tumor other than breast or prostate	-	254	265	-	247	766
039	prostate	-	214	218	-	208	640
Total	all	145	1099	1007	631	455	3,337

For the primary safety population, the applicant provided all data available until the data base lock on 2/28/01 for the time to death and renal function deterioration analyses.

The applicant provided safety data for an additional 493 patients from 8 studies and study extensions as the “supportive safety population.” For this supportive population, only 27 patients received zoledronate 4 mg; 61 received < 4 mg; 197 received zoledronate 8/4 mg; 22 received zoledronate 8 mg, and 186 received Aredia 90 mg i.v.

Study 506 is a clinical pharmacology study in 19 cancer patients with varying renal function, to provide information on dosing for this special population.

The cut-off date of February 28, 2001, was used for reporting data on deaths and serious adverse events (SAEs) in trials for other indications. Applicant’s table 1-3 summarizes ongoing trials and trials in other indications.

Applicant table 1-3

Table 1-3. Summary of ongoing trials and trials in other indications

Study No.	Purpose & Design	Type of Control	No. of Patients	Population
<u>Completed trials</u>				
001, 002	Efficacy and safety	None, placebo	16, 176	Paget's disease of bone
701 (terminated)	Randomized, double-blind	placebo	6	primary breast cancer
AT01 (closed)	Double-blind	placebo	20	renal transplant
041	Treatment of osteoporosis: Randomized, double-blind, dose-ranging	placebo	351	women with postmenopausal osteoporosis
US03 (closed)	Osteoporosis: open, randomized	active (Fosamax®)	12	patients on corticosteroids
036, 037	HCM, double-blind, randomized	Aredia	149, 138	cancer with HCM
CJ/HC1	open, phase 1, dose escalation	none	33	cancer with HCM
<u>Ongoing trials</u>				
010 Extension	Long-term safety: randomized, double-blind	active (Aredia)	704	breast cancer, multiple myeloma
011 Extension	Long-term safety: randomized, double-blind	placebo	101	solid tumor other than breast or prostate
039 Phase 2	Long-term safety: randomized, double-blind	placebo	204	prostate cancer
506 Extension (ongoing)	Open safety extension of PK trial	none	2	cancer patients with varying degrees of renal function
IA03 Extension 1	Long-term safety, open	Aredia	141	breast cancer/multiple myeloma
704	Prevention of bone metastases: randomized, double-blind	placebo	386	prostate cancer
705	Prevention of osteoporosis: randomized, double-blind	placebo	107	M0 prostate cancer
IB01	Disease-free survival: open, randomized	None	328	Stage I/II breast cancer; hormonal therapy
041E	Extension of postmenopausal osteoporosis study 041	placebo	280	postmenopausal osteoporosis
060	Compassionate use	None	3	multiple myeloma
Aus-01, Aus-02, Aus-03, Zol-GB-01, DE-01, 1501 ^a	Aus (33); GB-01 (26); DE-01 (7) 1501 (68)	None	134	Various

^a Local phase IV studies in Australia, Great Britain, Germany, and Japan; not filed to the IND.

Applicant table 2-1 summarizes the duration of exposure of the primary safety population to zoledronate and controls.

Applicant table 2-1

Table 2-1. Summary statistics for duration of exposure – primary safety population

	Zol < 4 mg	Zol 4 mg	Zol 8/4 mg	Aredia 90 mg	Placebo
No. of patients	145	1099	1007	631	455
Mean (months)	7.53	8.50	8.12	9.64	6.44
SD	2.88	4.77	4.80	3.90	4.92
Median (months)	9.04	9.07	8.61	11.96	5.43
Range (months)	0.04 – 12.29	0.04 – 18.54	0.04 – 18.82	0.04 – 15.82	0.04 – 18.07

Source: Post-text table 4.2-1.

The mean and median duration of exposure were shortest for the placebo group, in part because placebo served as the control for the study (#011) with the shortest duration of treatment, 9 months. The mean and median exposure for zoledronate 4 mg was 8.5 and 9.07 months, respectively, similar to zoledronate 8/4 mg, and slightly shorter than for Aredia.

Applicant table 2-2 summarizes additional information about duration of exposure for the primary safety population.

Applicant table 2-2

Table 2-2. Summary of duration of exposure – primary safety population

Months ^a	Zol < 4 mg	Zol 4 mg	Zol 8/4 mg	Aredia 90 mg	Placebo
No. of patients	145 (100.0)	1099 (100)	1007 (100)	631 (100)	455 (100)
< 3	16 (11.0)	193 (17.6)	206 (20.5)	66 (10.5)	142 (31.2)
3 to < 6	19 (13.1)	174 (15.8)	152 (15.1)	58 (9.2)	95 (20.9)
6 to < 10	96 (66.2)	235 (21.4)	204 (20.3)	133 (21.1)	122 (26.8)
10 to < 12	13 (9.0)	69 (6.3)	87 (8.6)	63 (10.0)	18 (4.0)
12 to < 15	1 (0.7)	350 (31.8)	303 (30.1)	308 (48.8)	20 (4.4)
15 to < 18	0 (0.0)	77 (7.0)	54 (5.4)	3 (0.5)	57 (12.5)
18 to < 24	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	1 (0.2)

^a duration from randomization: (last known date patient took study medication – Visit 2 date + 1)/28

Source: Post-text table 4.2-2.

The duration of exposure was at least 12 months for 38.9% of zoledronate 4 mg patients, 35.6% for zoledronate 8/4 mg, and 49.3% for Aredia patients.

For the three phase 3 trials, patients were to be randomized to zoledronate treatment arms of 4mg and 8 mg. After it was determined that 8 mg was associated with excess renal toxicity, no patient received more than 4 mg per dose and the 8 mg arm was renamed “8/4 mg”. This occurred June 2000. The percentage of infusions in the 8/4 mg groups that was actually 4 mg was 10% for #039 (prostate cancer), 20% for #010 (multiple myeloma and breast cancer, and 22% for #11 (miscellaneous solid tumors).

In June 1999, amendments to studies 039, 010, and 011 increased the infusion time from 5 to 15 minutes, which was shown to decrease the renal toxicity of zoledronate. See individual study safety reviews, which are contained in the Appendix, for details of the separate renal safety analyses done for patients according to whether they were randomized pre or post the 15-minute infusion amendment. Applicant table 2-4 demonstrates the total number of patients and infusions and the total number of 15-minute infusions by study.

Applicant table 2-4

Table 2-4. Total infusions and 15-minute infusions by study

Study	All patients		15-minute infusion		Zol 4 mg 15-minute infusions	
	no. of patients	no. of infusions	no. of patients	no. of infusions	no. of patients	no. of infusions
007	288	2486	0	0	0	0
010	1643	22565	830	10310	281	3610
011	766	5474	571	4026	186	1355
039	640	9048	274	3589	97	1330
Total	3337	39573	1675	17925	564	6295

Source: Post-text table 4.2-4

In studies 010, 011, and 039, 69.4%, 26.3% and 53.6% of patients, respectively, received at least twelve 15-minute infusions (from applicant table 2-5).

Detailed reviews of the individual studies, 010, 011, 039 (see Appendix for details), show a balance among treatment arms of age and baseline renal function. Applicant table 3-1 shows a summary of demographic information for the pooled primary safety population

Applicant table 3-1

Table 3-1. Summary of demographics – primary safety population

	Zol < 4 mg	Zol 4 mg	Zol 8/4 mg	Aredia 90 mg	Placebo
Total no. of patients	145 (100)	1099 (100)	1007 (100)	631 (100)	455 (100)
Sex (n, %)					
male	42 (29.0)	494 (44.9)	500 (49.7)	103 (16.3)	367 (80.7)
female	103 (71.0)	605 (55.1)	507 (50.3)	528 (83.7)	88 (19.3)
Race (n, %)					
white	124 (85.5)	962 (87.5)	863 (85.7)	544 (86.2)	395 (86.8)
black	10 (6.9)	77 (7.0)	76 (7.5)	56 (8.9)	31 (6.8)
other	11 (7.6)	60 (5.5)	68 (6.8)	31 (4.9)	29 (6.4)
Age (years)					
mean ± SD	57.1 ± 13.07	62.7 ± 11.86	62.1 ± 12.05	58.6 ± 12.55	66.8 ± 10.82
median	56.0	63.0	63.0	58.0	69.0
Age (n, %)					
≤ 60	85 (58.6)	462 (42.0)	433 (43.0)	354 (56.1)	113 (24.8)
> 60	60 (41.4)	637 (58.0)	574 (57.0)	277 (43.9)	342 (75.2)
Weight (kg)					
no. of patients	144	1069	983	614	452
mean ± SD	74.5 ± 15.50	75.0 ± 16.10	75.3 ± 16.43	73.6 ± 16.45	77.0 ± 17.09
median	73.1	73.2	74.0	71.9	75.2
Primary cancer site					
breast	84 (57.9)	418 (38.0)	364 (36.1)	435 (68.9)	0 (0.0)
multiple myeloma	61 (42.1)	213 (19.4)	160 (15.9)	196 (31.1)	0 (0.0)
prostate	0 (0.0)	214 (19.5)	218 (21.6)	0 (0.0)	208 (45.7)
lung	0 (0.0)	124 (11.3)	134 (13.3)	0 (0.0)	123 (27.0)
renal cell	0 (0.0)	27 (2.5)	28 (2.8)	0 (0.0)	19 (4.2)
other	0 (0.0)	103 (9.4)	103 (10.2)	0 (0.0)	105 (23.1)
Baseline serum creatinine					
< 1.4 mg/dL	135 (93.1)	981 (89.3)	875 (86.9)	585 (92.7)	390 (85.7)
≥ 1.4 mg/dL	10 (6.9)	110 (10.0)	123 (12.2)	40 (6.3)	58 (12.7)
missing	0 (0.0)	8 (0.7)	9 (0.9)	6 (1.0)	7 (1.5)

Source: Post-text table 2.2-1.

The imbalance in gender for the pooled population of patients treated with placebo and Aredia relates to the design of the studies, with placebo controlling the prostate study and Aredia controlling the breast cancer (and myeloma) study.

Prior to the start of the study drug, 90% or more of patients were taking antineoplastic therapies. After the start of the study drug, the percentage of patients receiving antineoplastic therapy was 42.6% for the placebo group, 74.3% for zoledronate 4 mg, 69.7% for zoledronate 8/4 mg. 94.8% for the Aredia group. The percentage of patients in these groups receiving cisplatin was 9%, 4.4%, 5.1%, and 0.6%, respectively.

4.3 Methods and specific findings of the safety review

Adverse events (AEs), serious adverse events (SAEs), laboratory studies and survival data were the main safety variables. Safety analysis was based on the type and frequency of adverse events and laboratory values outside of pre-determined ranges. Results were tabulated. Data was cut at the end of the study drug period, which was the end of the core study phase or 28 days following the last study medication. However, any available data was included up to the date of the data base lock for time to death or time to renal deterioration analyses.

Clinical study reports for the three phase 3 trials used the IMN dictionary to code adverse events. AEs are reported using MedDRA preferred terms. AEs were mapped from the IMN preferred terms to the corresponding MedDRA terms.

Following the occurrence of 3 renal failure SAEs in patients receiving zoledronate 8 mg, a Renal Advisory Board (RAB) was formed and amendments were made to the protocol. The effect on renal function was analyzed according to the number of patients who experienced renal adverse events using selected terms suggested by the RAB and the number of patients who met pre-defined criteria of renal deterioration. Kaplan-Meier curves were used to describe the time course to first renal function deterioration.

The “all terms criteria” from the RAB used to describe renal AEs and SAEs are as follows:

- Anuria
- Bladder retention
- Creatinine blood increased
- Hematuria
- Hydronephrosis
- Hyperuricemia
- Micturition frequency
- Nephritis
- Nephrolithiasis
- Nephropathy toxic
- Nephrotic syndrome
- Obstructive uropathy, urethral obstruction or urethral disorder
- Oliguria
- Proteinuria
- Pyelonephritis
- Renal calculus
- Renal failure acute
- Renal function abnormal
- Renal insufficiency
- Renal tubular disorder
- Tumor lysis syndrome
- Uremia
- Urinary retention

Baseline serum creatinine was considered normal if <1.4 mg/dL and abnormal if \geq 1.4mg/dL. Renal function deterioration was defined as any of the following:

- Normal baseline with change from baseline \geq 0.5 mg/dL
- Abnormal baseline with change from baseline \geq 1.0 mg/dL
- Post-baseline value \geq 2 time the baseline value.

Reviewer's comments:

The Applicant has provided an Integrated Summary of Safety with data pooled for the three randomized phase 3 trials (039, 10, 11) plus study 007. Study 007 is a phase 2 study in breast cancer and multiple myeloma patients comparing zoledronate 0.4 mg, 2 mg, and 4 mg i.v. over 5 minutes with Aredia as control. This last study adds little to the safety analysis since only 67 patients received the recommended 4 mg zoledronate dose and all zoledronate infusions were 5 minutes, rather than the recommended 15-minute infusion. Comparison of the major findings of each of the phase 3 studies with each other seems more useful than pooling the data for 4 studies without reference to the specific control in each case and the type of malignant disease. Furthermore, pooling the safety data without reference to duration of infusion significantly obscures the fact that the safety of zoledronate was improved when infused over 15 minutes rather than over 5 minutes.

For detailed safety information pertaining to each of the phase 3 randomized trials analyzed separately, refer to the Appendix. Some of the major points will be reviewed here, as well.

The major safety concern identified in the randomized trials is increased risk of renal function deterioration, which is dose-related and increases with duration of therapy. Most incidences were mild and reversible, with rare incidences of acute renal failure. During the course of the studies, the renal safety of zoledronate was improved by prolonging the infusion time to 15 minutes (instead of 5 minutes) and eliminating the 8 mg dose. The safety of the 4 mg dose was improved further by requiring assessment of serum creatinine before each dose and holding zoledronate for renal deterioration, until the return of creatinine to within 10% of the baseline.

When compared with Aredia 90 mg i.v. over 2 hours, zoledronate 4 mg i.v. over 15 minutes every 3-4 weeks in patients with breast cancer or multiple myeloma (study #010), the incidence of renal deterioration was similar (8.8% and 8.2%, respectively). It was 18.6% for zoledronate 8/4 mg. The incidence of and time to first renal deterioration for patients with prostate cancer (study #039) and solid tumor malignancies other than prostate and breast (#011) was higher than placebo, but the difference was not statistically significant. For prostate cancer patients treated with zoledronate 4 mg infused over 15 minutes, the incidence of renal deterioration was 15.2% compared with zoledronate 8/4 mg (20.7%) and placebo (11.5%). For patients with solid tumor malignancies other than prostate and breast cancer (#11), the incidence of renal deterioration was 10.9% for zoledronate 4 mg, 11.6% for zoledronate 8/4 mg and 6.7% for placebo. In all studies, deterioration of renal function was observed in patients with normal baseline creatinine and in patients with abnormal creatinine (≥ 1.4 -3.0). The prostate cancer patients (#39) with abnormal creatinine had a higher incidence of deterioration when treated with zoledronate or placebo, but there were only a small number of patients in this group, so the significance is uncertain. There were *fewer* patients with abnormal baseline creatinine in study #010 (breast/myeloma) who showed deterioration with zoledronate 4mg, compared with those with normal baseline creatinine. For study #011, the deterioration of renal function with zoledronate 4mg was similar for both baseline creatinine groups.

Symptoms felt possibly to be associated with bisphosphonates as a class, such as arthralgias, pyrexia, as well as electrolyte disturbances, were noted for zoledronate and Aredia, but were not clinically problematic. The incidence of eye-related AEs and injection site problems is less for zoledronate than Aredia.

Anemia was slightly more common with zoledronate 4 mg, compared with placebo. In the prostate study (#039), the incidence of anemia in the zoledronate groups was approximately 27% compared with 17.8% for placebo. In the miscellaneous solid tumor study (#011), anemia was present in 7.9% of the zoledronate 4 mg group and 3.6% of the placebo group. In the Aredia-controlled study (#010, breast/myeloma), more patients in the zoledronate 4 mg group had a decrease of $> 25\%$ from baseline hemoglobin. This is of uncertain significance

4.4 Adequacy of safety testing

Zoledronate has been tested adequately for safety for the population studied. The randomized trials have established safety in a broad spectrum of malignancies for long-term therapy.

4.5 Summary of critical safety findings and limitations of data

Zoledronate 4 mg i.v. over 15 minutes every 3-4 weeks has an acceptable safety profile, and is comparable in toxicity to Aredia 90 mg i.v. over 2 hours every 3-4 weeks as an adjuvant to standard anticancer therapy in patients with bone metastases from breast cancer and lesions of multiple myeloma. Zoledronate 4 mg i.v. over 15 minutes every 3 weeks has an acceptable safety profile, but is more toxic than placebo when used as an adjuvant to standard anticancer therapy in patients with prostate cancer and other solid tumors.

The risk of renal deterioration with zoledronate is greater than placebo, but similar to Aredia. It must be infused over not less than 15 minutes in a volume of 100ml, and clinical monitoring of serum creatinine should be done before each dose to minimize renal risk. The risk of renal toxicity increases with duration of therapy (# of infusions). Caution is indicated for patients with elevated baseline creatinine, particularly since the study population excluded patients with creatinine > 3.0 and the drug is excreted unchanged by the kidneys. The study population did not have extensive concomitant exposure to other potentially nephrotoxic drugs. As the treatment population is expanded, it will be necessary to monitor for possible synergistic nephrotoxic drug effects.