

4.2 Tables of Clinical Studies

The following table provides the basic characteristics of the 4 studies conducted in patients with Paget's disease. In addition to these 4 studies, data from an ongoing, partially-blinded study (2301) of approximately 7700 in postmenopausal women with osteoporosis provide important safety information for this review.

Study	Study objective, population	Patients	Study Duration	Medication, Dosing scheme	Type of control
Large efficacy trials					
2304	phase III, double-blind, randomized safety & efficacy in Paget's disease	172	6 months	1 x 5 mg Zoledronic acid (15 min i.v. infusion) 30 mg risedronate/day (60 days)	active control
2305	phase III, double-blind, randomized safety & efficacy in Paget's disease	185	6 months	1 x 5 mg Zoledronic acid (15 min i.v. infusion) 30 mg risedronate/day (60 days)	active control
Large dose-ranging trial					
002	phase II, double-blind, randomized dose-ranging trial in Paget's disease	176	3 months	1 x 50, 100, 200, or 400 µg Zoledronic acid , 1 x placebo (60 min i.v. infusion)	placebo control
Small dose-ranging trial					
001	phase I, open-label, rising dose trial in Paget's disease	16	14 days	1 x 24, 72, 216, or 400 µg Zoledronic acid (60 min i.v. infusion)	no control

4.3 Review Strategy

The studies that provide the majority of the data upon which this reviewer is basing a decision regarding the balance of benefits to risks of zoledronic acid in the treatment of Paget's disease are the phase 2 study 002, the phase 3 studies 2304 and 2305, and the ongoing phase 3 study 2301.

4.4 Data Quality and Integrity

The Division of Scientific Investigations (DSI) was asked to inspect the larger of several North American clinical sites. In a recently completed consult, DSI reported no major violations with the sites inspected.

4.5 Compliance with Good Clinical Practices

The trials appear to have been conducted in accordance with the accepted ethical standards.

4.6 Financial Disclosures

1. Compensation made to the investigator in which the value of compensation could be affected by study outcome.

None reported.

2. A proprietary interest in the tested product, including, but not limited to, a patent, trademark, copyright or licensing agreement.

None reported.

3. Any equity interest in the sponsor of a covered study, i.e., any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices.

None reported.

4. Any equity interest in a publicly held company that exceeds \$50,000 in value.

None reported.

5. Significant payments of other sorts, which are payments that have a cumulative monetary value of \$25,000 or more made by the sponsor of a covered study to the investigator or the investigators' institution to support activities of the investigator exclusive of the costs of conducting the clinical study or other clinical studies, (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the clinical investigator is carrying out the study and for 1 year following completion of the study.

~~_____~~ Amount under negotiations.

~~_____~~ stipend for research fellow.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

See review by Dr. Sandra Suarez for details of the pharmacokinetics data.

As described in the approved, zoledronic acid labeling, single or multiple (q 28 days) 5-minute or 15-minute infusions of 2, 4, 8 or 16 mg zoledronic acid were given to 64 patients with cancer and bone metastases. The post-infusion decline of zoledronic acid concentrations in plasma was consistent with a triphasic process showing a rapid decrease from peak concentrations at end-of-infusion to <1% of C_{max} 24 hours post infusion with population half-lives of $t_{1/2(\alpha)}$ 0.24 hours and $t_{1/2(\beta)}$ 1.87 hours for the early disposition phases of the drug. The terminal elimination

phase of zoledronic acid was prolonged, with very low concentrations in plasma between Days 2 and 28 post infusion, and a terminal elimination half-life $t_{1/2(\text{gamma})}$ of 146 hours. The area under the plasma concentration versus time curve ($\text{AUC}_{0-24\text{h}}$) of zoledronic acid was dose proportional from 2 to 16 mg. The accumulation of zoledronic acid measured over three cycles was low, with mean $\text{AUC}_{0-24\text{h}}$ ratios for cycles 2 and 3 versus 1 of 1.13 ± 0.30 and 1.16 ± 0.36 , respectively.

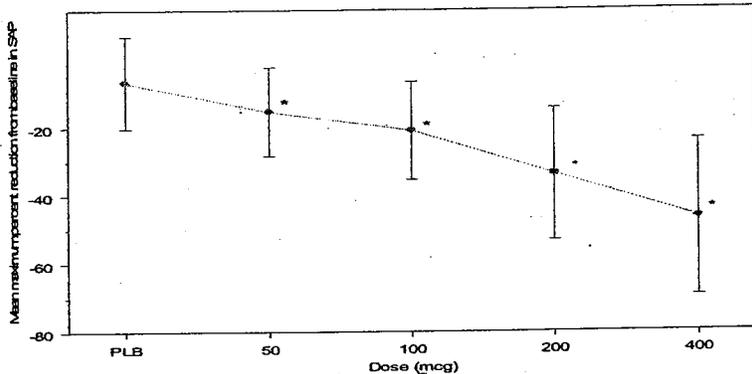
Zoledronic acid does not inhibit human P450 enzymes *in vitro*. Zoledronic acid does not undergo biotransformation *in vivo*. In animal studies, <3% of the administered intravenous dose was found in the feces, with the balance either recovered in the urine or taken up by bone, indicating that the drug is eliminated intact via the kidney. Following an intravenous dose of 20 nCi ^{14}C -zoledronic acid in a patient with cancer and bone metastases, only a single radioactive species with chromatographic properties identical to those of parent drug was recovered in urine, which suggests that zoledronic acid is not metabolized.

In 64 patients with cancer and bone metastases on average (\pm s.d.) $39 \pm 16\%$ of the administered zoledronic acid dose was recovered in the urine within 24 hours, with only trace amounts of drug found in urine post Day 2. The cumulative percent of drug excreted in the urine over 0-24 hours was independent of dose. The balance of drug not recovered in urine over 0-24 hours, representing drug presumably bound to bone, is slowly released back into the systemic circulation, giving rise to the observed prolonged low plasma concentrations. The 0-24 hour renal clearance of zoledronic acid was 3.7 ± 2.0 L/h.

Zoledronic acid clearance was independent of dose but dependent upon the patient's creatinine clearance. In a study in patients with cancer and bone metastases, increasing the infusion time of a 4-mg dose of zoledronic acid from 5 minutes ($n=5$) to 15 minutes ($n=7$) resulted in a 34% decrease in the zoledronic acid concentration at the end of the infusion ([mean \pm SD] 403 ± 118 ng/mL vs 264 ± 86 ng/mL) and a 10% increase in the total AUC (378 ± 116 ng \times h/mL vs 420 ± 218 ng \times h/mL). The difference between the AUC means was not statistically significant.

5.2 Pharmacodynamics

In the phase 2 study 002, intravenous dose of 50 ug, 100 ug, 200 ug, and 400 ug zoledronic acid or placebo were administered over 60 minutes to patients with Paget's disease. The pharmacodynamic marker relevant to Paget's disease of bone and measured in this study was serum alkaline phosphatase (SAP). The mean (SD) for maximum percent reductions from baseline in SAP is shown in the following figure (taken from Dr. Suarez's review).



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Over the range studied, there is a direct relationship between dose of zoledronic acid and suppression of SAP. It is noteworthy that there are no pharmacodynamic data for doses of zoledronic acid between 400 ug to < 5 mg.

See section 7.2.3 of this review for an additional discussion of the dose-response data.

5.3 Exposure-Response Relationships

See section 5.2.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The sponsor is proposing that zoledronic acid be indicated for the treatment of Paget's disease of bone in men and women.

6.1.1 Methods

Studies 2304 and 2305, randomized, double-blind, active-controlled 6-month trials, provide the efficacy data upon which this Reviewer determined the efficacy of zoledronic acid in the treatment of Paget's disease of bone. The two studies were conducted under identical protocols, as described below.

6.1.2 General Discussion of Endpoints

As with drugs previously approved for the treatment of Paget's disease of bone, the primary efficacy endpoint in the zoledronic acid studies was serum bone-specific alkaline phosphatase (SAP). Specifically, the efficacy endpoint was defined as the proportion of patients in the zoledronic acid and risedronate comparator group who either had normalization or a reduction of at least 75% from baseline of their SAP at the end of six months. While the level of SAP

correlates directly with the severity and extent of disease in patients with Paget's, there is no evidence that this Reviewer is aware of which indicates that normalization of SAP with bisphosphonate therapy prevents the morbid outcomes such as fractures or retards progression of the underlying disease. Nonetheless, SAP is an important marker that physicians follow to evaluate patients' clinical status and is a reasonable parameter upon which to base regulatory approval.

6.1.3 Study Design

The pivotal studies were randomized, double-blind, active-controlled 6-month trials comparing the efficacy of a single 5 mg dose of zoledronic acid administered during a 15-minute intravenous injection to 30 mg qd x 60 days of orally administered risedronate, the approved regimen of this bisphosphonate for Paget's disease. Each individual trial was powered to test whether zoledronic acid was non-inferior to risedronate. Non-inferiority was considered if the lower bound of the two-sided 95% confidence interval for the difference between zoledronic acid and risedronate in the proportion of responders exceeded -0.16.

The non-inferiority criterion of -0.16 for the difference of proportions was based on the efficacy results from the pivotal studies conducted to support FDA approval of risedronate for the treatment of Paget's disease. The non-inferiority margin of -0.16 allows 75% of the treatment effect demonstrated by risedronate relative to etidronate to be preserved. In other words, -0.16 is approximately 25% of the observed difference between etidronate and risedronate which was minus 0.65.

If non-inferiority was demonstrated, superiority was then tested using a logistic regression model with treatment and baseline SAP (above or below 3xULN) as explanatory variables. The secondary efficacy variables were:

- Relative change in serum CTX (bone resorption marker) at Day 10;
- Relative change in urine α -CTX (bone resorption marker) at Day 10;
- Relative change in serum SAP (bone formation marker) at Day 28;
- Change in BPI-SF pain severity over time;
- Change in BPI-SF pain interference over time;
- Proportion of subjects who achieved normalization at Day 28;
- Time to first therapeutic response.

The principal analysis for the primary efficacy variable was performed on the modified intent-to-treat (MITT) population. The MITT population was defined as all randomized patients with both a baseline and at least one post-baseline SAP measurement.

Patients in the pivotal trials who met the definition of a therapeutic response at the end of the core study (Day 182/Month 6) were asked to participate in the extended observation period, for follow-up every 6 months to measure SAP until levels returned to within 20% of baseline. The extended observation period is ongoing, and results are based on available data as of a cut-off

date of approximately 3 months prior to submission of this NDA (18-Jun-2004). For the majority of patients, follow-up occurred within 1 year of the end of the core period. The median follow-up time was 6 months; the maximum was 547 days. Data are provided for the time to first loss of therapeutic response, time to first partial disease relapse, and time to first disease relapse.

Elemental calcium (500 mg) and vitamin D₂ was to be taken by mouth with food (twice daily) beginning at least five days prior to administration of zoledronic acid and during the trial. Since calcium may interfere with the absorption of risedronate, it was to be taken at a different time of day. Calcium carbonate was the preferred form of calcium. If calcium carbonate was not well tolerated, another form of oral calcium was acceptable. In addition, each patient took multiple vitamin supplements containing between 400 and 1000 IU of vitamin D daily; the actual amount varied and was determined by the investigators.

Inclusion and exclusion criteria included the following:

Inclusion criteria

- Male or female patients 30 years and above at the time of entry into the trial who have Paget's disease of bone. Females of child-bearing potential may have been enrolled if they had a negative serum pregnancy test prior to study entry and if they agreed to use acceptable methods of contraception during the study.
- Confirmed diagnosis of Paget's disease of the bone (i.e., by x-ray, magnetic resonance imaging, computerized tomography, radioisotope imaging, etc.).
- Serum alkaline phosphatase level at least two times the upper limit of the normal reference range.
- A normal or not clinically significantly abnormal ECG result during the past 6 months.
- Washout period for other therapies prior to trial drug administration at Visit 2: 90 days for calcitonin and 180 days for any bisphosphonate.
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Exclusion criteria

- Treatment with any investigational drug within the past 30 days.
- History of noncompliance to medical regimens and patients who are considered unreliable.
- Any disease or therapy which would interfere with the procedures or data collection trial.
- Severe liver disease that would affect alkaline phosphatase levels such as hepatitis, primary biliary sclerosis, and cirrhosis.
- History of any of the following: hypersensitivity to bisphosphonates, clinically upper gastrointestinal disorders that could interfere with compliance, urticaria disease with continuing clinically significant abnormality, diabetic nephropathy retinopathy.
- WBC < 3.5 x 10³/mm³, platelets < 125 x 10³/mm³ or any other clinically significant laboratory abnormality.
- Calculated creatinine clearance < 30 mL/min at baseline or urine protein level without evidence of contamination or bacteruria.
- Evidence of vitamin D deficiency (serum 25(OH) D of <15 ng/mL).

- Patients with allergies to tetracycline or any of its derivatives were to be the bone biopsy procedure.
- Active primary hyperparathyroidism.
- Patients with a new diagnosis or active treatment for any malignancy less than 12 months prior to study entry.

The baseline demographic and disease characteristics of the zoledronic acid and risedronate groups were generally well-matched, as shown in the following two tables.

Baseline Demographic Characteristics – Studies 2304 and 2305 (ITT)				
	Study 2304		Study 2305	
	Zoledronic Acid n=90	Risedronate n=82	Zoledronic Acid N=92	Risedronate n=93
Sex – n (%)				
Male	62 (68.9)	61 (74.4)	62 (67.4)	57 (61.3)
Female	28 (31.1)	21 (25.6)	30 (32.6)	36 (38.7)
Race – n (%)				
Caucasian	84 (93.3)	80 (97.6)	84 (91.3)	84 (90.3)
Black	6 (6.7)	2 (2.4)	3 (3.3)	3 (3.2)
Other	0 (0.0)	0 (0.0)	5 (5.4)	6 (6.5)
Age (years)				
Mean (SD)	70.4 (10.25)	72.1 (9.91)	71.3 (9.42)	68.2 (11.15)
Median	72.0	74.0	72.5	70.0
Range	42.0 – 94.0	44.0 – 87.0	45.0 – 92.0	34.0 – 88.0
Age – n (%)				
<65 years	25 (27.8)	17 (20.7)	21 (22.8)	29 (31.2)
≥65 years	65 (72.2)	65 (79.3)	71 (77.2)	64 (68.8)
Weight (kg)				
Mean (SD)	78.5 (16.44)	78.8 (14.74)	76.7 (13.25)	78.4 (17.06)
Median	77.6	77.7	78.0	77.3
Range	39.8 – 132.7	48.0 – 121.1	49.5 – 110.0	44.2 – 133.0

Baseline Disease Characteristics – Studies 2304 and 2305 (ITT)				
	Study 2304		Study 2305	
	Zoledronic Acid	Risedronate	Zoledronic Acid	Risedronate
	(N=90)	(N=82)	(N=92)	(N=93)
Baseline SAP (U/L)				
Mean (SD)	424.5 (335.35)	423.0 (267.35)	431.0 (308.11)	427.4 (348.56)
Median	329.0	321.0	342.5	301.0

Baseline Disease Characteristics – Studies 2304 and 2305 (ITT)

	Study 2304		Study 2305	
	Zoledronic Acid (N=90)	Risedronate (N=82)	Zoledronic Acid (N=92)	Risedronate (N=93)
Range	229.0 - 2822.0	214.0 - 1971.0	230.0 - 2338.0	222.0 - 2377.0
Baseline SAP – n (%)				
< 3xULN	47 (52.2)	45 (54.9)	46 (50.0)	56 (60.2)
≥3xULN	43 (47.8)	37 (45.1)	46 (50.0)	36 (38.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
Creatinine Clearance at Baseline (mL/min)				
Mean (SD)	86.8 (36.51)	84.5 (36.34)	84.2 (28.75)	89.2 (30.26)
Median	77.7	79.2	81.6	88.2
Range	30.6 -217.8	29.4 -228.0	(36.0 - 180.0)	(34.2 - 192.6)
Creatinine Clearance at Baseline – n (%)				
< 30 mL/min	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
30 to < 40 mL/min	3 (3.3)	2 (2.4)	2 (2.2)	1 (1.1)
40 to 50 mL/min	10 (11.1)	7 (8.5)	8 (8.7)	9 (9.7)
> 50 mL/min	77 (85.6)	72 (87.8)	82 (89.1)	83 (89.2)
Last Paget's Disease Therapy Before Randomization - n (%)				
Bisphosphonates	39 (43.3)	39 (47.6)	50 (54.3)	52 (55.9)
Oral	23 (25.6)	28 (34.1)	33 (35.9)	35 (37.6)
IV	13 (14.4)	10 (12.2)	14 (15.2)	16 (17.2)
Clodronate	3 (3.3)	1 (1.2)	3 (3.3)	1 (1.1)
Other	2 (2.2)	2 (2.4)	6 (6.5)	5 (5.4)
None	49 (54.4)	41 (50.0)	36 (39.1)	36 (38.7)
Washout for Bisphosphonates – n (%)				
<180 days	1 (1.1)	0 (0.0)	2 (2.2)	2 (2.2)
180 to < 365 days	4 (4.4)	1 (1.2)	5 (5.4)	3 (3.2)
≥365 days	34 (37.8)	38 (46.3)	43 (46.7)	47 (50.5)
25(OH)D	Zoledronic Acid (2304 & 2305)		Risedronate (2304 & 2305)	
Mean (SD) (nmol/L)	62 (22)		68 (50)	
Mean (ng/ml)	25		27	

Approximately 93% of the subjects in each treatment group completed the 6-month trials. The most common reasons for failure to complete the studies were adverse event (1.1% -2.4%)

protocol violations (0.0% - 3.3%), withdrew consent (1.1% - 3.3%), and lost to follow up (0.0% - 2.4%).

6.1.4 Efficacy Findings

In general, the results of the efficacy outcome analyses were similar for the two pivotal studies; therefore, pooled data from both trials will be provided in this section.

Primary Efficacy Outcome: At Day 182, 169/176 (96%) of the patients in the zoledronic acid group and 127/171 (74%) of the patients in the risedronate group achieved a therapeutic response ($p < 0.001$). The point estimate of the difference between groups in response rates was 22% with a 95% CI of 14%, 30%. From a statistical standpoint, these results demonstrate that zoledronic acid was non-inferior to risedronate (i.e., lower bound of the 95% confidence interval for the difference between groups was above -16%), as well as superior.

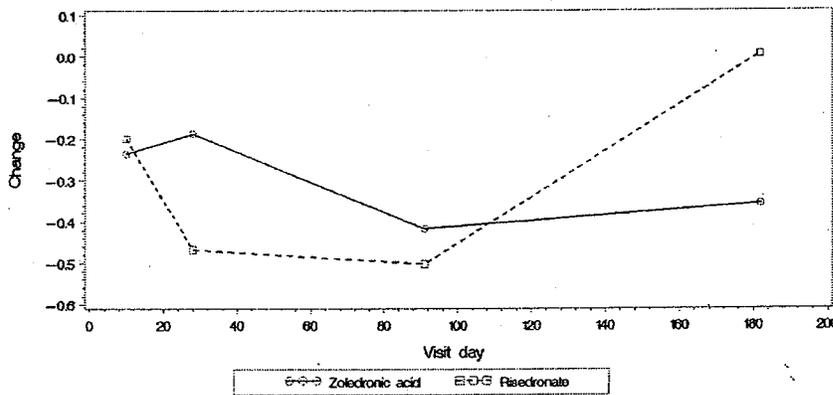
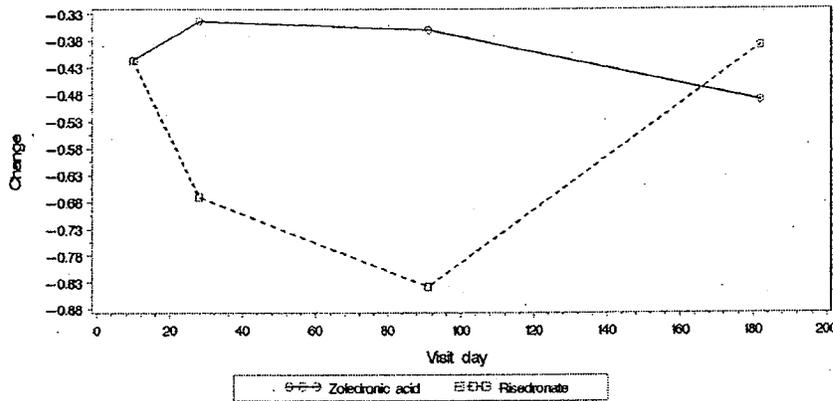
Eighty-nine percent of the zoledronic acid subjects and 58% of the risedronate subjects had normalization of SAP levels by Day 182. Seven percent of the zoledronic acid and 16% of the risedronate subjects had > 75% reduction in SAP excess only at Day 182.

In the Paget's registration trials for risedronate, 77% of patients treated with 30 mg x 2 months had normalization of their SAP levels by Day 180.

Secondary Efficacy Outcomes: The relative changes in serum CTX at Day 10, urine α -CTX at Day 10, and serum SAP at Day 28 were all statistically significantly greater in the zoledronic acid compared with the risedronate group.

Although the within-treatment differences for the changes in scores for BPI-SF pain severity and pain interference were statistically significant (all $p < 0.05$); the between-treatment comparisons for the changes in scores for BPI-SF pain severity and pain interference were not statistically significantly different (p-values 0.3 and 0.9, respectively).

The following two figures depict the pattern of change in the pain severity (top panel) and pain interference (bottom panel) measures for the two treatment groups.



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The proportion of patients who had a normalization of SAP by Day 28 was 13/176 (7%) in the zoledronic acid group and 1/170 (0.5%) in the risedronate group ($p < 0.001$).

The median time to first therapeutic response was 63 days in the zoledronic acid group and 107 days in the risedronate group ($p < 0.001$).

Long-Term Assessment of Efficacy: Following the core 6-month trial, subjects who achieved a therapeutic response and were willing to continue in the study were followed and had their SAP levels checked at 6-month intervals to assess long-term efficacy. At the initiation of the extended observation studies blinding was continued. After database lock for studies 2304 and 2305, the treatment codes were made available to the investigators. The extended observation period continues as of the filing of this NDA. Three parameters, defined below, were used to evaluate long-term efficacy:

- First loss of therapeutic response: the occurrence of a SAP level no longer meets the criteria of a therapeutic response.
- First partial disease relapse: an increase in SAP of at least 50% from the SAP measurement at month 6 and at least 1.25 x UNL

- First disease relapse: the occurrence of a SAP level that was within 20% of the baseline SAP value.

For the majority of patients, follow-up occurred within one year of the end of the core study period. The median follow-up time was 6 months.

The evaluations of long-term efficacy included 113 patients from the zoledronic acid group and 82 from the risedronate group. To date, 21 of the risedronate-treated subjects and one of the zoledronic acid-treated patients lost therapeutic response during the extended observation period (p=0.001). Eleven patients in the risedronate group and one in the zoledronic acid group experienced a partial disease relapse (p=0.01). One risedronate subject and none of the zoledronic acid subjects experienced a relapse of disease.

Efficacy Analyses in Demographic and Disease Subgroups: The primary efficacy outcome variable was assessed by number of previous Paget's treatment cycles, age, gender, race, baseline SAP, last Paget's therapy, and the presence or absence of pain at screening.

Number of Previous Treatment Cycles: The mean number of previous treatment cycles was approximately 1.5 for both groups. Roughly 45% of the patients entered the trial without any previous pharmacological treatment for Paget's. An additional 25% from each group received 1 treatment cycle prior to study entry. About 15% received 2-3 previous treatment cycles and approximately 13% received more than 3 treatment cycles. The following table provides the results of the primary efficacy analysis by previous treatment cycles.

Primary Efficacy Outcome by Number of Previous Treatment Cycles					
Studies 2304 and 2305 Combined					
Subgroup	Zoledronic acid n/N (Proportion)	Risedronate n/N (Proportion)	Difference ¹ (95% CI)	p-value ² for treatment difference	p-value ³ for subgroup interaction
Previous treatment cycles					
None	80/82 (0.98)	65/76 (0.86)	0.12 (0.02, 0.22)	0.0075	0.3553
1	41/45 (0.91)	32/46 (0.70)	0.22 (0.03, 0.40)	0.0098	
2-3	24/24 (1.00)	16/27 (0.59)	0.41 (0.18, 0.64)	0.0005	
>3	24/25 (0.96)	14/22 (0.64)	0.32 (0.06, 0.59)	0.0020	

¹ Difference is zoledronic acid minus risedronate; 95% CI for the difference is based on the normal approximation to the binomial.
² p-value is based on a Mantel-Haenszel test controlling for study for each category.
³ p-value is based on a Breslow-Day test with the subgroup as a controlling factor.
 Studies: 2304, 2305

Comment: It is clear from the above data that the largest differences in response rates between the zoledronic acid and risedronate groups are in the subjects who received previous pharmacological treatment prior to study entry.

Age: The response rates for those < 65 years, 65-74 years, and \geq 75 years were 100%, 97%, and 93% for the respective zoledronic acid groups and 82%, 78%, and 66% for the respective risedronate groups.

Gender: The response rate for females was 97% and 95% for males in the zoledronic acid group and 74% and 75% for the females and males in the risedronate group, respectively.

Race: There were too few patients other than Caucasians to perform meaningful analyses by race.

Baseline SAP: The response rates for those with baseline SAP levels < 3xULN were 97% in the zoledronic acid group and 75% in the risedronate group. For those patients with baseline SAP levels \geq 3xULN, the response rates were 95% and 74% for those in the zoledronic acid and risedronate groups, respectively.

Last Paget's Therapy: For those patients whose last Paget's therapy was an oral bisphosphonate, the response rate was 96% for the zoledronic acid-treated subjects and 55% for the risedronate subjects. For those whose previous therapy was an intravenous bisphosphonate, the response rates were 88% and 81% for the zoledronic acid and risedronate participants, respectively. For those who received clodronate previously, 100% of the subjects treated with zoledronic acid and risedronate responded. For patients who had not been previously treated for Paget's, the response rates were 98% and 86%, respectively, for the zoledronic acid and risedronate groups.

Symptomatic Pain at Screening: Of the patients who did not report pain at screening, 100% of the zoledronic acid and 82% of the risedronate-treated subjects responded. For the roughly 60% of all patients who did have pain at screening, 94% of the zoledronic acid subjects and 70% of the risedronate patients responded to therapy.

6.1.5 Clinical Microbiology

See review by Dr. John Metcalfe

6.1.6 Efficacy Conclusions

Novartis has provided substantial evidence to support the efficacy of a single 5 mg intravenous dose of zoledronic acid in the treatment of Paget's disease. This dosing regimen was statistically significantly more efficacious than therapy with 2 months of 30 mg daily risedronate. The data provided in this application also indicate that a single 5 mg dose of zoledronic acid provides a greater duration of therapeutic response than dose the risedronate regimen. Although both drugs reduced pain scores, the differences between groups were not statistically significant.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This integrated review of safety focuses on the results from the two pivotal Paget's disease trials, 2304 and 2305. Ancillary safety evaluations come from phase 1 and 2 Paget's disease studies, two phase 2 osteoporosis trials, and from one ongoing phase 3 osteoporosis study. Study 2301 is a randomized, placebo-controlled trial of more than 7000 postmenopausal women, and as such, safety data from this study, while partially blinded (treatment groups are designated A and B), will be the focus of the safety assessment from the ancillary data.

Regarding nomenclature, the following abbreviations will be used throughout this review:

- 1) Paget's Studies = the two pivotal Paget's disease studies 2304 and 2305, as well as the phase 1 and 2 studies 001 and 002.
- 2) Studies 2304 and 2305 = the two pivotal phase 3 Paget's disease studies 2304 and 2305.
- 3) Study 2301 = the ongoing postmenopausal osteoporosis fracture trial involving more than 7000 women.

Note: In study 2301, at baseline all subjects had their creatinine clearance (CrCl) calculated using the Cockcroft equation. If a subject's CrCl was less than 30 ml/min, they were excluded from the study. Prior to each dose (Month 12 and 24), serum creatinine, CrCl, and body weight were measured and patients were not to receive study drug if the CrCl was below 30 ml/min. As of the cutoff date for this submission, all of the subjects in each group received infusion #1 and roughly 51% of the subjects in each group had received a second infusion.

7.1.1 Deaths

Paget's Studies: There were four deaths - all occurred in study 002. The causes of death were listed as: DVT, pneumonia, esophageal cancer, and MI.

Study 2301: The incidence of deaths as of the cutoff date were 1.1% and 0.8% in treatment groups A and B, respectively.

7.1.2 Other Serious Adverse Events

Paget's studies: There were a total of 28 SAEs; 7 occurring in the 2 earlier trials using sub therapeutic doses of zoledronic acid, 9 occurring in zoledronic acid 5 mg group, 11 occurring in the risedronate group, and 1 occurring on placebo in Protocol 002. There was no suggestion that one particular SAE occurred at a greater frequency with zoledronic acid use than with risedronate or placebo.

Study 2301: The incidence of SAEs was 12.5% in treatment group A and 11.5% in group B. Although the overall frequency of SAEs was slightly higher (1%) in treatment group A, there

was no suggestion that any specific SAE associated with any particular organ class occurred more frequently with treatment A. A higher frequency of SAEs (≥ 5 patient difference) with treatment A vs. treatment B were observed for the following organ classes: cardiac disorders (2.4% vs. 2.2%), with ≥ 5 patient difference seen for atrial fibrillation (16 vs. 8 patients), acute myocardial infarction (8 vs. 2 patients) - [note for preferred term "myocardial infarction" the frequency was higher in treatment group B (21 patients) than in treatment group A (12 patients)], gastrointestinal disorders (2.2% vs. 1.6%), a difference of ≥ 5 patients seen for vomiting (11 vs. 5 patients) and upper abdominal pain (6 vs. 1 patients); general disorders and administrative site conditions (0.9% vs. 0.6%), a difference of ≥ 5 patients being seen for pyrexia (9 vs. 2 patients) and asthenia (8 vs. 3 patients); infections and infestations (2.4% vs. 1.9%), a difference of ≥ 5 patients seen for acute bronchitis (7 vs. 1 patients); metabolism and nutritional disorders (0.5% vs. 0.3%); musculoskeletal and connective tissue disorders (1.4% vs. 1.2%) a difference of ≥ 5 patients seen with arthralgia (9 vs. 3 patients), myalgia (5 vs. 0 patients); nervous system disorders (2.3% vs. 1.8%) with a difference of ≥ 5 patients seen for cerebrovascular accident (17 vs. 10 patients); psychiatric disorders (0.3% vs. 0.1%) A lower frequency of SAEs (≥ 5 patients) with treatment A vs. treatment B was observed for the following organ classes: endocrine (0.05% vs. 0.2%); hepato-biliary disorders (0.3% vs. 0.7%); neoplasms (1.5% vs. 1.7%); respiratory, thoracic and mediastinal disorders (0.7% vs. 0.9%).

Of the 485 SAEs in treatment group A and 446 SAEs in group B, the majority occurred more than 30 days after study drug infusion, with 90 and 59 SAEs occurring within 30 days for treatment group A and B, respectively.

The number of SAEs occurring within the first 3 days after study drug administration was low in both groups (31 [0.8%] in treatment group A, 14 [0.4%] in group B), with no SAE related to a specific preferred term occurring in more than 0.13% of patients in either group. The small difference in overall frequency was accounted for by a slightly higher number of SAEs of pyrexia (5 vs. 2 patients); myalgia (4 vs. 0 patients); arthralgia (3 vs. 0 patients); and dizziness (3 vs. 0 patients).

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Paget's Studies: There was a very low incidence of patient drop outs ~ 4% or less for the zoledronic, risedronate, and placebo groups.

7.1.3.2 Adverse events associated with dropouts

Paget's Studies: Eight zoledronic acid and 2 risedronate patients discontinued from the studies due to an adverse event; all took place in the two phase 3 trials. The Preferred Terms reported in the zoledronic acid groups included peripheral edema, pyrexia, vomiting, dyspepsia, asthenia, abdominal pain, and hypocalcemia (n=1). The Preferred Terms reported in the risedronate groups

included hypocalcemia (n=1) and confusional state. The majority of these adverse events occurred within 10 days of receiving the initial dose of study medication.

7.1.3.3 Other significant adverse events

Renal Abnormalities

Because zoledronic acid has been associated with renal injury (i.e., increases in serum creatinine), a specific evaluation of renal-related adverse events was conducted by Novartis.

Paget's Studies: There were 2 patients with reports of renal-related AEs in the zoledronic acid groups (creatinine clearance decreased and urinary retention) and 3 patients in the risedronate group (hematuria x 2 and renal impairment).

Renal abnormalities (defined as urine protein >2+ on dipstick and /or serum creatinine increase by >0.5 mg/dL) occurred in four zoledronic acid subjects, two risedronate subjects, and none of the placebo patients. Review of the case narratives for these reports does not provide strong support for a causal relationship between the events and use of either drug.

Study 2301: No cases of urine protein >2+ on dipstick and /or serum creatinine increase by >0.5 mg/dL have been reported for patients in Treatment groups A or B.

Upper GI Abnormalities

Bisphosphonates, primarily oral formulations, have been linked in post-approval assessments with an increased incidence of upper GI AEs.

Paget's Studies: Upper GI AEs occurred in 18.6% and 16.3% of patients in the zoledronic acid 5 mg and risedronate groups, respectively. Other than small differences in the incidence of nausea (higher for zoledronic acid 5 mg) or upper abdominal pain (higher for risedronate) between the groups, the individual upper GI AEs were evenly distributed across study groups.

7.1.4 Other Search Strategies

Because bisphosphonates, particularly intravenously-administered ones, are associated with symptoms consistent with an acute phase reaction, special attention was paid to the following adverse events reported within a few days of zoledronic acid administration: pyrexia, influenza-like symptoms, arthralgia, fatigue, rigors, and myalgia.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

According to Novartis, the investigational sites were instructed to ask patients at every visit after screening whether or not they had any adverse events to report.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The adverse event categorization and use of preferred terms appears to have been appropriate.

7.1.5.3 Incidence of common adverse events

Studies 2304 and 2305: The incidence of adverse events was 83% vs. 77% in the zoledronic acid and risedronate groups, respectively.

7.1.5.4 Common adverse event tables

Paget's Studies: The following table provides the common adverse events ($\geq 5\%$ incidence) in patients from the Paget's Studies.

	Adverse Events that Occurred in at Least 5% of Patients in any Group from the Paget's Studies			
	Phase III studies		Phase I/II studies	
	Zoledronic acid 5 mg n (%)	Risedronate n (%)	Zoledronic acid 24-400 µg n (%)	Placebo n (%)
Patients studied				
Total no. studied	177 (100)	172 (100)	157 (100)	35 (100)
Total no. with an AE	146 (82.5)	133 (77.3)	120 (76.4)	29 (82.9)
Adverse events				
Headache	19 (10.7)	17 (9.9)	16 (10.2)	4 (11.4)
Influenza-like illness	19 (10.7)	10 (5.8)	10 (6.4)	0 (0.0)
Arthralgia	16 (9.0)	19 (11.0)	25 (15.9)	9 (25.7)
Nausea	16 (9.0)	11 (6.4)	7 (4.5)	2 (5.7)
Bone pain	15 (8.5)	8 (4.7)	14 (8.9)	3 (8.6)
Dizziness	15 (8.5)	7 (4.1)	4 (2.5)	3 (8.6)
Pyrexia	15 (8.5)	3 (1.7)	3 (1.9)	0 (0.0)
Fatigue	14 (7.9)	7 (4.1)	16 (10.2)	1 (2.9)
Rigors	14 (7.9)	2 (1.2)	4 (2.5)	0 (0.0)
Influenza	13 (7.3)	8 (4.7)	0 (0.0)	0 (0.0)
Myalgia	13 (7.3)	7 (4.1)	3 (1.9)	0 (0.0)
Pain in extremity	13 (7.3)	13 (7.6)	17 (10.8)	6 (17.1)
Diarrhea	11 (6.2)	10 (5.8)	1 (0.6)	3 (8.6)
Nasopharyngitis	11 (6.2)	14 (8.1)	6 (3.8)	2 (5.7)
Constipation	10 (5.6)	9 (5.2)	1 (0.6)	1 (2.9)
Dyspepsia	9 (5.1)	6 (3.5)	2 (1.3)	0 (0.0)
Fall	9 (5.1)	5 (2.9)	0 (0.0)	0 (0.0)
Lethargy	9 (5.1)	1 (0.6)	3 (1.9)	1 (2.9)

Adverse Events that Occurred in at Least 5% of Patients in any Group from the Paget's Studies

	Phase III studies		Phase I/II studies	
	Zoledronic acid 5 mg	Risedronate	Zoledronic acid 24-400 µg	Placebo
Back pain	7 (4.0)	12 (7.0)	22 (14.0)	3 (8.6)
Edema peripheral	5 (2.8)	1 (0.6)	3 (1.9)	5 (14.3)
Asthenia	4 (2.3)	1 (0.6)	2 (1.3)	2 (5.7)
Cough	4 (2.3)	8 (4.7)	4 (2.5)	2 (5.7)
Paraesthesia	4 (2.3)	0 (0.0)	3 (1.9)	2 (5.7)
Hot flush	3 (1.7)	1 (0.6)	1 (0.6)	2 (5.7)
Upper resp. tract inf.	3 (1.7)	6 (3.5)	10 (6.4)	3 (8.6)

7.1.5.5 Identifying common and drug-related adverse events

Paget's Studies: Based on existing data for intravenously administered bisphosphonates, the following adverse events are biologically plausibly related to zoledronic acid use: influenza-like illness, nausea, bone pain, pyrexia, rigors, influenza, myalgia, and lethargy.

The following table provides the adverse events that occurred with an incidence of at least 2% in either group and were suspected by the investigators to be "drug-related."

Adverse Events that with an Incidence of at least 2% Patients in Either Group and Thought to be Drug-Related by the Study Investigators

	Phase III studies		Phase I/II studies	
	Zoledronic acid 5 mg n (%)	Risedronate n (%)	Zoledronic acid 24-400 µg n (%)	Placebo n (%)
Patients studied				
Total no. studied	177 (100)	172 (100)	157 (100)	35 (100)
Total no. with an AE	92 (52.0)	43 (25.0)	65 (41.4)	16 (45.7)
Adverse events				
Influenza-like illness	16 (9.0)	9 (5.2)	4 (2.5)	0 (0.0)
Pyrexia	13 (7.3)	1 (0.6)	3 (1.9)	0 (0.0)
Rigors	13 (7.3)	1 (0.6)	4 (2.5)	0 (0.0)
Headache	12 (6.8)	6 (3.5)	7 (4.5)	2 (5.7)
Myalgia	11 (6.2)	6 (3.5)	3 (1.9)	0 (0.0)
Nausea	10 (5.6)	3 (1.7)	6 (3.8)	1 (2.9)
Bone pain	9 (5.1)	2 (1.2)	8 (5.1)	2 (5.7)
Fatigue	9 (5.1)	3 (1.7)	12 (7.6)	0 (0.0)
Arthralgia	7 (4.0)	3 (1.7)	16 (10.2)	3 (8.6)
Lethargy	7 (4.0)	1 (0.6)	1 (0.6)	1 (2.9)
Influenza	6 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)
Pain	6 (3.4)	4 (2.3)	2 (1.3)	0 (0.0)
Hypocalcemia	5 (2.8)	1 (0.6)	0 (0.0)	0 (0.0)
Asthenia	4 (2.3)	1 (0.6)	2 (1.3)	0 (0.0)
Diarrhea	4 (2.3)	0 (0.0)	1 (0.6)	1 (2.9)
Dyspepsia	4 (2.3)	4 (2.3)	0 (0.0)	0 (0.0)
Dyspnea	4 (2.3)	0 (0.0)	1 (0.6)	0 (0.0)
Back pain	3 (1.7)	2 (1.2)	13 (8.3)	1 (2.9)

Adverse Events that with an Incidence of at least 2% Patients in Either Group and Thought to be Drug-Related by the Study Investigators

	Phase III studies		Phase I/II studies	
	Zoledronic acid 5 mg n (%)	Risedronate n (%)	Zoledronic acid 24-400 µg n (%)	Placebo n (%)
Paraesthesia	2 (1.1)	0 (0.0)	3 (1.9)	1 (2.9)
Body temperature increased	1 (0.6)	2 (1.2)	4 (2.5)	0 (0.0)
Hot flush	1 (0.6)	0 (0.0)	1 (0.6)	2 (5.7)
Night sweats	1 (0.6)	0 (0.0)	0 (0.0)	1 (2.9)
Chest wall pain	0 (0.0)	0 (0.0)	2 (1.3)	1 (2.9)
Flushing	0 (0.0)	0 (0.0)	2 (1.3)	1 (2.9)
Injection site reaction	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)
Muscle cramp	0 (0.0)	1 (0.6)	4 (2.5)	0 (0.0)
Edema peripheral	0 (0.0)	0 (0.0)	1 (0.6)	1 (2.9)
Pain in extremity	0 (0.0)	2 (1.2)	11 (7.0)	3 (8.6)

7.1.5.6 Additional analyses and explorations

Paget's Studies: The following adverse events occurred with a greater incidence in the zoledronic acid vs. the risedronate groups during the first three days after zoledronic acid administration: influenza-like symptoms, myalgia, pyrexia, fatigue, headache, nausea, and arthralgia.

Study 2301: The following table provides a summary of important partially-blinded safety information from Study 2301, an ongoing trial of over 7000 postmenopausal women with osteoporosis.

Number (%) of Subjects Who Died, Had Other Serious or Clinically Significant AEs or Discontinued Because of Them - Ongoing Study in Post-Menopausal Osteoporosis - 2301

	Treatment A n=3876	Treatment B n=3866
	n (%)	n (%)
Serious or significant AEs	2789 (72.0)	2265 (58.6)
Death	44 (1.1)	31 (0.8)
SAEs	485 (12.5)	446 (11.5)
Discontinuation due to SAEs	69 (1.8)	52 (1.3)
Discontinuation due to non-serious AEs	27 (0.7)	15 (0.4)
Lab abnormalities leading to premature discontinuation	1 (0.0)	2 (0.1)
AEs causing concomitant medication taken	2466 (63.6)	2147 (55.5)
AEs due to IV study drug administration (1)	1248 (32.2)	239 (6.2)
Renal AEs leading to deterioration of renal function	37 (1.0)	26 (0.7)
Hypocalcemia* (numbers from 12-day safety update)	7 (0.2)	0 (0.0)

Source: (1) Adverse events classified in this group are any occurrences of pyrexia, myalgia, arthralgia, bone pain, and influenza-like illness occurring within 3 days of study drug infusion.

* There was no standard definition of hypocalcemia, but patients were not to be dosed if their serum calcium level went below 8.0 mg/dl. Of the 5 patients in treatment group A who had a Day 10 serum calcium value, two were below normal. Four of the 7 patients did not have serum calcium levels drawn, even though they were recorded as having hypocalcemia (based on symptoms).

A total of 37 subjects in treatment group A and 26 in treatment group B had AEs related to deterioration in kidney function. Nineteen of treatment group A and 7 of treatment group B subjects developed increases in serum creatinine (120-day safety update). In the majority of these cases, the increases in serum creatinine occurred soon after receiving the study drug. Most of the increases were transient. Two of the 19 patients in Treatment group A received intravenous fluids in response to their increased creatinine levels. Six (0.15%) and 5 (0.13%) of the patients in treatment groups A and B, respectively, had renal impairment. Five (0.13%) and 4 (0.10%) of the treatment group A and B subjects, respectively, developed acute renal failure. And one treatment group A subject and none of the treatment group B subjects developed azotemia.

7.1.6 Less Common Adverse Events

Some of the less common adverse events that occurred with a greater incidence in the zoledronic acid groups compared with the risedronate groups include peripheral edema (2.8% vs. 0.6%), asthenia (2.3% vs. 0.6%), paraesthesia (2.3% vs. 0.0%), and hot flush (1.7% vs. 0.6%)

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Studies 2304 and 2305: The following laboratory parameters were obtained during the pivotal studies:

- Hematology at Baseline and Day 182: hematocrit, hemoglobin, platelet count, RBC, WBC, percent basophils, eosinophils, neutrophils, monocytes and lymphocytes
- Biochemistry at Baseline, Days 10, 63, 182: glucose, creatinine, BUN, total protein, AST, ALT, GGT, alkaline phosphatase, sodium, potassium, uric acid, chloride, phosphate, magnesium, albumin, calcium, bicarbonate, calculated creatinine clearance (Cockcroft-Gault equation)
- Urinalysis at Baseline and Days 10 and 182: protein, pH, specific gravity

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The two pivotal Paget's disease studies were active-controlled with risedronate.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Studies 2304 and 2305: Changes in hematology parameters from baseline to Day 182 are reported for the zoledronic acid and risedronate groups.

For the biochemistry parameters, comparisons between zoledronic acid and risedronate were made at post-infusion Days 10, 63, and 182. While the Day 182 values are provided below, this Reviewer examined the other time points, and provide comments if clinically meaningful changes between groups were noted.

The baseline values for the following parameters were not statistically significantly different between the two treatment groups.

- Basophils: The mean changes from baseline to Day 182 were 0.0% and 0.1% in the zoledronic acid and risedronate groups, respectively.
- Platelets: The mean changes from baseline to Day 182 were 1.7 10E9/L and -1.9 10E9/L in the zoledronic acid and risedronate groups, respectively.
- Eosinophils: The mean changes from baseline to Day 182 were 0.3% and 0.1% in the zoledronic acid and risedronate groups, respectively.
- Lymphocytes: The mean changes from baseline to Day 182 were 1.1% and 0.5% in the zoledronic acid and risedronate groups, respectively.
- Monocytes: The mean changes from baseline to Day 182 were 0.1% and 0.3% in the zoledronic acid and risedronate groups, respectively.
- Neutrophils: The mean changes from baseline to Day 182 were -1.5% and 0.9% in the zoledronic acid and risedronate groups, respectively.
- WBC: The mean changes from baseline to Day 182 were 0.1 10E9/L in each group.
- RBC: There were no changes in the mean values for this parameter in either group.
- Hematocrit: There were no mean changes in either group from baseline to Day 182.
- Hemoglobin: The mean changes from baseline to Day 182 were -0.6 g/L and -1.5 g/L in the zoledronic acid and risedronate groups, respectively.
- Albumin: The mean changes from baseline to Day 182 were -0.1 g/L and -0.3 g/L in the zoledronic acid and risedronate groups, respectively.
- BUN: The mean changes from baseline to Day 182 were 0.2 mmol/L in each group.

- Serum Calcium: There were no changes in the mean values for this parameter in either group at the Day 182 time point. At Day 10 post-infusion, the mean changes were -0.2 mmol/L and -0.1 mmol/L in the zoledronic acid and risedronate groups, respectively.
- Serum Chloride: The mean changes from baseline to Day 182 were 0.7 mmol/L and 0.1 mmol/L in the zoledronic acid and risedronate groups, respectively.
- Creatinine Clearance: At Day 10, the mean changes were 5.4 ml/min and -0.6 ml/min in the zoledronic acid and risedronate groups, respectively. At Day 182, the mean changes were -9.0 ml/min and -2.0 ml/min in the zoledronic acid and risedronate groups, respectively.
- Serum Creatinine: At Day 10, the mean changes were -4.4 umol/L and -0.1 umol/L in the zoledronic acid and risedronate groups, respectively. At Day 182, the mean changes were 3.7 umol/L and 1.1 umol/L in the zoledronic acid and risedronate groups, respectively.
- Serum Glucose: The mean changes at Day 182 were 0.1 mmol/L and -0.1 mmol/L in the zoledronic acid and risedronate groups, respectively.
- Serum Magnesium: There were no changes in the mean values for this parameter in either treatment group, at any of the post-infusion time points.
- Serum Phosphate: There were no changes in the mean values for this parameter in either group at Day 182.
- Serum Potassium: The mean changes at Day 182 were 0.0 mmol/L and -0.1 mmol/L in the zoledronic acid and risedronate groups, respectively.
- Serum iPTH: The mean changes at Day 182 were 0.7 pmol/L and 0.2 pmol/L in the zoledronic acid and risedronate groups, respectively.
- AST: The mean changes at Day 182 were -3.6 U/L and -1.9 U/L in the zoledronic acid and risedronate groups, respectively.
- ALT: The mean changes at Day 182 were 0.7 U/L and 0.5 U/L in the zoledronic acid and risedronate groups, respectively.
- Serum Sodium: The mean changes at Day 182 were -0.5 mmol/L and 0.8 mmol/L in the zoledronic acid and risedronate groups, respectively.
- Total Protein: The mean changes at Day 182 were 0.1 g/L and -0.3 g/L in the zoledronic acid and risedronate groups, respectively.

- Serum Uric Acid: At Day 10, the mean changes were -31.1 umol/L and -11.1 umol/L in the zoledronic acid and risedronate groups, respectively. At Day 63, the mean changes were -13.0 umol/L and -14.0 umol/L in the zoledronic acid and risedronate groups, respectively. At Day 182, the mean changes were -7.1 umol/L and -4.7 umol/L in the zoledronic acid and risedronate groups, respectively.

Comment: When Novartis was asked to provide data on changes in serum levels of LDH and total bilirubin, they responded that bilirubin was not measured "due to the lack of any signal in the previous studies and no known mechanism for liver toxicity for the class of bisphosphonates or zoledronic acid." Review of the summaries of data from the trials of patients with cancer and hypercalcemia of malignancy do not suggest that treatment with zoledronic acid was associated with an increased risk for clinically significant elevations of serum bilirubin compared with treatment with placebo or pamidronate. The lack of data on serum LDH from previous trials of zoledronic acid and from the Paget's studies is probably not important given the availability of data on hepatic transaminases.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Studies 2304 and 2305: Definitions of high and low laboratory parameters can be found in the Appendix.

- Platelets: At Day 182, 2 (1.3%) of the zoledronic acid and 1 (0.7%) of the risedronate subjects who had normal baseline platelet levels had high levels.
- Eosinophils: At Day 182, 1 (0.6%) of the zoledronic acid and 4 (2.6%) of the risedronate subjects who had normal baseline eosinophil levels had high levels.
- Hematocrit: At Day 182, 3 (1.9%) of the zoledronic acid and 3 (2.0%) of the risedronate subjects who had normal baseline hematocrit levels had low levels.
- Hemoglobin: At Day 182, 3 (1.9%) of the zoledronic acid and 6 (3.9%) of the risedronate subjects who had normal baseline hemoglobin levels had low levels.
- Lymphocytes: At Day 182, 3 (1.9%) of the zoledronic acid and 3 (2.0%) of the risedronate subjects who had normal baseline lymphocyte levels had low levels.
- Neutrophils: At Day 182, 7 (4.4%) of the zoledronic acid and 1 (0.7%) of the risedronate subjects who had normal neutrophil levels had high levels.
- RBC: At Day 182, 2 (1.3%) of the zoledronic acid and none of the risedronate subjects who had normal baseline RBC levels had low levels.
- WBC: At Day 182, 4 (2.5%) of the zoledronic acid and 3 (2.0%) of the risedronate subjects who had normal baseline WBC levels had high levels. One (0.6%) of the zoledronic acid subjects and 1 (0.7%) of the risedronate subjects who had normal baseline WBC levels had low levels at Day 182.
- BUN: At Day 10, none of the zoledronic acid and 2 (1.3%) of the risedronate subjects who had normal baseline BUN levels had high levels. At Day 63, 5 (3.0%) of the zoledronic acid and 5 (3%) of the risedronate subjects who had normal baseline BUN levels had high levels. Numbers similar to those at Day 63 were noted at Day 182 for both treatment groups.

- Creatinine Clearance: At Day 10, 7 (4.5%) of the zoledronic acid and 10 (6.3%) of the risedronate subjects who had normal baseline creatinine levels had low levels. At Day 182, none of the zoledronic acid and none of the risedronate subjects who had normal baseline levels had low creatinine clearance values.
- Creatinine: At Day 10, none of the subjects in either group who had normal baseline values for serum creatinine had high values. Of the 3 subjects in the zoledronic acid group who had high baseline serum creatinine values, 2 had high values at Day 10. One risedronate subject had a high baseline creatinine level, which remained high at Day 10. At Day 63, 2 (1.2%) of the zoledronic subjects and 1 (0.6%) of the risedronate subjects who had normal baseline creatinine values had high values. Of the 4 zoledronic acid subjects who had high baseline creatinine values, 3 had high levels at Day 63. One risedronate subject who had a high baseline creatinine also had a high value at Day 63. At Day 182, 2 (1.2%) of the zoledronic acid subjects and 1 (0.6%) of the risedronate subjects who had normal baseline creatinine levels had high levels.
- Calcium: At Day 10, 32 (20%) of the zoledronic acid and 4 (2.5%) of the risedronate subjects who had normal serum calcium levels at baseline had low levels. At Day 63, 4 (2.4%) of the zoledronic acid and 8 (4.8%) of the risedronate subjects who had normal baseline calcium levels had low levels. At Day 182, none of the subjects in either group had low serum calcium levels.
- Magnesium: At Day 10, 1 (0.6%) of the zoledronic acid and none of the risedronate subjects who had normal baseline magnesium levels had low levels. At Day 10, 10 (6.4%) of the zoledronic acid and 5 (3.1%) of the risedronate subjects who had normal baseline values had high serum magnesium levels. At Day 63, none of the subjects in either group who had normal baseline values had low levels. Six (3.6%) of the zoledronic acid and 4 (2.4%) of the risedronate subjects with normal baseline magnesium levels had high levels at Day 63. At Day 182, 9 (5.4%) of the zoledronic acid and 2 (1.3%) of the risedronate subjects with normal baseline levels had high levels.
- Phosphate: At Day 10, 28 (18%) of the zoledronic acid and 2 (1.3%) of the risedronate subjects with normal baseline values had low levels.
- iPTH: At Day 91, 18 (12%) of the zoledronic acid and 20 (13%) of the risedronate subjects with normal baseline iPTH levels had high levels. At Day 182, 5 (3.2%) of the zoledronic acid and 4 (2.6%) of the risedronate subjects with normal baseline values had high values.
- AST: At Day 10, 4 (2.7%) of the zoledronic acid and 10 (6.5%) of the risedronate subjects with normal baseline values had high values. At Day 63, none of the zoledronic acid and 7 (4.3%) of the risedronate subjects with normal baseline values had high values. At Day 182, 1 (0.6%) of the zoledronic acid and 3 (1.9%) of the risedronate subjects with normal baseline values had high values.
- ALT: At Day 10, 8 (5.3%) of the zoledronic acid and 5 (3.2%) of the risedronate subjects who had normal baseline values had high values. At Day 63, 5 (3.0%) of the zoledronic acid and 7 (4.2%) of the risedronate subjects who had normal baseline values had high values. At Day 182, 7 (4.2%) of the zoledronic acid and 8 (5.1%) of the risedronate subjects with normal baseline values had high values.

- Uric Acid: At Day 10, 2 (1.3%) of the zoledronic acid and 5 (3.1%) of the risedronate subjects who had normal baseline values had high values.

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

Previous clinical trials demonstrated that treatment with a single 4 mg infusion of zoledronic acid caused reductions in serum concentrations of calcium and phosphate, and increases in serum creatinine, with nadirs observed 9-11 days post-infusion. In this section, focus is paid to the "notably" low serum calcium and phosphate and high serum creatinine levels observed during Studies 2304 and 2305.

Serum Calcium: Five zoledronic acid and one risedronate-treated subject developed a serum calcium level < 1.87 mmol/L at any time during the two trials.

Serum Phosphate: None of the patients in either group developed a serum phosphorus level that was notably low.

Serum Creatinine: One zoledronic acid and none of the risedronate-treated subjects developed a serum creatinine > 221 umol/L at any time during the two trials.

7.1.7.4 Additional analyses and explorations

This section provides additional analyses of low serum calcium and phosphorus levels and high serum creatinine levels.

Serum Calcium

Studies 2304 and 2305: The following table shows the serum calcium levels at various time points during the studies for the 32 zoledronic acid and the 4 risedronate subjects who had normal baseline serum calcium levels and then developed a calcium concentration < 2.1 mmol/L at or near Day 10 post-dose.

The absolute and relative risks of hypocalcemia at Day 10 post-dose for the zoledronic acid and risedronate groups were: 32/151 (21%) vs. 5/156 (3.0%); RR = 6.6 (2.8, 19.4)

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**Demographic Characteristics of the Subjects who Developed
 Low Serum Calcium Levels At or Near Day 10 Post-Infusion**

Subject	Country	Age	Sex	Race	Calcium Baseline	Calcium Day 10	Calcium Day 29	Calcium Day 63	Calcium Day 92	Calcium Day 182
Zoledronic Acid Group										
005	Aus	75	F	W						
062	Aus	78	M	W						
071	Aus	84	M	W						
183	Aus	79	M	W						
012	Aus	73	M	W						
120	Aus	70	M	W						
155	Aus	51	M	W						
175	Aus	83	F	W						
204	Aus	56	M	W						
258	Aus	66	M	W						
303	Aus	70	M	W						
297	Aus	55	M	W						
061	Can	68	M	V						
179	Can	62	M	W						
083	GBR	80	F	W						
235	GBR	47	F	B						
086	NZL	78	M	W						
088	NZL	73	M	W						
187	NZL	72	M	W						
232	NZL	72	M	W						
233	NZL	73	F	W						
293	Aus	68	M	W						
114	Aus	84	F	W						
094	Aus	51	M	W						
349	ESP	71	F	W						
026	GBR	76	M	W						
075	NZL	77	M	W						
142	NZL	78	F	W						
303	NZL	63	M	W						
145	USA	64	F	W						
002	USA	78	M	W						
181	ZAF	74	F	O						
Risedronate Group*										
039	Aus	76	M	W						
152	Aus	78	F	W						
261	Aus	72	F	W						
239	ZAF	73	F	O						

Lower limit of normal for serum calcium is 2.1 mmol/L

The actual day the calcium level was drawn may vary ± a few days

*An additional patient who received risedronate developed a serum calcium of 5.4 mg/dl during the Day 9-11 visit. Because the blood was analyzed at a local lab, the information was not included in the above table.

The vast majority of the patients in both groups who developed low serum calcium levels were reportedly without symptoms and few received specific interventions to correct their low levels.

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 {Zoledronic Acid for Paget's disease}

Study 2301: Six (0.2%) of the subjects from treatment group A and 1 from treatment group B (<0.1%) developed serum calcium levels < 1.87 mmol/L.

Serum Phosphorus

Studies 2304 and 2305: The following table shows the serum phosphorus levels at various time points during the studies for the 18 zoledronic acid and the 2 risedronate subjects who had normal baseline serum phosphate levels and then developed a phosphate concentration < 0.71 mmol/L at or near Day 10 post-dose.

The absolute and relative risks of hypophosphatemia at Day 10 post-dose for the zoledronic acid and risedronate groups were: 28/157 (18%) vs. 2/159 (1.3%); RR = 14.2 (4.1, 108.6)

Demographic Characteristics of the Subjects who Developed Low Serum Phosphorus Levels At or Near Day 10 Post-Infusion

Subject	Country	Age	Sex	Race	PO4 Baseline	PO4 Day 10	PO4 Day 29	PO4 Day 63	PO4 Day 92	PO4 Day 182
Zoledronic Acid Group										
012	Aus	73	M	W						
204	Aus	56	M	W						
258	Aus	66	M	W						
303	Aus	70	M	W						
004	Can	58	M	W						
010	Can	60	M	W						
061	Can	68	M	W						
099	Can	64	M	W						
102	Can	82	M	W						
113	Can	58	M	W						
083	GBR	80	F	W						
235	GBR	47	F	B						
093	GBR	72	M	W						
291	GBR	88	M	W						
088	NZL	73	M	W						
233	NZL	73	F	W						
274	USA	84	M	W						
114	Aus	84	F	W						
094	Aus	51	M	W						
212	Aus	61	M	W						
201	ESP	70	M	W						
369	FRA	77	F	B						
204	GBR	88	F	W						
347	GBR	75	M	W						
075	NZL	77	M	W						
137	USA	76	F	W						
353	USA	77	M	W						
235	ZAF	71	M	O						
Risedronate Group										
096	AUS	65	M	W						
288	AUS	58	M	W						

Lower limit of normal for PO4 is 0.71 mmol/L
The actual day the calcium level was drawn may vary \pm a few days

Most if not all of the subjects who developed low serum phosphorus concentrations spontaneously normalized their levels.

Serum calcium and phosphorus levels at Day 63: In the trials that served as the basis of approval of risedronate for Paget's disease, the regimen of 30 mg per day x 2 months led to nadirs in serum calcium and phosphorus levels at or near Day 56. This suggests that the nadir for serum calcium and phosphorus levels in the subjects treated with risedronate in the zoledronic acid studies should have occurred near the Day 63 time point.

Of the subjects who had normal serum calcium levels at baseline, 4 (2.4%) of the zoledronic acid subjects and 8 (4.8%) of the risedronate subjects had low serum calcium levels at Day 63. Of the subjects who had normal serum phosphorus levels at baseline, 1 (0.6%) of the zoledronic acid subjects and none of the risedronate subjects had low serum phosphorus levels at Day 63.

In the pivotal Paget's studies for alendronate, in which 40 mg was administered daily for 6 months, serum calcium and phosphorus were measured at Months 1, 3 and 6. The nadirs for these two minerals appeared to have occurred at the Month 1 time point. The mean reductions in serum calcium and phosphorus at Month 1 were -0.45 mg/dl and -0.47 mg/dl, respectively. In the zoledronic acid trials, the Day 10 mean reductions in serum calcium and phosphorus were -0.8 mg/dl and -1.7 mg/dl, respectively. Further, approximately 19% of the alendronate treated subjects developed serum calcium levels below 8.5 mg/dl, compared with approximately 32% of the zoledronic acid subjects. One (1.5%) of the alendronate patients developed a serum calcium level below 8.0 mg/dl vs. 12 (8%) of the zoledronic acid-treated participants.

Study 2301: A total of 40 (1.1%) of the subjects in Treatment group A and 10 (0.3%) of the subjects in Treatment group B developed serum phosphorus values below 0.71 mmol/L at Day 10 (120-day safety update).

Comment: The above data indicate that a significantly greater percentage of patients treated with zoledronic acid compared with risedronate developed mostly asymptomatic hypocalcemia and hypophosphatemia within the first two weeks post-dosing. Given the potent antiresorptive action of a single 5 mg infusion of zoledronic acid compared with daily oral doses of other bisphosphonates, these findings are not surprising. Novartis states that to the best of their knowledge, of the 32 patients who developed low calcium levels at Day 10, 3 patients received specific interventions in an attempt to increase their low levels (e.g., instructed to take calcium supplements after it was discovered that they were not taking as directed). The rest of the subjects presumably normalized their serum calcium and phosphorus levels spontaneously.

Unfortunately, Novartis does not have data regarding the specific amounts of daily calcium or vitamin D the subjects actually took. Without this information it is not possible to determine if the increased frequency of hypocalcemia and hypophosphatemia in the

zoledronic acid-treated patients was related to poor compliance with, or inadequate doses of, the calcium and vitamin D supplements, or whether the results are simply due to the antiresorptive potency of the drug.

Renal Abnormalities and Adverse Events

Studies 2304 and 2305: As discussed in the below paragraphs, there were 5 reported adverse renal events, two occurring in the zoledronic acid 5 mg group and three in the risedronate group.

One patient (0455/00109) in the zoledronic acid 5 mg group had a clinically notable increase in serum creatinine, defined as a post-baseline value that increased by at least 0.05 mg/dl. Creatinine for this patient had been above the normal range at screening (189 $\mu\text{mol/L}$) and remained high for the following two visits (200- 212 $\mu\text{mol/L}$, Days 13 & 63). The high levels were attributed to congestive heart failure as well as to the treatment course, especially diuretics and ACE-inhibitors. Creatinine had decreased by the time of the first visit of the extension observation period. See Appendix for details of this case.

One patient (0452/00213) in the 5 mg zoledronic acid group had urinary retention which was moderate in severity, and related to a progression of urethral stenosis stemming from previous prostate surgery for benign prostatic hypertrophy. There was no evidence of renal compromise in this patient. This event did not require the patient to be discontinued from the study.

Three patients in the risedronate group had AEs associated with renal deterioration: hematuria in two patients and renal impairment in one. For the two patients with hematuria, both events were mild in severity, and did not require patients' discontinuation from the study. For the patient with renal impairment (0605/00199), the event was serious, and moderate in severity. The patient had several other serious AEs and was discontinued from the study as a result of the AE of confusion.

The following table provides the number and percentage of subjects in each group who developed at least +1 urinary protein (by dipstick) at any time post-baseline.

Baseline CrCl ml/min	Subjects Who Developed +1 or greater Urinary Protein by Dipstick					
	Zoledronic Acid			Risedronate		
	N	n	%	N	n	%
< 40	5	0	0	4	0	0
40 - 50	18	0	0	15	0	0
> 50	148	12	8.1	150	10	6.7
All Subjects	171	12	7	169	10	5.9

Study 2301: Three (0.1%) of the subjects in treatment group A and 2 (<0.1%) of the subjects in treatment group B developed serum creatinine values > 221 $\mu\text{mol/L}$. Ten (0.5%) and 7 (0.3%) had an increase in serum creatinine > 0.5 mg/dl 9-11 days post-infusion #1. A total of 12 of treatment group A subjects vs. 6 of treatment group B subjects had an increase in serum creatinine > 0.5 mg/dl 9-11 days post-infusion #2 (120-day safety update). The largest increase

in either group was 0.8 mg/dl and most increases were followed by lower serum creatinine values upon follow up assessments. Six (0.3%) of treatment group A subjects and 3 (0.1%) of treatment group B subjects had > 2+ protein urine on dipstick 9-11 days post-infusion #1. A total of 4 (0.3%) of treatment group A subjects vs. 1 (0.1%) of treatment group B subjects had > 2+ protein urine on dipstick 9-11 days post-infusion #2. Only one of the patients in Treatment group A and none in group B had an abnormal level of protein in their 24-hour urine sample. The narrative for this patient, as provided by Novartis, is provided below.

Patient ID USA/580/00042 – 84-year-old female from Treatment group A. The patient had a 3+ urine protein dipstick result at her MV5A visit (taken 4 Dec 03). The patient had 2+ urine protein dipstick results on all her previous lab visits. A local 24 h urine collection, performed on 15 Dec 04 confirmed the proteinuria suspicion (900mg protein /24h urine collection were reported). The patient had been advised to see a nephrologist. There was no change in health status and patient did not report any symptoms consistent with an acute phase reaction before or after the infusion. The patient had not developed a disease during the screening period. In the opinion of the investigator a relationship between the event and the study medication is possibly suspected. The nephrologist suspects hypertensive nephrosclerosis; he pointed out that the proteinuria by dipstick is quite variable depending upon the concentration of the urine. A renal ultrasound had also been performed and was reported as “essentially normal”. A recheck of renal function was planned. The patient herself reported no complaints, except some back discomfort.

The following table provides the number (%) of patients with renal adverse events from Study 2301.

Number (%) of Subjects with Renal Function AEs – Ongoing Study 2301		
	Treatment A	Treatment B
	n (%)	n (%)
Subjects studied		
Total no. of subjects studied	3876	3866
Total no. of subjects with deterioration of renal function AEs	37 (0.95)	26 (0.67)
Deterioration of renal function AEs		
Blood creatinine increased	12 (0.31)	4 (0.10)
Creatinine renal clearance decreased	11 (0.28)	10 (0.26)
Renal impairment	6 (0.15)	5 (0.13)
Proteinuria	5 (0.13)	4 (0.10)
Renal failure acute	4 (0.10)	3 (0.08)
Azotemia	1 (0.03)	0 (0.00)
Glomerulonephritis acute	1 (0.03)	0 (0.00)
Nephritis	1 (0.03)	0 (0.00)
Oliguria	1 (0.03)	0 (0.00)

Eye Abnormalities

Paget's Studies: There were more eye abnormalities in subjects treatment with zoledronic acid compared with those treated with risedronate or placebo – see Table in Appendix for listing of actual events.

Study 2301: There have been 10 cases of eye pain and 5 cases of uveitis in treatment group A and there have been 3 cases of eye pain and no cases of uveitis in group B.

Comment: Bisphosphonates including pamidronate, clodronate, and alendronate have been linked to the development of various eye abnormalities including uveitis and scleritis. Whether zoledronic acid poses a greater risk for eye abnormalities such as uveitis than other bisphosphonates is unknown at this time and would probably require a large head-to-head trial to accurately answer the question.

Osteonecrosis

Studies 2304 and 2305: no cases of osteonecrosis of the jaw were reported from these two studies, or in any of the zoledronic acid studies of patients with “benign” bone disease.

Study 2301: There have been no cases of osteonecrosis of the jaw in either group. There have been two SAEs of aseptic necrosis of the femoral head, one in each treatment group; both patients had a recent history of a hip fracture. Furthermore, there has been one additional case of knee necrosis in treatment group A.

Comment: A large number of MedWatch reports of osteonecrosis of the jaw have been submitted to Agency during the past year. Most of the cases have been in patients being treated for cancer with either pamidronate or zoledronic acid. There are very few cases of osteonecrosis from patients taking alendronate or risedronate for osteoporosis. The Division of Oncology Drug Products is convening their advisory committee on March 4, 2005, to discuss the risk bisphosphonates, primarily those administered intravenously, pose for osteonecrosis of the jaw in patients being treated for cancer.

Gastrointestinal Events

Studies 2304 and 2305: There were a total of 33 (19%) and 28 (16%) upper GI adverse events reported in the zoledronic acid and risedronate groups, respectively. Nausea (9.0% vs. 6.4%); dyspepsia (5.1% vs. 3.5%); abdominal distention (2.3% vs. 1.2%); and vomiting (2.3% vs. 1.7%) occurred more commonly in the zoledronic acid compared with the risedronate groups.

7.1.7.5 Special assessments

Bone Biopsy Data

In study 2304, a small subgroup of patients consented to having bone biopsies at Visit 7 (Day 182). In general, 6 weeks prior to Visit 7, patients received tetracycline capsules and were instructed to take 250 mg four times a day for 3 days, followed by 14 days without tetracycline, and then 3 additional days of the drug. Within 5 to 14 days of the second label ingestion, a transilial bone biopsy was performed according to a standard procedure. Once obtained, the bone specimens were shipped to _____, and subsequently sent to the _____.

There were 7 (5 male) zoledronic acid subjects and 4 (all male) risedronate subjects who took part in the bone biopsy substudy. The mean age of the zoledronic acid subjects was 72 years; whereas it was 64 years for the risedronate-treated subjects. All of these subjects were Caucasian.

Eleven biopsies (7 zoledronic acid and 4 risedronate) were evaluable (contained both cortices with intact trabecular bone and marrow) out of a total of 22 specimens. The 11 non-evaluable specimens consisted of insufficient tissue, containing only one cortex and a few trabecular fragments.

Three additional biopsy specimens were excluded from the per-protocol analyses because they were not obtained from the area of the bone prespecified in the protocol.

Other than finding areas of woven bone, a histological characteristic of Paget's disease, there were no reports of abnormal bone histology (e.g., mineralization defects) in specimens from either treatment group.

The following table provides the histomorphometric variables of interest from the two treatment groups.

Histomorphometric Variables					
Variable	Zoledronic Acid		Risedronate		P-value
	N	Mean	N	Mean	
Osteoid Thickness (Um)	5	4.9	3	5.3	0.4
Wall Thickness (Um)	5	28.6	3	43	0.07
Trabecular Thickness (Um)	5	184	3	171	1.0
Mineral Apposition Rate (um/d)	4	0.57	3	0.52	0.2
Mineralization Lag Time (days)	4	270	3	79	0.6
Activation Frequency (#/year)	4	0.05	3	0.43	0.2

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

In Studies 2304 and 2305, blood pressure, pulse, temperature, and body weight were measured at Baseline and Day 182.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The following vital sign data are provided for Studies 2304 and 2305 combined. Comparisons are made with risedronate.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

The mean changes in sitting systolic blood pressure from baseline to Day 182 were -1.2 mmHg and -2.1 mmHg in the zoledronic acid and risedronate groups, respectively.

The mean changes in sitting diastolic blood pressure from baseline to Day 182 were 1.1 mmHg and 0.7 mmHg in the zoledronic acid and risedronate groups, respectively.

The mean changes in sitting pulse rate from baseline to Day 182 were -0.2 bpm and -0.3 bpm in the zoledronic acid and risedronate groups, respectively.

The mean changes in body weight from baseline to Day 182 were 0.3 kg and 0.4 kg in the zoledronic acid and risedronate groups, respectively.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Blood Pressure and Pulse: The following table provides the number and percentage of patients in each treatment group who at any time during the trials was observed to have an outlier value for systolic or diastolic blood pressure or pulse rate.

Number and Percentage of Subjects with Significant Increase or Decrease from Baseline in Vital Signs at Any Time During Studies 2304 and 2305								
Parameter	Criteria	Zoledronic acid 5 mg			Risedronate			
		N	n	%	N	n	%	
Pulse (bpm)	Increase of > 10 units	173	20	11.6	167	18	10.8	
	Decrease of > 10 units	173	26	15.0	167	21	12.6	
Systolic BP (mmHg)	Increase of > 15 units	175	28	16.0	167	25	15.0	

Number and Percentage of Subjects with Significant Increase or Decrease from Baseline in Vital Signs at Any Time During Studies 2304 and 2305

Parameter	Criteria	Zoledronic acid 5 mg			Risedronate		
		N	n	%	N	n	%
Diastolic BP (mmHg)	Decrease of > 15 units	175	35	20.0	167	34	20.4
	Increase of > 10 units	175	19	10.9	167	15	9.0
	Decrease of > 10 units	175	18	10.3	167	12	7.2

Body Weight: Approximately 3.0% of the zoledronic acid subjects and 4.0% of the risedronate subjects had an increase in body weight of > 7% during the two pivotal trials. One point seven percent and 1.2% of the zoledronic acid and risedronate subjects, respectively, had decreases in body weight of > 7% during the two pivotal Paget's trials.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

No patient in either of the pivotal Paget's trials discontinued prematurely due to an abnormal vital sign.

7.1.8.4 Additional analyses and explorations

Acute-Phase Reaction

Bisphosphonates, primarily those administered by intravenous injection, have been associated with an acute-phase reaction that generally occurs within days of the infusion and typically includes symptoms such as fever, myalgia, and joint pain

Studies 2304 and 2305: Seventeen (10%) of the zoledronic acid and 7 (4%) of the risedronate subjects reported influenza-like illness within 3 days of the initial dose of study medications. Pyrexia was reported by 13 (7%) and 1 (0.6%) of the zoledronic acid and risedronate groups, respectively.

Study 2301: Six-hundred-forty subjects (17%) in Treatment group A and 71 (2%) in Treatment group B reported pyrexia (there was no standard definition of pyrexia used in the trial); 380 (8%) and 54 (1%) of Treatment group A and B subjects, respectively, reported myalgia; 284 (7%) and 51 (1%) of subjects in groups A and B, respectively, reported influenza-like illness; 239 (6%) of group A subjects reported arthralgia and 54 (1%) of group B did so; bone pain was reported by 160 (4%) of group A patients and by 33 (1%) of group B subjects. Approximately half of these events occurred on Day 1, half on Day 2, and a few on Day 3.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

No signals of cardiovascular toxicity in preclinical studies and no clinically significant changes in ECGs were noted in zoledronic acid compared with placebo or active-comparator treated subjects in the pivotal studies that supported approval of the drug for the treatment of hypercalcemia of malignancy and bone metastases. Moreover, oral and intravenous bisphosphonates, as a class have not been implicated in causing cardiac abnormalities. Given the aforementioned, and since ECGs are currently being obtained in a large zoledronic acid osteoporosis fracture trial, no routine ECG monitoring was done in the pivotal Paget's disease studies.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

See section 7.1.9.1

7.1.9.3 Standard analyses and explorations of ECG data

See section 7.1.9.1

7.1.9.4 Additional analyses and explorations

Not Applicable.

7.1.10 Immunogenicity

As of January 25, 2005, Novartis' Clinical Safety and Epidemiology Group received 25 (21 postmarketing and 4 clinical trial) reports suspicious for anaphylaxis or suspected anaphylaxis with zoledronic acid. The time between zoledronic acid administration and the onset of the first symptoms, was generally during the administration or within 24 hours of receiving study drug.

Brief narratives for these cases are provided in the Appendix.

The currently approved labeling for zoledronic acid contains precautionary language regarding the occurrence of bronchoconstriction in patients with aspirin sensitive asthma following treatment with bisphosphonates. No cases of bronchoconstriction have been reported to date with zoledronic acid.

7.1.11 Human Carcinogenicity

This Reviewer is not aware of any studies that have systematically examined whether zoledronic acid increases or decreases the risk of cancer. Data from preclinical studies do not suggest that

zoledronic acid is genotoxic or oncogenic. In fact, some animal data suggest that bisphosphonates have antiangiogenic properties, which could reduce the metastatic potential of some primary tumors⁴.

7.1.12 Special Safety Studies

Bone biopsies were obtained in a subset of Paget's patients who participated in Study 2304.

See section 7.1.7.5 of this review for additional details.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There are no data to suggest that bisphosphonates as a class or zoledronic acid in particular are associated with withdrawal phenomena or have any potential for abuse, as use of this term applies to centrally-active compounds such as amphetamines.

7.1.14 Human Reproduction and Pregnancy Data

Not surprisingly given the age of the subjects in the Paget's trials and the predominance of males, no pregnancies were reported. The Division believes that there is a theoretical risk of fetal harm if a pregnant woman were exposed to a bisphosphonate. Class labeling that addresses this theoretical risk has been enacted for all bisphosphonates. The Pregnancy subsection of the Precautions section of the bisphosphonate labels now includes the following language:

Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied.

As of January 25, 2005, Novartis' Clinical Safety and Epidemiology Group has received seven (6 post-marketing and one clinical trial) reports of exposure with zoledronic acid during pregnancy: The short summaries of these reports are provided in the Appendix.

7.1.15 Assessment of Effect on Growth

There is currently an ongoing study comparing the efficacy and safety of zoledronic acid to pamidronate in the treatment of osteogenesis imperfecta in pediatric patients. When completed, this trial will provide some data on the effects of zoledronic acid on linear growth, albeit in a small subset of children with an underlying bone disorder.

7.1.16 Overdose Experience

The following information is provided in the currently approved zoledronic acid labeling:

There is no experience of acute overdose with Zometa® (zoledronic acid) Injection. Two patients received Zometa 32 mg over 5 minutes in clinical trials. Neither patient experienced any clinical or laboratory toxicity. Overdosage may cause clinically significant hypocalcemia, hypophosphatemia, and hypomagnesemia. Clinically relevant reductions in serum levels of calcium, phosphorus, and magnesium should be corrected by intravenous administration of calcium gluconate, potassium or sodium phosphate, and magnesium sulfate, respectively.

In an open-label study of zoledronic acid 4 mg in breast-cancer patients, a female patient received a single 48-mg dose of zoledronic acid in error. Two days after the overdose the patient experienced a single episode of hyperthermia (38°C), which resolved after treatment. All other evaluations were normal, and the patient was discharged seven days after the overdose.

A patient with Non-Hodgkin's lymphoma received zoledronic acid 4 mg daily on four successive days for a total dose of 16 mg. The patient developed paresthesia and abnormal liver function tests with increased GGT (nearly 100U/L, each value unknown). The outcome of this case is not known.

7.1.17 Postmarketing and Foreign Experience

At the time of this NDA submission, zoledronic acid is not approved for the treatment of Paget's disease of bone in any country. A marketing application was submitted in April 2004 to the European Agency for Evaluation of Medicinal Products (EMA) in the European Union (EU) for the use of zoledronic acid as a treatment for Paget's disease and is currently under review via the Centralized Procedure. There have been no Health Authority or manufacturer withdrawal actions taken for zoledronic acid for safety or efficacy reasons in any country.

Zoledronic acid is approved and marketed for the following two oncology-related indications outside the United States (89 countries worldwide):

1. Hypercalcemia of malignancy (HCM)
2. Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumor-induced hypercalcemia) in patients with advanced malignancies involving bone.

Two pharmaceutical forms of zoledronic acid exist outside the United States, the originally developed 4 mg powder and solvent for solution for infusion and the 4 mg/5 mL concentrate for solution for infusion. The final solution for infusion (which is administered i.v. to the patient) resulting from either pharmaceutical form is equivalent. Zoledronic acid powder was first registered in Canada on 21 August 2000, for the indication of hypercalcemia of malignancy (HCM). The EU authorization via the Centralized Procedure for this indication was received on 20 March 2001. The second indication was first registered in Malta on 13 August 2001. European approval was received on 19 July 2002. Zoledronic acid concentrate was first approved in Australia on 24 March 2003, and the EU authorization via the Centralized Procedure was granted on 24 March 2003.

As discussed in section 7.2.2.2 below, osteonecrosis of the jaw (ONJ) has been identified as an adverse event (primarily in patients being treated for cancer) that is very likely related to the use

of zoledronic acid (and intravenous pamidronate). The Division of Oncology Drug Products plans to convene its Advisory Committee in March 2005 to discuss this issue in greater detail.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Paget's Disease Studies: Studies 2304 and 2305 were randomized, double-blind, active-controlled 6-month phase 3 studies involving approximately 350 patients with Paget's disease of the bone. Study 002 was a randomized, double-blind, placebo-controlled 3-month phase 2 study of 176 patients with Paget's disease and study 001 was an open-label 14-day study of 16 patients with Paget's disease. Data from Studies 2304 and 2305 provide the majority of the safety data for the Paget's population.

7.2.1.2 Demographics

The following table provides the baseline demographic characteristics, which were well-matched between groups, for the patients enrolled in the Paget's studies. The population was predominately Caucasian, male, and over the age of 65 years, as would be expected of patients with this disease.

	Phase III studies		Phase I/II studies	
	Zoledronic acid 5 mg N=177	Risedronate N=172	Zoledronic acid < 5 mg (24-400 µg) N=157	Placebo N=35
Sex n (%)				
Male	122 (68.9)	117 (68.0)	93 (59.2)	24 (68.6)
Female	55 (31.1)	55 (32.0)	64 (40.8)	11 (31.4)
Race n(%)				
Caucasian	164 (92.7)	162 (94.2)	140 (89.2)	34 (97.1)
Black	8 (4.5)	4 (2.3)	14 (8.9)	1 (2.9)
Other	5 (2.8)	6 (3.5)	3 (1.9)	0 (0.0)
Age group (years) n(%)				
<65	45 (25.4)	46 (26.7)	37 (23.6)	6 (17.1)
≥65	132 (74.6)	126 (73.3)	120 (76.4)	29 (82.9)
Age (years)				
n	177	172	157	35
mean (SD)	70.8 (9.90)	70.0 (10.79)	70.4 (8.34)	72.0 (10.48)
median	72.0	72.0	71.0	74.0
range	42.0-94.0	34.0-88.0	42.0-88.0	33.0-88.0

As shown below, disease characteristics were balanced between the zoledronic and placebo and risedronate comparator groups. Approximately 50% of the subjects in the phase 3 trials had baseline Alk Phos levels $\geq 3x$ ULN; the majority had calculated CrCl rates of > 50 mL/min; and nearly half had never received drug treatment for their Paget's disease prior to entry into these studies.

Disease characteristics by treatment for Subjects Enrolled in the Paget's Phase 1 - 3 Studies

	Phase III studies		Phase I/II Studies	
	Zoledronic acid 5 mg N=177	Risedronate N=172	Zoledronic acid <5 mg (24-400 ug) N=157	Placebo N=35
Baseline serum alkaline phosphatase (U/L)				
mean (SD)	430.6 (324.86)	426.6 (313.89)	581.9 (376.24)	540.6 (402.83)
median	339.0	305.0	444.0	389.0
range	229.0 - 2822.0	214.0 - 2377.0	213.0 - 2310.0	236.0 - 2362.0
Baseline serum alkaline phosphatase				
<3xULN	Σ			∩
$\geq 3x$ ULN				
missing				
Calculated creatinine clearance at baseline (mL/min)				
mean (SD)	85.3 (33.11)	87.0 (33.13)	70.4 (23.90)	70.4 (23.76)
median	80.4	83.1	67.5	68.0
range	30.6 - 217.8	29.4 - 228.0	29.0 - 153.0	33.0 - 145.0
Calculated creatinine clearance at baseline (mL/min)				
<30	0 (0.0)	1 (0.6)	1 (0.6)	0 (0.0)
30 - <40	5 (2.8)	3 (1.7)	11 (7.0)	2 (5.7)
40-50	18 (10.2)	15 (8.7)	15 (9.6)	4 (11.4)
>50	154 (87.0)	153 (89.0)	107 (68.2)	21 (60.0)
missing	0 (0.0)	0 (0.0)	23 (14.6)	8 (22.9)
Last Paget's disease therapy before randomization				
Bisphosphonates				
oral	∩			∩
iv				
clodronate (iv or oral)				
Others				
None				
Bisphosphonates washout (days)				
<180				
180 - <365	∩			∩
≥ 365				

7.2.1.3 Extent of exposure (dose/duration)

In the two phase 3 trials, the mean duration of treatment was approximately 60 days, with over 90% of the subjects in each treatment group reporting 90% or greater compliance with study drug administration.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Four studies of patients with osteoporosis provide ancillary safety data. Study 0041 was a randomized, placebo-controlled, double-blind 12-month phase 2 study of 351 women with postmenopausal osteoporosis. Approximately 280 of the 351 subjects enrolled in a 12-month open-label extension study. Study 2310 is an ongoing randomized, double-blind, placebo-controlled 24-month phase 3 study of approximately 1700 men and women who have sustained a hip fracture. Study 2301 is an ongoing, randomized, double-blind, placebo-controlled 36-month, phase 3 study of more than 7000 women with postmenopausal osteoporosis who are receiving annual 5 mg doses of zoledronic acid. This study, which remains partially blinded (treatment groups A and B), provides the largest exposure to zoledronic acid and placebo in a non-oncology population and is referred to frequently in this review.

7.2.2.2 Postmarketing experience

The most significant adverse event reported with use of zoledronic acid post-marketing is osteonecrosis of the jaw (ONJ). Using the AERS database, the Office of Drug Safety has provided the Divisions of Metabolic and Endocrine and Oncology Drugs with consults evaluating reports of osteonecrosis associated with use of zoledronic acid, pamidronate, and the oral bisphosphonates. The vast majority of cases of ONJ have occurred in patients with cancer who often had additional risk factors for the condition such as anemia, radiation treatment, etc. As of this writing, a Change Being Effected labeling supplement is being reviewed by the Division of Metabolic and Endocrine Drugs. The supplement proposes the addition of precautionary language regarding ONJ to the zoledronic acid and pamidronate labels. For more information on this topic, readers are referred to a paper by Ruggiero, et al., entitled Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases, published in the *Oral Maxillofac Surg.* 2004 May;62(5):527-34.

7.2.2.3 Literature

A list of the published papers that were reviewed can be found at the end of this review.

7.2.3 Adequacy of Overall Clinical Experience

The phase 2 data for zoledronic acid in Paget's disease come from 2 studies. In the larger of the two, the effects of 50 ug, 100 ug, 200 ug, and 400 ug of zoledronic acid (administered over 1 hour) on levels of serum alkaline phosphatase were examined in approximately 140 patients. The results indicated all doses of zoledronic acid decreased SAP levels, in a dose-related manner, by a statistically significantly greater amount than did placebo.

Although Novartis argues, based on changes in markers of bone resorption and formation in patients with osteoporosis, that a single 5 mg dose of zoledronic acid is appropriate for the

treatment of Paget's disease, the fact remains that the company does not know if doses lower than 5 mg (say, 3 mg) would prove efficacious in Paget's disease.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

As would be predicted based on its mechanism of action, zoledronic acid produces transient decreases in serum calcium levels, with nadir levels noted one to two weeks post-dose. In the pivotal Paget's studies, the mean changes from baseline to Day 10 in levels of serum calcium were -0.2 mmol/L in the zoledronic acid group and -0.1 mmol/L in the risedronate group. Mean changes of these magnitudes would not be expected to significantly prolong the QTc interval.

7.2.5 Adequacy of Routine Clinical Testing

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

See section 5 of this review and Dr. Suarez's review of this application for details of the pharmacokinetic properties of zoledronic acid.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

By including measurements at Day 10 post-infusion, the company designed the two pivotal Paget's trials to adequately assess the risk for renal injury and hypocalcemia.

7.2.8 Assessment of Quality and Completeness of Data

To the extent that the available information provides for such an evaluation, the data provided in this submission appear to be complete and of good quality.

7.2.9 Additional Submissions, Including Safety Update

On 19 January, 2005, Novartis submitted a 120-day safety update for the Paget's NDA. This update extends the period of patient observation from a cutoff date of 1 March 2004 to 1 July 2004.

No new studies in patients with Paget's disease have been initiated since submission of the original NDA. Serious AE information from the extension phases of studies 2304 and 2305 are provided in this safety update.

In addition to the extension phases of studies 2304 and 2305, updated safety information comes primarily from three trials:

1. 0041E2: A now completed phase 2 open-label extension study in postmenopausal women with osteoporosis.

2. 2301: An ongoing, partially blinded phase 3 trial evaluating the fracture efficacy of zoledronic acid in postmenopausal women.
3. 2202: An ongoing, open-label trial of the efficacy and safety of zoledronic acid vs. pamidronate in pediatric patients with osteogenesis imperfecta.

On note, four studies in patients without cancer started prior to 1 July 2004; however, the company reports that no deaths, serious AEs, or other clinically significant adverse events were reported for any of these studies as of the 1 July 2004 cutoff date.

Studies 2304 and 2305: During the extension phases of studies 2304 and 2305 there were two deaths in zoledronic-acid treated subjects and none in the risedronate-treated subjects. One death was attributed to a myocardial infarction in an 86-year-old subject and the other death was coded as due to mitral valve incompetence in an 83-year-old patient. There were three risedronate-treated patients who reported serious AEs (esophageal cancer, fracture of the humerus, and progression of hypertension) and one patient with a serious AE from the zoledronic acid group (pneumonia).

Study 0041E2: There were no deaths reported during this open-label study. As noted in the below table, one patient developed an increase in serum creatinine from baseline > 0.5 mg/dl, although the increased value was not confirmed upon repeat measurement; one developed a creatinine clearance < 30 ml/min; and 5 subjects developed urine protein > 2+ or ≥ 250 mg/dl. From the information provided in the narratives for these subjects, particularly the temporal relationship between the last dose of zoledronic acid and the occurrence of the proteinuria, it is this Reviewer's opinion that the drug was not causally related to the renal events.

Study 0041E2 - Pre-Specified Renal Abnormalities

	2 years of zoledronic acid		3 years of zoledronic acid		5 years of zoledronic acid	
	N	n (%)	N	n (%)	N	n (%)
Total no. of patients with a protocol-defined renal abnormality	19	2 (10.5)	78	2 (2.6)	22	2 (9.1)
Creatinine clearance < 30 mL/min	19	1 (5.3)	78	0	22	0
Increase in serum creatinine from baseline > 44.2 umol/L	19	1 (5.3)	78	0	22	0
Urine protein > 2+ or ≥250 mg/dL	19	1 (5.3)	78	2 (2.6)	22	2 (9.1)

Note: The treatment groups pertain to the total number of years of zoledronic acid treatment across the core, extension 1, and extension 2 studies.

N = number of patients with a relevant post-baseline absolute or change from baseline value.

Three patients were reported to have had renal adverse events coded as renal impairment:

- Patient 3-1554 (in the 5-year treatment group) had a baseline creatinine clearance of 69 mL/min. At month 48, a creatinine clearance of 60 mL/min was reported as an adverse event.

- Patient 3-1555 (in the 3-year treatment group) had a creatinine clearance of 56 mL/min at baseline. At month 48, a creatinine clearance of 54 mL/min was reported as mild renal impairment by the investigator.
- Patient 3-1559 (in the 2-year treatment group) had a baseline creatinine clearance value of 72 mL/min. At month 48, a creatinine clearance of 60 mL/min was reported as an adverse event.

Study 2301: The following table provides an updated summary of deaths, serious AEs, and other clinically important information from the ongoing osteoporosis treatment trial 2301.

Study 2301 - Number (%) of Subjects Who Died, Had Other Serious or Clinically Significant AEs or Discontinued Because of an AE		
	Treatment A	Treatment B
	n (%)	n (%)
Total		
Serious or significant AEs	3031 (78.2)	2626 (67.9)
Death	55 (1.4)	44 (1.1)
SAEs	584 (15.1)	564 (14.6)
Discontinuation due to SAEs	86 (2.2)	65 (1.7)
Discontinuation due to non-serious AEs	31 (0.8)	20 (0.5)
Lab abnormalities leading to premature discontinuation	1 (<0.1)	2 (0.1)
AEs causing concomitant medication taken	2748 (70.9)	2505 (64.8)
AEs due to IV study drug administration	1277 (32.9)	251 (6.5)
Renal AEs leading to deterioration of renal function	57 (1.5)	44 (1.1)
Hypocalcemia (< 8.0 mg/dl)	7 (0.2)	0 (0.0)

Adverse events classified in this group are any occurrences of pyrexia, myalgia, arthralgia, bone pain, and influenza-like illness occurring within 3 days of study drug infusion

Study 2202: There have been no deaths in this study. There were 6 cases of hypocalcemia reported as serious AEs in the safety update; all subjects received zoledronic acid.

Comment: Compared to the data provided in the original NDA submission, the data provided in the 120-day safety update do not raise any new concerns. In study 2301, which provides the largest patient exposure to zoledronic acid, as expected, there remains a slight imbalance between treatment groups in the incidence of renal adverse events leading to deterioration of renal function. Regarding hypocalcemia, in the original submission there were 4 reports of hypocalcemia in treatment group A and none in treatment group B; the numbers are now 7 vs. 0.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Hypocalcemia and Hypophosphatemia: Paget's disease is characterized by excessive bone turnover, a process that requires an ample supply of calcium and phosphorus, since these are core components of mineralized bone. One of the known effects of bisphosphonate treatment in

patients with Paget's disease is a transient lowering of serum calcium and phosphorus concentrations. This is the result of decreased bone resorption coupled with a continued increase in bone formation (at least in the short-term).

The body responds to the mismatch between supply and demand of calcium and phosphorus in the following ways. Decreased levels of serum calcium increase the release of PTH, which in turn triggers 3 mechanisms: 1) increased synthesis of serum 1, 25 vitamin D which increases the absorption of calcium and phosphorus from the small intestine; 2) increased release of calcium and phosphorus from bone directly by PTH, and 3) increased reabsorption of calcium and increased excretion of phosphorus by the kidney.

In the two pivotal trials reviewed herein, 21% of subjects treated with zoledronic acid vs. 3.0% of patients treated with risedronate developed hypocalcemia by Day 10. Eighteen percent vs. 1.3% of zoledronic acid and risedronate-treated patients, respectively, developed hypophosphatemia by Day 10.

In the active-controlled trial used to support approval of risedronate for the treatment of Paget's disease, in which patients received 30 mg of risedronate daily for 2 months, transient decreases in serum calcium and phosphorus concentrations were noted, with nadirs occurring between days 30 to 60. It thus makes sense to examine the changes in serum calcium and phosphorus that occurred at the Day 63 time point in the zoledronic acid trials.

Of the subjects who had normal serum calcium levels at baseline, 2.4% of the zoledronic acid subjects and 4.8% of the risedronate subjects had low serum calcium levels at Day 63. Of the subjects who had normal serum phosphorus levels at baseline, 0.6% of the zoledronic acid subjects and none of the risedronate subjects had low serum phosphorus levels at Day 63.

In the pivotal Paget's studies for alendronate, in which 40 mg was administered daily for 6 months, serum calcium and phosphorus were measured at Months 1, 3 and 6. The nadirs for these two minerals appeared to have occurred at Month 1. The mean reductions in serum calcium and phosphorus at Month 1 were -0.45 mg/dl and -0.47 mg/dl, respectively. In the zoledronic acid trials, the mean reductions in serum calcium and phosphorus at Day 10 were -0.8 mg/dl and -1.7 mg/dl, respectively. Further, approximately 19% of the alendronate-treated subjects developed serum calcium levels below 8.5 mg/dl, compared with approximately 32% of the zoledronic acid subjects. One (1.5%) of the alendronate patients developed a serum calcium level below 8.0 mg/dl vs. 12 (8%) of the zoledronic acid-treated participants.

Notwithstanding the difficulties of comparing data from different trials, taken together, the available evidence indicates that the risk for developing mild-to-severe hypocalcemia and hypophosphatemia is greater with zoledronic acid than with risedronate and probably alendronate. Moreover, since patients treated with zoledronic acid appear to develop hypocalcemia much more rapidly than those treated with oral bisphosphonates, this *may* put them at even greater risk for symptomatic hypocalcemia and hypophosphatemia.

Although none of the patients with low levels of serum calcium or phosphorus developed severe clinical sequelae such as seizure, cardiac arrhythmia, hemolysis, or rhabdomyolysis, a number of patients did develop markedly low calcium and phosphorus levels. It stands to reason, then, that if the drug were used in a broader range of Paget's patients, many of whom will have additional risk factors for hypocalcemia such as vitamin D deficiency and concomitant use of medications such as furosemide, an unacceptably high number of patients may suffer ill clinical consequences from a single 5 mg infusion of zoledronic acid. This brings to the fore the importance of characterizing the effects that supplemental calcium and vitamin D have on the occurrence of hypocalcemia and hypophosphatemia.

While it is reasonable to assume that the risk for developing low serum levels of calcium and phosphorus would be reduced by supplementing patients with calcium and vitamin D a few days prior to and a couple of weeks following dosing with zoledronic acid, this has yet to be empirically tested. Patients in the zoledronic acid trials were *instructed* to take 500 mg BID of supplemental calcium and 400 to 1000 IU per day of vitamin D during the studies, but the sponsor did not collect data to verify if, when, or how much of the supplements were actually taken.

In response to the Division's concern about the calcium and phosphorus data, Novartis proposed to handle the problem through labeling, as detailed below.

The page contains several large, handwritten scribbles and marks. On the left side, there are four distinct, somewhat abstract shapes drawn with a black pen. On the right side, there are three larger, more complex scribbles that appear to be stylized or illegible marks. These marks are scattered across the lower half of the page, below the main text.

Given the increased risks for developing hypocalcemia and hypophosphatemia with zoledronic acid compared with risedronate and most likely alendronate – two approved and effective therapies for Paget's – I believe Novartis should provide empiric evidence that supplementation with calcium and vitamin D significantly reduces the risk for developing hypocalcemia and hypophosphatemia following treatment with zoledronic acid before the drug is approved.

Until Novartis provides such evidence, this Reviewer does not believe that the data in the NDA support a favorable balance of benefits to risks for the 5 mg dose of zoledronic acid when used to treat Paget's disease of bone.

Acute-Phase Reaction: A constellation of adverse events which resemble those that occur during an acute-phase reaction have been reported in patients when treated with bisphosphonates, primarily by injection. As described in section 7.1.8.4 of this review, the symptom complex includes but is not limited to influenza-like illness, pyrexia, rigors, myalgia, fatigue, arthralgia, lethargy, and headache. The majority of these symptoms occurred within 72 hours of receiving the zoledronic acid infusion. The occurrence of an acute-phase reaction following drug administration is not a serious safety concern, although it may increase the odds that the patient refuses a second dose. Novartis is currently conducting a study to examine the efficacy of pre-treatment with ibuprofen or Tylenol to reduce the incidence of the symptoms of the acute-phase reaction following intravenous administration of zoledronic acid.

Renal Injury: Increases in serum creatinine, which in some cases progressed to frank renal failure, have occurred in patients treated with zoledronic acid, principally in those with an underlying malignancy who received q 3-4 week dosing. The risk of renal injury (i.e., increased serum creatinine) appears to be most strongly related to the dose and rate of infusion of zoledronic acid and to baseline renal function, with decreased creatinine clearance conferring greater risk. The currently approved zoledronic acid labeling includes precautionary language regarding renal toxicity and also includes recommendations to enhance renal safety, such as reducing the dose for patients with impaired baseline renal function. There was no evidence of an increased risk for renal injury following a single 5 mg dose of zoledronic acid in the patients with Paget's trials reviewed herein, albeit the sample size is relatively small.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

For the Paget's disease indication, pooling of data from the two pivotal studies, 2304 and 2305, provide the most accurate estimate of zoledronic acid's efficacy and safety relative to treatment with risedronate. Partially-blinded safety data from the ongoing osteoporosis treatment trial, 2301, provide useful information due to the size of the database. As of the date of filing of this NDA, over 7000 postmenopausal women had received one infusion of 5 mg zoledronic acid or

placebo, and approximately half of these subjects have also received a second, annual dose of drug or placebo.

7.4.1.2 Combining data

In the following section, results of exploratory analyses of pooled data from the Paget's studies 2304 and 2305 are provided.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Not applicable, as a single dose was used in the pivotal Paget's trials.

7.4.2.2 Explorations for time dependency for adverse findings

In an analysis of adverse events that occurred within 3 days of drug administration, the following events, many of which could be considered part of an acute phase reaction, were reported by a greater percentage of patients in the zoledronic acid vs. the risedronate group: Influenza-like illness, myalgia, pyrexia, fatigue, headache, rigors, bone pain, arthralgia, nausea, back pain, and dizziness.

In an analysis of adverse events that occurred after 3 days of drug administration, the following events were reported more frequently by the risedronate vs. the zoledronic acid groups: influenza-like illness, headache, nausea, arthralgia, and back pain.

7.4.2.3 Explorations for drug-demographic interactions

When analyzed by age above and below 72 years, hypocalcemia was reported in 6 (6.5%) of the zoledronic acid and none of the risedronate subjects at or above 72 years of age. In the subjects less than 72 years, 1 (1.2%) risedronate subject and none of the zoledronic acid subjects developed hypocalcemia. Other adverse events occurred with a different frequency between zoledronic acid vs. risedronate treated groups in those subjects > 72 vs. < 72 years, however it is difficult to determine if these differences are clinically significant.

When analyzed by gender, there were a number of adverse events that occurred with a different frequency between zoledronic acid vs. risedronate treated groups in males vs. females, and vice versa. It is difficult to determine if these differences between genders are clinically meaningful, however.

Analyses by race are not feasible given that the majority of patients in the trials were Caucasian.

7.4.2.4 Explorations for drug-disease interactions

Not performed due to the homogeneity of the subjects in terms of concomitant disease states at baseline.

7.4.2.5 Explorations for drug-drug interactions

An analysis was performed on the incidence of GI adverse events in subjects treated with and without concomitant NSAID/ASA use. Nausea and dyspepsia occurred in a greater number and percentage of zoledronic acid subjects compared with risedronate subjects in patients *without* concomitant use of NSAID/ASA, than in subjects with concomitant use of NSAID/ASA. The between-treatment group differences in the incidence rates for nausea and dyspepsia were 7% and 4% (in favor of zoledronic acid) in those subjects without concomitant use of NSAID/ASA, and 1% and 1% (in favor of risedronate) in those subjects not taking NSAID/ASA.

7.4.3 Causality Determination

Hypocalcemia, hypophosphatemia, and symptoms of acute phase reaction are without a doubt causally related to treatment with zoledronic acid.

Hypocalcemia: Based on the pharmacodynamic action of zoledronic acid to reduce osteoclast function in Paget's patients, of whom most have very high bone turnover, the development hypocalcemia following drug administration is not unexpected. Cases have been reported in Paget's patients treated with oral and intravenous bisphosphonates. However, the data from this application indicate that the risk for hypocalcemia in patients with Paget's disease is much greater following treatment with zoledronic acid than risedronate and most likely alendronate. Although most of the cases of hypocalcemia were reportedly asymptomatic and normalized without intervention, this Reviewer believes the efficacy of calcium and/or vitamin D supplementation at the time of dosing should be formally tested before this application is approved.

Hypophosphatemia: As mentioned above, it is not unusual for patients to develop low serum levels of phosphate following treatment with bisphosphonates. In the two pivotal Paget's trials, 18% of zoledronic acid and 1.3% of risedronate subjects developed low serum phosphate levels at Day 10 post-infusion. Serum phosphorus values below 1.5 mg/dl are generally considered severe and can be associated with symptoms such as muscle weakness and cardiac dysfunction. The lowest phosphate value observed in the current submission was 1.4 mg/dl in a patient treated with zoledronic acid. Most of the reductions were modest (1.6 to 2.1 mg/dl), were not associated with symptoms, and did not require intervention to normalize.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

There is no question that a single 5 mg dose of zoledronic acid is an effective dose to reduce levels of serum alkaline phosphatase in patients with Paget's disease. It is quite possible though that lower doses of the drug would produce sustained suppression of SAP levels without increasing the risk for hypocalcemia or hypophosphatemia to the extent seen with a 5 mg dose.

8.2 Drug-Drug Interactions

See Biopharmaceutics review for details of drug-drug interactions.

8.3 Special Populations

New language was recently added to the zoledronic acid labeling to provide special dosing instructions (i.e., reduced dose) for cancer patients with reduced renal function. These instructions should be followed by all patients with reduced renal function treated with zoledronic acid.

8.4 Pediatrics

At the time of this writing, a study comparing zoledronic acid to pamidronate in the treatment of pediatric patients with osteogenesis imperfecta is ongoing. Paget's disease of the bone is a (nearly) exclusively adult disease.

8.5 Advisory Committee Meeting

An Advisory Committee meeting was not considered necessary for this application.

8.6 Literature Review

A number of publications on zoledronic acid and Paget's disease were identified via a search of PubMed. These articles were reviewed and are referenced at the end of this document.

Of particular interest, a recently published study by Hogler et al (reference #15), indicates that single intravenous doses of zoledronic acid of 0.02 to 0.05 mg/kg are associated with statistically significant reductions in serum calcium and phosphorus within 72 hours post-dose in pediatric patients with a variety of bone disorders. Of note, these reductions in serum calcium were noted despite the fact that all patients were supplemented with 2 gram of elemental calcium per day for at least 10 days, starting 5 to 7 days before the infusion. Mean baseline 25OHD levels were 19 nmol/L – a level considered insufficient by many experts.

8.7 Postmarketing Risk Management Plan

Based on the findings from the requested calcium and vitamin D supplementation study, a risk management plan will be formulated.

8.8 Other Relevant Materials

Novartis is proposing a second trade name, Aclasta, for the Paget's disease indication. The Division of Medication Errors and Technical Support reviewed the results of a trade name survey commissioned by Novartis and concluded that there is no good evidence to suggest that the use of a second trade name for the Paget's indication, in addition to the current trade name, Zometa, used for the oncology indications, will reduce the risk for medication errors.

9 OVERALL ASSESSMENT

9.1 Conclusions

Adequate evidence has been provided to support the efficacy of a single 5 mg intravenous infusion of zoledronic acid in the treatment of Paget's disease of bone. Inadequate evidence, however, has been provided to support the safety of a single 5 mg dose of zoledronic acid in the treatment of Paget's disease. Nearly one-fifth of all subjects treated with zoledronic acid, and very few treated with risedronate, developed hypocalcemia and/or hypophosphatemia within 7 to 14 days post-dosing.

9.2 Recommendation on Regulatory Action

Approvable, pending demonstration that short-term supplementation with calcium and vitamin D reduces to an "acceptable" level the risk for hypocalcemia and hypophosphatemia following treatment with a 5 mg intravenous dose of zoledronic acid.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Details of a risk management strategy will be defined by the outcome of a calcium and vitamin D supplementation study.

9.3.2 Required Phase 4 Commitments

None

Clinical Review
{E. Colman, MD}
{NDA 21-817}
{Zoledronic Acid for Paget's disease}

9.3.3 Other Phase 4 Requests

None

9.4 Labeling Review

A full review of the labeling will be conducted prior to the approval of the application.

9.5 Comments to Applicant

See administrative record for an account of all comments and questions submitted to the applicant during review of this application.

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10 APPENDICES

10.1 Review of Individual Study Reports

Clinical Trial #1 - ZOL446K 2304

Title: Randomized, double-blind, safety and efficacy trial with intravenous zoledronic acid for the treatment of Paget's disease of bone using risedronate as a comparator.

Study Centers: 6 Australia, 6 Canada, 2 New Zealand, 6 United Kingdom, 12 United States and 1 in Spain.

Study Period: First patient enrolled: 25-Jan-2002 Last patient completed: 26-Mar-2004

Study Objectives: The primary efficacy objective of this trial was to show non-inferiority of the test drug, zoledronic acid, to the active control, risedronate, with respect to the proportion of patients who achieved therapeutic response. A therapeutic response was defined as a reduction of at least 75% from baseline in total serum alkaline phosphatase excess (difference between measured level and midpoint to the normal range) or normalization of serum alkaline phosphatase at the end of six months.

The secondary efficacy objective was to assess the effect of i.v. zoledronic acid 5.0 mg (once) and oral risedronate 30 mg o.d. (60 days) in diminishing serum c-telopeptide (CTX) and urine α -CTX.

Design: This was an international multicenter, randomized, double-blind trial. Each patient was randomized to receive either one zoledronic acid 5.0 mg i.v. infusion (15 minutes) and 60 days of oral placebo o.d., or one i.v. placebo infusion (15 minutes) and 60 days of oral risedronate 30 mg o.d. It was planned to randomize 88 patients to each treatment group.

The formal portion of the study consisted of 7 Study Visits, with Visits 3-7 occurring near Days 10, 28, 63, 91, and 182, respectively.

At Visit 7, each patient was identified by the investigator as either a responder or non-responder to treatment for entry into the extended observation period. A responder was defined as a patient who had $\geq 75\%$ decrease from baseline in serum alkaline phosphatase (SAP) excess (difference between measured level and midpoint of normal range) or SAP within the normal range at 6 months. A non-responder was defined as a patient who had $< 75\%$ decrease from baseline in SAP excess and whose SAP was above the ULN at 6 months. Each investigator was blinded to all efficacy laboratory values (serum bone turnover markers) throughout the trial except for SAP excess at Visit 1 (baseline) and Visit 7. Using these values multiplied the baseline SAP excess value at Visit 1 by 0.25 and provided the results to the

investigator. Each investigator made the determination that a patient entered the extended observation phase if the following conditions were satisfied.

If $(X_{To}) (0.25) \geq Y_{T7}$ or $(Y_{T7} + \text{Midpoint of normal range}) \leq \text{ULN}$ where X_{To} = baseline SAP excess Y_{T7} = Visit 7 SAP excess

Patients who completed the study and were identified as responders entered the extended observation phase for continued monitoring. All responders are to return to the investigator every 6 months to measure SAP and will continue to be monitored until the SAP level returns to within 20% of baseline, or the investigator re-initiates therapy to treat the Paget's disease. Following Amendment 4 (dated 19-Jan-2004), additional bone marker data (serum CTx, serum PINP, and urine α -CTx) were also to be collected. The results of the extended observation period will be presented in a separate report. Patients identified as non-responders ended study participation at Visit 7.

A transiliac crest bone biopsy was performed at designated sites, for those patients who volunteered to participate and who completed 6 months of the study. It was planned that up to approximately 20 patients would have a bone biopsy performed at Visit 7. Patients who elected to participate were presented with the informed consent for the bone biopsy procedure at Visit 6. Those who signed the form were asked to return approximately 6 weeks prior to Visit 7 for the tetracycline HCl capsules and instructions. However, if a patient could not return for another visit prior to Visit 7, the tetracycline HCl and instructions could be dispensed at Visit 6. If the tetracycline HCl was provided at Visit 6, the investigator was to call and remind the patient to begin taking the tetracycline capsules at the appropriate time. The investigator verified compliance.

Patient Population: The trial population consisted of patients with a prior confirmed diagnosis of Paget's disease of bone, with a serum alkaline phosphatase ≥ 2 times the upper limit of normal.

Inclusion criteria:

- Male or female patients 30 years and above at the time of entry into the trial who have Paget's disease of bone. Females of child-bearing potential may have been enrolled if they had a negative serum pregnancy test prior to study entry and if they agreed to use acceptable methods of contraception during the study.
- Confirmed diagnosis of Paget's disease of the bone (i.e., by x-ray, magnetic resonance imaging, computerized tomography, radioisotope imaging, etc.).
- Serum alkaline phosphatase level at least two times the upper limit of the normal reference range.
- A normal or not clinically significantly abnormal ECG result during the past 6 months.
- Washout period for other therapies prior to trial drug administration at Visit 2: 90 days for calcitonin and 180 days for any bisphosphonate (washout period changed from 365 to 180 days via Amendment 3, dated 21-Oct-2002).

Exclusion criteria:

- Treatment with any investigational drug within the past 30 days.
- History of noncompliance to medical regimens and patients who are considered potentially unreliable.

- Any disease or therapy which would interfere with the procedures or data collection of this trial.
- Severe liver disease that would affect alkaline phosphatase levels such as hepatitis, primary biliary sclerosis, and cirrhosis.
- History of any of the following: hypersensitivity to bisphosphonates, clinically significant upper gastrointestinal disorders that could interfere with compliance, uritis or uveitis, renal disease with continuing clinically significant abnormality, diabetic nephropathy or retinopathy.
- WBC $< 3.5 \times 10^3/\text{mm}^3$, platelets $< 125 \times 10^3/\text{mm}^3$ or any other clinically significant laboratory abnormality.
- Calculated creatinine clearance $< 30 \text{ mL/min}$ at baseline or urine protein level $\geq 2+$ protein without evidence of contamination or bacteruria (urine protein level criteria added via Amendment 2, dated 29-May-2002).
- Evidence of vitamin D deficiency (serum 25(OH) D of $< 15 \text{ ng/mL}$).
- Patients with allergies to tetracycline or any of its derivatives were to be excluded from the bone biopsy procedure.
- Active primary hyperparathyroidism (added via Amendment 2, dated 29-May-2002).
- Patients with a new diagnosis or active treatment for any malignancy less than or equal to 12 months prior to study entry (Amendment 3, dated 21-Oct-2002).

Treatment Groups: Zoledronic acid and matching placebo was given intravenously to each patient as a slow infusion over 15 minutes. A peripheral intravenous site was used for the infusion. The bore of the needle or angio-catheter used to insert the intravenous line was 20 to 22 gauge. Risedronate and matching oral placebo capsules were administered once per day for 60 consecutive days. Risedronate and matching oral placebo capsules were to be taken at least 30 minutes before the first food or drink of the day, other than water. Risedronate or oral placebo was to be taken in an upright position with a full glass (6 to 8 oz) of plain water. Lying down was to be avoided for at least 30 minutes after taking risedronate or oral placebo.

Elemental calcium (500 mg) was to be taken by mouth with food (twice daily) beginning at least five days prior to administration of zoledronic acid and during the trial. Since calcium may interfere with the absorption of risedronate, it was to be taken at a different time of day. Calcium carbonate was the preferred form of calcium. If calcium carbonate was not well tolerated, another form of oral calcium was acceptable. In addition, each patient took multiple vitamin supplements containing between 400 and 1000 IU of vitamin D daily. Calcium and the multiple vitamins were dispensed as a 3-month supply and were supplied by the investigator. All patients were to receive calcium and multiple vitamin supplies at appropriate Visits. Patients were instructed to take one dose (500 mg) of calcium twice a day with food, or according to the information provided by the manufacturer and one multiple vitamin per day.

Statistical Analyses: The primary efficacy objective of this study was to show non-inferiority of zoledronic acid relative to risedronate with respect to the primary efficacy variable, proportion of patients who achieved therapeutic response at six months. The null hypothesis tested was that the proportion of patients who achieved therapeutic response at 6 months was 0.16 lower in the zoledronic acid group than in the risedronate group while the alternative hypothesis was that proportion of patients who achieved therapeutic response at 6 months in the zoledronic acid group was greater than or equal to the proportion of patients who achieved therapeutic response in the risedronate group minus 0.16. Non-inferiority of zoledronic acid relative to risedronate was concluded if the lower limit of the two-sided 95% confidence interval for the difference in proportions (zoledronic acid minus risedronate) was greater than -0.16 . A 95% confidence interval for the difference in the proportion of patients who achieved therapeutic response at six months was constructed based on the normal approximation to the binomial.

In addition, as a pre-planned strategy to test the superiority of zoledronic acid over risedronate, if non-inferiority of zoledronic acid relative to risedronate was demonstrated, between treatment differences in proportion of patients who achieved therapeutic response at 6 months was evaluated using a logistic regression model with treatment and baseline SAP (categorized as $< 3xULN$ or $\geq 3xULN$) as explanatory variables. In case the logistic regression model did not converge, the lower limit of the two-sided 95% confidence interval was used to assess the superiority of zoledronic acid over risedronate based on the normal approximation to the binomial. The p-values reported for the model were computed from the likelihood ratio tests. The 95% confidence interval for the treatment effect was obtained based on the profile likelihood assuming asymptotic normality. Then, the estimate of the treatment effect and the 95% confidence interval limits were exponentiated to express the results in terms of the odds ratio.

The odds ratio measured the odds of a zoledronic acid-treated patient responding to treatment relative to the odds of a risedronate-treated patient responding to treatment. An odds ratio > 1 implies that a zoledronic acid-treated patient is more likely to respond to treatment than a risedronate-treated patient. The presence of treatment-by-baseline SAP interactions was also assessed. A treatment-by-baseline SAP explanatory variable was added separately to the primary logistic regression model. The least squares estimate of the treatment effect and its standard error were then used to construct the 95% confidence interval for the log odds ratio and then were exponentiated to express the results in terms of the odds ratio. If the p-value was less than or equal to 0.1000 for the interaction term, then further work was done (tabular and/or graphical methods) to look for a possible explanation to the differences across subgroups. A tabular representation of the proportion of responders by country and other demographic subgroups (age, gender, race, and previous Paget's Therapy) was also presented.

The primary analysis of primary efficacy variable was based on the Modified ITT population using the LOCF approach for missing values, i.e., for all patients with baseline and at least one post-baseline measurement, the last post-baseline measurement prior to the visit window, independently of being in any previous visit window, was carried forward to all subsequent visits with missing observation(s). The analysis was repeated on the per-protocol population using the LOCF approach for missing values. The logistic regression model was repeated on both populations using only patients with available data within Day 182 visit window, i.e., noimputation for missing values.

Protocol Amendments:

Amendment No. 1 (13-Dec-2001) was finalized prior to the enrollment of the first patient in the study. The purpose of this amendment was to incorporate changes requested by FDA and the EMEA.

- The objectives and statistical justifications were modified to reflect the FDA's suggestion to pool the results of studies CZOL446H2304 and CZOL446H2305. Modifications were made to the planned statistical methods.
- The wording of the primary efficacy variable was modified.
- The bone marker urine α -CTx was added as an additional secondary efficacy objective.

- Inclusion criteria of "prior x-ray confirmation of Paget's" was changed to include other means of confirmation (e.g., magnetic resonance imaging, computerized tomography, radioisotope imaging, etc.).
- Inclusion criteria for washout period of bisphosphonates was changed from 180 to 365 days.

Amendment No. 2 (29-May-2002). The purpose of this amendment was to incorporate changes requested by the FDA.

- The objectives and statistical justifications/methods modified under Amendment No. 1 (see first bullet above) were changed back to those of the original protocol.
- The wording of the primary efficacy variable modified under Amendment No. 1 (see second bullet above) was changed back to that of the original protocol.
- Two exclusion criteria were added: active primary hyperparathyroidism and invasive malignancy. The renal function exclusion criteria was expanded (calculated creatinine clearance of < 30 mL/min at baseline or urine protein level \geq 2+ protein).

Amendment No. 3 (21-Oct-2002). The purpose of this amendment was to make the following changes to the protocol:

- The inclusion criteria for the bisphosphonate washout period was changed from 365 days to 180 days.
- The exclusion criteria for malignancies was replaced with an updated version more suitable to the study.

Amendment No. 4 (19-Jan-2004). The purpose of this amendment was to have additional bone marker assessments (serum CTx, urine α -CTx, and PINP) performed every six months during the extended observation period, coinciding with the collection of SAP.

Results

Patient Demographics: The groups were well matched for baseline demographic characteristics with no statistically significant differences between groups. The mean age was 71 years (range 42 – 94 years); about 75% of the patients were 65 years of age or older; 72% of the subjects were male; and 95% were Caucasian. The following table provides the baseline disease characteristics for the two groups.

Baseline Disease Characteristics - Study 2304			
	Zoledronic Acid n=90	Risedronate n=82	P-value*
Serum Alk Phos (U/L)	425 (range 229 – 2822)	423 (range 214 – 1917)	0.97
SAP % < 3xULN	52%	55%	0.76
SAP % ≥ 3xULN	48%	45%	
Calculated CrCl (mL/min)	87	85	0.68
Last Paget's disease Tx			0.70
Oral Bisphosphonate	26%	34%	
IV Bisphosphonate	14%	12%	
Clodronate	3%	1%	
None	54%	50%	
Washout Bisphosphonate			0.20
< 180 days	1%	0%	
180 < 365 days	4%	1%	
> 365 days	38%	46%	
Duration of Disease (yr)	8.2 (0.07 – 30)	9.4 (0.05, 39)	0.45

*Based on one-way analysis of variance for continuous variables and the Fisher exact test for categorical variables.

Patient Disposition: A total of 90 patients were randomized to zoledronic acid and 82 to risedronate. Eighty-six and 76 subjects in the zoledronic acid and risedronate groups, respectively, completed the study. Full details of patient disposition per group are provided in the following table.

Summary of Patient Disposition			
	Zoledronic acid n (%)	Risedronate n (%)	p-value
Total no. of patients - n(%)			
ITT	90 (100)	82 (100)	
Completed	86 (95.6)	76 (92.7)	
Discontinuations – n(%)			
Total	4 (4.4)	6 (7.3)	
Primary reason			
Adverse event	2 (2.2)	2 (2.4)	
Protocol violations	1 (1.1)	0 (0.0)	
Patient withdrew consent	1 (1.1)	2 (2.4)	
Lost to follow up	0 (0.0)	2 (2.4)	

Protocol Violations: As shown in the Table below, the most common protocol violations were compliance with capsules > 110% and compliance with capsules < 90%. The number of patients in each treatment group with compliance > 110% or < 90% were similar.

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Exclusions from the Per Protocol Population

	Zoledronic acid N=90 n (%)	Risedronate N=82 n (%)
Protocol violation		
Compliance with oral study medication <90% or >110%	12 (13.3)	13 (15.9)
No baseline or post-baseline SAP measurement	2 (2.2)	0 (0.0)
Baseline SAP < 2xULN	1 (1.1)	2 (2.4)
Randomized but did not take study drug	1 (1.1)	0 (0.0)
Washout period for calcitonin < 90 days or bisphosphonates < 180 days	1 (1.1)	0 (0.0)
Wrong study treatment during whole study	1 (1.1)	0 (0.0)
Baseline creatinine clearance <30 mL/min ¹	0 (0.0)	1 (1.2)
Switch of study treatment during study	0 (0.0)	1 (1.2)

Comment: It is unlikely that the number, type, and distribution of protocol violations between groups would have materially affected the efficacy or safety analyses.

Concomitant Medications: The following table provides the more commonly taken concomitant medications for subjects in both treatment groups.

Concomitant Medications (at least 10% patients for any group)

Preferred term	Zoledronic acid (N=89) n (%)	Risedronate (N=82) n (%)
Total no. of patients receiving any concomitant medication	88 (100.0)	90 (100.0)
Paracetamol	44 (49.4)	30 (36.6)
Ergocalciferol	37 (41.6)	28 (34.1)
Lekovit Ca	37 (41.6)	30 (36.6)
Acetylsalicylic acid	27 (30.3)	34 (41.5)
Calcium	25 (28.1)	18 (22.0)
Calcium carbonate	16 (18.0)	17 (20.7)
Amlodipine	11 (12.4)	2 (2.4)
Celecoxib	11 (12.4)	4 (4.9)
Atorvastatin	9 (10.1)	10 (12.2)
Ibuprofen	8 (9.0)	9 (11.0)
Furosemide	7 (7.9)	9 (11.0)
Omeprazole	4 (4.5)	10 (12.2)
Rofecoxib	3 (3.4)	9 (11.0)
Amoxicillin	2 (2.2)	10 (12.2)

Preferred terms are sorted in decreasing order of frequency with respect to zoledronic acid group.

Primary Efficacy Endpoint: The primary efficacy variable was the proportion of patients who achieved therapeutic response at 6 months. A therapeutic response was defined as a reduction of at least 75% from baseline (Visit 1) in SAP excess (difference between measured level and midpoint to the normal range) or normalization of SAP.

As seen in the Table below, a statistically significantly greater percentage of patients treated with a single dose of zoledronic acid vs. risedronate achieved a therapeutic response at Month 6.

The proportion of patients who achieved therapeutic response at 6 months was 0.97 for zoledronic acid compared to 0.73 for risedronate. The lower limit of the two sided 95% CI for the difference between the treatment groups was greater than -0.16, meeting the non-inferiority criterion for zoledronic acid relative to risedronate.

Proportion of Patients who Achieved Therapeutic Response at 6 Months					
Treatment	N	Proportion	Difference ¹ 95% CI	Odds ratio ² 95% CI	p-value ³
Zoledronic acid	88	0.97	0.23 (0.12, 0.35)	10.37 (3.40, 45.21)	< 0.0001
Risedronate	82	0.73			

¹ difference of zoledronic acid minus risedronate
² Odds ratio of zoledronic acid over risedronate and its 95% CI is based on the logistic regression model
³ P-value given by the likelihood ratio test for the treatment comparison in the logistic regression model

Subgroup Analyses: In general, the differences in response rates for the two treatment groups were similar for various subgroups as they were for the overall populations, with the notable exception of those patients whose previous treatment for Paget's disease was an IV bisphosphonate. These patients had response rates in this study of approximately 80% in both treatment groups. It should also be noted that those patients who were previously treated with risedronate had very poor responses to risedronate therapy in this study.

Secondary Efficacy Endpoints: See Integrated Summary of Efficacy

Safety: See Integrated Summary of Safety

Clinical Trial #2 - ZOL446K 2305

Title: Randomized, double-blind, safety and efficacy trial with intravenous zoledronic acid for the treatment of Paget's disease of bone using risedronate as a comparator.

Study Centers: 5 Australia, 2 Belgium, 1 Canada, 8 France, 5 Germany, 1 New Zealand, 1 South Africa, 9 Spain, 3 United Kingdom, and 10 United States.

Study Period: First patient enrolled: 22-Apr-2002 Last patient completed: 02-Dec-2003

Study Objectives: The primary efficacy objective of this trial was to show non-inferiority of the test drug, zoledronic acid, to the active control, risedronate, with respect to the proportion of

patients who achieved therapeutic response. A therapeutic response was defined as a reduction of at least 75% from baseline in total serum alkaline phosphatase excess (difference between measured level and midpoint to the normal range) or normalization of serum alkaline phosphatase at the end of six months.

The secondary efficacy objective was to assess the effect of i.v. zoledronic acid 5.0 mg (once) and oral risedronate 30 mg o.d. (60 days) in diminishing serum c-telopeptide (CTX) and urine α -CTX.

Design: This was an international multicenter, randomized, double-blind trial. Each patient was randomized to receive either one zoledronic acid 5.0 mg i.v. infusion (15 minutes) and 60 days of oral placebo o.d., or one i.v. placebo infusion (15 minutes) and 60 days of oral risedronate 30 mg o.d. It was planned to randomize 88 patients to each treatment group.

The formal portion of the study consisted of 7 Study Visits, with Visits 3-7 occurring near Days 10, 28, 63, 91, and 182, respectively.

At Visit 7, each patient was identified by the investigator as either a responder or non-responder to treatment for entry into the extended observation period. A responder was defined as a patient who had $\geq 75\%$ decrease from baseline in serum alkaline phosphatase (SAP) excess (difference between measured level and midpoint of normal range) or SAP within the normal range at 6 months. A non-responder was defined as a patient who had $< 75\%$ decrease from baseline in SAP excess and whose SAP was above the ULN at 6 months. Each investigator was blinded to all efficacy laboratory values (serum bone turnover markers) throughout the trial except for SAP excess at Visit 1 (baseline) and Visit 7. Using these values, _____ multiplied the baseline SAP excess value at Visit 1 by 0.25 and provided the results to the investigator. Each investigator made the determination that a patient entered the extended observation phase if the following conditions were satisfied.

If $(X_{To}) (0.25) \geq Y_{T7}$ or $(Y_{T7} + \text{Midpoint of normal range}) \leq \text{ULN}$ where X_{To} = baseline SAP excess Y_{T7} = Visit 7 SAP excess

Patients who completed the study and were identified as responders entered the extended observation phase for continued monitoring. All responders are to return to the investigator every 6 months to measure SAP and will continue to be monitored until the SAP level returns to within 20% of baseline, or the investigator re-initiates therapy to treat the Paget's disease. Following Amendment 4 (dated 19-Jan-2004), additional bone marker data (serum CTx, serum P1NP, and urine α -CTx) were also to be collected. The results of the extended observation period will be presented in a separate report. Patients identified as non-responders ended study participation at Visit 7.

A transiliac crest bone biopsy was performed at designated sites, for those patients who volunteered to participate and who completed 6 months of the study. It was planned that up to approximately 20 patients would have a bone biopsy performed at Visit 7. Patients who elected to participate were presented with the informed consent for the bone biopsy

procedure at Visit 6. Those who signed the form were asked to return approximately 6 weeks prior to Visit 7 for the tetracycline HCl capsules and instructions. However, if a patient could not return for another visit prior to Visit 7, the tetracycline HCl and instructions could be dispensed at Visit 6. If the tetracycline HCl was provided at Visit 6, the investigator was to call and remind the patient to begin taking the tetracycline capsules at the appropriate time. The investigator verified compliance.

Patient Population: The trial population consisted of patients with prior confirmed diagnosis of Paget's disease of bone with a serum alkaline phosphatase ≥ 2 times the upper limit of normal.

Inclusion criteria:

- Male or female patients 30 years and above at the time of entry into the trial who have Paget's disease of bone. Females of child-bearing potential may have been enrolled if they had a negative serum pregnancy test prior to study entry and if they agreed to use acceptable methods of contraception during the study.
- Confirmed diagnosis of Paget's disease of the bone (i.e., by x-ray, magnetic resonance imaging, computerized tomography, radioisotope imaging, etc.).
- Serum alkaline phosphatase level at least two times the upper limit of the normal reference range.
- A normal or not clinically significantly abnormal ECG result during the past 6 months.
- Washout period for other therapies prior to trial drug administration at Visit 2: 90 days for calcitonin and 180 days for any bisphosphonate (washout period changed from 365 to 180 days via Amendment 3, dated 21-Oct-2002).

Exclusion criteria:

- Treatment with any investigational drug within the past 30 days.
- History of noncompliance to medical regimens and patients who are considered potentially unreliable.
- Any disease or therapy which would interfere with the procedures or data collection of this trial.
- Severe liver disease that would affect alkaline phosphatase levels such as hepatitis, primary biliary sclerosis, and cirrhosis.
- History of any of the following: hypersensitivity to bisphosphonates, clinically significant upper gastrointestinal disorders that could interfere with compliance, uritis or uveitis, renal disease with continuing clinically significant abnormality, diabetic nephropathy or retinopathy.
- WBC $< 3.5 \times 10^3/\text{mm}^3$, platelets $< 125 \times 10^3/\text{mm}^3$ or any other clinically significant laboratory abnormality.
- Calculated creatinine clearance $< 30 \text{ mL/min}$ at baseline or urine protein level $\geq 2+$ protein without evidence of contamination or bacteruria (urine protein level criteria added via Amendment 2, dated 29-May-2002).
- Evidence of vitamin D deficiency (serum 25(OH) D of $< 15 \text{ ng/mL}$).
- Patients with allergies to tetracycline or any of its derivatives were to be excluded from the bone biopsy procedure.
- Active primary hyperparathyroidism (added via Amendment 2, dated 29-May-2002).
- Patients with a new diagnosis or active treatment for any malignancy less than or equal to 12 months prior to study entry (Amendment 3, dated 21-Oct-2002).

Treatment Groups: Zoledronic acid and matching placebo was given intravenously to each patient as a slow infusion over 15 minutes. A peripheral intravenous site was used for the infusion. The bore of the needle or angio-catheter used to insert the intravenous line was 20 to 22 gauge. Risedronate and matching oral placebo capsules were administered once per day for 60 consecutive days. Risedronate and matching oral placebo capsules were to be taken at least 30 minutes before the first food or drink of the day, other than water. Risedronate or oral placebo

was to be taken in an upright position with a full glass (6 to 8 oz) of plain water. Lying down was to be avoided for at least 30 minutes after taking risedronate or oral placebo.

Elemental calcium (500 mg) was to be taken by mouth with food (twice daily) beginning at least five days prior to administration of zoledronic acid and during the trial. Since calcium may interfere with the absorption of risedronate, it was to be taken at a different time of day. Calcium carbonate was the preferred form of calcium. If calcium carbonate was not well tolerated, another form of oral calcium was acceptable. In addition, each patient took multiple vitamin supplements containing between 400 and 1000 IU of vitamin D daily. Calcium and the multiple vitamins were dispensed as a 3-month supply and were supplied by the investigator. All patients were to receive calcium and multiple vitamin supplies at appropriate Visits. Patients were instructed to take one dose (500 mg) of calcium twice a day with food, or according to the information provided by the manufacturer and one multiple vitamin per day.

Statistical Analyses: The primary efficacy objective of this study was to show non-inferiority of zoledronic acid relative to risedronate with respect to the primary efficacy variable, proportion of patients who achieved therapeutic response at six months. The null hypothesis tested was that the proportion of patients who achieved therapeutic response at 6 months was 0.16 lower in the zoledronic acid group than in the risedronate group while the alternative hypothesis was that proportion of patients who achieved therapeutic response at 6 months in the zoledronic acid group was greater than or equal to the proportion of patients who achieved therapeutic response in the risedronate group minus 0.16. Non-inferiority of zoledronic acid relative to risedronate was concluded if the lower limit of the two-sided 95% confidence interval for the difference in proportions (zoledronic acid minus risedronate) was greater than -0.16 . A 95% confidence interval for the difference in the proportion of patients who achieved therapeutic response at six months was constructed based on the normal approximation to the binomial.

In addition, as a pre-planned strategy to test the superiority of zoledronic acid over risedronate, if non-inferiority of zoledronic acid relative to risedronate was demonstrated, between treatment differences in proportion of patients who achieved therapeutic response at 6 months was evaluated using a logistic regression model with treatment and baseline SAP (categorized as $< 3 \times \text{ULN}$ or $\geq 3 \times \text{ULN}$) as explanatory variables. In case the logistic regression model did not converge, the lower limit of the two-sided 95% confidence interval was used to assess the superiority of zoledronic acid over risedronate based on the normal approximation to the binomial. The p-values reported for the model were computed from the likelihood ratio tests. The 95% confidence interval for the treatment effect was obtained based on the profile likelihood assuming asymptotic normality. Then, the estimate of the treatment effect and the 95% confidence interval limits were exponentiated to express the results in terms of the odds ratio.

The odds ratio measured the odds of a zoledronic acid-treated patient responding to treatment relative to the odds of a risedronate-treated patient responding to treatment. An odds ratio > 1 implies that a zoledronic acid-treated patient is more likely to respond to treatment than a risedronate-treated patient. The presence of treatment-by-baseline SAP interactions was also assessed. A treatment-by-baseline SAP explanatory variable was added separately to the primary logistic regression model. The least squares estimate of the treatment effect and its standard error

were then used to construct the 95% confidence interval for the log odds ratio and then were exponentiated to express the results in terms of the odds ratio. If the p-value was less than or equal to 0.1000 for the interaction term, then further work was done (tabular and/or graphical methods) to look for a possible explanation to the differences across subgroups. A tabular representation of the proportion of responders by country and other demographic subgroups (age, gender, race, and previous Paget's Therapy) was also presented.

The primary analysis of primary efficacy variable was based on the Modified ITT population using the LOCF approach for missing values, i.e., for all patients with baseline and at least one post-baseline measurement, the last post-baseline measurement prior to the visit window, independently of being in any previous visit window, was carried forward to all subsequent visits with missing observation(s). The analysis was repeated on the per-protocol population using the LOCF approach for missing values. The logistic regression model was repeated on both populations using only patients with available data within Day 182 visit window, i.e., noimputation for missing values.

Protocol Amendments:

Amendment No. 1 (01-Feb-2002). Amendment No. 1 was finalized prior to the enrollment of the first patient in the study.

- An exclusion criterion was added for history of invasive malignancy,
- A directive was added for the administration of risedonate, in accordance with the approved package insert.
- Clarifications to the statistical analysis were made.

Amendment No. 2 (08-Aug-2002). The purpose of this amendment was to incorporate changes requested by the FDA.

- An exclusion criterion was added for active primary hyperparathyroidism.
- The renal function exclusion criterion was expanded (calculated creatinine clearance of <30 mL/min at baseline or urine protein level $\geq 2+$ protein).
- Clarifications regarding the administration of the intravenous study medication were made.

Amendment No. 3 (31-Oct-2002). The purpose of this amendment was to make corrections to the exclusion criteria regarding patients with malignancies and the washout period for previous bisphosphonate treatment.

Amendment no. 4 (13-Jan-2004). The purpose of this amendment was to have additional bone marker assessments (serum CTx, urine α -CTx, and P1NP) performed during the extended observation period.

Results

Baseline Patient Demographics: Aside from age, which was statistically significantly greater in the zoledronic acid vs. the risedronate group, the baseline demographic characteristics were similar for the two groups (Table below). Approximately 64% of the patients were male, 91%

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were Caucasian, and the mean age was 71 years in the zoledronic acid group compared with 68 years in the risedronate group.

Baseline Disease Characteristics			
	Zoledronic Acid n=90	Risedronate n=82	*P-value
Serum Alk Phos (U/L)	431	427	0.94
SAP % < 3xULN	50%	60%	0.18
SAP % ≥ 3xULN	50%	39%	
Calculated CrCl (mL/min)	84	89	0.25
Last Paget's disease Tx			0.90
Oral Bisphosphonate	36%	38%	
IV Bisphosphonate	15%	17%	
Clodronate	3%	1%	
None	39%	39%	
Washout Bisphosphonate			0.80
< 180 days	2%	2%	
180 < 365 days	5%	3%	
> 365 days	47%	51%	
Duration of Disease (yr)	10.4 (0.02, 39)	9.6 (0.03, 42)	0.72

*Based on one-way analysis of variance for continuous variables and the Fisher exact test for categorical variables.

Patient Disposition: A total of 92 patients were randomized to the zoledronic acid group and 93 to the risedronate group. Eighty-five and 89 patients from the zoledronic acid and risedronate groups, respectively, completed the 6-month study. Full details of patient disposition per group are provided in the following table

	Zoledronic acid n (%)	Risedronate n (%)
Total no. of patients - n(%)		
ITT	92 (100%)	93 (100%)
Completed	85 (92%)	89 (96%)
Discontinuations – n(%)		
Total	7 (8%)	4 (4%)
Primary reason		
Adverse event	1 (1%)	0
Protocol violations	3 (3%)	2 (2%)
Patient withdrew consent	3 (3%)	2 (2%)

Protocol Violations: As shown in the following table, the zoledronic acid group had a greater number of patients who reportedly had compliance with oral study medication that was below 90%.

Exclusions from per protocol population

	Zoledronic acid N=92 n (%)	Risedronate N=93 n (%)
Total no. with at least one major protocol violation	23 (25.0)	12 (12.9)
Protocol violation		
Compliance with oral study medication <90% or >110%	17 (18.5)	6 (6.5)
No baseline or post-baseline SAP measurement	4 (4.3)	4 (4.3)
Randomized but did not take study drug	4 (4.3)	3 (3.2)
Washout period for calcitonin < 90 days or bisphosphonates < 180 days	2 (2.2)	2 (2.2)
Baseline SAP < 2xULN	0 (0.0)	1 (1.1)

Concomitant Medications: The most commonly taken concomitant medications (i.e., $\geq 10\%$ of patients in either treatment group) were various formulations of calcium and vitamin D, over-the-counter pain relievers (paracetamol, acetylsalicylic acid, and ibuprofen), and omeprazole.

Comment: It is highly unlikely that the protocol violations or the concomitant medication use for the two groups materially influenced the efficacy or safety outcomes from the study.

Primary Efficacy Endpoint: The primary efficacy variable was the proportion of patients who achieved therapeutic response at 6 months. A therapeutic response was defined as a reduction of at least 75% from baseline (Visit 1) in SAP excess (difference between measured level and midpoint to the normal range) or normalization of SAP.

The proportion of patients who achieved therapeutic response at 6 months was 0.95 for zoledronic acid compared to 0.75 for risedronate. The lower limit of the one-sided 97.5% CI (or two-sided 95% CI) for the difference between the treatment groups was greater than -0.16, meeting the non-inferiority criterion of zoledronic acid relative to risedronate. In addition, in testing for superiority, the lower limit of the confidence interval was greater than 0 indicating that zoledronic acid had a significantly higher proportion of patients who achieved therapeutic response.

Subgroup Analyses: In general, the response rates for zoledronic acid and risedronate observed in the pre-defined subgroups were similar to those of the overall analysis.

Secondary Efficacy Outcomes: See Integrated Summary of Efficacy

Safety Review: See Integrated Summary of Safety

Appendix (con't)

Criteria for clinically notable laboratory parameters.

Clinically Notable Criteria for Selected Laboratory Parameters		
	Less Than	Greater Than
Albumin	25 g/L	60 g/L
Bilirubin (Total)	0 µmol/L	43 µmol/L
Blood Urea Nitrogen (BUN)	0.7 mmol/L	14.3 mmol/L
Calcium	1.87 mmol/L	2.89 mmol/L
Chloride	85 mmol/L	119 mmol/L
Creatinine	18 µmol/L	221 µmol/L
Sodium	125 mmol/L	154 mmol/L
Potassium	3 mmol/L	6 mmol/L
SGOT	0 U/L	100 U/L
SGPT	0 U/L	110 U/L
LDH	0 U/L	500 U/L
Total Protein	40 g/L	95 g/L
Uric Acid	89 µmol/L	595 µmol/L
Hemoglobin	100 g/L	200 g/L
Hematocrit	30%	60%
RBC	3.3 10E12/L	6.6 10E12/L
WBC	3.0 10E9/L	15.0 10E9/L
Platelet	100 10E9/L	600 10E9/L

Narrative for patient 0455/00109 who developed a 0.05 mg/dl increase in post-baseline serum creatinine.

Patient: 61 years old male, Caucasian, 84.7 kg, 173cm **Treatment group:** Zoledronic acid

The patient's relevant medical history includes tuberculosis (1987),-smoking (since 1957 and still active), alcoholism, high blood pressure and pneumonia (all on 1999). In addition, the patient suffered from congestive heart failure (CHF) since 1999 with one hospitalization due to a dyspnoea worsening episode in — At that moment, an echocardiographic assessment showed dilated cardiomyopathy based on the following criteria: DDLV 70.3 mm DSLV 62.5, ejection fraction of 23%, thickness TIV 11.4 mm, PP 11.9 mm. Left auricula 40 mm. Aortic root: 30mm. Doppler flow showed mitral regurgitation flow degree I-II.

This patient was referred by his rheumatologist and was screened in the trial on 16-Oct-2002 and Calcium/Vitamin D supplements were started. At the study start, the patient was taking furosemide, perindopril and Potassium supplements.

The laboratory assessment results at screening showed high levels of serum creatinine (2.1 mg/dL; ref ranges: 0.5-1.5 mg/dL), urea nitrogen (41 mg/dL, ref range: 4-29 mg/dL) and uric

acid 10.7 mg/dL ref range: 2.5-8.3mg/dL). These abnormal levels were attributed to CHF as well as to the treatment in course, especially diuretics and ACE-inhibitors. The creatinine clearance value was low (43 mL/min, ref range: 85-125 mL/min) but not exclusionary as per protocol criteria. At screening visit, the patient denied current alcohol consumption.

The study intravenous infusion was done on 6-Nov-2002 and the oral study medication intake started the following day.

Twelve days after IV infusion (visit 3, 18-Nov), the creatinine level increased to 2.3 mg/dL and continued elevation through the core protocol period (2.4 and 3.8 mg/dL at visits 5 & 7, respectively). The creatinine clearance decreased slightly at visit 3 (41 mL/min). Serum uric acid levels decreased at all post-randomization visits when compared to the screening value. The urea nitrogen levels were decreased at visits 3 and 5 but increased at visit 7. The patient completed the trial double-blind phase, was a responder and entered the extension observation period. The investigator confirmed that no local laboratory assessments were performed since the completion of the core protocol portion. This patient is being followed-up by his primary care physician.

As follow-up, some laboratory assessments were conducted at the first visit of the trial extension observation period (2-Dec-2003) and showed decreased serum creatinine clearance (28 mL/min) and urea nitrogen levels. The creatinine clearance decrease is mainly related to the patient weight diminution (by 10 kg) which would be linked to the cardiovascular prescription according to the investigator.

Because creatinine levels have been raising and there has been a decrease in the weight value, further assessments are planned to be performed: Creatinine clearance (24 hrs urine), complete biochemistry panel (including creatinine, serum uric acid, total protein, urea nitrogen, and electrolytes), Urine cytology, urine electrolytes and renal ultrasound.

The clinical and biochemical assessments indicated above were performed on 3-Mar-2004 at the site and a local lab, respectively.

Physical examination: weight: 77.2 kg; height: 173 cm; blood pressure: 135/85 mm Hg.

Blood Chemistry: Glucose: 100 (60-110 mg/dL); Urea 83 (15-50 mg/dL); BUN 38.7 (7.0-21.0 mg/dL); Uric acid 6.6 (3.4-7.0 mg/dL); Sodium 139 (135-147 mEq/L); Potassium 5.27 (3.5- 5.1 mEq/L); Chloride 105 (87-110 mEq/L); Total bilirubin 0.4 (0-1.2 mg/dL); Direct bilirubin 0.1 (0-0.4 mg/dL); Total protein 7.9 (6.4-8.2 g/dL); Albumin 4.9 (3.5-5.2 g/dL); Calcium 10.1 (8.4-10.3 mg/dL); Phosphate 4 (2.5-5 mg/dL); ASAT 13 (<45UI/L); ALAT 16 (<45 UI/L); Alkaline Phosphatase 102 (40-129 UI/L); GGT 29 (8-61 UI/L); LDH 285 (211-423 UI/L); CK 63 (0-170 UI/L); Total cholesterol 245 (0-200 mg/dL); Triglycerides 198 (35-200 mg/dL).

Urine chemistry: Diuresis 720 min (12-h): 1600 mL; Blood creatinine: 3.23 (0-1.3 mg/dL); Urine creatinine: 51.3 mg/dL; Urine sodium (excretion): 225.60 mEq/720 min; Urine Potassium: 38.61 mEq/720 min; Urine Chloride: 187.20 mEq/720 min; 24-hour Urine Creatinine Clearance: 35.29 mL/min (70-120 mL/min)

Urine cytology: Benign

Ultrasound:

- Abdominal examination: normal.
- Kidneys: normal sized.
- Bile ducts and vesicle, pancreas, spleen, abdominal vessels and retroperitoneal space were within normal limits.
- Bladder: replete, with smooth wall. Prostate: 27x42x30 mm, with a volume of 18 cm³.

According to the investigator, the patient's condition is stable and no new clinical event was reported. The patient denied any alcohol intake. The concomitant medication intake remains unchanged and the patient's cardiac clinical status is stable. However, the blood pressure level remained high, that could explain the abnormal renal function.

According to the investigator, the clinical significance of renal function impairment in this patient would be probably due to bad control of high blood pressure, arising from the sclerosed-hypertensive form of nephropathy and progressing to renal failure.

The investigator concluded that the renal function damage is probably related to his basal disease (renal failure) and bad control of his high blood pressure. Furthermore, as the study drug has been administrated once, several months ago, the deterioration of renal function is unlikely related to this drug. However a relationship between the study medication and impairment of his renal function could not be completely excluded.

Relevant concomitant medications: Nolotil, Seguril and Coversil.

Eye Abnormalities from Phase 2 and 3 Paget's Studies

Eye disorders	Zol < 5 mg	Zol 5 mg	Risedronate	Placebo
Total	9(5.7)	8(4.5)	3(1.7)	0(0.0)
Eye pain	0(0.0)	2(1.1)	0(0.0)	0(0.0)
Acquired night blindness	0(0.0)	1(0.6)	0(0.0)	0(0.0)
Conjunctivitis	0(0.0)	1(0.6)	1(0.6)	0(0.0)
Eye irritation	1(0.6)	1(0.6)	0(0.0)	0(0.0)
Eye redness	1(0.6)	1(0.6)	0(0.0)	0(0.0)
Keratoconjunctivitis	0(0.0)	1(0.6)	0(0.0)	0(0.0)
Sicca				
Photopsia	0(0.0)	1(0.6)	0(0.0)	0(0.0)
Vision blurred	2(1.3)	1(0.6)	1(0.6)	0(0.0)
Blepharitis	0(0.0)	0(0.0)	1(0.6)	0(0.0)
Conjunctival disorder	1(0.6)	0(0.0)	0(0.0)	0(0.0)
Conjunctival hemorrhage	2(1.3)	0(0.0)	0(0.0)	0(0.0)
Entopion	0(0.0)	0(0.0)	1(0.6)	0(0.0)
Eye discharge	1(0.6)	0(0.0)	0(0.0)	0(0.0)
Eye disorder	1(0.6)	0(0.0)	0(0.0)	0(0.0)
Eye pruritus	1(0.6)	0(0.0)	0(0.0)	0(0.0)
Lacrimation increased	1(0.6)	0(0.0)	0(0.0)	0(0.0)

Brief narratives for the cases of "anaphylaxis" discussed in section 7.1.10

Case IDs (incl age, gender, indication)	Onset after therapy initiation	Reported main events	Treatment Outcome Other
PHBS2004GR11864 (75 yrs, male with prostate cancer) [Serious SR]	After 12 hrs (1 st infusion)	Tongue edema with difficulty to speak clearly, swallow and breath	Methylprednisolone Complete recovery Just before Zometa infusion pt received one Voltaren (diclofenac) ampoule for flu-like syndrome
PHBS2002AU06105 (39 yrs, male with ankylosing spondylitis) [Serious SR]	Almost immediately after Zometa administration (1 st infusion)	Anaphylactoid reaction with flushed face, swelling of face, swelling of trachea, nauseated (lasted about 60 minutes)	Hydrocortisone Metoclopramide Promethazine Complete recovery on same day
PHBS2002SE02471 (72 yrs, male with prophylaxis against skeletal cancer) [Serious SR]	During Zometa infusion (1 st infusion)	Allergic reaction (urticarial) with conjunctivitis, swollen eyes, eye pain, headache	Cromoglicate Complete recovery Alendronate was stopped 48 hrs prior to Zometa infusion
PHBS2003BE02365 (70 yrs, gender unkn with breast cancer) [Non-serious SR]	After a few minutes (1 st infusion)	Allergy with swollen eyelids, redness face and eyes, nausea, vomiting	Dexchlorpheniramine Methylprednisolone Alizapride Complete recovery Re-challenge negative
PHBS2003BE13316 (50 yrs, female with breast cancer) [Non-serious SR]	After about 5 minutes of Zometa infusion (After "over a year")	"Acute reaction" with retrosternal pain and dyspnea (lasted about 30 minutes)	Complete recovery Phenergan and dexamethasone given prior to next Zometa infusion (Rechallenge negative)

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Case IDs (incl age, gender, indication)	Onset after therapy initiation	Reported main events	Treatment Outcome Other
PHBS2003ES12025 (44 yrs, female with breast cancer) [Serious SR]	Minutes after the Zometa infusion (After 215 days)	Anaphylactic reaction with shortness of breath, "diffuse drowning sensation", facial and cervical redness, swollen face and neck	Corticosteroids Antihistamines Adrenalin Complete recovery Previous history of allergic reactions (unspecified) Concomitant docetaxel, NSAID's, omeprazole, paracetamol
PHBS2004BR02993 (Age unkn, female with breast cancer) [Serious SR]	Unspecified	Allergic reaction with urticaria, rubor, pruritus, glottis spasm, dyspnea, "whistle", cutaneous erythema	Dexamethasone Fexofenadine Complete recovery Rechallenge positive (2 nd infusion)
PHBS2004IE12616 (Age, gender and indication unkn) [Non-serious SR]	"While taking Zometa"	Hypersensitivity reaction with profuse allergic dermatitis	Not reported
PHEH2001US08982 (65 yrs, male with hypercalcemia of malignancy) [Non-serious SR]	After 3 cc infusion of Zometa (1 st infusion)	"Hypersensitivity reaction" with chest tightness	Hydrocortisone Diphenhydramine Complete recovery
PHEH2003US00568 (Age unkn, female with bone metastases) [Serious SR]	Unspecified (1 st infusion)	Severe allergic reaction with difficulty breathing, tongue swelling, elevated pCO ₂ , uncontrolled bowel movements	Steroids Complete recovery
PHEH2003US08411 (60 yrs, female with multiple myeloma) [Non-serious SR]	Shortly after Zometa infusion (1 st infusion)	"Suspected allergic reaction" with itchiness all over body and rash"	Diphenhydramine Complete recovery Concomitant celecoxib, cyclophosphamide, estradiol/testosterone, dextropropoxyphene, mometasone, medroxyprogesterone, carisoprodol, diazepam

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Case IDs (incl age, gender, indication)	Onset after therapy initiation	Reported main events	Treatment Outcome Other
PHEH2004US03701 (83 yrs, male with prostate cancer) [Non-serious SR]	On same day as Zometa infusion (1 st infusion)	Allergic reaction with rash and wheals (abdomen, extremities), "broke out with welts across chest"	Diphenhydramine Complete recovery Concomitant tamsulosin, atorvastatin, metoprolol, amlodipine, technetium TC ^{99M} teboroxime
PHFR2003GB02078 (72 yrs, female with multiple myeloma) [Serious SR]	Within 5 minutes of Zometa infusion (After 207 days)	"Possible anaphylaxis" with vomiting, rigors, awful feeling	Hydrocortisone Chlorphenamine Concomitant ciprofloxacin, diclofenac, melphalan History of hypersensitivity
PHNU2002DE03266 (70 yrs, male) [Serious SR]	About 30 minutes after Zometa infusion was finished (1 st infusion)	"Suspected anaphylactic reaction" with severe obstructive bronchospasm, dyspnea, hot flushes, chills, fever (lasted about 7 hrs)	Prednisolone Fenoterol/ ipratropium bromide Aminophylline Oxygen Complete recovery Co-suspect paracetamol History of pulmonary tuberculosis and pneumonia and currently suffering from pleural effusions
PHNU2003DE02543 (67 yrs, male with bone metastases) [Serious SR]	About 10 minutes after Zometa infusion was finished (1 st infusion)	"Suspected anaphylaxis" with hypotension, tachycardia, sweating attack	Treatment not reported Complete recovery
PHEH2002US05512 (55 yrs, female with osteoporosis) [Serious SR]	About 10 hrs after Zometa infusion (1 st infusion)	Acute allergic reaction with chills/ shaking chills/ shaky feeling, shortness of breath/ dyspnea at rest/ labored breathing, throat tightness/ swelling, shaking	Methylprednisolone Diphenhydramine Condition improving
PHBS2003AT04076 (Age and indication unkn, female) [Serious SR]	Unspecified (After 4 th or 5 th infusion)	Anaphylactic reaction Tumor lysis syndrome	Not reported Related to tumor lysis syndrome

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Case IDs (incl age, gender, indication)	Onset after therapy initiation	Reported main events	Treatment Outcome Other
PHBS2002IT11122 (73 yrs, male with osteitis condensans) [Non-serious SR]	Unspecified, after a single infusion	Angioedema face and neck Rheumatic polymyalgia	Not reported Complete recovery
PHEH2003US11241 (71 yrs, female with bone metastases) [Non-serious SR]	On same day as Zometa infusion (1 st infusion)	Marked allergic reaction with semi-generalized rash mainly on chest (torso) and also buttocks and thighs	Treatment not reported Unchanged at time of reporting Skin allergies to many substances
PHFR2003GB03609 (Age, gender and indication unkn) [Serious SR]	Unspecified	Angioedema	Not reported
PHNR2004AU00639 (55 yrs, female with bone metastases) [Serious SR]	After the 2 nd Zometa infusion	Angioedema	Not reported
PHHO2004DE02513 (77 yrs, male with prostate cancer) CZOL446E DE07 [Serious suspected CT]	18-20 hrs after 1 st Zometa infusion	Allergic distress with serious dyspnea, sweating, shivering, bone pain (lasting 2-3 hrs)	Treatment not reported Complete recovery Concomitant acetylsalicylic acid, enalapril, furosemide, ibuprofen, metoprolol, simvastatin History of diabetes mellitus, peripheral occlusion of arteries
PHHO2004GB02695 (37 yrs, female with breast cancer) CZOL446G2408 [Serious suspected CT]	About 2.5 hrs after administration of Zometa (1 st infusion)	Anaphylactic reaction with swelled face, flushing, periorbital edema, vomiting	Hydrocortisone Chlorphenamine Cyclizine Complete recovery Co-suspect 5-FU, epirubicin, cyclophosphamide, cyclizine, dexamethasone; Concomitant insulin, ondansetron
PHHO2002FR07902 (64 yrs, male with multiple myeloma) CZOL446GFR01 (ZOOM) [Serious suspected CT]	On next day (1 st infusion)	Hypersensitivity reaction with fever, urticaria, rhinitis	Treatment not reported Complete recovery Concomitant cyclophosphamide

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Case IDs (incl age, gender, indication)	Onset after therapy initiation	Reported main events	Treatment Outcome Other
PHEH1999US18303 (69 yrs, female with breast cancer) Protocol 010 [Serious suspected CT]	On the evening of the 1 st dose	Angioedema of the face	Treatment not reported Condition improving History of penicillin allergy

Reports of exposure to zoledronic acid during pregnancy.

Spontaneous reports

PHBS2002AU09429 A 38 year-old patient a received a single dose of Zometa for severe renal osteodystrophy and experienced a temperature of 41 degrees C within hours. The patient was hospitalized for 24 hours and received treatment with antibiotics as it was suspected the patient was experiencing an infection. It was also reported that the patient is pregnant. She was receiving concomitant IV Raccaltrol (calcitriol) and erythropoietin.

PHEH2003US06416 A 38 year-old patient was administered Zometa for bone metastases. The patient has a complicated concomitant medication regimen. An unspecified time after she started therapy it was discovered that the "patient is 8 to 9 weeks pregnant". She received letrozole, trastuzumab, warfarin, goserelin and ACE inhibitor as co-medications.

PHNU2002DE03851 A 39 year-old physician who was seven months pregnant had a momentary skin contact with Zometa infusion solution on her hands when she administered medication. The course of pregnancy was without complications and that she delivered a healthy male baby (3230 g; APGAR: 9).

PHEH2003US01283 A 40 year-old patient with metastatic breast cancer received a single dose of Zometa. At the time of the infusion the patient was approximately 2 1/2 weeks pregnant. The physician stated that chorionic villi sampling results showed DE NOVO balanced translocation of chromosomes 1 and 8 and was "not considered to be balanced with a 6% risk of severe retardation anomalies." The patient delivered a normal male infant via caesarean section. The infant weighed 7 lb. 11 oz. with no abnormalities and Apgar scores of 8, 9 and 9 at 1, 5 and 10 minutes, respectively. The physician reported the patient had no adverse effects during pregnancy.

PHBS2004AT02888 A 35 year-old patient with fibrous dysplasia of the bones was switched to Zometa after 2.5 years treatment with Aredia. Four weeks before her last Zometa administration (once per half a year), she noticed that she was pregnant. This patient had a voluntary abortion due to private reasons, time unknown (first 3 months?).

PHBS2004GR14917 A 33 year-old patient with metastatic breast cancer received 5 courses FEC regimen. At the time of the first chemotherapy course, she was in menstruation phase, so she did not undergo a pregnancy test. During the 23rd week after the chemotherapy initiation, the patient underwent analgesic radiotherapy because of a persistent low back pain. A total dosage of 28 Gy

was delivered in the lumbar part and in the thoracic part. After the end of radiotherapy, tamoxifen and zoledronic acid (every 28 days) were administered. The patient did not accept further chemotherapy. When the patient came into the hospital for the administration of the third cycle of zoledronic acid (33 weeks after the first chemotherapy course), an ultrasound examination showed pregnancy with gestation age of 28 weeks that the patient did not know of. Eventually she had "symptoms of premature delivery" and during the 35th week of her pregnancy, the patient gave birth to a healthy girl by caesarian section. The authors stated that the cesarian section was preferred, because the expulsion phase of labor would have been hazardous and difficult due to painful bone metastases of the thoracic and lumbar spine. The infant's weight was found to be of normal birthweight for gestation age (2070 g), the height 46 cm, and the head perimeter 33 cm. The delivery had no complications; the Apgar score of the infant both in 1 and 5 min was 10. All hematological and biochemistry parameters of the neonate were within normal ranges for her age. Approximately 12 months after delivery, no disorder, congenital abnormality, or disease of the infant was observed.

PHEH2002US10610 A patient with unknown age on Zometa therapy for metastatic breast cancer became pregnant. No therapy dates or dosage was provided. The patient was scheduled to terminate pregnancy. No other details provided.

Clinical trial case

PHHO2004AT01093

A patient with unknown age and with hormone sensitive breast cancer commenced Arimidex plus zoledronic acid on 13 Sep 2002. Sixteen months later (19 January 2004) she was 19 weeks pregnant. Study medication was temporarily interrupted. She received also goserelin as co-medication. Delivery occurred on 27 May 2004 and the investigator stated that the outcome of the pregnancy was: 'normal, no complication'.

10.2 Line-by-Line Labeling Review

Pending approval of the NDA.

REFERENCES

1. Ishizuka S, Kurihara N, Miura D, et al. Vitamin D antagonist, TEI-9647, inhibits osteoclast formation induced by 1 alpha, 25-dihydroxyvitamin D3 from pagetic bone marrow cells. *Journal of Steroid Biochemistry and Molecular Biology*. 2004; 89-90:331-4.
2. Menna C. 1,25-dihydroxyvitamin D3 hypersensitivity of osteoclast precursors from patients with Paget's Disease. *Journal of Bone and Mineral Research*. 2000; 15:228-236.
3. Reddy SV, Kurihara NK, Menna C, et al. Paget's disease of bone: a disease of the osteoclast. *Rev Endocr Metab Disord*. 2001;2:195-201.
4. Markowitz GS, Fine PL, Stack JL, Kunis CL, Radhakrishnan J, Palecki W, Park J, Nasr SH, Hoh S, Siegel DS, D'Agati VD. Toxic acute tubular necrosis following treatment with zoledronate (Zometa). *Kidney Int*. 2003 Jul;64(1):281-9.
5. Theriault RL. Zoledronic acid (Zometa) use in bone disease. *Expert Rev Anticancer Ther*. 2003 Apr;3(2):157-66.
6. Croucher P, et al. The anti-tumor potential of zoledronic acid. *Breast*. 2003 Aug;12 Suppl 2:S30-6.
7. Chung G, Keen RW. Zoledronate treatment in active Paget's disease. *Ann Rheum Dis*. 2003 Mar;62(3):275-6.
8. Fournier P, Boissier S, Filleur S, Guglielmi J, Cabon F, Colombel M, Clezardin P. Bisphosphonates inhibit angiogenesis in vitro and testosterone-stimulated vascular regrowth in the ventral prostate in castrated rats. *Cancer Res*. 2002 Nov 15;62(22):6538-44.
9. Widler L, Jaeggi KA, Glatt M, Muller K, Bachmann R, Bisping M, et al. Highly potent geminal bisphosphonates. From pamidronate disodium (Aredia) to zoledronic acid (Zometa). *J Med Chem*. 2002 Aug 15;45(17):3721-38.
10. Garnero P, Christgau S, Delmas PD. The bisphosphonate zoledronate decreases type II collagen breakdown in patients with Paget's disease of bone. *Bone*. 2001 May;28(5):461-4.
11. Buckler H, Fraser W, Hosking D, Ryan W, Maricic MJ, Singer F, et al. Single infusion of zoledronate in Paget's disease of bone: a placebo-controlled, dose-ranging study. *Bone*. 1999 May;24(5 Suppl):81S-85S.
12. Garnero P, Gineyts E, Schaffer AV, Seaman J, Delmas PD. Measurement of urinary excretion of nonisomerized and beta-isomerized forms of type I collagen breakdown products to monitor the effects of the bisphosphonate zoledronate in Paget's disease. *Arthritis Rheum*. 1998 Feb;41(2):354-60.
13. Arden-Cordone M, Siris ES, Lyles KW, Knieriem A, Newton RA, Schaffer V, et al. Antiresorptive effect of a single infusion of microgram quantities of zoledronate in Paget's disease of bone. *Calcif Tissue Int*. 1997 May;60(5):415-8.
14. Siris E. Zoledronate in the treatment of Paget's disease. *Br J Clin Pract Suppl*. 1996 Sep;87:19-20; discussion 22.
15. Delmas PD. Zoledronate. *Br J Clin Pract Suppl*. 1996 Sep;87:15 discussion 22.
16. Hogler W, et al. Short-term safety assessment in the use of intravenous zoledronic acid in children. *J Pediatr*. 2004;145:701-4.
17. Peter R, et al. Severe hypocalcemia after being given intravenous bisphosphonate. *BMJ*. 2004 Feb 7;328:335-6.

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/s/

Eric Colman
3/18/05 01:48:06 PM
MEDICAL OFFICER

David Orloff
3/18/05 03:10:04 PM
MEDICAL OFFICER
Concur with Dr. Colman on need to address hypocalcemia/hypophosphatemia
risk before approval for tx of Paget's. AE