CENTER FOR DRUG EVALUATION AND RESEARCH

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

MEDICAL REVIEW(S)

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

FDA MEDICAL OFFICER REVIEW OF A NEW DRUG APPLICATION

NDA NUMBER:	**21-386**
DRUG NAME:	**Zometa® (zoledronic acid for injection)**
INDICATION:	**Treatment of Bone Metastases**
SPONSOR:	**Novartis**
CLINICAL REVIEWERS:	**Amna Ibrahim,M.D.(Studies 011 & 039)**
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	Nancy Scher, M.D. (Safety review)

APPEARS THIS WAY
ON ORIGINAL

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1 Recommendations

1.1 Recommendation on Approvability

We recommend approval of Zoledronate for the following indication:

> "the treatment of patients with multiple myeloma and documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy"

This recommendation is based on review of the clinical data, discussions with the staff of the Division of Oncology Drug Products, and advice from the Oncologic Drugs Advisory Committee (ODAC).

Zoledronate decreases the morbidity of patients with Multiple Myeloma and patients with metastases from solid tumors. In clinical studies, both the number of patients with skeletal events and the time to first skeletal event were decreased with Zoledronate treatment relative to placebo. Risks from Zoledronate treatment include a low incidence of renal insufficiency at the recommended regimen.

Zometa is well tolerated in doses of 4 mg. infused over 15 minutes every three to four weeks. A 1700 patient study in patients with either myeloma or bone metastases from breast cancer demonstrated that Zoledronate and Aredia have similar benefits and side effects.

1.2 Recommendation on Phase 4 Studies and/or Risk Management Steps

We recommend the following phase 4 commitments:

- Renal toxicity has been observed in patients treated with both thalidomide and Zoledronate. We recommend a drug-drug interaction study to evaluate the effect of thalidomide on the pharmacokinetics and safety of Zoledronate in patients with multiple myeloma.

- Inadequate information is available to guide dosing of Zoledronate in patients with bone metastases and severe renal impairment. We recommend a phase 4 pharmacokinetic, safety and efficacy study in patients with renal dysfunction and serum creatinine ≥ 3 mg/dl. The dose of Zoledronate to be administered should be adjusted to match the $AUC_{0\text{-}24h}$ in patients with normal renal function, and safety, efficacy and biomarker suppression should be assessed. A suitable patient population may be patients with multiple myeloma.

2 Summary of Clinical Findings

2.1 Brief Overview of Clinical Program

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) and 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 and 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 8 mg 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).

2.2 Efficacy

The results from these studies and the supporting data were submitted to the FDA on August 21, 2001 and, after FDA review, were discussed with the Oncologic Drugs Advisory Committee (ODAC) on January 31, 2002. The efficacy results are summarized in the following tables 1 & 2

Table 1: Placebo Controlled Studies 039 (Prostate Cancer) and 011 (Other Solid Tumors)

Study	Study Arm	Analysis of proportion of patients with an SRE			Analysis of time to first SRE		
		Proportion	Difference & 95% CI	P value	Median Time to First SRE	HR 95% CI	P value
Prostate Cancer (039)	Zol 4mg	33%	-11 (-20, -2)	0.021	NR	0.66 (0.48, 0.90)	0.009
	Zol 8mg	38%	-6 (-15, 4)	0.222	3363	0.91 (0.68, 1.23)	0.541
	Placebo	44%	—	—	322	—	—
Solid Tumors (011)	Zol 4mg	38%	-6 (-15, 2)	0.127	230	0.73 (0.56, 0.97)	0.026
	Zol 8mg	35%	-9 (-18, -1)	0.023	219	0.74 (0.56, 0.98)	0.035
	Placebo	44%	—	—	163	—	—

Table 2: Active Control Study 010 (Myeloma and Breast Cancer)

Study	Study Arm	Analysis of proportion of patients with an SRE			Analysis of time to first SRE		
		Proportion	Difference & 95% CI	P value	Time to First SRE (HR)	95% CI	P value
Myeloma & Breast CA (010)	Zol 4mg	44%	-2 (-7.9, 3.7)	0.461	0.92	(0.77,1.09)	0.31
	Zol 8mg	46%	0 (-6.1, 5.8)	0.963	0.99	(0.83,1.18)	0.91
	Aredia	46%	—	—	—	—	—

The results and ODAC recommendations are discussed below for each of the three studies.

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, $\log_e$ 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. The major problems that were debated internally, and were also presented to ODAC, were:

- Unsupportive evidence provided by efficacy analyses of the 8/4 mg arm.
- Prostate Cancer produces predominantly osteoblastic metastases, where as the only prior approval of a bisphosphonate was for Aredia in Breast cancer and Multiple Myeloma. In these diseases, the bone metastases are predominantly osteolytic. The question arose whether results from studies 010 and 011 could support the finding in the Zol. 4 mg arm.
- Lack of clinical data in published literature to support the efficacy of the Zol. 4 mg arm in this new indication

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 ODAC voted that Zol. 4 mg demonstrated "substantial evidence of efficacy" for the following reasons:

- Osteoclast activation appears to be the underlying mechanism of action for both osteolytic and osteobastic metastases.
- The overall efficacy results in the three studies were similar to each other.
- The exploratory analyses such as the pooled analysis of Zol. 4 mg + Zol. 8/4 mg suggested efficacy of Zoledronate.

For these reasons, zoledronate is being recommended for approval for prostate cancer.

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. Furthermore, incorrect randomization makes conclusions based on subsets inaccurate.

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

Table 3: 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

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 Zoledronate 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.

The main issues for this indication were:

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

The ODAC committee members voted that there was "substantial evidence" that Zol 4 mg is effective in the population studied. An improvement of over 2 months in time to first SRE in a population of patients with a median survival of less than 6 months represents clinical benefit. Even though results from the Zol 4 mg arm failed to achieve statistical significance relative to placebo for the primary endpoint, (proportion of patients with SRE, 37% versus 44% respectively, p = 0.106), there was a statistically significant finding in the closely related secondary endpoint (time to SRE), there were statistically significant findings from the Zol 8/4 mg arm in prostate cancer for both the primary and secondary efficacy analyses, and there was support from trials in multiple myeloma, breast cancer, and prostate cancer.

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 *constancy 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.

At the time these results were presented to the ODAC, the FDA review team believed they represented substantial evidence of efficacy. The ODAC agreed, voting 11-0, that they do.

2.2 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.

2.3 Dosing

The recommended dose of zoledronate in patients with multiple myeloma and metastatic bone lesions from solid tumors is 4 mg infused over 15 minutes every three or four weeks. Patients should take an oral calcium supplement (500 mg) and a multivitamin containing vitamin D 400 IU daily. Serum creatinine should be measured before each dose of zoledronate and treatment should be withheld for renal deterioration. In the clinical studies, renal deterioration was defined as an increase in creatinine of 0.5 mg/dL for patients with baseline creatinine less than 1.4 mg/dL or an increase of 1.0 mg/dL for patients with baseline creatinine of 1.4 mg/dL or higher. Zoledronate was held until return of the creatinine to within 10% of baseline.

The studies were amended twice because of renal toxicity. The duration of infusion was increased from 5 minutes to 15 minutes and the infusion volume was increased from 50 to 100 ml, with improvement of the toxicity profile. Subsequently, after all patients were accrued, the dose was reduced for those patients in the 8 mg arms to 4 mg (8/4 mg arm), with further decrease in renal toxicity.

Patients were excluded from the bone metastases trials for serum creatinine greater than 3.0 mg/dL. Patients were excluded from the hypercalcemia of malignancy (HCM) trials for creatinine greater than 4.5 mg/dL. For HCM, therapy would ordinarily be short-term, and

patients would be less likely exposed to the cumulative risk of renal deterioration over time associated with long-term therapy with zoledronate.

Safety and pharmacokinetic data are limited in patients with severe renal impairment. At this time, there is no clinical data available to permit dose modification for patients with severe renal impairment, who were excluded from the clinical trials.

WARNINGS must emphasize that single doses of zoledronate should not exceed 4 mg; the duration of infusion should be no less than 15 minutes; baseline creatinine should be obtained and patients with severe renal impairment excluded (see above); serum creatinine should be assessed before each dose and the dose held for renal deterioration.

2.4 Special Populations

- Gender. Gender has no apparent effect on safety or efficacy of Zoledronate. Efficacy was established in tumors that occur only in men (prostate cancer), predominantly in women (breast cancer), and in both (multiple myeloma and other solid tumors).

- Age. In the bone metastases trials, more than 50% of the patients treated with zoledronate were older than age 60. The controlled clinical studies in multiple myeloma and bone metastases showed similar efficacy and safety in older and younger patients. Pharmocokinetics of zoledronate were not affected by age in patients who ranged from 38 to 84 years. Because decreased renal function occurs more commonly in the elderly, special care should be taken to monitor renal function.

- Race. The pharmacokinetics of zoledronic acid were not affected by race in patients with cancer bone metastases.

- Pediatrics. The safety and effectiveness of Zoledronate in pediatric patients have not been established. Because of long-term retention in bone, Zoledronate should only be used in children if the potential benefit outweighs the potential risk. No studies are planned in children because of the potential effect of Zoledronate on bone remodeling in children.

- Pregnancy and Nursing Mothers. Zoledronate should not be used during pregnancy. In reproductive studies in the pregnant rat, subcutaneous doses equivalent to 2.4 or 4.8 times the human systemic exposure (an i.v. dose of 4 mg based on an AUC comparison) resulted in pre- and post-implantation losses, decreases in viable fetuses and fetal skeletal, visceral and external malformations. It is not known whether Zoledronate is excreted in human milk. Because many drugs are excreted in human milk, and because Zoledronate binds to bone long-term, Zoledronate should not be administered to a nursing woman.

- Renal insufficiency. 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. As discussed in the pharmacokinetics section of the Zoledronate labeling, based on a population pharmacokinetic model, the risk of renal deterioration increases with Zoledronate AUC, and is doubled at a creatinine clearance of 10 ml/min.

Drug-Drug interactions. An increased rate of renal insufficiency was noted in multiple myeloma patients taking concomitant thalidomide and Zoledronate 8 mg.

Clinical Review Section

Clinical Review

1 Introduction and Background

1.1 Established and Proposed Trade Name of Drug, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

1.1.1 Established Name:
Zoledronic acid for injection

1.1.2 Proposed Trade Name:
Zometa®

1.1.3 Drug Class:
Bisphosphonate

1.1.3 Applicant's Proposed Indication

The following is the wording of the proposed indication:

> "Zoledronate 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

[redacted]

[redacted]

1.1.4 Dose, Regimens

The recommended dose of Zoledronate in patients with multiple myeloma and bone mesastases from solid tumors is 4 mg diluted in 100 ml. of normal saline or 5% dextrose water infused over no less than 15 minutes.

Increased renal toxicity was associated with a shorter infusion duration (5 minutes) and with a higher dose (8 mg). The former concern is expressed in the following excerpt from the dosage and administration section of the Zoledronate label:

" *Method of Administration* DUE TO THE RISK OF CLINICALLY SIGNIFICANT DETERIORATION IN RENAL FUNCTION, WHICH MAY PROGRESS TO RENAL FAILURE, SINGLE DOSES OF

ZOLEDRONATE 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 [redacted]

1.1.5 Age Groups

The mean age of the patient was 59 years. Patients ranged from 25 to 95 years of age in the three trials.

1.2 State of Armamentarium for Indication(s)

Pamidronate is the only bisphosphonate approved by FDA for treatment of patients with multiple myeloma and bone metasteses. The history of the pamidronate approval process provides is pertinent to evaluation of the zoledronate NDA: first, the pamidronate studies provide strong rationale that biphosphonates 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 biphosphonate 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 biphosphonates 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.

Clinical Review Section

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 185	P 195	A 185	P 195	A 185	P 195	A 182	P 189	A 182	P 189	A 182	P 189
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.

1.3 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. ——— was submitted to the Division of Metabolic and Endocrinology Drug Products (DMEDP) for treatment of HCM while ——— 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 20001, 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.

A related [redacted] was submitted to the Division of Metabolic and Endocrinology Drug Products (HFD-510) for Zoledronate for the indication of hypercalcemia. An NDA was submitted to HFD-510 in 12/99. An approvable letter was sent in September 2000 (after cardio-renal consult) and the drug was approved in August 2001 for hypercalcemia. Subsequently, an efficacy supplement has been submitted to DODP for the use of Zoledronate to [redacted]

The Phase III protocol for Zoledronate was submitted under [redacted] in April 30, 1998. The primary analysis timepoint was 15 months, although analyses will be performed at 3, 6, 9, 12, and 15 months. The *primary efficacy variable* is the *proportion of patients with any SRE* during the first 15 months of the study. Phase III protocol for similar indication [redacted] May 21st, 1998, and for [redacted] was submitted on September 28, 1998.

After reports of increased incidence of renal failure, all protocols were amended in 6/99 to increase the infusion volume from 50- 100 ml, and the infusion duration was increased from 5 to 15 minutes. Another amendment in 6/00 eliminated the 8 mg dose of Zoledronate from all protocols because of an excess number of cases of renal failure. The adjuvant studies of Zoledronate were placed on clinical hold, and early prostate cancer studies (patients with no

other evidence of disease other than rising PSA) were put on a partial hold. Trials in patients with metastatic disease were not placed on hold because of the more favorable risk to benefit ratio in this populaion.

The sponsor informed [redacted]

[redacted] The nature of good clinical practice violations should be included.

1.4 Other Relevant Information

Zoledronate has been approved for tumor-induced hypercalcemia in 46 countries including the US. It has not been approved in any country to [redacted]

1.5 Important Issues with Pharmacologically Related Agents

Aredia is a bisphophonate that has been approved for tumor-induced hypercalcemia as well as to reduce skeletal morbidity in patients with existing skeletal metastases. Concerns were raised recently regarding renal toxicity associated with this drug. In general, this class of drugs is well tolerated.

2 Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, and Microbiology.

Because zoledronate was previously approved by FDA for treatment of hypercalcemia of malignancy, most important non-medical issues were addressed in earlier NDA reviews. However, review of animal pharmacology and toxicology data supports additional precautions for pregnant and nursing patients. In reproductive studies in the pregnant rat, subcutaneous doses equivalent to 2.4 or 4.8 times the human systemic exposure (an i.v. dose of 4 mg based on an AUC comparison) resulted in pre- and post-implantation losses, decreases in viable fetuses and fetal skeletal, visceral and external malformations. Based on these data, we recommend changing the pregnancy labeling classification from C to D and stating in the warnings section of labeling that zoledronate should not be used during pregnancy.

It is not known whether zoledronate is excreted in human milk. However, because many drugs are excreted in human milk, and because zoledronate binds to bone long-term, we recommend zoledronate not be administered to a nursing woman.

3 Human Pharmacokinetics and Pharmacodynamics

3.1 Pharmacokinetics

The following excerpt from the FDA biopharmaceutics review summarizes the relevant pharmacokinetic data.

Zoledronate is characterized by a three-compartment pharmacokinetic model. Zoledronate possesses a "distributive" phase that is characterized by a half-life (α-$t_{1/2}$) of 0.24 hrs, a β-$t_{1/2}$ of 1.87 hours and γ-$t_{1/2}$ of 146 hours. The terminal elimination phase is characterized by prolonged period in which Zoledronate concentrations are generally only slightly higher than the limit of quantification of the assay. It is believed that Zoledronate is slowly released back into the circulation following initial rapid sequestration in the bone. The β-$t_{1/2}$ serves as the effective half-life for the drug, and exposure is described in terms of a twenty-four hour period ($AUC_{0\text{-}24h}$) instead of $AUC_{0\text{-}\infty}$ because of the inaccuracy in determining the terminal elimination phase of the drug.

The Applicant demonstrated that Zoledronate does not inhibit cytochrome P-450 isozymes in vitro, and consequently, did not study P-450 based in vivo drug-drug interactions. Protein binding was originally reported as 22%, but then amended to 56%. The latter figure was derived from a single male volunteer and the original estimate of protein binding is likely more accurate. ^{14}C-labeled studies of Zoledronate in vivo resulted in the recovery of a single radioactive species, which indicated that Zoledronate itself was not metabolized in vivo. This result suggested that hepatic metabolism of Zoledronate does not occur in vivo, and therefore, the effect of hepatic impairment on Zoledronate pharmacokinetics or pharmacodynamics was not studied.

Studies of radio-labeled and unlabeled Zoledronate (64 patients; 503/503E, J001, 506/506E) indicated that renal excretion was the main route of elimination. Within 24 hours of dosing 39 ± 16% of Zoledronate was recovered in the urine. However, it should be noted that fecal recovery of Zoledronate was not reported.

The clearance of Zoledronate, determined by a population pharmacokinetic analysis, was reportedly dependent upon creatinine clearance, age, sex, weight. The FDA re-analysis indicates that CL is dependent upon creatinine clearance alone. Age, race, were not significant cofactors. Weight improved the assessment of volume of distribution. Clearance was approximately 7 L/hr.

The applicant conducted a renal impairment study of Zoledronate in patients with normal, mild or moderate impairment. The results indicated that the $AUC_{0\text{-}24h}$ of Zoledronate increased by 20% with mild impairment and 50% with moderate impairment. In the only patient with severe renal impairment studied, the $AUC_{0\text{-}24h}$ increased by 60% when creatinine clearance decreased from 46 to 9.1 ml/min. The FDA PK/PD analysis indicated that drug efficacy was independent of dose, but Zoledronate did reduce the likelihood of a skeletal related event. Furthermore, the risk of a renal event was correlated with creatinine clearance and Zoledronate AUC. Ther efore, use of Zoledronate is not recommended in patients with severe renal impairment.

3.2 Pharmacodynamics

No clinical pharmacology studies were done in healthy volunteers. The clinical PK and PD of Zoledronate were determined in three studies (J001, 503/503E, 506) in 64 cancer patients with bone metastasis. PD data was also obtained from safety and dose finding studies (003, 007, 035, IA03) and clinical efficacy trials 010, 011 and 039. Serum/plasma markers tested were bone specific alkaline phosphatase, C-terminal telopeptide of type I collagen, N-terminal telopeptide of type I collagen, osteocalcin, PTH and 1,25-dihydroxy vitamin D3 were studied. Calcium, hydroxyproline, pyridinoline, deoxypyridinoline and N-terminal telopeptide of type I collagen were tested in the urine.

Per Applicant, doses in the range of 0.1 mg to 0.4 mg administered to cancer patients with bone metastases produced little or no inhibitory effects on serum and urinary markers of bone resorption. At doses $\geq$ 4 mg, strong inhibition of bone markers of absoroption was noted to >3 to 4 weeks post dose, whereas doses $\leq$ 2 mg showed a lesser consistency in prolongation of inhibitory effect past 3 to 4 weeks, and a generally smaller decline from baseline postdose. However, because of large interpatient variability in the bone marker data, and the high zoledronic acid doses in most studies, a clear cut dose response and duration response relationship could not be established.

4 Description of Clinical Data and Sources

4.1 Overall Data

The clinical data was reviewed as provided by the Applicant in the NDA submission, from volumes 1, 92, 93, 9798, 106, 107, and 112. The electronic submission was analyzed. In particular, the raw data sets, as well as the derived datasets were used for primary, secondary and exploratory analysis of studies 011 and 039.

Literature was reviewed for bone metastasis in prostate cancer. There is a lack of literature describing skeletal events for prostate cancer, and in general for all solid tumors. A literature review for prostate cancer is provided in section 2.4.4.

4.2 Tables Listing the Clinical Trials

Four double-blind, multi-institutional, randomized studies were conducted and are summarized in the following table:

Table 4: Listing of Clinical Trials

Study No.	Tumor Type	Patients randomized	Primary efficacy measure
011	Bone mets from any solid tumors other than breast and prostate cancer	N =773 Zol:4mg =257 Zol:4/8mg =266 Placebo =250	Proportion of patients having at least one SRE (excluding TIH)
039	Bone mets from Prostate cancer	N =643 Zol:4mg =214 Zol:4/8mg =221 Placebo =208	Proportion of patients having at least one SRE (excluding TIH)
010	Bone mets from Breast cancer or Multiple Myeloma	N =1648 Zol:4mg =564 Zol:4/8mg =526 Aredia =558	Proportion of patients having at least one SRE (excluding TIH)
007	Bone mets from breast cancer or Multiple Myeloma	N =280 Zol:0.4mg =68 Zol:2mg =72 Zol:4mg =67 Aredia =73	Proportion of patients having radiation to the bone

4.3 Postmarketing Experience

Postmarketing experience for zoledronate is from treatment of hypercalcemia (HCM), a disorder treated at the same dose (4mg) as that proposed for treating bone metastases, treatment is usually limited to only one or at most a few doses. Per Applicant, by the time of submission of

this NDA, approximately 1472 patients have had received zoledronate for HCM and only two spontaneous reports had been received; neither report was serious.

5 Clinical Review Methods

5.1 How the Review was Conducted

There was a single trial submitted for each indication. Study 010 was conducted in patients with Multiple Myeloma and breast cancer bone metastases, study 011 in patients with bone metastases from solid tumors other than breast cancer and prostate cancer, and study 039 in patient with bone metastases from prostate cancer. Efficacy and safety of each trial were reviewed separately. Three clinical reviewers were involved. They were:

Efficacy review of protocol 010: Dr. Grant Williams M.D.
Efficacy review of protocols 011 and 039: Dr. Amna Ibrahim M.D.
Safety review of protocols 010, 011 and 039: Dr. Nancy Scher M.D.

The study reports and data were reviewed. Electronic raw and derived datasets were used to verify the Applicant's analyses and claims.

5.2 Overview of Materials Consulted in Review

FDA reviewed the original protocols and their amendments and study reports submitted by the Applicant. Electronic datasets were submitted and were used extensively for analysis. FDA requested numerous additional analyses during the review process. Results of these analyses were selectively verified using the electronic datasets.

5.3 Overview of Methods Used to Evaluate Data Quality and Integrity

FDA's Division of Scientific Investigation (DSI) audited selected centers assess data quality and integrity. Sites that accrued the largest number of patients were selected for DSI audit. Inspections were completed at the following sites. DSI determined that study conduct and data quality from these sites were acceptable.

The sites inspected were:
1- Leonard Kalman M.D., Miami, Florida
2- J.Thaddeus Beck M.D., Fayetteville, Arkansas
3- Lee Rosen M.D. (Principal Investigator), Los Angeles, California and [redacted]
4- David Gordon M.D., San Antonio, Texas

5.4 Were Trials Conducted in Accordance with Accepted Ethical Standards

The trials were conducted in accordance with the accepted ethical standard.

5.5 Evaluation of Financial Disclosure

The Financial Disclosure Rule states that for NDAs or sNDAs submitted on or after February 2, 1999, the applicant must disclose whether the following financial arrangements were made with the investigators:

- Compensation affected by the outcome of the clinical studies
- Significant equity interest in the sponsor of a covered study (exceeds $50,000 during the time the investigator conducts the study and for 1 year following completion)
- Proprietary interest in the tested product (patent, trademark, copyright, licensing agreement)
- Significant payments of other sorts (payments to the investigator or the institution of > $25,000, exclusive of study costs during the time the investigator conducts the study and for 1 year following completion)

If these arrangements have been made, the applicant must disclose the arrangements and state what has been done to minimize the potential for bias.

Disclosures

The Applicant asked investigators whether such arrangements had been made. The Applicant got a response from 73% to 85% of the US investigators, whereas only 42% to 49% of the non-US investigators respond for the three main clinical studies. Form 3454 was submitted with the application. The following responses were received from investigators:

- Compensation affected by the outcome of the clinical studies:

- Proprietary interest in the tested product (patent, trademark, copyright, licensing agreement)

- Honoraria, Grants and Consulting fees

Reviewer's assessment

The phase 3 studies are blinded, and randomized studies. Therefore it is not expected that the investigator's financial interests would affect the outcome of the study. The submitted information seems to be adequate and the reviewer believes it to be in compliance with financial disclosure requirements.

Clinical Review Section

6 Integrated Review of Efficacy

6.1 Brief Statement of Conclusions

Zoledronate efficacy is supported by three randomized studies in patients with multiple myeloma or 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) and 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 and 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 8 mg 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 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).

The efficacy results are summarized in the following tables 5 and 6

Table 5: Placebo Controlled Studies 039 (Prostate Cancer) and 011 (Other Solid Tumors)

Study	Study Arm	Analysis of proportion of patients with an SRE			Analysis of time to first SRE		
		Proportion	Difference & 95% CI	P value	Median Time to First SRE	HR 95% CI	P value
Prostate Cancer (039)	Zol 4mg	33%	-11 (-20, -2)	0.021	NR	0.66 (0.48, 0.90)	0.009
	Zol 8mg	38%	-6 (-15, 4)	0.222	363	0.91 (0.68, 1.23)	0.541
	Placebo	44%	—	—	322	—	—
Solid Tumors (011)	Zol 4mg	38%	-6 (-15, 2)	0.127	230	0.73 (0.56, 0.97)	0.026
	Zol 8mg	35%	-9 (-18, -1)	0.023	219	0.74 (0.56, 0.98)	0.035
	Placebo	44%	—	—	163	—	—

Table 6: Active Control Study 010 (Myeloma and Breast Cancer)

Study	Study Arm	Analysis of proportion of patients with an SRE			Analysis of time to first SRE		
		Proportion	Difference & 95% CI	P value	Time to First SRE (HR)	95% CI	P value
Myeloma & Breast CA (010)	Zol 4mg	44%	-2 (-7.9, 3.7)	0.461	0.92	(0.77,1.09)	0.31
	Zol 8mg	46%	0 (-6.1, 5.8)	0.963	0.99	(0.83,1.18)	0.91
	Aredia	46%	—	—	—	—	—

The results from these studies and the supporting data were submitted to the FDA onAugust 21st, 2001 and, after FDA review, were discussed with the Oncologic Drugs Advisory Committee (ODAC) on January 31, 2002. While there were review issues with each of the trials, when viewed together, the efficacy results were mutually supportive. ODAC voted that each of these studies represented substantial evidence of zoledronate 4 mg efficacy for the patients treated, and we concur with these findings. Below are the main issues and conclusions for each of these studies.

Prostate cancer

The 643 patients entering Study 039 were required to have PSA progression while on first-line hormonal therapy for prostate cancer metastatic to bone. Efficacy results showed significantly less skeletal morbidity on the Zol 4 mg 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), although the proportions analysis and a reviewer exploratory analysis of symptomatic SREs did trend 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, $\log_e$ of baseline PSA, and baseline analgesic scores), the findings from the Zol 8/4 remained unchanged, although the p value decreased.

The main issue discussed before ODAC were

- Unsupportive evidence provided by efficacy analyses of the 8/4 mg arm.
- Prostate Cancer produces predominantly osteoblastic metastases, where as the only prior approval of a bisphosphonate was for Aredia in Breast cancer and Multiple Myeloma. In these diseases, the bone metastases are predominantly osteolytic. The question arose whether results from studies 010 and 011 could support the finding in the Zol. 4 mg arm.
- Lack of clinical data in published literature to support the efficacy of the Zol. 4 mg arm in this new indication

The ODAC voted that zol. 4 mg demonstrated "substantial evidence of efficacy" for the following reasons:

- Osteoclast activation appears to be the underlying mechanism of action for both osteolytic and osteobastic metastases.
- The overall efficacy results in the three studies were similar to each other.
- The exploratory analyses such as the pooled analysis of Zol. 4 + Zol. 8/4 mg suggested efficacy of zoledronate.

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 (Zol 4), zoledronate 8/4 mg (Zol 8/4), or placebo to evaluate zoledronate's effect on SREs. Randomization was stratified according to cancer type as either *NSCLC* or *other tumors*. Stratification was imperfect, with a number of other tumor types incorrectly included in the *NSCLC* stratum. However, there was no evidence that the randomization process itself was compromised.

The main issues for this indication were:

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

Design Flaws

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

Efficacy Results

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

Time to first SRE was 67 days longer in the 4mg arm than placebo (230 days versus 163 days respectively, p = 0.026) and was also significantly longer for Zol 8/4.

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

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

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

We concur with the ODAC conclusions. An improvement of over 2 months in time to first SRE in a population of patients with a median survival of less than 6 months represents clinical benefit. Even though results from the Zol 4 failed to achieve statistical significance relative to placebo for the primary endpoint, (proportion of patients with SRE, 37% versus 44% respectively, p = 0.106), there was a statistically significant finding in the closely related secondary endpoint (time to SRE), there were statistically significant findings from the Zol 8/4 primary and secondary analyses in prostate cancer, and there was support from trials in multiple myeloma, breast cancer, and prostate cancer.

Myeloma and Breast Cancer

Study 010 was an international, multicenter, stratified, double-blind, study that randomized patients 1:1:1 to Zol 4 mg, Zol 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 *constancy 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

As discussed in detail in the review, each of these differences were carefully examined, and none of them appeared to violate the constancy assumption. At the time these results were presented to the ODAC, the FDA review team believed they represented substantial evidence of efficacy. The ODAC agreed, voting 11-0, that they do.

6.2 General Approach to Review of the Efficacy of the Drug

Four double-blind, multi-institutional, randomized studies were submitted. They are given in Table 3. Study 007 was a dose ranging study, with a different primary endpoint and was not reviewed for efficacy. Studies 010, 011 and 039 were reviewed in detail. Study 010 was a non-inferiority comparing Zoledronate to Aredia (pamidronate) in Breast Cancer and Multiple Myeloma. Studies 011 and 039 were placebo-controlled.

Table 7: Studies submitted to support Efficacy of Zoledronate

Study No.	Tumor Type	Patients randomized	Primary efficacy measure
011	Bone mets from any solid tumors other than breast and prostate cancer	N =773 Zol:4mg =257 Zol:4/8mg =266 Placebo =250	Proportion of patients having at least one SRE (excluding TIH)
039	Bone mets from Prostate cancer	N =643 Zol:4mg =214 Zol:4/8mg =221 Placebo =208	Proportion of patients having at least one SRE (excluding TIH)
010	Bone mets from Breast cancer or Multiple Myeloma	N =1648 Zol:4mg =564 Zol:4/8mg =526 Aredia =558	Proportion of patients having at least one SRE (excluding TIH)
007	Bone mets from breast cancer or Multiple Myeloma	N =280 Zol:0.4mg =68 Zol:2mg =72 Zol:4mg =67 Aredia =73	Proportion of patients having radiation to the bone

Skeletal related events (SREs) include pathological fractures, spinal cord compression, radiation therapy to the bone and surgery. Chemotherapy change due to pain was included as an SRE in the prostate cancer study only.

6.3 Detailed Review of Trials by Indication

Placebo Controlled Trial #039 in Prostate Cancer

6.3.1 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 Zoledronate'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-relate 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 Zoledronate.

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.

Prognostic factors for SREs

Prognostic factors for SREs are not well-described in literature. In the Aredia studies for Multiple Myeloma and Breast Cancer, prognostic factors included a history of having a previous SRE and time since diagnosis of bone metastasis.

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. Zoledronate 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 Zoledronate should be used in combination with antineoplastic therapy, the inclusion criteria for Study 039 did not require continuation of antineoplastic therapy and this 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:
"Zoledronic acid 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 and with biochemical progression of disease (e.g. a rising PSA) while on first-line hormonal therapy for metastatic disease. Documentation of androgen suppression (serum testosterone < 50 ng/ml) was required.

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. SREs 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/creatininee 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.

Clinical Review Section

-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

Table 8: 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 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 Zoledronate 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 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, 1960 infusions (24%) were administered prior to amendment 2 over 5 minutes. Six thousand and seventy three infusions (76%) were administered over 15 minutes.

Table 9: No. of infusions affected by amendment 2 for Study 039*

Infusion Duration	Total infusions	Placebo	Zol. 4 mg	Zol. 8/4 mg
5 minutes	1960 24%	679	637	644
15 minutes	6073 76%	1933	2116	2024

*based on the amendment date

APPEARS THIS WAY
ON ORIGINAL

Table 10: Duration of Infusion by visit number for Study 039*

Visit #	Total infusions	5 minute infusion			15 minute infusion		
		4 mg	8/4 mg	Placebo	4 mg	8/4 mg	Placebo
2	640	116	126	124	97	93	84
3	613	103	104	114	98	104	90
4	575	85	86	97	100	113	94
5	553	73	73	83	106	115	103
6	525	63	56	70	111	122	103
7	498	53	47	51	115	123	109
8	465	32	39	42	118	124	110
9	436	28	29	34	112	120	113
10	410	27	27	26	108	115	107
11	382	21	20	16	108	110	107
12	361	16	12	12	106	110	105
13	342	11	8	7	107	109	100
14	329	6	6	3	108	105	101
15	293	3	4	0	102	90	94
16	284	0	3	0	102	89	90
17	262	0	2	0	98	80	82
18	243	0	1	0	95	73	74
19	223	0	1	0	87	62	73
20	212	0	0	0	85	60	67
21	195	0	0	0	77	55	63
22	192	0	0	0	76	52	64

*based on the amendment date.

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.

Table 11: Actual dose administered due to amendment 4

Dose administered	Total infusions	Placebo	Zol.4 mg	Zol.8/4 mg
Placebo	2609	2609	0	0
4 mg	3023	3	2752	268
8 mg	2401	0	1	2400

Table 12: Dose of 4 mg administered in patients in each arm per visit

Visit no.	Total no. of infusions	Placebo	Zol. 4 mg	Zol. 8/4 mg
2	214	1	212	1
3	204	2	201	1
4	186	0	185	1
5	181	0	179	2
6	175	0	174	1
7	169	0	168	1
8	151	0	150	1
9	141	0	140	1
10	136	0	135	1
11	131	0	129	2
12	124	0	122	2
13	132	0	118	14
14	131	0	114	17
15	124	0	105	19
16	126	0	102	24
17	125	0	98	27
18	126	0	95	31
19	115	0	87	28
20	117	0	85	32
21	106	0	77	29
22	109	0	76	33

Efficacy Results of Study 039

Patient Disposition

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, Uraguay 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:

Table 13: Demography

Treatment arm	Placebo	Zol. 4 mg	Zol. 8/4 mg
No of patients	208	214	221
Age range	37-90	45-90	43-90
Median	73	72	72
Age ≤ 60 years	15	19	19
Age > 60 years	193	196	201
Time from initial diagnosis to randomization N	208	214	218
Median (months)	56.9	51.8	60.6
Range (months)	1 - 250	3 - 283	8 - 280
Time from initial diagnosis to diagnosis of bone mets N	207	214	217
Median (months)	19.6	19.6	26.6
Range (months)	0 - 216	0 - 228	0 - 215
Time from first bone mets to randomization N	115	114	132
Median (months)	12.3	5.8	5.4
Range (months)	0 - 111	0 - 121	0 - 87
Prior history of bone metastasis	92	99	87
No prior history of bone metastasis	116	115	134
No. of bone metastasis per patient			
median	4	4	4
range	—	—	—
Previous SRE N	208	214	218
Yes	78 37.5%	66 30%	70 32%
No	130 62%	148 69%	148 68%
Number of extraskeletal organs involved			
0	3	2	2
1	182	176	188
2	18	33	24
3	5	3	6
4	0	0	1
Race			
Caucasian	172	178	186
Black	19	24	19
Oriental	2	3	1
Other	15	9	15
Performance status			
0	93	86	98
1	97	112	103