

Please refer to the "Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505 A of the Federal Food, Drug and Cosmetic Act".

Novartis Response:

Additional Novartis overhead (attachment #5)

FDA Response:

- The interim analysis and stopping rules should be pre-specified in the protocol.

ACTION ITEMS:

1. Novartis should submit a copy of the 2 - year carcinogenicity studies to and to HFD-510 who will be conducting the lead review of the studies.
2. Novartis will submit a PK/PD development plan for review.

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Protocol CZOL 4469701

The following comments and requests for information were provided to the sponsor but not discussed at the meeting.

A. Comments on the statistical plan—major issues

1. The FDA statistical reviewer will provide comments on this protocol.
2. The primary endpoint of "bone metastasis-free survival" does not by itself represent clinical benefit. Selection of this endpoint assumes that delaying the occurrence of bone metastases is better than prescribing biphosphonate therapy at the time of bone recurrence. Patients with breast cancer usually die of visceral metastases, not skeletal involvement. The sponsor will need to demonstrate that prophylactic treatment with zoledronate results in less skeletal-related morbidity and greater patient benefit than treating established bone metastases with zoledronate. One possibility is to randomize patients to receive adjuvant zoledronate or placebo, then administer open-label zoledronate when bone metastases develop. Skeletal morbidity endpoints, similar to those used in the pamidronate trials, could be evaluated. Zoledronate is a relatively non-toxic medication, but the trial, if positive, would result in the treatment of all breast cancer patients with an elevated BSP level with an IV medication given monthly. The IV route of administration and monthly visits could cause a potential decrement in quality of life and some associated toxicity that must be weighed against the benefits of delaying asymptomatic metastases. The percentage of the treated population in whom metastases are delayed will be important to evaluate as well.
3. Bone metastasis-free survival may be a useful secondary endpoint. Defining "bone metastasis-free survival" as the time to development of bone metastases or death due to any cause creates a composite endpoint. You state in the package that a survival benefit for zoledronate in this trial is not anticipated. The endpoint should be defined as the time to the development of bone metastases; deaths should be censored.
4. The timepoints selected for the analysis may not be appropriate. BSP levels appear to correlate with the subsequent development of bone metastases (in several published articles), but do not predict when bone metastases will occur. The statistical plan and power calculations are based on the assumption that 50% of the placebo group will have bone metastases within 2 years. This assumption may be incorrect, and the ability to detect a difference between the two groups may be compromised by lack of power and few events at the specified timepoints. Also, patients with bone metastases have a median survival of 4 years; survival analysis at 2 and 4 years is also unlikely to detect a difference between arms.
5. Stratification by type of adjuvant therapy is appropriate. However, there is a demonstrated survival advantage with the addition of paclitaxel to anthracycline-based chemotherapy. An imbalance between treatment arms in patients treated with AC compared to patients

treated with AC followed by paclitaxel could affect the study results. Additional stratification should be considered.

Stratification by node negative or node positive status may not be sufficient to ensure balanced treatment arms. The risk of recurrence (regardless of site) is increased in node positive patients and is also dependent on the number of nodes involved. Stratification by type of adjuvant treatment will not fully address this issue. For example, a patient treated with chemotherapy is likely to be at higher risk than a patient treated with hormonal therapy. However, a patient with 2 positive nodes and a patient with 10 positive nodes will both receive chemotherapy and despite treatment, will have different risks for recurrence.

B. Comments on the statistical plan—as written

1. The Agency will consider the primary analysis to be the unadjusted analysis. The use of the Cox regression model will be considered exploratory. The sponsor has pre-specified the prognostic factors; all are relevant or potentially relevant to recurrence and the protocol treatment. The sponsor may wish to consider adding the number of nodes, rather than only the TNM status.
2. Patients who receive a bisphosphonate or transplant will be censored at the time the treatment is given. This approach assumes that data from these patients are "missing at random" with respect to bone metastases-free survival. This assumption may be incorrect.
 - Bisphosphonates may be prescribed for patients with bone metastases diagnosed by bone scan alone. You can address this problem by giving open-label zoledronate at the time of bone recurrence and following patients for skeletal morbidity. You should take steps to minimize crossover since there is no good way to deal with this problem. It will become an issue of data quality.
 - High-dose chemotherapy with peripheral stem cell transplant/autologous bone marrow transplant may not be recommended at random. It will be given to patients who have a partial or complete response to chemotherapy; it is likely that these patients will have few or no bone metastases. If only a few patients select this option, it is unlikely to affect the study. If a significant number of patients choose this option, it could affect study results. We recommend performing an analysis that censors these patients. If a significant number of patients have a transplant, analyses to evaluate the robustness of the results may be considered.
3. In the analysis of the proportion of patients with bone metastases, patients with early termination or who are lost to follow-up should be censored at the last visit.
4. Why will the proportion of patients who develop metastatic bone disease or die within 2 and 4 study years be compared with the Cochran-Mantel-Haenszel test rather than the logrank test?

5. Please clarify the alpha that will be used for statistical significance at the second and third analyses.
6. There is no prospectively defined procedure for determining number and location of bone metastases, which is listed as a secondary endpoint. The sponsor should specify whether lesions will be counted from the bone scan, from radiographs, or from CT/MRI scans. Use of different modalities will result in different lesion counts in the same patient. It can be difficult to count all sites on a bone scan, since extensive bony disease may appear confluent or involve large or small portions of an individual bone.
7. "Recurrence" is defined in Appendix 6 as local recurrence in the ipsilateral breast after breast-conserving surgery, local recurrence after mastectomy, regional recurrence (ipsilateral internal mammary, supraclavicular, infraclavicular, axillary nodes or axillary soft tissues), and distant recurrence. The diagnosis of a second malignancy is also considered as recurrence.

The sponsor may wish to re-evaluate the inclusion of in-breast recurrence in this definition. Patients with an in-breast recurrence can be treated with mastectomy and have survivals that are similar to patients treated with initial mastectomy. An in-breast recurrence does not alter survival, although it may be a predictive factor for subsequent systemic relapse. Removing these patients from the study might affect the trial results: patients may still develop an in-breast recurrence (if zoledronate has no effect in the breast), but might have a decreased rate of bone metastases with additional treatment. Conversely, patients on placebo with IBTR may have an increased rate of bony recurrence; keeping these patients on study may further enrich the study population.

The development of a second primary may confound the source of subsequent bone metastases. Subsequent therapy for the new primary may confound the study results. It is reasonable (although not required) to consider the development of a second primary as an off-study criterion.

C. Comments on eligibility

1. The eligibility criteria state that patients must have had complete primary tumor resection, but that the BSP level must be obtained preoperatively. What is the rationale for obtaining a preoperative, rather than postoperative, BSP level? You may have problems with accrual, as surgeons will need to discuss the study with a patient and obtain the BSP level, but medical oncologists will administer the treatment and follow-up phases. This factor may not be an issue at Dr. Dial's site (he obtained preoperative BSP levels on 388 patients in 2 years) but may affect other centers and the relevance of the results to the general population.

2. The sponsor may wish to exclude all Stage IIIB patients, not only inflammatory breast cancer patients, because of their worse prognosis. While they are at increased risk for bone metastases, they are also at high risk for visceral disease and local complications that often require additional local therapies such as surgery and radiation.

D. General comments

1. _____
2. Chemistries will be obtained at the stated intervals. The protocol indicates that total and bone specific alkaline phosphatase values will remain blinded unless the total or bone-specific result is $\geq 2 \times \text{ULN}$. The sponsor should clarify whether all laboratory studies will be performed centrally or locally.
3. The most recent follow-up guidelines from ASCO do not recommend routine bloodwork for breast cancer patient follow-up. Blinding of alkaline phosphatase values should not present an ethical or practice dilemma. Investigators may obtain an alkaline phosphatase whenever they feel it is indicated for patient management. The sponsor may wish to underscore the importance of maintaining the blind and adhering to the protocol as written to avoid unblinding for a non-medical indication.
4. The sponsor should clarify whether serum BSP values will be performed at a central laboratory. Central processing is preferable in order to ensure consistent methodology.
5. Given that zoledronate is given intravenously on a monthly schedule for two years, the sponsor may wish to consider some measure of quality of life in this trial.
6. The sponsor should clarify when study drug therapy will begin (e.g., on the first day of adjuvant therapy administration, after chemotherapy is completed, after radiotherapy is completed).
7. The sponsor should clarify in the protocol how patients with a positive bone scan and negative films will be treated. For example, a patient with known liver metastases and a bone scan consistent with bone metastases, even in the absence of radiographic evidence of metastases, might be offered pamidronate.

The meeting was concluded at 4pm. There were no unresolved issues or discussion points.

IS, 5/4/99
Ann Staten, RD Date
Project Manager
Minutes preparer

Concurrence Chair: IS 4/24/99
Susan Flamm Honig, MD Date
Medical Officer

Attachments: Novartis overheads- Attachments 1, 2, 3, 4, and 5.

Attachment 6 - Novartis development plan summary

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Attachment 1



**Clinical Relevance of
Preventing/Delaying Bone Metastases**

- In breast cancer, bone is the only site of metastases for years in approximately 20% of patients. These patients may be cured by bisphosphonates.

Information on this slide is based on
the results of the study
April 15, 2002



**Clinical Relevance of
Preventing/Delaying Bone Metastases**

- Bone is the primary site of metastatic disease in 80% of prostate cancer patients. These patients should have their performance status maintained by delaying the onset of bone metastases.

Information on this slide is based on
the results of the study
April 15, 2002



Clinical Relevance of Preventing/Delaying Bone Metastases

- **The majority of bone metastases are symptomatic**
 - Bone scanning in 316 early breast cancer (T1 or T2 lesions) patients yielded only one patient with an asymptomatic bone metastases.
 - Bone scanning in patients with metastatic breast (N=131) and prostate (N=64) cancer yielded asymptomatic sites in 21% and 22%.
 - Median time to skeletal related event in metastatic breast cancer trials is 6 mos.

Source: American Society
of Clinical Oncology
April 15, 1999



Bone Metastases-Free Survival

- **Clodronate adjuvant breast publications (Diel NEJM 1998, Powles ASCO 1998) demonstrate a decrease in bone metastases**
- **Controversy as to whether visceral metastases can be prevented by bisphosphonates**
- **Primary endpoint most likely to demonstrate a benefit to the patient selected**

Source: American Society
of Clinical Oncology
April 15, 1999



Bone Metastases-Free Survival

- Bone metastases-free survival is a surrogate marker for survival and may be used as the basis of an accelerated approval with full approval based upon disease-free and overall survival.
- Disease-free and overall survival are collected for a minimum of 4 years in breast cancer and 2 years in prostate cancer.

Statistical Significance of Results
Challenges of Monitoring
June 16, 2001



Bone Metastases-Free Survival

- Objective of Prevention Program is to demonstrate an improvement in BM-free survival
- Not explore the utility of zoledronate for the treatment of bone metastases in patients who were previously treated with zoledronate to prevent/delay bone metastases.

Statistical Significance of Results
Challenges of Monitoring
June 16, 2001

NOVARTIS

Bone Metastases-Free Survival

- Zoledronate should already be commercially available and there would not be a need for open label bone metastases treatment in the prevention program.

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April 16, 2002

NOVARTIS

Alternate Proposal for Endpoints in Adjuvant Breast (0701) and Recurrent Prostate Cancer (0704) Trials

- **Endpoints**
 - Time to bone metastases-free survival
 - Maintenance of Karnofsky Performance Status
 - ≥ 12 months difference between zoledronate and placebo in breast cancer
 - ≥ 4 months difference in prostate cancer
 - QOL as measured by EURO-QOL EQ-5D

Document: 000000-01 Novartis
Confidentiality of Novartis
April 16, 2002



Timeline for Zoledronate Program

<u>Indication</u>	<u>Submission</u>
TIH	Dec. 99
Treatment of BM	
• prostate, lung	2Q01
• broad label	2Q02
Adjuvant Treatment of BM	
• breast	1Q04
• prostate	1Q05

Document Number: Z-1000
Revision: 01/00
Date: 11/00

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Study Design of Protocol 0701 (Breast cancer)

Oncology

- Assumptions for sample size calculation:
 - 50% of the placebo patients will develop bone metastases or die at the end of 2 years (hazard rate of 0.3466/year),
 - Zoledronate treatment will reduce the placebo hazard rate by 1/3 (hazard rate of 0.2311/year),
 - 2 years accrual, 2 years treatment, 2 years follow-up, primary efficacy analysis at the end of core phase (~4 years),
 - 5%/year of loss to follow-up in both treatment arms,
 - 80% power with 5% (2-sided) significance level.
- 400 patients (220 events) are planned for this study.
- 1 interim analysis and 1 analysis at the end of follow-up (~6 yrs)

Attachment 2



Interactive Voice Randomization System (IVRS) Probability of Institutional Balancing

Oncology

The result of preliminary calculation of probability of institution balancing is as follows:

No. of Patient Randomized at a Study Center	Acceptable Level of Imbalance	Prob. of Institutional Imbalance
8	2	8.98%
	3	5.56%
10	2	10.00%
	3	6.11%

Attachment 2

Attachment 4



Recurrent Prostate Cancer Population

Oncology

- Delete androgen-independent
- Redefine as:
 - rising PSA in recurrent prostate cancer patients treated with LHRH agonists

Interim Analysis (continued)

Oncology

- **Time of interim analysis**
Protocol 0701: When the 110th event occurs,
Protocol 0704: When the 206th event occurs.
- **When the p-value associated with the interim analysis is less than the Nominal level of 0.005, decision on terminating the study will be jointly made by DMB and Novartis.**

Attachment 5

**(ATTACHMENT 6)
Clinical Development**

ZOLEDRONATE

(CGP 42448, ZOL448)

End-of-Phase II Briefing Documentation

- **Prevention of Bone Metastases**

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1. Introduction

Zoledronate is a third generation bisphosphonate compound. Bisphosphonates have been used in oncology to treat tumor-induced hypercalcemia (TTH) and to prevent or palliate skeletal complications associated with malignant bone involvement because of their ability to inhibit osteoclastic bone resorption. Pamidronate (Aredia®), a second generation bisphosphonate, is approved for TTH (60 - 90 mg in moderate hypercalcemia and 90 mg in severe hypercalcemia) therapy and for the treatment of patients with lytic bone lesions (90 mg) associated with multiple myeloma or breast cancer. Doses of pamidronate up to 90 mg are approved to be infused intravenously over 2-24 hours. The major advantages of zoledronate compared to pamidronate and other bisphosphonates are the greater potency of zoledronate to inhibit osteoclastic bone resorption and the larger therapeutic ratio between drug concentrations which cause the desired inhibition of bone resorption and those that cause the unwanted inhibition of bone mineralization. In addition, preclinical data indicate that zoledronate's greater potency to inhibit osteoclastic function is not associated with enhanced untoward renal effects compared to other bisphosphonates. These characteristics should result in a low dose of zoledronate providing greater inhibition of bone resorption and similar or improved safety profile and a more convenient administration (a 5 minute intravenous infusion or a less than one minute intravenous bolus) compared to 60 - 90 mg of pamidronate.

1.1. Oncology development program

The broad clinical objectives for the zoledronate oncology development program are to demonstrate that zoledronate is effective therapy for the following clinical indications: 1) the treatment of TTH, 2) the treatment of patients with bone metastases arising from any cancer type, and 3) the prevention of bone metastases in breast cancer and prostate cancers. A table summarizing completed and ongoing studies is included in Appendix 1.

2. Overview of the program for prevention of bone metastases

2.1. Rationale for program

2.1.1. Preclinical

Zoledronate is a new, third generation bisphosphonate with an imidazole substituent and is one of the most potent inhibitors of osteoclastic bone resorption known to date. Most of the available preclinical data on zoledronate relate to the inhibition of osteoclastic bone resorption *in vitro* and in animal models of benign bone disease. In mouse calvarial cultures stimulated with 1,25-dihydroxyvitamin D₃, zoledronate potently inhibited osteoclastic bone resorption with an IC₅₀ value of 2 nM (Green et al., 1994). Similar IC₅₀ values were obtained following stimulation with PTH, PTHrP, IL-1-beta or PGE₂, indicating that zoledronate should be a highly effective inhibitor of elevated bone resorption regardless of the underlying pathophysiology.

Direct effects of zoledronate on bone metabolism *in vivo* were first demonstrated by measuring radiographic density of the proximal tibial metaphysis in young, growing rats after 10 days bisphosphonate treatment. In this model both zoledronate and pamidronate produced a dose-

dependent increase in bone density with ED_{50} values of 1.7 and 390 $\mu\text{g}/\text{kg}/\text{day}$ s.c., respectively (Green et al., 1994). In a histomorphometric study in young rats, zoledronate caused a dose-dependent suppression of bone turnover, and was 100 times more potent than pamidronate (Pataki et al., 1997). The renal and intestinal tolerability profile of zoledronate in rats was similar to that of an identical dose of pamidronate, indicating a greater therapeutic index for zoledronate (Green et al., 1997a and b). Short term treatment of rats with zoledronate (0.03 to 5 $\mu\text{g}/\text{kg}/\text{week}$ s.c.) prevented osteopenia due to estrogen deficiency or adjuvant arthritis in the distal femur and lumbar vertebrae. Alendronate and pamidronate had comparable effects at doses one and two orders of magnitude greater, respectively (Müller et al., 1998).

Long-term administration of zoledronate at doses of 0.5 to 12.5 $\mu\text{g}/\text{kg}/\text{week}$ s.c. for 16 months to ovariectomized adult rhesus monkeys has been shown to maintain bone mass and mechanical integrity without any adverse clinical effects (Binkley et al., 1998; Grynpas et al., 1998). A 6-month interim analysis of bone biopsies from these animals showed a dose-dependent suppression of cancellous bone turnover with no detrimental effect on bone mineralization (Bare et al., 1997).

In addition to the well established inhibitory effects of bisphosphonates on osteoclastic bone resorption in benign bone disease, preclinical evidence also indicates that they may be useful for the treatment and prevention of bone metastases. Recent attention has focused on direct effects of these compounds on various stages of the metastatic cascade as well as on the interaction between tumor cells and osteoclasts.

Opinion leaders in the field of metastatic bone disease refer to the "vicious cycle", a paracrine loop by which tumor cells produce factors (predominantly PTHrP, but also IL-1, IL-6 and TNF α) that induce osteoclastic bone resorption which in turn causes a release of growth factors from the bone matrix that promote the growth and activity of the tumor cells (Mundy, 1997). Thus, the osteoclast has been identified as a site for therapeutic intervention in the bone metastatic process. Bisphosphonate therapy could interrupt the "vicious cycle" by preventing the release of tumor growth factors from the bone matrix through inhibition of osteoclastic bone resorption. Several growth factors (TGF-beta, IGF-1 and IL, PDGF, and bFGF), which have the potential to modulate tumor growth and activity, have been identified in bone matrix and conditioned media from resorbing bone. In animal models of bone metastases, the pivotal role of PTHrP and TGF-beta in disease progression has been elegantly demonstrated by the use of neutralizing antibodies to PTHrP and tumor cells with an inactive TGF-beta receptor (Guise et al., 1996). Moreover, preliminary data indicate that bisphosphonates, in addition to inhibiting osteoclastic bone resorption, can also directly down-regulate TGF-beta mRNA in human osteosarcoma cells, reducing their proliferation and inducing apoptosis (Shehata et al., 1997).

The formation of a bone metastasis from a distant primary tumor is a multistep process comprising several discrete stages, each of which involves specific interactions between the tumor cells and the surrounding tissue. First, tumor cells must detach from the primary site, invade the adjacent tissue and migrate via the tumor capillaries into the general circulation. This procedure is reversed at the metastatic site where tumor cells, arrested in an embolism in a capillary bed, leave the vasculature and enter the bone marrow cavity. For this to occur, tumor

cells must first attach to the basement membrane by specific adhesion molecules, then disrupt the membrane by secreting proteolytic enzymes and migrate through it, driven by a chemotactic signal from the underlying tissue. Once in the tissue stroma, the tumor cells proliferate to form secondary metastases with neovascularization, and interact with their local bone microenvironment in a paracrine manner as described above. Clearly, each of these stages in the metastatic cascade offers a potential target for pharmacologic intervention and a growing body of data indicates that bisphosphonates can indeed affect the process at several levels.

Platelets, activated by tumor cells, are intimately involved in the initial thrombus formation prior to the adhesion and extravasation of tumor cells through the capillary walls at a new metastatic site. Zoledronate and ibandronate have been shown to decrease thrombin generation by human osteosarcoma cells and subsequently to reduce platelet aggregation *in vitro* (Marion et al., 1998). These preliminary findings raise the exciting possibility that amino-bisphosphonates may inhibit this initial trigger for the extravasation of tumor cells.

There is also evidence that bisphosphonates can inhibit matrix degradation and invasion by tumor cells *in vitro*. Pretreatment of human prostate and breast cancer cells with zoledronate (10^{-12} to 10^{-6} M) for 24 hours has been reported to inhibit cell invasion into Matrigel (a laminin-rich extracellular matrix) without exerting any cytotoxic or apoptotic effects (Boissier et al., 1998). These authors suggested that bisphosphonates may inhibit matrix-degrading proteinases secreted by the tumor cells. This proposal has yet to be fully explored but alendronate has been shown to inhibit the production of two matrix metalloproteinases (MMP-2 and MMP-9) by human prostate cancer cells *in vitro* and *in vivo* without affecting enzymatic activity *per se* (Stearns & Wang, 1996; Stearns, 1998). Further support of the concept is provided by the finding that combined treatment with a bisphosphonate and a tissue inhibitor of the matrix metalloproteinase-2 (TIMP-2) was more effective than either agent alone at inhibiting osteolytic lesions caused by human breast cancer cells in nude mice (Yoneda et al., 1997). Recent *in vitro* studies have indicated that the nitrogen-containing bisphosphonates inhibit the adhesion of tumor cells to mineralized and non-mineralized extracellular matrices. Pretreatment of both human prostate and breast carcinoma cell lines with pamidronate, NE-10244 (a heterocyclic compound structurally similar to zoledronate), or ibandronate was observed to reduce tumor cell adhesion to bone matrices in a concentration-dependent manner with IC_{50} values in the range of 10^{-10} to 10^{-8} M, respectively (Boissier et al., 1997). In similar experiments, the attachment and spreading of human breast cancer cells to cortical and trabecular bone slices could also be inhibited by pretreatment of the bone slices with ibandronate, alendronate or pamidronate (van der Pluijm et al., 1996). The non-amino-bisphosphonates clodronate and etidronate had little or no effect in these test systems at comparable concentrations. Interestingly, both these studies showed a correlation between the potency of a compound as an inhibitor of osteoclastic bone resorption and its potency as an inhibitor of tumor cell adhesion to bone matrix. In the absence of any direct cytostatic or cytotoxic effects, the mechanism by which amino-bisphosphonates inhibit tumor cell adhesion to bone matrix remains unknown, modulation of cell adhesion molecules such as cadherin, laminin and the integrins is probably involved. This view is supported by *in vitro* studies with human osteoclast-like cells which showed that alendronate treatment (10^{-10} to 10^{-8} M) reduced by 50%

adhesion to specific extracellular matrices containing the integrin RGD sequence (Colucci et al., 1998).

Numerous studies during the past 15 years in a variety of animal models have clearly demonstrated that bisphosphonates reduce tumor-induced osteolysis, measured either as the number of lesions or radiographic area. The tumor cells studied, their routes of administration and the host animals used are summarized in the below.

Animal models used to study of the effect of bisphosphonates on tumor-induced osteolysis

Tumor cell	Host animal	Route	Compound	Reference
Walker 256 rat carcinosarcoma	syngeneic rats	i.a. left iliac artery	pamidronate	Jung et al., 1984
mouse 5T2 multiple myeloma	syngeneic C57BL mice	lv.	pamidronate	Radi et al., 1985
Walker 256 rat carcinosarcoma	syngeneic rats	bone marrow cavity	pamidronate	Wingen et al., 1986
human prostate adenocarcinoma	BALB/c nude mice	s.c. over calvaria	pamidronate, etidronate	Nemoto et al., 1990
mouse bladder MBT-2 carcinoma	syngeneic mice	s.c. over calvaria	pamidronate, etidronate	Nemoto et al., 1991
rat R3327 prostate carcinoma	syngeneic rats	lv. with caval vein clamped	pamidronate	Yu-Cheng et al., 1992
rat breast adenoma ENU 1564	syngeneic rats	left cardiac ventricle	risedronate	Hall & Stoica, 1994
human breast carcinoma MDA-231	BALB/c nude mice	left cardiac ventricle	risedronate	Sasaki et al., 1995
human PC-3ML prostate cancer cells	SCID mice	lv. tail vein	etidronate	Stearns & Wang, 1996
human breast carcinoma MDA-231	BALB/c nude mice	left cardiac ventricle	YH-529	Sasaki et al., 1998

The work of Sasaki et al. (1995, 1998) is particularly relevant to the proposed use of zoledronate in the prevention setting since risedronate and YH-529 are heterocyclic compounds with a structure similar to that of zoledronate, and both compounds were efficacious not only in a treatment protocol but also when used for the prevention of bone metastases. Although the efficacy of bisphosphonates in these models is generally thought to be due primarily to inhibition of osteoclastic activity leading to an indirect suppression of metastatic growth, direct effects on tumor cells have also been implicated. Recent data indicate that zoledronate, pamidronate and YM-175 promote apoptosis of human myeloma cell lines *in vitro* (Shipman et al., 1997; Aparicio et al., 1998), similar to the effects observed on osteoclasts *in vitro* and *in vivo* with risedronate, pamidronate and (Hughes et al., 1995).

As alluded to above, angiogenesis is vital for the growth of primary tumors and their secondary metastases, however the effects of bisphosphonates on this process have not yet been systematically investigated. One preliminary report has described potent inhibition by pamidronate of capillary development in the chick chorioallantoic membrane assay (Steiner et al., 1991). In order to pursue this finding further, several studies have recently been initiated to investigate the effect of zoledronate and other potent bisphosphonates on tumor angiogenesis *in vivo*.

In summary, the preclinical data indicate that zoledronate has great potential for the prevention of bone metastases since 1) zoledronate is an extremely potent inhibitor of osteoclastic bone resorption which should block the paracrine release of growth factors at the metastatic site, 2) zoledronate produces apoptosis in tumor cells and osteoclasts, 3) zoledronate and other nitrogen-containing bisphosphonates have been shown to affect various stages of the metastatic cascade *in vitro*, and 4) nitrogen-containing bisphosphonates are known to suppress the growth and spread of bone metastases in animals injected with cells derived from human tumors. Moreover, the high therapeutic index for zoledronate predicted for the tolerability profile should permit the clinical use of higher doses with greater pharmacological efficacy than those currently used for pamidronate. This is an important point since, at present, we only have *in vivo* dose-response data for bisphosphonates on the inhibition of osteoclastic activity; a different dose-response relationship, requiring higher doses, may pertain for direct effects on tumor cells and the metastatic cascade. In the long-term study with ovariectomized monkeys, a maximal dose of 12.5 $\mu\text{g}/\text{kg}/\text{week}$ (corresponding to 3.25 mg/65 kg/month) was administered to prevent fully the benign osteopenia induced by estrogen deficiency. On the basis of these considerations it would seem prudent to use a higher dose in the malignant setting where the levels of osteoclastic activity and bone turnover are likely to be far above those found in benign bone disease.

2.1.2. Clinical safety and efficacy of zoledronate

A summary of completed Phase I studies is included in the Investigators' Brochure.

Trials in the treatment of bone metastases are summarized below. Complete safety listings for 8 mg of zoledronate can be found in Appendix 3.

Protocol 003 was an open-label, dose-ranging trial of zoledronate in cancer patients with osteolytic bone metastases. The dose levels investigated ranged from 0.1 - 8 mg. Zoledronate was administered as an i.v. infusion every four weeks for three months. The zoledronate was given as a 5-30 minute infusion (patients in the 4 and 8 mg dosing groups received zoledronate as a 5-minute infusion). There were 59 patients enrolled and 52 completed the core phase which was three months in duration. This trial has recently completed. The most commonly reported adverse events were transient increases in bone pain, fatigue, rigors, anemia, nausea, anorexia, constipation, and dyspnea. The safety profile of zoledronate is consistent with that of pamidronate. A complete listing of events is provided in Appendix 3.

The efficacy data indicate that zoledronate 8 mg more effectively and more consistently inhibits markers of bone resorption than lower doses, as shown below in Table 2.1.2-1.

Table 2.1.2-1. Median % change in deoxy pyridinoline/creatinine ratio from baseline

Zoledronate dose	N	1 week %	4 weeks %	8 weeks %	12 weeks %
0.1 mg	7	-14	+18	-5	-11
0.2 mg	8	-20	-9	-3	-19
0.4 mg	8	-8	-16	-18	-4
0.8 mg	7	-41	-7	-17	-13
1.5 mg	10	-28	-32	-27	-44
2.0 mg	8	-38	-30	-40	-27
4.0 mg	7	-40	-21	-3	-35
8.0 mg	7	-44	-48	-47	-53

Protocol 003 Extension. There were a total of 29 patients enrolled in the 003 Extension trial. Three patients remain in study to date and zoledronate has been well tolerated. The maximum duration of treatment for patients in the 003 Extension is 27 months.

Protocol 035 was an open-label fixed ascending dose ranging trial of intravenous zoledronate in patients with any cancer and bone metastases. Patients have received 1 - 16 mg dose of zoledronate; all dose levels have been well-tolerated. As of February 1999, 44 patients had been entered in the core trial (single dose) and 42 completed the eight week follow-up phase. Analysis regarding efficacy (lowering of biochemical parameters of bone resorption) has not been completed. Toxicities observed in patients receiving 8 mg are listed in Appendix 3. The most frequently reported events were bone pain, fever, nausea, diarrhea, URI, edema, and fatigue. The safety profile of zoledronate is similar to that of pamidronate.

Protocol 035 Extension. There were a total of 35 patients enrolled in the 035 Extension trial and 22 are continuing to receive treatment.

Zoledronate 035 Extension Enrollment (as of February 28, 1999)

Dose Group	No. of pts. enrolled	No. of pts discontinued	No. of pts continuing
1 mg	5	5	0
2 mg	7	5	2
4 mg	6	1	5
8 mg	8	1	7
16 mg	9	1	8
Total	35	13	22

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Dose Group	No. enrolled	3 mos.	6 mos.	9 mos.	12 mos.
1 mg	5	2	2		
2 mg	7		1	3	2
4 mg	6	1	2	3	
8 mg	8		7		
16 mg	9	6			

All of the five 1 mg patients have discontinued. One patient was on study less than 3 months. There are two of the seven 2 mg patients continuing (both of these patients have been on for more than one year). One patient was on study less than 3 months.

Five of the six 4 mg patients are continuing.

Seven of the eight 8 mg patients are continuing. One patient was on study less than 3 months.

Three 16 mg patients are on study less than three months.

Protocol 007 was a phase II, double-blind, randomized, dose ranging, multi-center trial in which 280 patients with osteolytic lesions due to either breast cancer or multiple myeloma were randomized to one of four treatment groups as follows: 68 patients into the zoledronate 0.4 mg group, 72 patients into the zoledronate 2.0 mg group, 67 patients into the zoledronate 4.0 mg group, and 73 patients into the Aredia 90 mg group. The grouping for safety and efficacy analyses was by treatment group. However, there were four patients who deviated from their assigned randomization. For safety analysis, all randomized patients were used. In case of randomization deviation, the patient was either assigned to the treatment group which he/she received the most dosage or if the dosage received was not specified in the protocol, the patient was assigned to the protocol specified treatment group whose dosage was lower than he/she received. For efficacy analysis, intent-to-treat patients were used, i.e. patients were assigned to the original treatment groups regardless what they received. Thus, the differences between the numbers of patients in each safety versus efficacy treatment groups. Study drug was administered for 9 months and then one month later, at month 10, patients were evaluated.

Adverse events, whether or not trial drug related that occurred in 15% or more of the patients are given in the following table:

No. of patients with most frequent AEs ($\geq 15\%$ for each group)

	Zol 0.4 mg n (%)	Zol 2.0 mg n (%)	Zol 4.0 mg n (%)	Aredia 80 mg n (%)
Patients studied				
Total no. of patients studied	68	73	66	73
Total no. of patients with an AE	68 (100)	72 (98.6)	66 (100)	73 (100)
Most frequent AEs				
Pain skeletal	30 (44.1)	40 (54.8)	30 (45.5)	44 (60.3)
Fatigue	17 (25.0)	18 (24.7)	27 (40.9)	24 (32.8)
Nausea	30 (44.1)	32 (43.8)	26 (39.4)	37 (50.7)
Vomiting	18 (23.5)	19 (26.0)	24 (36.4)	25 (34.2)
Headache	10 (14.7)	20 (27.4)	21 (31.8)	21 (28.8)
Anorexia	12 (17.6)	13 (17.8)	18 (27.3)	8 (11.0)
Diarrhea	18 (26.5)	10 (13.7)	18 (27.3)	18 (24.7)
Dyspnea	10 (14.7)	8 (11.0)	18 (27.3)	12 (16.4)
Fever	20 (29.4)	20 (27.4)	17 (25.8)	14 (19.2)
Infection viral	14 (20.6)	11 (15.1)	17 (25.8)	18 (24.7)
Anemia	15 (22.1)	16 (21.9)	16 (24.2)	15 (20.5)
Arthralgia	13 (19.1)	10 (13.7)	16 (24.2)	12 (16.4)
Constipation	10 (14.7)	16 (21.9)	16 (24.2)	15 (20.5)
Coughing	12 (17.6)	11 (15.1)	15 (22.7)	19 (26.0)
Dyspepsia	11 (16.2)	13 (17.8)	14 (21.2)	12 (16.4)
Pain abdominal	15 (22.1)	12 (16.4)	10 (15.2)	13 (17.8)

To date, there have been six patients who have experienced serious adverse experiences which were considered to be related to trial drug. One patient experienced severe generalized aches and pains the day after the first trial drug infusion (2 day duration). These symptoms resolved and the patient remains on trial. (Such acute phase reactions appear to be a one-time occurrence and may be prevented by premedication with acetaminophen). A second patient was hospitalized due to hypocalcemia (headache and confusion) eight days after her first trial drug infusion. The patient was treated with two infusions of calcium chloride three weeks apart. The patient recovered and continued in the trial. A third patient experienced renal calculi after 108 days of therapy. The patient was hospitalized for two days and underwent shock wave lithotripsy. The patient completely recovered and continued in the trial. A fourth patient complained of fatigue and malaise, possibly due to deteriorating renal function after 204 days of receiving study drug. The event occurred 19 days after the last dose of study medication. A fifth patient complained of musculoskeletal aches, pyrexia and vomiting associated with neutropenia. Study medication was discontinued due to this event. The sixth patient was discontinued from the trial after experiencing a severe allergic skin reaction which was noted two days after the first trial drug infusion. This patient completely recovered from the allergic reaction within four days.

The primary efficacy variable for this study was the proportion of patients requiring radiation therapy to bone in the 10 month observation period. The study defined effectiveness in a treatment group if less than 30 % (upper limit of the 95% confidence interval) of the patients had radiation therapy to bone. The primary objective was to determine if a dose-response relationship for zoledronate treatment, in addition to standard antineoplastic therapy, exists. Secondary objectives were to assess the efficacy of zoledronate therapy versus that of 90 mg of Aredia in regard to prevention of skeletal-related events (radiation therapy to bone, pathologic fractures, surgery to bone, spinal cord compression), improvement of bone mineral density, and inhibition of markers of bone resorption.

All of the treatment groups except zoledronate 0.4 mg met the defined criterion for effectiveness. The results in regard to the proportion of patients who had radiation therapy to bone are as follows:

Proportion of patients with radiation to bone

	Zol 0.4 mg	Zol 2.0 mg	Zol 4.0 mg	Aredia 90 mg
Proportion	16/68 (24%)	14/72 (19%)	14/67 (21%)	13/73 (18%)
P-Values vs Aredia	0.306	0.780	0.635	
P-Values vs zol 0.4 mg		0.428	0.605	

There were no statistically significant differences between any of the treatment groups.

The proportion of breast cancer patients having radiation therapy to bone was also greatest in the zoledronate 0.4 mg group. Few radiation events occurred in the myeloma patients. Less events than expected occurred in the myeloma group, where as the expected number of events occurred in the breast cancer group.

Proportion of patients with radiation to bone (breast cancer patients)

	Zol 0.4 mg	Zol 2.0 mg	Zol 4.0 mg	Aredia 90 mg
Proportion	13/39 (33%)	13/45 (29%)	11/42 (26%)	11/46 (24%)
P-Values vs Aredia	0.339	0.592	0.806	
P-Values vs zol 0.4 mg		0.662	0.484	

Proportion of patients with radiation to bone (myeloma patients)

	Zol 0.4 mg	Zol 2.0 mg	Zol 4.0 mg	Aredia 90 mg
Proportion	3/29 (10%)	1/27 (4%)	3/25 (12%)	2/27 (7%)
P-Values vs Aredia	0.703	0.556	0.578	
P-Values vs zol 0.4 mg		0.339	0.848	

The proportion of patients having at least one skeletal-related event was greatest in the zoledronate 0.4 mg group overall and for breast cancer patients. Little difference between treatment groups was observed for the myeloma patients.

Proportion of patients with any skeletal-related events

	Zol 0.4 mg	Zol 2.0 mg	Zol 4.0 mg	Aredia 90 mg
Proportion	30/68 (44%)	23/72 (32%)	22/67 (33%)	22/73 (30%)
P-Values vs Aredia	0.059	0.802	0.729	
P-Values vs zol 0.4 mg		0.093	0.139	

Proportion of patients with any skeletal-related events (breast cancer patients)

	Zol 0.4 mg	Zol 2.0 mg	Zol 4.0 mg	Aredia 90 mg
Proportion	22/39 (56%)	18/45 (40%)	15/42 (36%)	16/46 (35%)
P-Values vs Aredia	0.047	0.609	0.928	
P-Values vs zol 0.4 mg		0.135	0.063	

Proportion of patients with any skeletal-related events (myeloma patients)

	Zol 0.4 mg	Zol 2.0 mg	Zol 4.0 mg	Aredia 90 mg
Proportion	8/29 (28%)	5/27 (19%)	7/25 (28%)	6/27 (22%)
P-Values vs Aredia	0.646	0.738	0.634	
P-Values vs zol 0.4 mg		0.426	0.973	

All treatment groups met the study defined criterion for effectiveness for percent increase from baseline in AP lumbar spine bone mineral density (i.e., BMD percent change from baseline statistically greater than 2%). The BMD increase in the 4.0 mg zoledronate group was statistically greater than that in the 0.4 mg zoledronate group. No other treatment group differences were significantly different.

Summary statistics of percent changes from baseline in AP lumbar spine

	Zol 0.4 mg	Zol 2.0 mg	Zol 4.0 mg	Aredia 90 mg
Mean	0.06	0.09	0.10	0.09
P-Values vs Aredia	0.068	0.902	0.786	
P-Values vs zol 0.4 mg		0.095	0.041	

Protocol 007 Extension (US), an open-label, extension trial of rapid intravenous infusion (5 minute) of zoledronate vs Aredia (pamidronate disodium) in cancer patients with osteolytic bone metastases is currently ongoing. The primary objective of this trial is to allow metastatic breast cancer and advanced multiple myeloma patients, who in the investigator's opinion may benefit from further bisphosphonate treatments, to receive either Aredia 90 mg or zoledronate 8 mg after completing their participation in the core dose-ranging trial. This is an amended protocol from the original extension protocol which allowed patients to receive only Aredia 90 mg after completion of the core protocol. Patients who received zoledronate, 0.4, 2 or 4 mg, administered iv over 5 minutes in 50 ml saline in the core trial will receive 8 mg of zoledronate every 4 weeks. Patients who received Aredia, 90 mg administered i.v. over 2 hours in 250 ml saline, every 4 weeks in the core trial will continue to receive 90 mg of Aredia. The double-blind status is maintained by normal saline controls. To date there have been 48 patients who have received zoledronate 8 mg for exposure times ranging from 2 to 15 months (Table 2.1.2-2.).

Table 2.1.2-2. Patient Exposure to 8 mg Zoledronate in Protocol 007 Extension

	< 3 months	3 months	6 months	9 months	12 months	15 months
No. of Patients	48	46	38	21	13	4

There has been one serious drug-related adverse experience in the 007E study. This event involved an elderly woman who developed chronic renal insufficiency after 20 months of monthly zoledronate therapy. She subsequently died from pneumonia with sepsis and an associated acute renal failure. Table 2.1.2-3 shows the adverse events occurring in 10% or more of the patients who received 8 mg of zoledronate. Appendix 3 lists all the AE's experienced by the patients who received 8 mg.

Table 2.1.2-3 007 Extension 8 mg dose group (Total 48 patients) Adverse Events Occurring in 10% or More of Patients

Body System	Adverse event by body system	No. of episodes	No. of pts with at least one episode
Body as a Whole	Fever	7	5
Digestive	Constipation	5	5
	Nausea	7	6
Musculoskeletal	Pain Skeletal	23	12
	Arthralgia	6	6
	Myalgia	5	5
Respiratory	Coughing	8	7

In summary, the safety profile of zoledronate is similar to that of pamidronate. The efficacy of zoledronate appears to be dose-dependent from the limited bone marker data available from the 003 trial.

2.1.3. Unmet clinical need

The skeleton is the third most favored site for metastasis of solid tumors. In the U.S. alone it is estimated that there are approximately 500,000 deaths per year from malignant disease, and that two-thirds to three-quarters of these patients have bone metastases at the time of death. In particular, breast cancer and prostate cancer almost always metastasize to the skeleton. In forty-seven percent of metastatic breast cancer patients, bone is the first site of distant disease. Patients may have bone only disease for months to years (Coleman RE 1987). Eighty percent (80%) of prostate cancer patients have metastatic disease limited to bone until their disease becomes end-stage (Scher 1994). Therapy that prevents or significantly delays (\geq four months for androgen-independent prostate, and \geq twelve months for adjuvant breast cancer) the occurrence of bone metastases will decrease morbidity from skeletal complications.

Currently, there is no bisphosphonate approved for the prevention/delay of bone metastases. However, at least two adjuvant trials of _____ in patients with breast cancer have reported positive results (Diel 1998 and Powles 1998a). These clinical data in the adjuvant breast setting suggest that both lytic and blastic metastases are prevented. There are, however, criticisms of these studies which need to be addressed.

The Diel trial demonstrated a decrease not only in bone metastases, but also in visceral metastases, for breast cancer patients in the adjuvant setting (Diel 1998). However, this was an open label trial and therefore its results may be biased. Editorial commentary on the Diel trial cited that the effect of bisphosphonates should not be generalized to the entire adjuvant breast cancer population, but limited to early-stage, hormone-dependent tumors which were most

heavily represented (Meli 1998). There were also criticisms of the stratification based only upon node negative versus positive rather than by number of involved nodes. No stratification based upon the type of adjuvant therapy was undertaken (Panasci 1998).

The Powles 1998 ASCO abstract also has shown an adjuvant treatment advantage for bisphosphonates in breast cancer. A full manuscript is yet to be published, but an update by Dr. Alexander Patterson at the NSABP meeting in December 1998 revealed some concern about an increased recurrence rate after clodronate was discontinued. There are multiple potential explanations for the fact that Powles saw a decrease incidence in the bone metastases and not in visceral recurrence as did the Diel trial. The obvious difference in the two trials is the populations enrolled Diel selected a subset of patients with micrometastatic disease in the marrow, whereas Powles included any patient with operable breast cancer. Even though the duration of — therapy was two years in both trials, the timing of the therapy differed between the two trials. Powles began therapy within six months of the primary diagnosis of breast cancer, whereas Diel began — at the same time as adjuvant therapy. Although the Powles trial was double-blind, compliance with oral medication has been raised as an issue which needs to be addressed in the complete manuscript.

In addition to the potential value of bisphosphonates in the delay/prevention of bone metastases in breast cancer, — has been documented to improve bone mineral density in breast cancer patients receiving systemic adjuvant therapy (Powles 1998). — given for one year following adjuvant chemotherapy and/or tamoxifen, improved the bone mineral density of the lumbar spine by 2.38% and of the hip by 0.74%. In a separate study, premenopausal women receiving adjuvant tamoxifen experienced a mean annual loss of 1.17% in the lumbar spine and 1.71% in the hip (Powles 1996). Although tamoxifen may slow bone loss when given as an adjuvant treatment for breast cancer, it does not stop bone mineral loss.

Several small studies have been published suggesting that bisphosphonates may be of benefit in decreasing pain and analgesic use in patients with prostate cancer metastatic to bone (Clarke 1992, Adami 1985, Masud 1989, Pelger 1989 and 1998, Purohit 1994, and Yu-Cheng 1992). A larger study with 300 patients employing clodronate failed to show such a benefit (Strang 1997).

Since bone destruction by metastatic disease is initially mediated by bone resorption, prevention of both lytic and blastic disease is possible with bisphosphonates (Kanis 1997). In tumor types other than breast and prostate cancer, some efficacy in the treatment of bone metastases has been reported with clodronate (Piga 1998). — treatment did not affect survival but demonstrated efficacy in symptom control and in the reduction of analgesic use.

In summary, there are currently no treatments approved for the prevention of bone metastases. The zoledronate program as outlined below addresses the need for double-blind placebo controlled trials as the initial registration trials in breast and prostate cancer. Since bisphosphonates may delay rather than prevent the occurrence of bone metastases the pivotal trials are designed with a primary endpoint of bone metastases-free survival. Even if an impact of zoledronate therapy on overall survival did not occur it is likely that the delay and/or

prevention of bone metastases would significantly impact on patients' quality of life. Performance status could be maintained by potentially reducing the disability and symptoms associated with bone metastases (Theriault 1999). This contention is supported by trials of pamidronate in patients with lytic bone metastases from breast cancer and multiple myeloma. A less rapid decline in ECOG performance status, decreased pain scores and analgesic use were observed in pamidronate-treated patients with lytic bone metastases compared with placebo-treated patients (Hortobagi 1996 and Berenson 1996).

2.2. Overview of program

Due to the nature of this indication, trials specifically investigating bone metastases prevention will be performed only in phase III. The phase III program will evaluate two populations, patients with breast cancer and patients with prostate cancer. The populations to be studied are a subset of adjuvant breast cancer patients with a high-risk of developing bone metastases and androgen-independent prostate cancer patients without radiologically evident metastases. One randomized, placebo-controlled trial in each patient population will be conducted to support registration. These studies (CZOL 0701 and CZOL 0704) are described in detail below.

Dosing considerations

A zoledronate dose of 8 mg monthly has been selected to be utilized in adjuvant registration trials. This selection is based on data from phase I and II studies. The phase I hypercalcemia trial (protocol CJ/HCl) showed a > 90% complete response with a 0.04 mg/kg dose (total dose range of 1.5 to 3.3 mg given intravenously). A complete response was defined as normocalcemia [corrected serum calcium level \leq 10.4 mg/dL (2.6 mmol/L)] obtained in up to 7 days after infusion. Higher doses were not investigated. The phase I bone metastases trial, protocol 035, showed that single doses of zoledronate up to 16 mg were safe and well tolerated. Another phase I trial, protocol 003, investigated a dose range of 0.1 - 8 mg and showed that multiple doses of zoledronate up to 8 mg given every four weeks for two months were safe and well tolerated. Data from protocol 003 indicate a positive dose response, with the greatest inhibition of markers of bone resorption and the greatest lowering of bone pain scores resulting from the 8 mg dose. These data suggest that 8 mg is more efficacious than 4 mg of zoledronate.

Long-term safety is addressed in protocol 007 (a phase II trial of patients with lytic bone metastases in patients with breast cancer and myeloma) in which zoledronate doses of 0.4, 2, and 4 mg are administered monthly for 9 cycles. The 4 mg dose appears to be well tolerated as long-term therapy and is similar in efficacy to 90 mg of Aredia[®]. Bisphosphonates are given on a four-week schedule because the duration of inhibition of markers of bone resorption has been observed to be approximately 3-4 weeks. This also appears to be true for zoledronate.

Additional safety data for the 8 mg dose will be available from the ongoing bone metastases treatment trials (Protocols # 4244603-039, 4244603-010, and 4244603-011) in May 1999 and will be reviewed by SWOG and the NCI before SWOG proceeds with an adjuvant breast trial.

Selection of Serum Bone Sialoprotein as a Prognostic Indicator for Development of Bone Metastases in Early Breast Cancer

Bone sialoprotein (BSP) is a glycoprotein that is important in cell-matrix adhesion and bone mineralization. Made by osteoblasts, osteoclasts, and by tumor cells, this protein may be found in primary breast and prostate cancers (Bellahcene 1994 and 1996; Waltregny 1998). Expression of BSP in the primary breast tumor correlates with the subsequent development of bone metastases (Bellahcene 1996). No correlation has been found between BSP and axillary node status, steroid receptor status, or age (Bellahcene 1996). BSP is elevated in the presence of bone metastases in patients with various primary carcinomas and with multiple myeloma, lymphoma, and malignant melanoma (Siebel 1996 and Withold 1996). In addition the serum BSP is elevated in patients with metabolic bone diseases, such as primary hyperparathyroidism (pHPT) and Paget's disease (Siebel 1996). Bisphosphonate treatment decreases BSP levels in the serum in patients with multiple myeloma (Withold 1996). Postmenopausal women have higher serum BSP levels than premenopausal women (Siebel 1996, Withold 1996).

No significant correlation was found for serum BSP and height, weight, body mass index, lumbar bone mineral density, serum calcium, albumin or creatinine values. The tables below summarize serum BSP data from the literature and its relationship to known markers of bone metabolism. Urinary pyridinoline (U-PYD) and urinary deoxypyridinoline (U-DPD) weakly correlated with serum BSP, while total serum alkaline phosphatase activity did not (Seibel 1996). There was no significant influence of liver or renal dysfunction (Withold 1996).

Serum Bone Sialoprotein Concentrations (Mean +/- SD) Withold 1996

	Any Metastatic Tumor with No Bone Mets (N=56)	Any Metastatic Tumor with Bone Mets (N=22)	Treated Myeloma (N=16)
Serum BSP $\mu\text{g/L}$	22.1 (6.7)	26.9 (9.4)	13.4 (7.5)
Serum Bone Alk Phos $\mu\text{g/L}$	7.7 (3.0)	17.6 (1.7)	2.4 (1.1)
U-DPD $\mu\text{mol/mmol Cr}$	6.6 (3.3)	11.7 (6.3)	5.4 (1.9)

Characteristics of Study Population and Markers of Bone Turnover (Seibel 1996)

	Men (N=75)	Premenopausal Women (N=20)	Postmenopausal Women (N=38)
Age years	59 (20-79)	44 (28-54)	68 (50-80)
Serum BSP ng/mL	9.6 (3.7-27.4)	6.7 (2.6-19.3)	11.9 (5.4-23.5)
Serum Alk Phos U/L	101 (65-311)	88 (51-135)	115 (78-196)
Serum Ca mmol/L	2.38 (2.16-2.62)	2.39 (2.17-2.59)	2.41 (2.25-2.72)
U-PYD *	20.8 (9.9-54.1)	19.6 (8.4-64.1)	28.2 (12.3-63.9)
U-DPD *	5.0 (2.0-11.1)	5.1 (1.9-17.1)	7.2 (3.3-14.6)

Diel reported the prognostic significance of serum BSP in early breast cancer (Stages I - III) patients prior to surgical resection of their primary tumor (Diel 1998). Based upon the 388 patients in this study, a serum BSP ≥ 24 ng/mL will be used as a selection criteria for early breast cancer patients at high-risk of developing bone metastases for the CZOL 701 study. The serum BSP assay methodology from Withold's publication will be used for the CZOL 0701 study. The upper limit of normal for this assay is 12 ng/mL. Validation of this surrogate marker for the risk of the development of bone metastases in the adjuvant breast setting will be performed using a large serum bank. If the CZOL 0701 trial is filed, it is understood that the kit used for serum BSP determinations would need to be registered in tandem under the appropriate national regulations covering medical devices. It is also understood that any potential label from the CZOL 701 trial would be restricted to the trial population.

Serum Bone Sialoprotein Concentrations (Mean) Diel 1998

	Pre-Op Primary Breast Ca, No Distant Metastases (360/388)	Pre-Op Primary Breast Cancer Visceral Mets (9/388)	Pre-Op Primary Breast Cancer now with Bone Mets (19/388)
Serum BSP μ g/L	11.2	10.5	53.1

Breast cancer trials

A pivotal trial will be conducted in a subset of breast cancer patients that are at high-risk for developing bone metastases based upon a surrogate marker, serum bone-sialoprotein (BSP). BSP ≥ 24 ng/mL has been identified (Diel, ASCO 1998) to be an important prognostic indicator in the adjuvant setting for the subsequent development of bone metastases. Validation of bone sialoprotein as a prognostic indicator in the adjuvant setting using a large serum bank will be performed by Novartis. A 200 patient serum bank from Georgetown University in Washington, D.C. and a 400 patient serum bank from the University of Heidelberg, FRG are in the process of being tested. In addition, approximately 100 healthy control sera will also be tested: 50 from premenopausal and 50 from post-menopausal women. If serum BSP cannot be validated as a prognostic indicator of bone metastases, then a node positive trial population will be considered instead by Novartis.

This protocol, 0701, is provided in Appendix 4. The study will accrue 400 patients, stratified by the nodal status (node negative versus node positive) and adjuvant therapy for the breast cancer (chemotherapy versus hormonal therapy versus combination chemotherapy and hormonal therapy) at study entry. An interactive voice response system (IVRS) with institutional balancing will be used for the randomization to balance the treatment assignments within a stratum for the study. The IVRS Project Specification is attached as Appendix 5. Each patient will be treated monthly for two years and followed for two years after therapy is completed. The primary endpoint of the trial is bone metastases-free survival after two years of treatment. It is anticipated that after two years bone metastases will have occurred in 50% of the placebo treated

patients and 37% of the zoledronate-treated patients. The initial filing will be based upon these data. Patients will be followed for two years after treatment is discontinued to assure that there is not a rebound effect (increase in metastases with no net benefit) after stopping zoledronate.

Additionally, an amendment is being prepared for the 0701 trial that will examine the bone mineral density in a subset of patients. The zoledronate and placebo arms will be compared for statistically significant difference in bone mineral density.

Discussions are underway with SWOG for an adjuvant treatment trial (stages I, II, and III disease). Preliminary communications with SWOG indicate that the trial could begin in late September 1999 and would require 3300 patients.

The treatment groups in the breast cancer trials will be zoledronate plus standard anticancer adjuvant therapy (chemotherapy, hormonal therapy or both) versus standard anticancer adjuvant therapy alone. It is anticipated that the zoledronate therapy would continue for two years in all adjuvant breast trials. The high-risk breast population trial that would comprise the initial submission will be placebo-controlled (Diel study), while the SWOG trial would be an open-label design. The primary endpoint of the Diel trial will be that zoledronate treatment improves the bone metastases-free survival of patients compared to standard adjuvant therapy alone. The primary endpoint of the SWOG trial will be disease-free survival.

Prostate cancer

Unlike breast cancer, there is no population of prostate cancer patients for whom adjuvant therapy is recommended. However, standard practice has evolved over the last 5-7 years so that most prostate cancer patients in the US and many prostate cancer patients in Europe and Canada begin androgen deprivation therapy with at least an LHRH agonist when biochemical progression (serum PSA elevation) occurs prior to the development of clinically apparent distant bone metastases. This hormonal therapy induces osteoporosis which can be severe. This osteoporosis can result in a fragile skeleton which has an impaired capacity to withstand bone destruction when clinically apparent bone metastases appear, and is perceived as medically relevant by both the urologic (surgical) and medical oncology communities.

One pivotal trial, 0704, will be conducted in patients with androgen-independent prostate cancer (based upon a rising PSA in the face of androgen ablation). These patients have either local recurrence or early metastatic disease, and do not represent a true adjuvant population. They will not have radiologically evident metastases at study entry. However, 80% of these patients will develop radiologically evident bone metastases within two years (median survival 3-4 years). Bone mineral density and fractures will be followed as secondary endpoints in this trial, as treatment of osteoporosis would be of clinical relevance in this androgen-deprived population. Patients will be treated with zoledronate or matching placebo until the occurrence of bone metastases. In addition to study medication, patients will continue LHRH agonist and receive "standard therapy" for their prostate cancer which may be either chemotherapy (e.g. estramustine-based regimens or mitoxantrone and prednisone) or further hormonal manipulations

(e.g. ketoconazole or aminoglutethimide and prednisone). Patients will be followed until the specified number of events (anticipated to be 412) occur in this 500 patient trial. The 0704 protocol is in preparation and the study synopsis is provided in Appendix 6.

Statistical considerations for 0701 (Adjuvant Breast)

Efficacy evaluation

The primary efficacy variable is bone metastases-free survival at the end of the core phase. The bone metastases-free survival is defined as time to development of bone metastases or death due to any cause and will be compared between the treatment groups using survival analysis methods, including Kaplan-Meier product-limit estimates of the "survival functions" and the stratified log-rank test. If a patient has not developed bone metastases nor died at the analysis time, this variable is censored at the time of last assessment. In the breast cancer population, if a patient received bisphosphonate and/or bone marrow transplant/stem cell rescue, this variable is censored at the time the use and/or the procedure is performed.

For 0701, the most important secondary primary end point is disease-free survival at the end of the core phase. The disease free survival is defined as the time to the death of any cause or recurrent breast cancer or any second primary cancer (aside from non-melanomatous skin cancer, carcinoma in situ of cervix, or lobular carcinoma in situ of the breast). The disease-free survival will be analyzed exactly the same as the primary end point.

Safety evaluation for 0701

Sample size and power considerations for Study 0701

The calculation of sample size is based on the assumption that the study has two years accrual, two years follow-up, a loss to follow-up rate of 0.05/year, and 50% patients will develop bone metastases or die (hazard rate of 0.3466/year) at the end of core (treatment portion of the study) phase in the placebo group. Using the proposed method by Lachin and Foulkes (1986), 366 patients are required (183 patients in each treatment group) to have a power of 80% to detect a 33% reduction in hazard rate of bone metastases or death (hazard ratio 0.6667 for zoledronate versus placebo) with a two-sided 5% level of significance. To allow for the efficiency loss introduced by the intent-to-treat population, it is recommended that 400 patients be randomized for the study.

Assuming a median survival of 3 years (hazard rate of 0.2310) in the placebo group, a sample size of 400 patients will have a power of 50% to detect a 23% reduction in hazard rate of death (hazard ratio 0.7692 for zoledronate versus placebo) with a two-sided 5% level of significance.

Data monitoring board and interim analysis plan for 0701 and 0704

The two Novartis pivotal studies (CZOL 0701 and CZOL 0704), will each have one interim analysis on the primary efficacy variable at the time 50% of the patients have developed bone metastases. The interim analysis will be performed with appropriate procedures to retain the blinding by a Novartis statistician who is not involved in any activities for the zoledronate project. The interim analysis results will be provided only to the designated Novartis personnel (e.g. Head of Oncology Therapeutic Area and Biostatistics) and an

The

If the p-value associated with the bone metastases-free survival is ≤ 0.005 , the decision on terminating the study will be jointly made by _____ and Novartis. This may include consultation with various health authorities. The significance level for the analysis at the end of the core phase will be adjusted to maintain the overall type I significance level at 0.05 level and the nominal two-sided p-values are 0.005 and 0.048 for the interim and the analysis at the end of core phase, respectively.

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Summary of studies and objectives**Registration Studies:**

Trial Code	Abbreviated Title	Treatment & Duration	Objectives
CZOL 446 0701 Dial (N=400)	Placebo-controlled trial in the prevention of bone mets in breast cancer patients at high-risk of developing bone mets based upon serum BSP	8 mg monthly 24 months	1° Improvement in bone metastases-free survival 2° Improvement in disease-free survival 2° Long-term safety in an adjuvant breast population
CZOL 446 0704 (N=500)	Placebo-controlled trial in the prevention of bone mets in prostate cancer patients at high-risk of developing bone mets	8 mg monthly until the development of bone metastases	1° Improvement in bone metastases-free survival 2° Improvement in BMD 2° Long-term safety

Additional Studies

SWOG (N=3300)	An open-label, randomized phase 3 trial in stages I-III breast cancer patients	8 mg monthly 24 months	1° Improvement in disease-free survival 2° Long-term safety in an adjuvant breast population
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APPEARS THIS WAY
ON ORIGINAL

3. Outline of pivotal trials

Protocol number / title:	CZOL 0701 (Diel): A randomized, double-blind, placebo-controlled study on the efficacy and tolerability of zoledronate in the prevention of bone metastases in patients with primary breast cancer and elevated BSP (Bone Sialoprotein) levels
Objective(s):	The primary objective is to determine whether the bone metastases-free survival is improved at the end of the treatment period in patients receiving intravenous zoledronate. Secondary objectives include safety and disease-free survival.
Design:	Prospective, randomized, double-blind, placebo-controlled multi-center study with parallel groups.
Number of Patients	400
Centers / Location	40 centers in Germany; 8 in France and 5 in Sweden
Patient Population:	Female patients with primary breast cancer with a pre-operative serum BSP ≥ 24 ng/ml and no evidence of metastatic disease.
Dosing / treatment plan:	Zoledronate 8 mg or placebo rapid i.v. (5 min) every 4 weeks for 2 years. There will be an additional 2 year follow-up period for a total of at least 4 years in the study.
Efficacy Endpoints:	Primary: bone metastases-free survival Secondary: Disease-free survival. Events include death from any cause, recurrence of breast cancer (locoregional or distant), any new primary cancer (except for carcinoma in situ of the uterine cervix, non-melanomatous skin cancer, or lobular carcinoma in situ of the breast)
Definition of Endpoints:	Bone metastases-free survival is the time to death from any cause or development of bone metastases Disease-free survival is the time to death of any cause, recurrent disease, or any new primary cancer
Safety Monitoring:	Adverse events, laboratory parameters of drug safety
Sample size / basis:	Assuming a 50% bone-metastases free rate at the end of 2 years treatment and a hazard ratio of 0.6667 between zoledronate and placebo, 366 patients is required to achieve 80% power with 0.05 significance level. To allow for the efficiency loss introduced by the intent-to-treat population and spending of the type I error at the interim analysis, it is recommended 400 patients be randomized for the study.
Analyses:	1 interim analysis and 2 other analyses at the end of core phase and the end of study, respectively.
Tests on primary and secondary endpoints:	Primary: stratified log-rank test Secondary: stratified log-rank test
Estimated start and completion dates:	March 1999 to December 2005

Protocol number / title: CZOL 0704 A randomized, double-blind, placebo-controlled study on the efficacy and tolerability of zoledronate in the prevention/delay of bone metastases in patients with biochemically recurrent, androgen-independent prostate cancer. These are asymptomatic patients with a rising PSA and without radiologically detectable bone or visceral metastases.

Objective(s): The primary objective is to determine whether the bone metastases-free survival is improved during the observation period in patients treated with intravenous zoledronate. Secondary objectives include safety and survival.

Design: Prospective, randomized, double-blind, placebo-controlled multi-center study with parallel groups.

Number of patients Centers / Location: 500 total patients
120; North and South America and Europe

Patient Population: Men with androgen-independent prostate cancer as evidenced by a rising PSA and without radiologically detectable bone or visceral metastases.

Treatment plan: 8 mg iv. every 3-4 weeks until patient develop bone metastases

Efficacy Endpoints: Primary: bone metastases-free survival
Secondary: percent change from baseline in BMD

Definition of Endpoints: Bone metastases-free survival is the time to death (cancer related death) or development of bone metastases

Safety Monitoring: Adverse events, laboratory parameters of drug safety

Sample size / basis: Assuming a 20% bone-metastases free rate at the end of 2 study years and a hazard ratio of 0.7142 between zoledronate and placebo, 348 patients is required to achieve 80% power with 0.05 significance level. To allow for the efficiency loss introduced by the intent-to-treat population, the minimum power required for the analysis of overall survival and spending of the type I error at the interim analysis, it is recommended that 500 patients be randomized for the study.

Analyses: 1 interim analysis and 2 other analyses at the end of core phase and the end of study, respectively.

Tests on primary and secondary endpoints: Primary: stratified log-rank test
Secondary: general linear model (t-test)

Estimated start and completion dates: September 1999 to December 2003

K1.2A



K1.2A

N21386



N21386

NDA 21-386

ZOMETA[®]

(zoledronic acid for injection)

Novartis Pharmaceuticals Corporation

Rec'd
5/16/02
9:13 AM

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Vol. 2 of 2

Number of Pages
Redacted 72



Draft Labeling
(not releasable)

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February 15, 2002

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Rockville, Maryland 20857

NDA 21-386

ZOMETA[®] (zoledronic acid for injection)

- Phase IV Commitment



Dear Dr. Pazdur,

Reference is made to our NDA 21-386 submitted on August 21, 2001. Reference is also made to the February 15, 2002 email from Debbie Vause, Project Manager, seeking agreement to two Phase IV Commitments.

We agree to the following Phase IV Commitments with the time frame provided:

1. Conduct a Phase IV pharmacokinetic, safety and efficacy study in patients with renal dysfunction and serum creatinine ≥ 3 mg/dl. The dose of Zometa to be administered should be adjusted to match the AUC 0-24 h 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.

Draft Protocol Submission Date: April 15, 2002
Target Final Submission to FDA: July 30, 2004

2. Conduct a drug-drug interaction study to evaluate the effect of thalidomide on the pharmacokinetics and safety of Zometa in patients with multiple myeloma.

Draft Protocol Submission Date: April 15, 2002
Target Final Submission to FDA: July 30, 2004

If you have any questions concerning this submission, please contact me at (973) 781-7712.

Sincerely,

Handwritten signature of Paula E. Rinaldi.

Paula E. Rinaldi
Director
Drug Regulatory Affairs

per:
cc: Debra Vause/HFD-150

Vause, Debra

From: paula.rinaldi@pharma.novartis.com
Sent: Wednesday, February 20, 2002 3:14 PM
To: vaused@cder.fda.gov
Subject: Novartis suggested changes to 15FEB02 Draft Label

Dear Debbie,

As discussed today, I am providing the following labeling changes suggested by Novartis, to the 15FEB02 Draft Label. Page numbers and line numbers noted, refer to the "changes accepted" copy of the package insert.

Page 6, Table 2 (line 168)
Study 010 treatment duration should be 12 months.
Reason: In this study, patients were dosed for 12 months, and received a final evaluation one month later, at 13 months. The 13th month treatment dose was given after the final evaluation for this study, and is part of the extension arm of the study.
Note in studies 039 and 011, the patient's final assessment was AFTER the last dose was given, at 15 months and 9 month respectively.

Page 8, INDICATIONS AND USAGE, Multiple Myeloma and Bone Metastases of Solid Tumor (line 219)
Suggest adding "patients with" before "documented bone metastases"
Therefore, the first sentence should read: Zometa is indicated for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy.

Page 10, Carcinogenesis, Mutagenesis, Impairment of Fertility, Mutagenesis,
last sentence (line 334).
correct typographical error
genototxic should be genotoxic

Page 12, ADVERSE REACTIONS, second paragraph (line 399).
correct typographical error
pruritis should be pruritus

Please let me know if you need any additional information.

Regards,

Paula E. Rinaldi
Novartis, Regulatory Affairs

Vause, Debra

From: paula.rinaldi@pharma.novartis.com
Sent: Thursday, February 21, 2002 1:31 PM
To: vaused@cdcr.fda.gov
Subject: Zometa Bone Mets - Draft Labeling comment



wssinfo.txt

Dear Debbie,

In follow-up to our telephone conversation today, there is one small change which probably should be made to the package insert:

In the DOSAGE AND ADMINISTRATION section, following the Preparation of Solution sub-section, there is a paragraph on Method of Administration. This paragraph should probably be a sub-section just like Preparation of Solution. Therefore, Method of Administration should be a sub-title, with a hard return, and the sentence starting DUE TO THE RISK (in bold) ... should start on the next line as shown below:

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)

Paula

**APPEARS THIS WAY
ON ORIGINAL**



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

**MEDICAL TEAM LEADER NDA SUMMARY AND
RECOMMENDATIONS**

NDA NUMBER: 21-386

DRUG NAME: Zometa® (zoledronic acid for injection)

**INDICATION: Treatment of Patients with Multiple Myeloma and
Patients with Bone Metastases from Solid Tumors**

APPLICANT: Novartis

MEDICAL TEAM LEADER: Grant Williams, M.D.

Table of Contents

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**APPEARS THIS WAY
ON ORIGINAL**

Introductory Comments:

I agree with the results and analyses documented in the FDA Medical Officer Review for this NDA. Please refer to it for additional details. For the most part, this document duplicates the Executive Summary of that review. In several areas, however, additional medical team leader perspective and discussion are presented.

1 Recommendations

1.1 Recommendation on Approvability

I recommend approval of Zometa® (zoledronic acid for injection, zoledronate) for the following indication:

"the treatment of patients with multiple myeloma and patients with 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 of patients with metastases from solid tumors. In two placebo-controlled clinical studies, both the number of patients with skeletal events and the time to first skeletal event were decreased relative to placebo. In addition, a 1700-patient active control study demonstrated similar efficacy and toxicity of zoledronate compared to pamidronate in patients with bone lesions from multiple myeloma or breast cancer.

Zoledronate, given by the approved dose and schedule (regimen of 4 mg. infused over 15 minutes every three to four weeks) is well tolerated. Risks from zoledronate treatment include a low incidence of renal insufficiency.

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_{0-24h} 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 multiple myeloma and bone metastases from solid tumors. In each of the studies the primary endpoint was the proportion of patients with skeletal-related events (SREs). SRE is an aggregate endpoint consisting of any of the following: 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.

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 Results

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.

**APPEARS THIS WAY
ON ORIGINAL**

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	0.67 (0.49, 0.91)	0.011
	Zol 8mg	38%	-6 (-15, 4)	0.22	363	0.91 (0.68, 1.23)	0.54
	Placebo	44%	---	---	321	---	---
Solid Tumors (011)	Zol 4mg	38%	-7 (-15, 2)	0.13	230	0.73 (0.56, 0.96)	0.023
	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)	0.46	0.92	(0.77, 1.09)	0.32
	Zol 8mg	46%	0 (-6.1, 5.8)	0.96	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 arm failed to demonstrate a statistically significant difference from placebo (Proportions: 38% vs. 44%, respectively, $p = 0.22$. Time to SRE: $p = 0.54$). The proportions analysis and a reviewer exploratory analysis of symptomatic SREs trended in favor of the Zol 8 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.

The study was a well-conducted, well-controlled trial. The findings from Zol 4 versus placebo comparison were quite convincing ($p = 0.021$) and not likely due to chance. The review issues with this study were:

- The unresponsive evidence provided by efficacy analyses of the Zol 8 mg arm versus placebo.
- Prostate Cancer produces predominantly osteoblastic metastases. The only prior evidence that bisphosphonates are effective in metastatic bone lesions is from experience with pamidronate, which is FDA approved for treatment of *osteolytic* metastases of breast cancer and multiple myeloma. A point of discussion for the ODAC was whether zoledronate efficacy demonstrated in predominantly osteolytic metastases [*other solid tumors* (Study 011) and *breast cancer and myeloma* (Study 010)] should be considered supportive of zoledronate efficacy in predominantly osteoblastic metastases of prostate cancer.

As noted above, the FDA review team found no good explanation for the lack of a positive finding in the comparison of Zol 8 to placebo. Patients on the Zol 8 arm remained blinded to treatment so that bias was unlikely. Furthermore, they received as many drug doses and were followed just as closely for SREs as patients on Zol 4 and placebo arms. The explanation that seems most likely to this reviewer is chance. For these NDA studies that had 80% statistical power, we expect a positive finding only four out of five times, and we expect a false negative finding one out of five times. This NDA had three trials, each with two different zoledronate doses, leading to six zoledronate-versus-placebo comparisons. Just based on probability, at least one negative comparison seems quite likely in this setting. An exploratory analysis pooling the results of Zol. 4 mg + Zol. 8 mg also supported the efficacy of zoledronate in this trial.

The second issue was whether zoledronate efficacy demonstrated in osteolytic bone metastases should be considered supportive of a prostate cancer treatment indication. This issue was discussed at length before ODAC. A persuasive argument was that osteoclast activation appears to be an important underlying mechanism for causing bone destruction and hence bone morbidity from both osteolytic and osteoblastic metastases. Zoledronate suppresses laboratory markers of bone resorption in patients with osteoblastic as well as in osteolytic disease

ODAC voted (Y-11, N-0) that evidence of zoledronate efficacy in patients with lytic metastases should be considered supportive of zoledronate efficacy in prostate cancer. ODAC then voted (Y-10, N-1) that the NDA trials collectively represent substantial evidence of Zometa (4 mg) efficacy in prostate cancer. I concur with these findings.

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 mg (Zol 8), 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 proportion of patients with an SRE was lower on Zol 4 than placebo, but the difference was not statistically significant (38% versus 44%, respectively, $p = 0.13$). The comparison of the Zol 8 to placebo showed a significant difference (35% versus 44% respectively, $p = 0.023$). Time to first SRE was 67 days longer for Zol 4 than placebo (230 days versus 163 days respectively, $p = 0.023$) and was also significantly longer for Zol 8. For the Zol 4 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 Zol 4 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 demonstrates convincingly that zoledronate 4 mg provides clinical benefit to the overall population studied. Although the Zol 4 improvement in the primary endpoint (proportions of patients with an SRE) was not statistically significant, improvement in the FDA-preferred secondary endpoint (time to first SRE) was. From the Zol 8 versus placebo comparison, both the primary and secondary SRE analyses were statistically significant, and were supportive.

Study 011 had limited statistical power to examine efficacy in subgroups of individual tumor types. An important review issue was whether results from Study 011 can be extrapolated to all solid tumors, e.g., whether zoledronate approval should extend to bone metastases of all solid tumors. Several findings support such a broad approval:

- The positive efficacy findings for both zoledronate arms of this study compared to placebo suggest that the underlying premise of Study 011 is true, that zoledronate has a beneficial effect on bone metastases from many different types of primary tumors.
- Strong trends are noted both in the lung cancer subgroups and in non-lung cancer subgroup of this study.
- Evidence of zoledronate activity from other NDA trials (010 and 039) in both blastic and lytic metastases provide additional support.

The ODAC voted (Y-11, N-0) that zoledronate should be indicated for patients with bone metastases from all solid tumors irrespective of the primary tumor. For the reasons noted above, I concur with this recommendation.

Myeloma and Breast Cancer

Study 010 was an international, multicenter, stratified, double-blind, study that randomized patients 1:1:1 to zoledronate 4 mg (Zol 4), zoledronate 8mg (Zol 8), 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 outlined 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 medical officer review, each of these differences was carefully examined, and none of them appeared to violate the constancy assumption. The FDA review team believes these data represent substantial evidence of efficacy of zoledronate in patients with multiple myeloma and patients with bone metastases from breast cancer. The ODAC agreed, voting 11-0 that they do.

Efficacy Conclusions

When viewed separately, each of the three randomized double-blind clinical trials can be criticized:

- In Study 039 (prostate cancer), efficacy analyses of the 8 mg zoledronate arm were not statistically positive.
- In Study 011 (solid tumors), the analysis of proportions of patients with SRE was not statistically positive. Also, the study did not have statistical power to evaluate efficacy in each tumor type.
- In Study 010 (myeloma and breast cancer), the study population was not identical to the historic population where the active control (pamidronate) was studied.

However, when one views the results in tables 1 and 2 of this review, one finds compelling evidence of zoledronate efficacy in patients with bone metastases in all tumors that commonly metastasize to bone. These efficacy results are mutually supportive and provide substantial evidence of efficacy for the proposed indication.

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 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. Pharmacokinetics 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.