World-Wide Regulatory Status

Zoledronate is not approved for any indication in any country.

Sponsor's Summary of Preclinical Pharmacology/Toxicology (see Dr. Kuijpers review)

Effects on bone metabolism in vitro

In cultures of murine calvarian bones stimulated with a variety of naturally occurring agents, zoledronate inhibits calcium release (IC50 2-7 nM) and is 100 times more potent than pamidronate. By the addition of calcium glycerophosphate to murine calvaria cultures, bone mineralization can be stimulated. In this system, all the bisphosphonates tested inhibited calcium incorporation with IC50 values of 10-30 uM. The ratios of IC50 values for the inhibition of calcium incorporation versus calcium release in vitro differ widely between compounds, with zoledronate having the highest value. This wide dissociation indicates that zoledronate can inhibit bone resorption in vitro without affecting bone mineralization.

Inhibition of hypercalcemia in the thyroparathyroidectomized (TPTX) rat

In the TPTX rat with hypercalcemia induced by vitamin D, zoledronate dose-dependently inhibits the acute hypercalcemia, achieving 100% efficacy at a dose of approx. 1.5 ug/kg sc With an ED50 of 72 ng/kg sc, zoledronate in 850 times more active than pamidronate, and more than 4 orders of magnitude more potent then either clodronate or etidronate. As with all other bisphosphonates, the oral bioavailability of zoledronate is very low and could not be increased by inclusion of the compound in beta-cyclodextrin complexes.

Although PTHrP, rather than vitamin D, is thought to be central to the pathogenesis of TIH, this rat Assay models the human disease in that the downstream events of elevated osteoclastic bone resorption and hypercalcemia are common to both. It could be argued that the observed hypocalcemic effect is due to effects on calcium metabolism in the gut or kidney rather than to direct inhibition of osteoclastic bone resorption. However, the close correlation between the inhibitory potency of a range of bisphosphonates in murine calvarian bone cultures in vitro and their inhibitory potency in hypercalcemic rats in vivo is evidence of the contrary.

Anti-tumor effects in vitro

In addition to inhibiting osteoclastic bone resorption, zoledronate also exerts direct effects on human tumor cells and on key steps in the metastatic process in vivo. Treatment of human myeloma cell lines, or primary myeloma cells from patients, with zoledronate (1-500 uM) rapidly induces apoptosis and inhibits cell proliferation in a time- and dose-dependent manner. Zoledronate exerts similar anti-tumor effects on the human epithelial carcinoma cell line, A431 and on human breast cancer cell lines.

Single dose toxicity

In rats a single intravenous injection of 1.6 mg/kg (twice the highest human dose on the basis of m2 body surface area) was well tolerated with no mortality, the only clinical sign being local irritation at the injection site.

Effect on the kidney

As per Dr. Kuijpers: Since renal toxicity is a clinical safety concern upon short term infusion of bisphosphonates, the renal findings in the single dose rat iv study are discussed in some more detail. In the acute iv rat study kidneys of one 0.6 mg/kg and five 6 mg/kg males were examined microscopically. One of the five 6 mg/kg animals died on Day 6 after dosing. The kidneys of this animal and of 3 other animals in this dose group showed renal changes of minimal to slight severity, consisting of tubular regeneration, dilation (in the cortex) and desquamation (in outer medulla), and of inflammation and/or fibrosis of the interstitium mainly in the inner stripe of the outer medulla. In the fifth male, kidneys were enlarged, pale and soft, and showed marked tubular and interstitial lesions that were similar to but much more severe than the lesions seen in the other animals in this group. In this animal there were also granulocytic casts in tubules of the outer medulla and in collecting ducts. The tubular lesions may be explained by the high renal clearance of the compound leading to the build up of large concentrations in the renal tubule.
The doses of 0.6 and 6 mg/kg in the rat give exposures of 3.5x and 35x the human exposure dose.

Repeat dose toxicity

In the repeat-dose parenteral studies of up to 1 year in rats (0.001-2 mg/kg, sc and 0.06-6 mg/kg iv) and dogs (0.005-1 mg/kg iv) zoledronate caused dose-dependent alterations in bone and soft tissues that were not unexpected. The rationale for applying the sc route in the rat studies was the consideration of the possible development of a transdermal therapeutic system with the test compound and the fact that intravenous administration was not feasible given the propensity of zoledronate to cause severe local skin and perivenous irritation. Upon profiling plasma AUC of total radioactivity or parent compound after iv and sc dosing, recent evidence indicates that sc administrated zoledronate is fully bioavailable in the rat model.

Effect on the bone

The most frequent and reproducible finding in toxicity studies consisted of increased primary spongiosa in the metaphyses of long bones in growing animals at nearly all doses, a finding that reflected the compound's pharmacological antiresorptive activity. Morphometric studies on bone from rats administered up to 0.01 mg/kg/day of zoledronate for 12 months and on bone from monkeys given doses up to 12.5 ug/kg/week sc for 16 months have shown that the compound does not produce any deleterious effects (e.g. mineralization defects). Biomechanical data from the 6/12-month iv dog study indicated improved bone quality. In this study there was a significant increase in density and improvement of the mechanical properties of trabecular bone after treatment for 6 months, particularly at 0.03 mg/kg. Similar effects were seen in whole vertebrae after 12 months of treatment as well as a possible improvement in some of the mechanical properties of cortical bone. The bone changes in the toxicology studies were still present after an appropriate recovery period.

Effect on the kidney

Zoledronate is concentrated and excreted via the kidney and as with bisphosphonates in general, there is the potential for zoledronate to produce renal injury. The ability of zoledronate and pamidronate to produce renal toxicity was compared in two short-term rat studies. At doses of 1.5 to 50 mg/kg, the ED100 value for zoledronate was 3.8 fold higher than that of pamidronate indicating a greater therapeutic range for zoledronate. Nevertheless, instances of renal tubular necrosis/regeneration and inflammation associated with altered clinical laboratory values occurred in both the rat and dog. As renal toxicity is always a concern, the following table provides the NOAELs for renal effects obtained in the critical iv animal toxicity studies. Results are expressed as multiples of the highest intended human dose of 8 mg.

SPECIES	NOAEL (MG/KG)	MULTIPLES OF 8 MG HUMAN DOSE•
Rat	1.6 (single dose)	2x
Rat	0.6 (6 doses total)	1x
Dog	2.0 (single dose)	8x
Dog	1.0 (daily x 10 days)	4x
Dog	0.2 (daily x 1 month	1x
Dog	0.01 (daily x 3 months)	0.04x
Dog	0.005 (every third day x 1 year)	0.02x

•based on body surface area for a 60 kg adult

Although the safety margins appear narrow in the longer term repeat-dose rat and dog studies when using this conservative method of comparison, the relevant single dose and subchronic studies in these species did not indicate renal effects at doses equivalent to or exceeding the highest intented human dose. Furthermore, the shorter term studies better reflect the clinical regimen since zoledronate will be administered to patients as a single dose of 4 c for the treatment of TIH or every three to four weeks for bone metastases.

Effect on other organ systems

At higher doses zoledronate produces toxicologically-significant irritant effects in other organs including the GI tract, liver, spleen, lungs and at iv injection sites. These included, but were not limited to: inflammation, hemorrhage and erosions in the GI tract; hepatocellular necrosis as well as hemorrhage and inflammation; inflammatory lesions in the lung; splenic inflammation and hemorrhage; and severe local skin inflammation at injection sites, particularly in the iv studies. In addition to altered renal parameters, the most common clinical pathology findings consisted of hypocalcemia and electrolyte imbalances, decreased (bone) alkaline phosphatase activity and increased ALT and AST (liver and bone).

Whereas direct GI tract mucosal irritation would be expected following oral administration of zoledronate, it is noteworthy that these effects were also seen after the parenteral route. Thus it is possible that iv administration produces a surge of locally high, transient compound concentrations in well-vascularized organs such as liver, kidney, spleen, lung, and GI tract. Other local factors may also be involved. For example, gastric intolerance may also be due to altered gastric secretion owing to reductions in plasma calcium and exacerbated by electrolyte imbalances. Interference with calcium-dependent processes in tissue mast cells that commonly reside in the GI and respiratory tracts and in the interstitial tissue of the liver may also incite inflammatory processes. Lastly, factors which may exacerbate the compound's effects in specific organs include a slightly longer retention time in kidney, liver, and spleen as well as the fact that the caustic properties of zoledronate are not ameliorated via metabolism. These soft tissue findings were largely or entirely reversible after an appropriate recovery period.

Sponsor's and Dr. Robert Shore's Summaries of Human Pharmacokinetcs and Pharmacodynamics
(See Dr. Robert Shore's review)

The pharmacokinetics (PK) and pharmacodynamics (PD) of zoledronate were studied in two separate clinical trials – 503 and J001 – in 32 cancer patients with bone metastases receiving a single dose of zoledronate in the range of 2-16 mg. Serial blood samples and quantitative urine collections were obtained up to 48 hours post dose, with spot samples obtained on days 8, 15, and 29 post dose.

Plasma concentrations of zoledronate were highest at the end of the infusion period, and showed a multiphasic decline to < 10% of peak after 4 hours and < 1% of peak after 24 hours post dose. The rapid, > 100-fold decrease in plasma concentrations was followed by a prolonged, gradual decline to concentrations < 0.1% of peak at day 29 post dose.

The pattern of early rapid decline in concentration, followed by a period of sustained, low drug concentrations, is typical of bisphosphonates. It is thought to result from rapid drug clearance by the kidney and bone, whereas, the return of drug to the systemic circulation, which results in the prolonged terminal elimination phase, is governed by the slow process of bone remodeling.

Mass balance and distribution studies of zoledronate in animals show that < 3% of an intravenous dose is found in the feces, that the drug is eliminated almost exclusively via the kidney into the urine, and that the large majority of drug not eliminated into the urine within a given collection period is located in bone. In the two human PK studies, there was an initial rapid, then very slow rate of the urinary excretion of zoledronate, paralleling the plasma concentration profile. The cumulative 0-24 hour urinary excretion of the drug was 48% —— range) and 42% —— range) in the two studies, reflecting consistency in the average PK results despite considerable interpatient variability. The urinary excretion data suggest that on average greater than half of the administered dose of zoledronate is taken up by bone. According to Dr. Shore, about 30-50% of a given zoledronate dose remains in the body for an extended period of time, probably in the bone.

The renal clearance assessed from the ratio of 0-24 hour urinary excretion/AUC was 4.0 L/h. The renal clearance and the urinary excretion of zoledronate were independent of dose in the range studied, 2 mg and 16 mg.

Zoledronate concentrations at the end of infusion, and the area under the plasma concentration vs. time curve (AUC) were dose proportional. Increasing the infusion period from 5 minutes to 15 minutes had no statistically significant effect on the drug exposure (AUC concentration vs. time curve), but expectedly lowered the zoledronate concentration at the end of infusion by about 30%.

Of note, Dr. Shore has highlighted that fact that the AUC for a 15-minute infusion of 4 mg of zoledronate is about 70% higher than when the same dose of drug is infused over 5 minutes.

From a population PK analysis of 32 patients indicates that the various half-lives of zoledronate are alpha: 0.23; beta: 1.75; and gamma: 167. These estimates pertain to a 70-kg adult with a creatinine clearance of 83 ml/min. As per Dr. Shore's review, it can be concluded that body weight is a covariate for central volume distribution, individual creatinine clearance is a covariate for total plasma clearance, and total plasma clearance is not affected by body weight, body mass index, age, gender, or race.

Additional analysis of the population PK data suggest that the plasma clearance of zoledronate in a patient with moderate renal impairment, creatinine clearance 30 ml/min, is projected to be about 3.5 fold lower than in a patient with normal renal function, creatinine clearance 120 ml/min. Of note, of the 32 patients from which PK were derived, the range of creatinine clearance was —— ml/min.

Conclusions:

- Over a 4-week period post dose, zoledronate shows a tri-phasic plasma concentration profile with population half lives t½alpha = 0.23 h; t½beta = 1.75 h; and t½gamma = 167 h.
- Renal clearance is the principal route of elimination.
- A total of 44% of a dose is excreted in the urine within 24 hours (with the remained slowly released from the bone).
- PK profile is dose proportional.
- Reduced creatinine clearance is associated with a decrease in zoledronate plasma clearance and an increase in systemic exposure.
- Zoledronate has low protein binding in the plasma.
- There is no hepatic clearance of zoledronate.

Clinical Data Source

Two clinical studies were conducted in support of approval of zoledronate in the treatment of TIH. Review of these studies follows.

Study 036

This study was conducted in 40 centers (12 in Australia, 3 in Belgium, 8 in Germany, 7 in France, 4 in the UK, 1 in Hungary, 3 in Italy, and 2 in Sweden) from December 1997 through October 1999.

Title: A randomized, double-blind study of two doses of zoledronate and Aredia 90 mg in the treatment of tumor-induced hypercalcemia.

Primary Objectives: To assess the efficacy and safety of 4mg and 8mg IV of zoledronate in the treatment of TIH and to compare the efficacy of both doses of zoledronate to 90mg IV of pamidronate.

Secondary Objectives: To assess: 1) the time to relapse of TIH; 2) the duration of response; 3) the change from baseline in corrected serum calcium at Day 10; 4) the percentage of patients with refractory TIH; and 5) the effectiveness of zoledronate 8mg as retreatment for patients whose TIH either relapsed during the course of this trial or was refractory to initial zoledronate/pamidronate treatment.

Study Design: This was a two-stage, multicenter, randomized, double-blind, double-dummy, parallel, dose-finding trial of zoledronate treatment for patients with TIH. In stage 1, patients were initially treated with either zoledronate or pamidronate. In stage 2, patients with TIH that was refractory to or had relapsed after initial treatment were retreated with 8mg of zoledronate, regardless of the drug and dose received in stage 1.

In stage 1, eligible patients were randomized to receive a single IV dose of zoledronate 4mg or 8mg, or pamidronate 90mg. If treatment resulted in a complete response (corrected serum calcium < 10.8 mg/dl), the patient was followed for eight weeks in stage 1 of the trial (to day 56) or until the patient's corrected serum calcium rose to a level $\geq$ 2.90 mmol/L (11.6 mg/dl), whichever occurred first. Patients in whom trial therapy had not achieved a complete response by day 10, but whose corrected serum calcium (CSC) concentration was < 11.6 mg/dl on day 10, continued to be followed in stage 1 of the trial to day 56 or until the patient's CSC rose to a level $\geq$ 11.6 mg/dl, whichever occurred first.

In stage 2, patients received retreatment with 8mg IV zoledronate if their TIH was refractory to initial zoledronate/pamidronate treatment, or if following the achievement of a complete a relapse of TIH to a CSC of $\geq$ 11.6 mg/dl occurred by day 56. If zoledronate retreatment resulted in a complete response, the patient was followed in stage 2 of the trial until relapse or for four weeks after retreatment, whichever occurred first. If a complete response was not achieved by day 10 or stage 2, the patient was discontinued from the trial.

To accommodate out-patient treatment, drugs were administered simultaneously with IV hydration (500 ml over 4 hours; see Drug Administration below). The administration of additional IV fluids following the completion of the required infusions designated by the protocol was at the discretion of the treating physician. To minimize the potential risk of nephrotoxicity due to the use of IV bisphosphonates in the presence of severe dehydration, patients presenting with severe volume depletion were to be initially excluded from the trial. However, these patients were eligible for the study if their CSC level remained $\geq$ 12.0 mg/dL after correction of volume depletion with IV fluids.

Drug Administration: Each IV dose of zoledronate was administered with 50 ml of 0.9% saline over 5 minutes. Patients randomized to pamidronate also received a matching placebo infusion of 50 ml of normal saline. Each IV dose of pamidronate was administered with 10 ml of sterile water and 240 ml of 0.9% saline over 2 hours. Patients randomized to zoledronate received a matching placebo infusion of 250 ml of normal saline.

Concomitant Medication: Standard antineoplastic therapies including marketed cytotoxic chemotherapy agents, hormonal agents, steroids, and biologic response modifier agents were permitted. Antineoplastic therapy was not to be changed within 7 days before and 10 days after Visit 1. Standard marketed cytokine/colony stimulating factor agents were also permitted. Marketed drugs/therapies except other bisphosphonates, calcitonin, gallium nitrate, mithramycin, thiazide diuretics, lithium, and vitamin D therapy were also allowed. Loop diuretics were not to be utilized in this trial from days 1 through 10, except when necessary to treat fluid overload secondary to the intravenous hydration therapy for hypercalcemia resulting in left ventricular cardiac failure.

Patient Population: A total of 144 subjects were randomized into this study. All patients had to be at least 18 years of age, have a histologically or cytologically confirmed diagnosis of cancer, and have a CSC $\geq$ 12.0 mg/dl. Participants were excluded for any of the following reasons:

- Received treatment with a bisphosphonate within 90 days prior to visit 1.
- Received treatment with calcitonin with 72 hours prior to visit 1.
- Received treatment with mithramycin within 14 days prior to visit 1.
- Received treatment gallium nitrate within 14 days prior to visit 1.
- Serum creatinine > 4.5 mg/dl.
- Unable to tolerate IV fluids (i.e., congestive heart failure).
- Presented with severe hydration.

Endpoints: The primary efficacy endpoint was the proportion of patients having a complete response defined as a lowering of CSC to $\leq$ 10.8 mg/dl by day 10. Secondary endpoints included:

- Duration of complete response, defined as days between occurrence of complete response and last CSC $\leq$ 10.8 mg/dl.
- Mean change in CSC level from baseline to Day 10.
- Proportion of patients with refractory TIH. Refractory TIH was defined as absence of lowering of CSC from baseline by $\geq$ 0.2 mg/dl by Day 4 or by $\geq$ 1.0 mg/dl by Day 7 or failure to achieve CSC < 11.6 mg/dl by Day 10. Further, patients without post-baseline CSC were considered refractory (e.g., patients who discontinued due to death without a post-baseline measurement). Patients who achieved a complete or partial response before Day 10 were not considered as refractory even if they became hypercalcemic again by Day 10.

Safety endpoints included regular assessment of adverse events, physical examination, vital signs, and standard laboratory tests including chemistry, hematology, and urinalysis. During stage 1, corrected serum calcium levels were determined on Days 1, 4, 7, 10, 14, 17, 21, 24, 28, 35, 42, 49, and 56. During stage 2, corrected serum calcium levels were determined on Days 1, 4, 7, 10, 14, 21, and 28. Serum PTH and PTHrP were measured at baseline.

Statistical Analyses (see statistical review by Dr. Choudhury for a detailed critique of statistical analyses): For stage 1 of the trial the sponsor has defined two patient populations: 1) per protocol – all randomized patients who received the IV infusion at baseline and satisfied the admission criteria for TIH; and 2) intent-to-treat (ITT) – all randomized patients who received the IV infusion at baseline of stage 1 of the trial. The per protocol population was designated as the primary data set for all efficacy analyses. For the analysis of safety, all randomized patients who received study drug were considered.

For stage 2, the per protocol population consisted of patients who received the IV infusion of zoledronate 8mg and whose CSC in stage 2 was $\geq$ 11.0 mg/dl. The intent-to-treat population included all patients who received the IV infusion of zoledronate at stage 2 baseline.

For the primary efficacy analysis, a dose of drug was considered efficacious if the lower bound of the 95% confidence interval (CI) for the proportion of patients who achieved a complete response by Day 10 was > 70%.

An ANCOVA model with baseline CSC as a covariate and treatment-by-baseline CSC as an interaction term was used to compare between treatment group changes in CSC from baseline to Day 10.

Results

Patient Disposition: A total of 149 patients were randomized to three treatment arms: 46 to Zol 4mg, 51 to Zol 8mg, and 52 to Pam 90mg. Approximately 90% of the subjects in the two Zol groups completed stage 1 (completed the Day 56 visit or had a complete response to treatment) compared with 75% of the Pam subjects. The most common reasons for discontinuation were death (3 Zol 4mg, 4 Zol 8mg, and 3 Pam 90mg) and unsatisfactory therapeutic effect (1 Zol 4mg, 1 Zol 8mg, and 9 Pam 90mg).

Reviewer Comment: The vast majority of patients (~70%) considered completers of Stage 1 were so deemed because they had satisfactory reductions in their serum calcium levels by Day 10. Most did not complete the Day 56 visit.

See ISE for additional details of disposition.

Protocol Violations: Of greatest concern to the primary efficacy analysis, 3 Zol 8mg patients and 2 Pam 90mg patients had CSC levels at baseline that were less than 12.0 mg/dl. These 5 subjects were excluded from the per protocol population. Also of interest, a total of 31 patients received a loop diuretic during days 1-10 on study. These subjects were not excluded from the per protocol analysis. This issue is discussed further below in the Concomitant Medications section.

Baseline Demographics: The following table provides the baseline demographic characteristics for subjects in the three treatment groups.

BASELINE DEMOGRAPHICS			
	Zol 4mg	Zol 8mg	Pam 90mg
	N=46	N=51	N=52
Age (range) (yrs)	61	59	59
% Female	57%	45%	48%
% Caucasian	100%	94%	94%
% Black	0%	2%	2%
Baseline CSC (mg/dl)	14.00	13.57	14.03
% with Breast Cancer	33%	26%	25%
% with Lung Cancer	20%	26%	19%
% with Renal Cancer	13%	12%	17%
% with Multiple Myeloma	9%	2%	8%
% with Bone Metastases	65%	60%	54%
Serum PTHrP			
% ≤ 2 pmol/L	65%	67%	60%
% > 2 pmol/L	26%	29%	31%
Mean (pmol/L)	1.57	1.74	2.15
Median Time from Cancer Diagnosis (months)	9.0	14.2	8.3

The groups were fairly well matched for important baseline characteristics such as age, gender, mean CSC level, mean PTHrP level, and time from cancer diagnosis, with no statistically significant differences among groups.

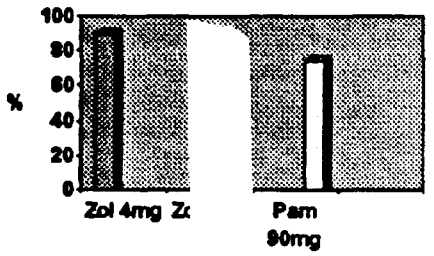
Concomitant Medications: In general, the three groups had similar patterns of use of concomitant medications during stage 1. As IV hydration (0.9% saline) can facilitate calcium excretion in the urine, it is important to note that the three groups received similar amounts of IV hydration during Days 1-10. Similarly, loop diuretics promote calcium loss in the urine and of note, 31 patients (8 in Zol 4mg, 11 in Zol 8mg, and 12 in Pam 90mg) received loop diuretics during Days 1-10.

Reviewer Questions: For each treatment group, what were the mean and median cumulative doses of loop diuretics received during days 1-10? And, do the results of the primary efficacy analysis differ significantly when these subjects are removed from the analysis. In response, the sponsor claims that information on dosage of loop diuretics was not recorded. However, when one compared the complete response rates between those patients who received diuretics to those that did not, the results were similar.

Primary Efficacy Outcome (per protocol population)

Complete Response Rates (serum CSC < 10.8 mg/dl by Day10): As shown in the figure below, the complete response rates for the Zol 4mg, Zol 8mg, and Pam 90mg were 89% (95% CI 80%, 98%), 90% (81%, 98%), and 74% (62%, 86%). Both doses of zoledronate were deemed efficacious because the lower bound of the 95% confidence interval for both doses was greater than 70% - the predefined criteria of efficacy. The 90-mg dose of pamidronate was deemed non-efficacious because the lower bound of the confidence interval for this dose was lower than 70%. Results were similar for the ITT population.

Complete Response at Day 10



APPEARS THIS WAY
ON ORIGINAL

Although this study was not powered to detect a statistically significant difference in complete response rates between the zoledronate and pamidronate doses, the comparison of response rates between the 4mg dose of zoledronate and the 90 mg dose of pamidronate was of borderline statistical significance (p=0.06).

As expected, irrespective of treatment group, the proportion of complete responders was lower for patients with levels of PTHrP greater than 2 pmol/L at baseline (77%) compared with those with PTHrP levels less than 2 pmol/L (89%).

Secondary Efficacy Outcomes (per protocol population)

Duration of Response: For those subjects who met the criteria for complete response, the median number of days from complete response to last CSC $\leq$ 10.8 mg/dl were "not reached," 43 days, and 22 days for the Zol 4mg, Zol 8mg, and Pam 90mg, respectively.

Change in CSC Levels from Baseline to Day 10: The mean reductions in CSC levels in the two zoledronate doses were –4.20 mg/dl and –4.24 mg/dl (4mg and 8mg) and –3.52 mg/dl for the pamidronate 90mg group. The differences between the zoledronate groups and the pamidronate group were significant at p<0.02.

APPEARS THIS WAY

Proportion of Patients with Refractory TIH: Whereas 6 subjects in the pamidronate group had refractory TIH, only one Zol 8mg subject and no Zol 4mg patients satisfied the criteria for refractory TIH. Of note, the one patient in the Zol 8mg group with refractory TIH was classified as so because of early death.

Retreatment of Relapsed or Refractory TIH (Stage 2): A total of 34 patients received a second dose of drug (zoledronate 8mg) during stage 2 of the study. The majority of these subjects (n=19) were originally treated with pamidronate, while 10 had received Zol 4mg and 5 Zol 8mg. Twenty-three of the 34 patients had a complete response in stage 1 and were retreated for relapsed hypercalcemia. Of the remaining subjects, 4 had refractory TIH, 6 had partial responses during stage 1, and 1 subject was unclassified.

At Day 10 of stage 2, 55.9% of the patients had a complete response following an 8mg dose of zoledronate. The mean change in CSC from baseline to Day 10 was -1.88 mg/dl. For the patients with a complete response, the median number of days to relapse was 13. Results were similar for the ITT analyses.

Safety Review

Because protocols 036 and 037 are identical in design, a review of zoledronate's safety profile from this trial will be discussed in the pooled analysis of 036 + 037 data in the Integrated Summary of Safety.

Sponsor's Conclusions

Zoledronate in single intravenous doses of 4 mg or 8 mg given as a 5 minute infusion, is highly effective in the initial treatment of tumor-induced hypercalcemia. Both doses of zoledronate were equally effective, and both appeared to be more effective than Aredia 90 mg, although the trial was not powered for between-group comparisons. Zoledronate 4 mg is the recommended dose for initial treatment of TIH.

[ ] Zoledronate is safe and well-tolerated at doses of 4 mg and given as a 5-minute intravenous infusion in patients with tumor-induced hypercalcemia. The overall safety profile of zoledronate 4 mg o was similar to that of Aredia 90 mg.

Study 037

This study was conducted in a total of 34 centers in the United States and Canada. The first patient was enrolled on January 7, 1998 and the last patient visit was October 4, 1999.

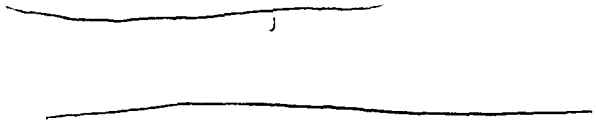
Title: A randomized, double-blind study of two doses of zoledronate and Aredia 90 mg in the treatment of tumor-induced hypercalcemia.

Primary Objectives: To assess the efficacy and safety of 4mg and 8mg IV of zoledronate in the treatment of TIH and to compare the efficacy of both doses of zoledronate to 90mg IV of pamidronate.

Secondary Objectives: To assess: 1) the time to relapse of TIH; 2) the duration of response; 3) the change from baseline in corrected serum calcium at Day 10; 4) the percentage of patients with refractory TIH; and 5) the effectiveness of zoledronate 8mg as retreatment for patients whose TIH either relapsed during the course of this trial or was refractory to initial zoledronate/pamidronate treatment.

Design: This was a two-stage, multicenter, randomized, double-blind, double-dummy, parallel, dose-finding trial of zoledronate treatment for patients with TIH. In stage 1, patients were initially treated with either zoledronate or pamidronate. In stage 2, patients with TIH that was refractory to or had relapsed after initial treatment were retreated with 8mg of zoledronate, regardless of the drug and dose received in stage 1.

In stage 1, eligible patients were randomized to receive a single IV dose of zoledronate 4mg or 8mg, or pamidronate 90mg. If treatment resulted in a complete response (corrected serum calcium < 10.8 mg/dl), the patient was followed for eight weeks in stage 1 of the trial (to day 56) or until the patient's corrected serum calcium rose to a level ≥ 2.90 mmol/L (11.6 mg/dl), whichever occurred first. Patients in whom trial therapy had not achieved a complete response by day 10, but whose corrected serum calcium (CSC) concentration was < 11.6 mg/dl on day 10, continued to be followed in stage 1 of the trial to day 56 or until the patient's CSC rose to a level ≥ 11.6 mg/dl, whichever occurred first.



To accommodate out-patient treatment, drugs were administered simultaneously with IV hydration (500 ml over 4 hours; see Drug Administration below). The administration of additional IV fluids following the completion of the required infusions designated by the protocol was at the discretion of the treating physician. To minimize the potential risk of nephrotoxicity due to the use of IV bisphosphonates in the presence of severe dehydration, patients presenting with severe volume depletion were to be initially excluded from the trial. However, these patients were eligible for the study if their CSC level remained ≥ 12.0 mg/dL after correction of volume depletion with IV fluids.

Drug Administration: Each IV dose of zoledronate was administered with 50 ml of 0.9% saline over 5 minutes. Patients randomized to pamidronate also received a matching placebo infusion of 50 ml of normal saline. Each IV dose of pamidronate was administered with 10 ml of sterile water and 240 ml of 0.9% saline over 2 hours. Patients randomized to zoledronate received a matching placebo infusion of 250 ml of normal saline.

Concomitant Medication: Standard antineoplastic therapies including marketed cytotoxic chemotherapy agents, hormonal agents, steroids, and biologic response modifier agents were permitted. Antineoplastic therapy was not to be changed within 7 days before and 10 days after Visit 1. Standard marketed cytokine/colony stimulating factor agents were also permitted. Marketed drugs/therapies except other bisphosphonates, calcitonin, gallium nitrate, mithramycin, thiazide diuretics, lithium, and vitamin D

therapy were also allowed. Loop diuretics were not to be utilized in this trial from days 1 through 10, except when necessary to treat fluid overload secondary to the intravenous hydration therapy for hypercalcemia resulting in left ventricular cardiac failure.

Patient Population: A total of 144 subjects were randomized into this study. All patients had to be at least 18 years of age, have a histologically or cytologically confirmed diagnosis of cancer, and have a CSC ≥ 12.0 mg/dl. Participants were excluded for any of the following reasons:

- Received treatment with a bisphosphonate within 90 days prior to visit 1.
- Received treatment with calcitonin with 72 hours prior to visit 1.
- Received treatment with mithramycin within 14 days prior to visit 1.
- Received treatment gallium nitrate within 14 days prior to visit 1.
- Serum creatinine > 4.5 mg/dl.
- Unable to tolerate IV fluids (i.e., congestive heart failure).
- Presented with severe hydration.

Endpoints: The primary efficacy endpoint was the proportion of patients having a complete response defined as a lowering of C$C to ≤ 10.8 mg/dl by day 10. Secondary endpoints included:

- Duration of complete response, defined as days between occurrence of complete response and last CSC ≤ 10.8 mg/dl.
- Mean change in CSC level from baseline to Day 10.
- Proportion of patients with refractory TIH. Refractory TIH was defined as absence of lowering of CSC from baseline by ≥ 0.2 mg/dl by Day 4 or by ≥ 1.0 mg/dl by Day 7 or failure to achieve CSC < 11.6 mg/dl by Day 10. Further, patients without post-baseline CSC were considered refractory (e.g., patients who discontinued due to death without a post-baseline measurement). Patients who achieved a complete or partial response before Day 10 were not considered as refractory even if they became hypercalcemic again by Day 10.

Safety endpoints included regular assessment of adverse events, physical examination, vital signs, and standard laboratory tests including chemistry, hematology, and urinalysis. During stage 1, corrected serum calcium levels were determined on Days 1, 4, 7, 10, 14, 17, 21, 24, 28, 35, 42, 49, and 56. During stage 2, corrected serum calcium levels were determined on Days 1, 4, 7, 10, 14, 21, and 28. Serum PTH and PTHrP were measured at baseline.

Statistical Analyses (see statistical review by Dr. Choudhury for a detailed critique of statistical analyses): For stage 1 of the trial the sponsor has defined two patient populations: 1) per protocol – all randomized patients who received the IV infusion at baseline and satisfied the admission criteria for TIH; and 2) intent-to-treat (ITT) – all randomized patients who received the IV infusion at baseline of stage 1 of the trial. The per protocol population was designated as the primary data set for all efficacy analyses. For the analysis of safety, all randomized patients who received study drug were considered.

For stage 2, the per protocol population consisted of patients who received the IV infusion of zoledronate and whose CSC in stage 2 was ≥ 11.0 mg/dl. The intent-to-treat population included all patients who received the IV infusion of zoledronate at stage 2 baseline.

For the primary efficacy analysis, a dose of drug was considered efficacious if the lower bound of the 95% confidence interval (CI) for the proportion of patients who achieved a complete response by Day 10 was > 70%.

An ANCOVA model with baseline CSC as a covariate and treatment-by-baseline CSC as an interaction term was used to compare between treatment group changes in CSC from baseline to Day 10.

Results

Patient Disposition: A total 138 patients were randomized into three groups: 40 to Zol 4mg, 47 to Zol and 51 to Pam 90mg. Ninety percent of the Zol 4mg subjects, 85% of the Zol 8mg subjects, and 73% of the Pam 90mg subjects completed stage 1 of the study. Like to 0036, the vast majority of subjects categorized as completing stage 1 were deemed so because they had a complete response by Day 10.

Protocol Violations: A total of 7 patients had major protocol violations: 3 Zol 8mg subjects and 2 Pam 90mg subjects did not have baseline CSC levels of at least 12 mg/dl; and two Zol 8mg subjects did not have a baseline calcium measurement. These 7 patients were excluded from the per protocol analyses. Thirty-six patients received a loop diuretic during the first 10 days.

Reviewer Questions: For each treatment group, what were the mean and median cumulative doses of loop diuretics received during days 1-10? And, do the results of the primary efficacy analysis differ significantly when these subjects are removed from the analysis

Baseline Demographics: The following table provides the baseline demographic characteristics of the study population.

BASELINE DEMOGRAPHICS			
	Zol 4mg	Zol 8mg	Pam 90mg
	N=40	N=47	N=51
Age (range) (yrs)	59	60	58 (25-87)
% Male	65%	79%	61%
% Caucasian	68%	57%	61%
% Black	28%	34%	31%
Baseline CSC (mg/dl)	13.9	13.5	13.7
% with Breast Cancer	18%	4%	6%
% with Lung Cancer	15%	30%	31%
% with Renal Cancer	8%	9%	4%
% with Head and Neck Cancer	18%	11%	16%
% with Multiple Myeloma	13%	11%	10%
% with Bone Metastases	48%	51%	41%
Serum PTHrP			
% ≤ 2 pmol/L	80%	66%	75%
% > 2 pmol/L	20%	21%	16%
Mean (pmol/L)	1.6	1.8	1.4
Median Time from Cancer Diagnosis (months)	12.3	4.6	5.8

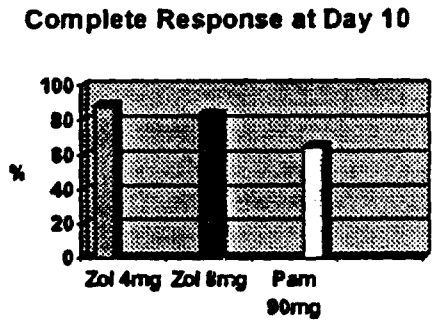
Aside from a greater percentage of patients in the zoledronate 4mg group with breast/hematological malignancies, the baseline characteristics of the three groups were well matched with no statistically significant differences. The imbalance in the type of cancer is unlikely to affect the study results.

Concomitant Medications: As in study 0036, a number of patients received loop diuretics during stage 1. In all, 36 subjects received furosemide during days 1-10 of stage 1: 14 (35%) of Zol 4mg subjects, 13 (31%) of Zol 8mg subjects, and 9 (18%) of the Pam 90mg subjects.

Reviewer Comment/Question: What were the mean and median cumulative doses of furosemide given to the 3 treatment groups? In response, the sponsor claims that information on dosage of loop diuretics was not recorded. However, when one compared the complete response rates between those patients who received diuretics to those that did not, the results were similar.

Primary Efficacy Outcome (per protocol population)

Complete Response Rates (serum CSC < 10.8 mg/dl by Day10): As shown in the figure below, the complete response rates for the Zol 4mg, Zol 8mg, and Pam 90mg were 88% (95% CI 77%, 98%), 83% (72, 95%), and 65% (52%, 79%). Both doses of zoledronate were deemed efficacious because the lower bound of the 95% confidence interval for both doses was greater than 70% - the predefined criteria of efficacy. The 90-mg dose of pamidronate was deemed non-efficacious because the lower bound of the



confidence interval for this dose was lower than 70%. Results were similar for the ITT population.

As mentioned for study 0036, this study was not designed to demonstrate statistical superiority of the zoledronate doses to the pamidronate dose; however, the percentage of patients in the Zol 4mg group who achieved a complete response by Day 10 was significantly greater than the percentage of patient in the Pam 90mg group ($p=0.02$). The difference between the Zol 8mg group and the Pam 90mg group was of borderline statistical significance ($p=0.07$). The two zoledronate doses did not differ significantly from one another. The results of the ITT analyses were similar to the per protocol calculations.

The level of PTHrP has been reported to affect response to treatment with hypocalcemic agents, with higher levels conferring more recalcitrant responses. While the response to treatment with Zol 4mg did not differ by baseline PTHrP levels above or below 2 pmol/L, the response was lower in the Zol 8mg group for those subjects with a baseline PTHrP level greater than 2 pmol/L compared with lower than 2 pmol/L. Baseline PTHrP levels did not significantly alter the response in the Pam 90mg group.

In general, a greater proportion of older ($\geq$ 65 yrs) vs. younger subjects in each treatment group achieved a complete response by Day 10. Gender or race did not meaningfully alter complete response rates, although the relatively small numbers of non-Caucasians render conclusions about race tenuous.

Secondary Efficacy Outcomes (per protocol population)

Duration of Response: For those subjects who met the criteria for complete response, the median number of days from complete response to last CSC $\leq$ 10.8 mg/dl were 27, 39, and 14 days for the Zol 4mg, Zol 8mg, and Pam 90mg, respectively.

Change in CSC Levels from Baseline to Day 10: The mean reductions in CSC levels in the two zoledronate doses were -3.72 mg/dl and -3.76 mg/dl (4mg and 8mg) and -3.16 mg/dl for the pamidronate 90mg group. The differences between the zoledronate groups and the pamidronate group were significant at $p<0.05$.

Proportion of Patients with Refractory TIH: One (2.5%) of Zol 4mg-treated patients, 3 (7.1%) of Zol 8mg-treated subjects, and 4 (8.2%) of Pam 90mg-treated patients were classified as having refractory TIH.

Retreatment of Relapsed or Refractory TIH (Stage 2): A total of 35 patients received a second dose of drug (zoledronate 8mg) during stage 2 of the study. The majority of these subjects, 19 were originally

treated with pamidronate, while 9 had received Zol 4mg and 7 Zol 8mg. Twenty-four of the 35 patients had a complete response in stage 1 and were retreated for relapsed hypercalcemia. Of the remaining subjects, 2 had refractory TIH, 7 had partial responses during stage 1, and 2 subjects were unclassified.

A total of 17 (49%) of the patients who required retreatment had a complete response by Day 10 of stage 2. The mean change from baseline to Day 10 in CSC for the entire stage 2 cohort was -1.72 mg/dl. The median duration of complete response was only 7 days. Results were similar for the ITT analyses.

The data from stage 2 clearly indicate that patients requiring a second course of treatment for TIH (either because of refractory status or relapse) are less responsive to retreatment with 8 mg of zoledronate.

Safety Review

Because protocols 036 and 037 are identical in design, a review of zoledronate's safety profile from this trial will be discussed in the pooled analysis of 036 + 037 data in the Integrated Summary of Safety

Sponsor's Conclusions

Zoledronate in single intravenous doses of 4 mg or 8 mg given as a 5 minute infusion, is highly effective in the initial treatment of tumor-induced hypercalcemia. Zoledronate 4 mg is the recommended dose for initial treatment of TIH. Both doses of zoledronate were equally effective, and were more effective than Aredia 90 mg. Although there were no differences in complete response rates between zoledronate doses, the 8 mg dose appeared to have a longer duration of action. Retreatment with 8 mg of zoledronate, although less effective than initial treatment, still provided a good response rate in a highly selected, difficult-to-treat patient population. Both doses of zoledronate were well-tolerated, with no unexpected adverse events.

Integrated Summary of Efficacy

Overview

This integrated summary of efficacy (ISE) is confined to an analysis of pooled data from the two primary studies - 036 and 037 - reviewed previously. Because the two studies followed identical protocols and the only difference between them was the location of conduct (036 conducted in Europe and Australia and 037 conducted in the US and Canada), a more rigorous estimate of the drug's efficacy will be obtained when the data from the two studies are combined.

Data from the phase I dose-ranging study (CJ/HCI) will not be included in the ISE because multiple doses other than the two studied in 036 and 037 were examined and the protocol differed significantly from the two primary studies.

Pooled Analysis of Zoledronate's Efficacy

It is important to note that the Sponsor pre-planned an analysis of pooled data from studies 036 and 037. The design and conduct of these studies are described above; however, to facilitate readers' review, this information will be provided here as well.

Objective: To examine whether a single 5-minute infusion of either dose of zoledronate (4 mg _ was not inferior to a 2-hour infusion of 90 mg of pamidronate with respect to the proportion of patients who became normocalcemic by Day 10 following drug administration. (non-inferior is discussed under analysis plan).

Design: These studies were two-stage, multicenter, randomized, double-blind, double-dummy, parallel, dose-finding trials of zoledronate treatment for patients with TIH. In stage 1, patients were initially treated with either zoledronate or pamidronate. In stage 2, patients with TIH that was refractory to or had relapsed after initial treatment were retreated with 8mg of zoledronate, regardless of the drug and dose received in stage 1.

In stage 1, eligible patients were randomized to receive a single IV dose of zoledronate 4mg o _ or pamidronate 90mg. If treatment resulted in a complete response (corrected serum calcium < 10.8 mg/dl), the patient was followed for eight weeks in stage 1 of the trial (to day 56) or until the patient's corrected serum calcium rose to a level ≥ 2.90 mmol/L (11.6 mg/dl), whichever occurred first. Patients in whom trial therapy had not achieved a complete response by day 10, but whose corrected serum calcium (CSC) concentration was < 11.6 mg/dl on day 10, continued to be followed in stage 1 of the trial to day 56 or until the patient's CSC rose to a level ≥ 11.6 mg/dl, whichever occurred first.

In stage 2, patients received retreatment with 8mg IV zoledronate if their TIH was refractory to initial zoledronate/pamidronate treatment, or if following the achievement of a complete a relapse of TIH to a CSC of ≥ 11.6 mg/dl occurred by day 56. If zoledronate retreatment resulted in a complete response, the patient was followed in stage 2 of the trial until relapse or for four weeks after retreatment, whichever occurred first. If a complete response was not achieved by day 10 or stage 2, the patient was discontinued from the trial.

To accommodate out-patient treatment, drugs were administered simultaneously with IV hydration (500 ml over 4 hours; see Drug Administration below). The administration of additional IV fluids following the completion of the required infusions designated by the protocol was at the discretion of the treating physician. To minimize the potential risk of nephrotoxicity due to the use of IV bisphosphonates in the presence of severe dehydration, patients presenting with severe volume depletion were to be initially excluded from the trial. However, these patients were eligible for the study if their CSC level remained ≥ 12.0 mg/dL after correction of volume depletion with IV fluids.

Drug Administration: Each IV dose of zoledronate was administered with 50 ml of 0.9% saline over 5 minutes. Patients randomized to pamidronate also received a matching placebo infusion of 50 ml of normal

saline. Each IV dose of pamidronate was administered with 10 ml of sterile water and 240 ml of 0.9% saline over 2 hours. Patients randomized to zoledronate received a matching placebo infusion of 250 ml of normal saline.

Patient Randomization: A total of 485 patients were screened for the two pivotal studies. A total of 287 subjects were randomized into studies 036 and 037. The most common reasons for not enrolling into the studies were: hyperparathyroidism, inappropriately low serum calcium level, administrative problems, and previous treatment with a bisphosphonate.

Patient Demographics: The following table provides the baseline characteristics for the study population.

BASELINE DEMOGRAPHICS POOLED ANALYSIS			
	Zol 4mg	Zol 8mg	Pam 90mg
	N=86	N=90	N=99
Age (yrs)	60	59	59
% Male	54%	67%	57%
% Caucasian	85%	78%	77%
% Black	13%	17%	17%
Baseline CSC (mg/dl)	13.96	13.67	13.95
% with Breast Cancer	26%	16%	15%
% with Lung Cancer	17%	23%	23%
% with Renal Cancer	11%	11%	11%
% with Head and Neck Cancer	11%	10%	12%
% with Multiple Myeloma	11%	6%	9%
% with Bone Metastases	57%	56%	46%
Serum PTHrP			
% ≤ 2 pmol/L	72%	66%	66%
% > 2 pmol/L	23%	28%	24%
Mean			
% Used Loop Diuretic in Stage I	26%	27%	21%

Patient Disposition

A detailed description of patient disposition for the subjects in studies 036 and 037 is provided in the table below. Disposition is presented for Day 10 and Day 56 of the trials.

PATIENT DISPOSITION DURING STAGE 1			
	ZOL 4MG N=86	ZOL 8MG N=98	PAM 90MG N=103
Day 10			
Completed	91%	87%	88%
Reason for D/C			
AE	1.2%	1.0%	1.0%
Unsatisfactory response	0	0	2.9%
Protocol violation	1.2%	0	0
Withdrew consent	2.3%	1.0%	3.9%
Death	4.7%	11.2%	3.9%
Day 56			
Completed	30%	28%	18%
Reason for D/C			
AE	4.7%	9.2%	7.8%
Lab abnormality	0	0	1.0%
Unsatisfactory response	22.1%	11.2%	36.9%

PATIENT DISPOSITION DURING STAGE 1			
	ZOL 4MG N=86	ZOL 8MG N=98	PAM 90MG N=103
Protocol violation	4.7%	0	3.9%
Withdrew consent	10.5%	14.3%	8.7%
LTF	5.8%	1.0%	1.9%
Administrative	2.3%	4.1%	1.0%
Death	18.6%	32.7%	19.4%

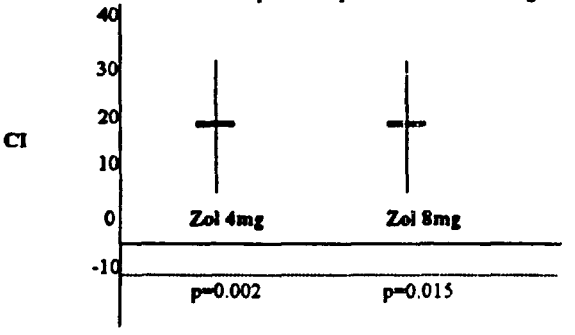
As can be seen in the above table, most of the subjects in all three groups completed the Day 10 evaluation, but not the Day 56 evaluation. The most common reasons for not completing the Day 56 evaluation were unsatisfactory response (largest proportion in the pamidronate group) and death (largest proportion in the zoledronate 8mg group).

Primary Efficacy Outcome

As pre-defined, zoledronate was to be deemed non-inferior to pamidronate if the 95% confidence interval of the difference between zoledronate and pamidronate in the percentage of complete responders was not above the –10% preset non-inferiority limit but also above 0%. (The 4 mg dose of zoledronate was to be declared non-inferior to pamidronate only if the 8 mg dose of zoledronate was also declared non-inferior.

As shown in the figure below, both doses of zoledronate were in fact shown to be statistically and clinically significantly superior to 90 mg of pamidronate.

95% Confidence Intervals for Complete Response Rates vs. 90 mg Pamidronate



Approximately 88% of the zoledronate 4 mg subjects and 87% of the zoledronate 8 mg subjects had complete responses by Day 10 following dosing, whereas 70% of the pamidronate-treated subjects had complete responses by Day 10 ($p<0.02$). The two zoledronate doses did not differ clinically or statistically.

It is reassuring that the results did not differ when minor protocol violators were excluded from the analysis. Approximately 86%, 86%, and 74% of the zoledronate 4mg and 8mg and pamidronate subjects, respectively, had complete response rates by Day 10 in the non-protocol violator analysis.

Secondary Efficacy Outcomes

Corrected Serum Calcium Values

Calcium levels decreased to a greater extent in both zoledronate groups compared with the pamidronate group at Days 4, 7, and 10 post-dosing. The actual values are shown in the following table.

MEAN CHANGES IN CORRECTED SERUM CALCIUM LEVELS FROM BASELINE TO DAYS 4, 7, AND 10 (MG/DL)					
	Zol 4mg	p vs. Pam	Zol 8 mg	p vs. Pam	Pam 90 mg
Day 4	-2.92	0.005	-2.80	0.05	-2.48
Day 7	-3.88	0.001	-3.84	0.003	-3.32
Day 10	-4.00	0.001	-4.00	0.001	-3.36

Time to Relapse

In an analysis of time to relapse, the subjects in the pamidronate group had a median time to relapse of 17 days, whereas the zoledronate 4 mg group subjects had a median time to relapse of 30 days ($p<0.05$ vs. Pam) and the 8 mg subjects had a median time to relapse of 40 days ($p<0.05$ vs.Pam).

Refractory TIH

Only one subject in the zoledronate 4 mg group developed refractory TIH. Four subjects in the zoledronate 8 mg group were refractory to treatment and 10 subjects in the pamidronate group did not respond to treatment. The difference in the proportion of subjects with refractory TIH was statistically significantly lower in the zoledronate 4 mg group (but not the 8 mg group) vs. the pamidronate group ($p=0.01$).

Response to Treatment for Various Subgroups of Patients

With respect to the primary efficacy variable, complete response at Day 10, four covariates were examined in a subgroup analysis. These covariates were presence of bone metastases at baseline (yes/no), primary cancer group (breast, hematologic, other), baseline CSC level (< 3.4 mmol/L, ≥ 3.4 mmol/L), and baseline PTHrP level (≤ 2 pmol/L, > 2 pmol/L). These variables were identified by Novartis prior to unblinding of the data. None of these factors had a significant influence on the complete response rate.

However, when considering time to relapse, a baseline CSC level < 3.4 mmol/L, a PTHrP level > 2 pmol/L, and the absence of bone metastases at baseline were all associated with shorter times to relapse. The presence of a higher baseline level of PTHrp and a shorter time to relapse makes sense biologically, whereas, a lower baseline level of CSC and the absence of bone metastases are at odds with what one would predict to be associated with shorter time to relapse of TIH. Because these are subgroup analyses the results need to be interpreted with caution.

Integrated Summary of Safety

Overview and Approach to Review

Two databases will be used to review the overall safety of zoledronate. Pooled data from the two pivotal TIH studies will be the primary focus of this safety review. The secondary dataset is comprised of completed studies evaluating the efficacy and safety of zoledronate in the treatment of bone metastases in cancer patients. Data will be provided as part of the written review for the TIH studies. Where appropriate (i.e., imbalance noted), data from the bone metastases studies will be discussed after the TIH data are presented. Further, some analysis will be based on data pooled from the TIH and metastases studies.

TIH Database

In addition to the two pivotal studies (036 and 037) previously described and reviewed, the pooled safety database for TIH includes 33 patients who were treated with a single infusion of zoledronate using doses ranging from 0.002 to 0.06 mg/kg with follow-up for 35 days (phase I study CJ/HC1). All doses in this phase I study were less than 4 mg. It should be noted that there was no placebo group in these studies. Study CJ/HC1 had no control group and studies 036 and 037 included 4-mg and 8-mg zoledronate groups and a 90-mg pamidronate group. Following initial treatment some subjects, irrespective of initial therapy, received re-treatment with 8 mg of zoledronate.

Demographics

A total of 33 patients were treated with < 4 mg of zoledronate, 86 with 4 mg of zoledronate, 98 with 8 mg of zoledronate, and 103 with 90 mg of pamidronate. Aside from a lower percentage of males (42%) in the < 4 mg group relative to the other doses (approx. 50% - 65%), the baseline demographics for subjects in the TIH database were comparable across dose groups. The mean age was about 60 years, most of the patients (~77%) were Caucasian, with breast and lung cancers the most common form of malignancy. Concomitant medication use was similar for all treatment groups, as was use of anti-neoplastic agents.

Of note, although patients were excluded if they had a serum creatinine > 4.5 mg/dl, approximately 1.0% to 4.0% of the zoledronate subjects and 1.0% to 11.0% of the pamidronate subjects had a history or ongoing diagnosis of one of the following renal conditions: uremia, abnormal renal function, or acute renal failure.

Drug Exposure

As for exposure to study drug, a total of 33 patients received a single dose of < 4 mg of zoledronate, 86 received a single dose of 4 mg of zoledronate, 98 received a single dose of 8 mg of zoledronate, and 103 received a single dose of 90 mg of pamidronate. Seventy subjects received retreatment with 8 mg of zoledronate during the second stage of studies 036 and 037.

Bone Metastases Database

The pooled bone metastases database was comprised of 2 phase 1 studies (003 and its extension and 035) and an additional phase II study (007 and its extension). Protocol 003 enrolled 59 patients with lytic bone lesions from various types of cancer. Zoledronate doses of 0.1 mg to 8.0 mg were given as a 5-minute infusion every four weeks for 3 months. Patients were subsequently enrolled in the 003 Extension (003E) trial, which allowed continued treatment every 3-4 weeks with the same dose of zoledronate previously received. Treatment duration was not specified in the extension trials but continued until the treating physician believed treatment was no longer in the patient's best interest, death or an adverse event resulted in discontinuation, or the patient withdrew consent.

Protocol 007 enrolled 280 patients with lytic bone lesions from myeloma and breast cancer. Patients were randomized to receive either zoledronate 0.4, 2.0, or 4.0 mg as a 5 minute infusion or pamidronate 90 mg given as a 2 hour infusion given every 3-4 weeks for 9 months. In the extension trial, 007E, patients

received 8 mg of zoledronate if previously treated with zoledronate or 90 mg of pamidronate if previously treated with pamidronate. A total of fifty patients received an 8 mg dose of zoledronate in the 007 trial extension after receiving a lower dose of zoledronate in the core protocol. This group is described as the "switched to 8 mg zoledronate" group. Protocol 035 enrolled 44 patients with lytic and/or blastic bone lesions from various types of cancer. Zoledronate single doses of 1 to 16 mg were given as a rapid iv bolus over 30 to 60 seconds. Only 10 patients received 16-mg zoledronate.

Demographics

In these studies a total of 168 patients received zoledronate < 4 mg, 65 received 4 mg of zoledronate, 17 received 8 mg of zoledronate, and 73 received pamidronate 90 mg. The zoledronate and pamidronate groups were comparable with respect to age, race, and body weight. The proportion of patients who were male was lower in the pamidronate group (14%) than in the zoledronate groups (26% to 59%). The mean age was approximately 60 years, 80% to 88% of the patients were Caucasian, and the mean weight was about 76 kg. Breast cancer (35% to 60%) was the most common malignancy, followed by multiple myeloma (30% to 40%). Concomitant medication use was similar for all treatment groups, as was use of anti-neoplastic agents [except for a lower percentage of patients in the zoledronate 8 mg group (59%) who were treated with any anti-neoplastic agent after study initiation when compared with the other groups (80% to 84%)].

Drug Exposure

Regarding exposure to study drug, patients in the bone metastases studies generally received treatment every 4 weeks. A total of 152 patients received < 4 mg of zoledronate for a mean of 8.6 months; 57 subjects received 4 mg of zoledronate for a mean of 7.9 months; 7 patients received 8 mg of zoledronate for a mean of 7.3 months; and 73 subjects received 90 mg of pamidronate for a mean of 13.3 months.

Deaths

Deaths are reported if they occurred during the trial or within 30 days of study discontinuation. As all of these subjects had a diagnosis of cancer, high rates of death during and within 30 days of study discontinuation are to be expected. Furthermore, since only a single dose of drug was administered during phase I of the TIH studies, it is unlikely that deaths would be significantly or discernibly influenced by drug treatment. Given that pamidronate is the most widely used bisphosphonate to treat TIH, it is reasonable to focus attention on comparing the rates of death between the zoledronate and pamidronate groups.

The percentage of patients who died in each of the four groups < 4 mg of zoledronate, 4 mg of zoledronate, 8 mg of zoledronate, and 90 mg of pamidronate were as follows: 30%, 19%, 33%, and 19%, respectively. (for the metastases studies, 18% of the zoledronate 8 mg subjects died compared with 14% of the pamidronate 90 mg subjects). Although the incidence of death was higher in the zoledronate 8 mg group, there was no discernable pattern or cause of death that suggested drug-relatedness.). The respiratory system was the most frequently cited system responsible for death in both the zoledronate 8-mg group (7%) and the pamidronate group (5%). None of the zoledronate 4-mg subjects were recorded as having died from a respiratory cause. (this pattern was not seen in the metastases studies).

The median survival times for the zoledronate 4mg and 8mg and pamidronate groups were 74, 57, and 70 days, respectively (the 95% confidence intervals overlapped, i.e., the rates were not statistically significantly different).

Serious Adverse Events

A total of 6%, 52%, 56%, and 42% of the < 4 mg zoledronate, the 4 mg zoledronate, the 8 mg zoledronate, and the 90 mg pamidronate subjects, respectively reported any serious adverse event. (In the metastases trials, the rates of serious adverse events were similar in the pamidronate and 4 mg zoledronate groups and much lower in the zoledronate 8 mg group). Progression of cancer with the most frequently recorded

serious adverse event, followed by dyspnea and sepsis. The pattern of reporting across treatment groups does not lend itself to any concern about an imbalance in one or more adverse events.

Adverse Events Leading to Discontinuation

Only two subjects discontinued due to adverse events: one subject in the zoledronate 4-mg group dropped out because of cardiac and renal failure, and the second patient, treated with pamidronate, from granulocytopenia. (In the metastases studies, a comparable proportion of patients in the zoledronate < 4 mg and 4-mg groups and the pamidronate group discontinued due to an adverse event: 19% to 14%. Twenty-four percent of the zoledronate 8 mg subjects discontinued because of an adverse event; however, only 17 patients total were treated with this dose, making it difficult to draw conclusions from this group. "Body as a whole" was the most frequently recorded system affected by the adverse event. There were no imbalances in body systems affected by the adverse events between the zoledronate 4 mg and 8 mg and pamidronate groups).

Overall Incidence of Adverse Events

Because cancer patients with TIH are a debilitated population, adverse events are reported with great frequency. The sponsor has chosen to present those adverse events that occurred with a frequency greater than 15% in any of the groups. This is a reasonable approach.

The following table provides the adverse event (> 15%) profiles for the treatment groups.

PERCENTAGE OF PATIENTS WITH MOST FREQUENT (> 15%) ADVERSE EVENTS IN TIH TRIALS				
	< 4 mg Zol	4 mg Zol	8 mg Zol	90 mg Pam
# patients	33	86	98	103
# patients with any AE	29 (88%)	81 (94%)	94 (96%)	95 (92%)
Fever	52%	44%	35%	33%
Progression of Cancer	0	16%	30%	20%
Anemia	15%	22%	28%	18%
Nausea	18%	29%	21%	27%
Constipation	3%	27%	19%	13%
Dyspnea	6%	22%	18%	19%
Confusion	12%	13%	15%	13%
Insomnia	0	15%	15%	10%
Vomiting	18%	14%	15%	17%
Hypokalemia	3%	12%	12%	16%
Diarrhea	0	17%	10%	17%
Abdominal Pain	9%	16%	7%	13%
Hypophosphatemia	21%	13%	5%	2%

For this patient population, the rates of adverse event reporting were similar for the zoledronate 4 mg and 8-mg groups compared with the pamidronate group. The lower rate of hypophosphatemia in the pamidronate group probably reflects the lower potency (on bone and mineral metabolism) of this bisphosphonate compared with zoledronate. (In the metastases studies, as expected, skeletal pain was the most frequently recorded adverse event in all groups. No significant imbalances across treatment groups were noted for the other reported adverse events).

Special Safety Issues

Bisphosphonates as a class have been associated with a number of adverse events. These include fever (for IV administered drugs), mineral/electrolyte abnormalities, renal failure, eye abnormalities, and

gastrointestinal problems (more so with oral agents). A review of these particular adverse events is provided in the following section.

Mineral/Electrolyte Abnormalities

Because of their mechanism of action on bone, treatment with bisphosphonates would generally be expected to result in some degree of mineral abnormalities – most commonly hypocalcemia and hypophosphatemia[1]. The table below provides the percentage of patients in each group who had one or more serum electrolyte/mineral abnormalities.

PERCENT OF PATIENTS WITH SERUM ELECTROLYTE/MINERAL ABNORMALITIES				
	< 4 mg n=33	Zol 4 mg n=86	Zol 8 mg n=98	Pam 90 mg n=103
% of Patients with any Abnormality	24%	33%	25%	27%
Hypokalemia	3%	12%	12%	16%
Hypocalcemia	12%	6%	8%	2%
Hypomagnesemia	3%	11%	6%	5%
Hypophosphatemia	21%	13%	5%	2%
Hyponatremia	0	4%	2%	7%

Compared with treatment with pamidronate, a higher percentage of patients treated with zoledronate (all doses) developed hypocalcemia and hypophosphatemia. This most likely reflects the greater potency of zoledronate on bone (mineral) metabolism relative to treatment with pamidronate. (A similar trend was seen in the bone metastases studies; although the small sample size in the 8 mg group limits ones ability to draw confident conclusions).

Upon further investigation it was noted that, whereas 12% of pamidronate-treated subjects developed marked hypophosphatemia (< 1.5 mg/dl), 29% and 22% of zoledronate 4 mg and 8 mg-treated patients, respectively, developed this critically low serum phosphorus level.

Of note, during stage 1, the mean number of days to the development of low serum calcium levels (< 8.5 mg/dl) was 12 for the two zoledronate groups and 15 for the pamidronate group. During stage 2, 8 subjects developed a low serum calcium level at a mean number of days of 15. Few subjects developed notably low serum calcium levels (< 7 mg/dl) during stages 1 or 2. Of those that did during stage 1, the mean number of days to this value was 12 for the zoledronate 8 mg subjects and the pamidronate subjects (only 1 subject in the zoledronate 4 mg group had a notably low serum calcium level and this occurred on Day 56). During stage 2, the one subject with a notably low serum calcium level developed this abnormality on Day 19. One subjects During stage 1, subjects in the zoledronate groups developed low serum phosphorus levels (< 2.0 mg/dl) at a mean number of days of about 10, while it was 9 days in the pamidronate group. During stage 2, 16 subjects in the retreatment group (8 mg of zoledronate) developed their first low serum phosphorus level at a mean of 9 days. A large number of patients developed notably low serum phosphorus levels (< 1.5 mg/dl) during both stages of the trial. During stage 1, the first notably low levels of phosphorus were measured after a mean number of 11 days for the zoledronate subjects and 14 days for the pamidronate subjects. During stage 2, a mean of 10 days passed before the first notably low level of phosphorus occurred.

In general, low levels of phosphorus and calcium did not occur until at least 4-6 days after receiving both doses of zoledronate and pamidronate drugs.

[1] Adami S. Adverse Effects of bisphosphonates. Drug Safety: March 1996.

Four of the 8 patients who experienced a notably low serum calcium level during stages 1 and 2 of studies 036 and 037 were treated with calcium supplements. A total of 56 patients experienced an episode of a notably low serum phosphorus level; 9 of these subjects were treated with sodium phosphate.

Renal Abnormalities (see consult from Dr. Douglas Throckmorton)

Acute renal failure has been reported following rapid intravenous administration of bisphosphonates[2]. In this overview, multiple COSTART terms, in addition to acute renal failure, will be evaluated for renal safety. A greater percentage of patients in the zoledronate 4 mg and 8 mg groups had renal adverse events compared with those treated with pamidronate. The table below outlines these data.

NUMBER OF PATIENTS WITH RENAL ADVERSE EVENTS				
	< 4 mg n=33	Zol 4 mg N=86	Zol 8 mg N=98	Pam 90 mg N=103
N and % of Patients with any Abnormality	1 (3%)	13 (15%)	14 (14%)	7 (7%)
Total Number of Adverse Events	1	15	13	8
Acute Renal Failure	0	1	1	0
Hyperuricemia	0	1	0	2
Anuria	0	0	1	0
Hematuria	0	1	2	2
Hydronephrosis	0	1	0	0
Micturition Frequency	0	1	0	1
Obstructive Uropathy	0	0	0	1
Pyelonephritis	0	1	0	0
Renal Function Abnormal	0	4	3	1
Uremia	0	2	4	0
Urinary Retention	1	3	2	1

If one restricts the analysis of renal adverse events to acute renal failure, renal function abnormal, and uremia, in aggregate, the percentages of patients in the zoledronate 4-mg and 8-mg and pamidronate groups with these disorders are 8.1%, 8.2%, and 0.97%, respectively. [There was no imbalance for the overall incidence of renal adverse events, or for the aggregate (acute renal failure, renal function abnormal, and uremia) of adverse events in the completed bone metastases studies].

It bears mention that there did not appear to be any significant imbalances between the zoledronate and pamidronate groups in the prevalence of baseline medical conditions that might increase the risk for renal failure. These conditions included hypertension, hyperuricemia, diabetes, nephrotoxic antineoplastics, or pre-existing renal dysfunction. This post-hoc assessment of the relative risk of renal failure in the zoledronate vs. the pamidronate groups could be criticized as an inadequate means to assess whether zoledronate has a higher potential for nephrotoxicity than pamidronate. Nonetheless, lumping all of the terms in the above table (some quite disparate from one another and not related physiologically to renal failure) also seems to be a less than ideal way to assess the renal safety profile of zoledronate.

Regarding laboratory assessment of renal function, 8% of the subjects in the zoledronate 4 mg group, 13% of the patients in the zoledronate 8 mg group, and 9% of the participants in the pamidronate group developed a serum creatinine > 4.5 mg/dl or had an increase of 0.5 mg/dl from baseline. [There was no imbalance in the proportion of patients in the zoledronate compared with the pamidronate groups that developed a clinically significant increase in serum creatinine].

On Thursday May 11, 2000 the Data Safety Monitoring Board (DSMB) met to discuss a summary of renal safety data from three ongoing bone metastases trials (studies 010, 011, and 039, see appendix for details of

[2] Bounameaux HM. Renal failure associated with intravenous diphosphonates. Lancet: I 1983.

these trials). Renal toxicity was assessed by examining the percentage of patients in each group who developed any of the following (data are included through January 2000):

1. Increase in serum creatinine of more than 0.5 mg/dl in patients with baseline levels < 1.4 mg/dl
2. Increase in serum creatinine of more than 1.0 mg/dl in patients with baseline levels ≥ 1.4 mg/dl
3. A doubling or more of the baseline serum creatinine

The following table provides the results from this analysis.

INCIDENCE OF INCREASED SERU CREATININE LEVEL				
PROTOCOL	TREATMENT GROUP	N	# EVENTS (%)	P-VALUE VS. PAM OR PLACEBO*
10	Zol 4mg	491	27 (5.5%)	0.04
	Zol 8mg	454	47 (10.4%)	<0.001
	Pam 90mg	482	13 (2.7%)	
11	Zol 4mg	181	13 (7.2%)	0.007
	Zol 8mg	184	14 (7.6%)	0.004
	Placebo	168	2 (1.2%)	
39	Zol 4mg	178	20 (11.2%)	0.3
	Zol 8mg	173	39 (22.5%)	<0.001
	Placebo	172	13 (7.6%)	

*Fisher's Exact test

There is no question that, relative to treatment with placebo and pamidronate, zoledronate (as used in these trials) is associated with an increased risk for renal toxicity – as assessed by serum creatinine levels. It is also obvious that the 8 mg dose of zoledronate is more injurious than the 4 mg dose. In the majority of cases, the creatinine level increased by 0.5 mg/dl to 2 mg/dl from the baseline value.

Additional analyses of interest were conducted on the data from the three metastases trials. In an exploratory analysis, age and baseline serum creatinine level were identified as significant predictors of renal function deterioration. Each year of advancing age and each increase of 0.1 mg/dl in baseline creatinine were associated with a 4% and 11% increase, respectively, in risk for renal deterioration.

Kaplan-Meier plots indicate that the risk for renal injury does generally not occur until after the second or third monthly dose. The data also support the assertion that risk for renal toxicity increases with continued exposure to the drug. It should be noted, however, that increases in serum creatinine did occur following a single injection of zoledronate.

When one examines the risk for renal toxicity by duration of drug infusion (5 vs.15 minutes) it is evident that the risk is higher with the shorter infusion time. Because C_{max} but not AUC increases when the drug is infused over 5 compared with 15 minutes, it is possible that peak concentration rather than total drug exposure is directly related to risk for renal injury.

[redacted]

At this point, it is safe to say that the use of zoledronate is associated with an increased risk for renal injury. Preliminary data indicate that the risk is directly related to multiple factors including dose, infusion time, duration of treatment, age of the patient, and baseline renal function.

Compared with patients treated for bone metastases, patients treated for TIH will, in general, require fewer infusions of zoledronate. Since the risk for renal injury is related in part to duration of treatment with zoledronate, TIH patients are a lower risk population. Nevertheless, some TIH patients will require multiple infusions and given that there are approved treatments (i.e., pamidronate) for TIH that are effective and present lower risk for renal toxicity, I believe additional data should be gathered and analyzed before zoledronate is approved.

It will be important to assess if and how the recently implemented renal surveillance program (i.e., frequent monitoring of serum creatinine) affects the risk for renal injury in the ongoing bone metastases trials.

Eye Abnormalities

The use of pamidronate (and other bisphosphonates) has been associated with uveitis, scleritis, and episcleritis in as many as 1 in 1000 patients[3] [4]. These adverse events appear to be dose related and are more likely to occur in patients with pre-existing inflammatory eye conditions. Few ophthalmologic adverse events were reported in the TIH studies and no cases of iritis, scleritis, or uveitis were reported. Conjunctivitis was the most frequently recorded adverse event, with two cases in the zoledronate 4 mg and 8 mg and pamidronate groups each. [In the metastases studies, the overall incidence of eye adverse events was similar among all groups. Once case of iritis and one case of scleritis were reported in these studies: one in the < 4 mg zoledronate group and the other in the zoledronate 4 mg group].

Fever

Perhaps related to an ability to increase circulating levels of IL-6, some of the bisphosphonates have been associated with a flu-like syndrome, with fever as a prominent component[5] [6]. Because fever can be a component of the carcinogenic process itself and many cancer patients develop infections accompanied by fever, attributing a febrile response to the administration of zoledronate in these studies can be difficult. With this in mind, the percentage of patients in each treatment group who developed fever during the studies was comparable. During stage 1, a total of 22% of the zoledronate 4 mg subjects, 21% of the zoledronate 8 mg subjects, and 18% of the pamidronate patients developed a fever within 48 hours of drug administration. Nine percent of the subjects retreated with zoledronate developed a fever within 48 hours of dosing. [Similar percentages of patients in the zoledronate and pamidronate groups developed fever in the metastases studies as well].

Gastrointestinal

Upper gastrointestinal (GI) adverse events have been associated with the use of bisphosphonates. These events range from mild complaints of dyspepsia, nausea, and vomiting to serious cases of erosive esophagitis[7] [8]. Since bisphosphonates may have a direct noxious effect on the GI mucosa, the risk for upper GI adverse events appears to be much greater for oral compared with IV administered drugs.

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[3] Macarol V. Pamidronate disodium and possible ocular adverse drug reactions. Am J Ophthalmol: 118 1994.

[4] Ghose K. Uveitis associated with pamidronate. Aust NZ J Med:24 1994.

[5] Adami S. The acute-phase response after bisphosphonate administration. Calcif Tissue Int: 41 1987.

[6] Schweitzer DH. Interleukin-6 and the acute-phase response during treatment of patients with Paget's disease with the nitrogen-containing bisphosphonate dimethylaminohydroxypropylidene bisphosphonate. J Bone Miner Res: 6-1995.

[7] Douglas DL. Drug treatment of primary hyperparathyroidism: use of clodronate disodium. BMJ: 286 1983.

Provided below is a table of gastrointestinal events that were recorded during studies 036 and 037.

NUMBER OF PATIENTS WITH GI ADVERSE EVENTS				
	< 4 mg n=33	Zol 4 mg N=86	Zol 8 mg N=98	Pam 90 mg N=103
% of Patients with any Abnormality	21%	43%	32%	35%
Total Number of Adverse Events	10	51	39	49
Melana	0	1	2	2
Duodenal ulcer	0	1	0	0
Dyspepsia	0	7	4	10
Dysphagia	0	8	4	3
Esop stricture	0	0	0	1
Esophagitis	0	3	1	0
Gastric ulcer	0	0	1	0
Gastritis	1	1	1	1
GE reflux	0	2	1	0
GI hemorrhage	0	2	2	1
Abdominal pain	3	14	7	13
Vomiting	6	12	15	17
Hematemesis	0	0	1	1

[Data from the bone metastases trials are similar to those presented in the above table]. The rates of reporting of the various GI adverse events were similar for the zoledronate and pamidronate groups. In cases were the incidence in the zoledronate groups was higher than in the pamidronate groups (i.e., dysphagia, abdominal pain), there was an absence of a dose-response in the zoledronate groups, making drug-causality less likely.

Serum Chemistry and Hematology Parameters

Abnormalities in serum electrolytes and minerals were previously reviewed. Therefore in this section abnormalities in liver function tests and serum hematology parameters will be discussed. Cutoff values of > 100 U/L were used to define clinically significant increases in SGOT and SGPT and > 2.0 mg/dl was used for total bilirubin. Clinically significant changes in hemoglobin, WBC, and platelets were defined as < 6.5 g/dL, < 0.5 x 10^9/L, and < 20 x 10^9/L, respectively. Given the patient population, these cutoff values seem reasonable.

A total of 24% of zoledronate 4 mg-treated patients, 17% of zoledronate 8 mg-treated subjects, and 17% of pamidronate-treated patients developed an SGOT value > 100 U/L. Fifteen and 13% of the two zoledronate groups had SGPT values > 100 U/L. Similarly, 13% of pamidronate-treated subjects developed SGPT values above this cutoff. A slightly higher percentage of zoledronate-treated patients (9-10%) developed total bilirubin levels > 2.0 mg/dL compared with 8% of the patients in the pamidronate group. [There were no differences between the zoledronate and pamidronate-treated groups in the proportion of patients with clinically significant increases in SGOT, SGPT, or total bilirubin].

Compared with 1% of the pamidronate subjects who developed a hemoglobin level < 6.5 g/dL, 3% of the subjects in the < 4 mg zoledronate group, 2.5% of the patients in the zoledronate 4 mg group, and 0% of the subjects in the zoledronate 8 mg group developed low hemoglobin levels. Although none of the pamidronate subjects developed a WBC count below 0.5 x 10^9/L, 4.9% and 1.1% of the zoledronate 4 mg and 8 mg subjects, respectively developed neutropenia (none of the < 4 mg zoledronate subjects became neutropenic). The highest proportion of patients who developed a low platelet count, as defined above, were in the zoledronate 4 mg group (5%), followed by 2% in the pamidronate group and 1% in the

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[8] Harink HIJ. Paget's disease of bone: early and late response to three different modes of treatment with aminohydroxypropylidene bisphosphonate. BMJ: 295 1987.

zoledronate 8 mg group, and none in the < 4 mg zoledronate group. [There were no significant differences between any of the groups for the hematology parameters in the metastases studies].

Vital Signs

(Changes in body temperature were discussed earlier in the ISS under Fever).

Blood Pressure and Pulse

There were no significant differences among the groups for the mean changes in blood pressure and pulse from baseline to Endpoint, or for the proportion of subjects in each group with clinically significant changes in blood pressure or pulse.

Body Weight

There were no meaningful differences among the groups for the changes in body weight during the trials. A similar and small proportion (1-3%) of patients in the zoledronate and pamidronate groups had an increase in weight from baseline to endpoint of > 10% and a similar proportion had a decrease in weight from baseline to Endpoint of > 10%. [Review of the data from the metastases trials did not reveal any significant differences between the zoledronate and pamidronate for vital signs or body weight].

Electrocardiograms

The TIH protocols did not require electrocardiograms.

120-Day Safety Update

Data from July 1, 1999 through February 29, 2000 are included in this update.

For patients enrolled in the 3 TIH and 3 bone metastases studies which comprised the safety data in the original December 1999 NDA submission, only 4 serious adverse events were reported after the database lock. This submission contains data from ongoing trials in a variety of patient populations and disease conditions such as metastatic prostate and breast cancer and postmenopausal osteoporosis. The largest study (n=1648) is a treatment of bone metastases in patients with multiple myeloma and breast cancer. These subjects are receiving zoledronate 4 mg or 8 mg or pamidronate 90 mg as iv infusions every 3-4 weeks for varying duration.

The 4 adverse events reported from the TIH trials (after the data lock) were distributed as follows: zoledronate 4 mg 2 (progression of cancer and superior vena cava syndrome), zoledronate 8 mg 1 (progression of cancer), and pamidronate 1 (dehydration).

Because most of the data in these ongoing trials remains blinded little can be said about drug-relatedness. Of note, in two open-label studies, out of a total of 7 patients who developed serious renal adverse events and treatment assignment is known at this time, 6 of these subjects received the 16 mg dose and the other patient received an 8 mg dose. No renal adverse events occurred in the subjects treated with 4 mg or lower. These data are certainly suggestive, although far from conclusive, of a dose-related toxicity. Perhaps fortunately, doses greater than 8 mg are not being studied in the ongoing or planned phase 3 trials.

Because data from ongoing trials remains blinded, no conclusions can be reached as to whether the safety profile of zoledronate has changed appreciably since review of the data in the original NDA submission.

Second Safety Update

Safety update data have been submitted in response to questions about the renal toxicity of zoledronate. This information is conveyed in the above review and in Dr. Throckmorton's consult.

Overall Conclusions and Summary

Two well-conducted studies assessed the relative efficacy and safety of 4mg and 8mg of IV zoledronate in the treatment of TIH. Compared with pamidronate, both doses of zoledronate were statistically significantly superior in terms of lowering serum calcium levels to within normal limits at 10 days following drug infusion (complete response). Approximately 12% to 18% more of the zoledronate-treated patients had complete responses than did the pamidronate-treated subjects. Unfortunately, the studies were not designed to compare the relative efficacy or safety of multiple doses of drug treatment, as used in patients with recalcitrant or recurrent TIH.

It is apparent that zoledronate is associated with an increased risk for renal toxicity. In the TIH trials a significantly larger number of patients in the zoledronate groups experienced a renal adverse event vs. those in the pamidronate group. There were no significant differences between the treatment groups in the incidence of clinically significant (as defined in the renal section of the ISS) elevations in serum creatinine, however. An opposite picture has emerged from the three ongoing bone metastases trials (010, 011, and 039). Here there was a clear increase in the risk for elevations in serum creatinine in the two zoledronate groups compared with the pamidronate or placebo groups, but not in the incidence of renal adverse events. These disparities are difficult to explain.

Preliminary analyses suggest that the risk for renal injury associated with zoledronate is related to dose, duration of use, length of infusion, age of the patient, and baseline renal function or creatinine level. Accordingly, the 8-mg dose has been eliminated from the zoledronate clinical program, the infusion time has been lengthened to 15 minutes, and an algorithm for renal monitoring has been implemented in the ongoing bone metastases trials. When these trials are completed in early 2001, it will be important to examine whether the above changes decreased the risk for renal toxicity.

Given that patients with TIH generally receive fewer doses of bisphosphonate therapy than patients with bone metastases, one may assume that their risk for renal injury with zoledronate will be lower. The serum creatinine data from the TIH and bone metastases trials support this assumption. Nevertheless, given the availability of "effective" therapy for TIH (i.e. pamidronate), I believe it would be prudent to delay approval of zoledronate until the ongoing bone metastases trials are completed and a comprehensive assessment of the drug's renal safety profile (including the affect of the recently implemented protocol changes) can be made.

Regulatory Recommendation

I recommend that this application be deemed approvable pending review of renal safety data from the ongoing bone metastases trials scheduled to be completed in early 2001.

/S/ -9/18/00
Eric Colman, MD

Appendix

Outline of Bone Metastases Trials (010, 011, 039)

Study 010 – Double-blind, active-controlled, multicenter study of IV zoledronate (4mg and 8mg as 5-minute infusions) vs. IV pamidronate (90mg as a 2-hour infusion) in the treatment of multiple myeloma and breast cancer patients with cancer-related bone lesions. First patient visit was in October 1998 and the last patient visit is anticipated to be January 2001. A total of approximately 1500 patients were randomized to infusions of drug every 3-4 weeks for 12 months. Patients with a baseline serum creatinine > 3 mg/dl were excluded. If patients develop TIH > 14 days after drug infusion they are to receive their next dose of study drug as treatment for the TIH. If TIH continues or recurs patients are to be withdrawn from the trial. Patients who develop TIH within 14 days of study drug administration are to be immediately terminated from the trial.

Study 011 – Double-blind, placebo-controlled, multicenter study of IV zoledronate (4mg and 8mg as 5-minute infusions) vs. placebo in the treatment of patients with bone metastases secondary to solid tumors other than breast or prostate cancer. First patient visit was in August 1998 and the last patient visit is anticipated to be in January 2001. A total of approximately 700 patients were randomized to infusions of drug every 3 weeks for 9 months. Patients who develop TIH are to be discontinued from the trial.

Study 039 – Double-blind, placebo-controlled, multicenter study of IV zoledronate (4mg and 8mg as 5-minute infusions) vs. placebo in the treatment of patients with bone lesions secondary to prostate cancer. More than 700 patients were randomized to infusions of drug every 3 weeks for 24 months. Patients with a serum creatinine > 3 mg/dl are excluded from trial participation.

In July 1999 the infusion time was extended from 5 to 15 minutes in all trials.