

#### 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

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#### 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  $\alpha$ -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  $\alpha$ -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  $\geq 2$  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  $\alpha$ -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  $\alpha$ -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
<b>Total no. of patients - n(%)</b>			
ITT	90 (100)	82 (100)	
Completed	86 (95.6)	76 (92.7)	
<b>Discontinuations – n(%)</b>			
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 (%)
<b>Protocol violation</b>		
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 <sup>1</sup>	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 (%)
<b>Total no. of patients receiving any concomitant medication</b>	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 <sup>1</sup> 95% CI	Odds ratio <sup>2</sup> 95% CI	p-value <sup>3</sup>
Zoledronic acid	88	0.97	0.23 (0.12, 0.35)	10.37 (3.40, 45.21)	< 0.0001
Risedronate	82	0.73			

<sup>1</sup> difference of zoledronic acid minus risedronate  
<sup>2</sup> Odds ratio of zoledronic acid over risedronate and its 95% CI is based on the logistic regression model  
<sup>3</sup> 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  $\alpha$ -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  $\alpha$ -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  $\geq 2$  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  $\alpha$ -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 (%)
<b>Total no. of patients - n(%)</b>		
ITT	92 (100%)	93 (100%)
Completed	85 (92%)	89 (96%)
<b>Discontinuations – n(%)</b>		
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 (%)
<b>Total no. with at least one major protocol violation</b>	23 (25.0)	12 (12.9)
<b>Protocol violation</b>		
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 cm<sup>3</sup>.

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 <sup>st</sup> 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 <sup>st</sup> 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 <sup>st</sup> 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 <sup>st</sup> 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 <sup>nd</sup> 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 <sup>st</sup> infusion)	"Hypersensitivity reaction" with chest tightness	Hydrocortisone Diphenhydramine  Complete recovery
PHEH2003US00568 (Age unkn, female with bone metastases) [Serious SR]	Unspecified (1 <sup>st</sup> infusion)	Severe allergic reaction with difficulty breathing, tongue swelling, elevated pCO <sub>2</sub> , uncontrolled bowel movements	Steroids  Complete recovery
PHEH2003US08411 (60 yrs, female with multiple myeloma) [Non-serious SR]	Shortly after Zometa infusion (1 <sup>st</sup> 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 <sup>st</sup> 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 <sup>99M</sup> 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 <sup>st</sup> 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 <sup>st</sup> 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 <sup>st</sup> 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 <sup>th</sup> or 5 <sup>th</sup> 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 <sup>st</sup> 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 <sup>nd</sup> Zometa infusion	Angioedema	Not reported
PHHO2004DE02513 (77 yrs, male with prostate cancer) CZOL446E DE07 [Serious suspected CT]	18-20 hrs after 1 <sup>st</sup> 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 <sup>st</sup> 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 <sup>st</sup> 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 <sup>st</sup> 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 Raccalrol (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.

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/s/

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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

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-817**

**CHEMISTRY REVIEW(S)**

## Memorandum

**Date:** 13-MAR-2007  
**From:** Su (Suong Tran), PhD, Pharmaceutical Assessment Lead, Branch II/DPA I/ONDQA  
**Through:** Blair Fraser, PhD, Director, DPA I/ONDQA  
**To:** NDA 21-817 NAME (zoledronic acid) Injection  
Letter date: 13-OCT-2006

**Subject:** Complete Response to the 22-FEB-2006 Approvable Letter

### Background:

- NDA 21-817 NAME (zoledronic acid) Injection was found Approvable on 22-FEB-2006 because of clinical deficiencies. The CMC recommendation at that time was "Approval" pending the DMETS' review of the proposed proprietary name. That recommendation included the review of CMC information in the package insert and packaging labels.
- The Complete Response dated 13-OCT-2006 includes labeling (copied at the end of this review).

### Reviewer's comments:

- Compared to the CMC information in the package insert and packaging labels that was previously found acceptable (refer to previous Chem. Reviews), the labeling submitted in the Complete Response has the revisions listed below. These revisions are acceptable. The text size of the established name is acceptable (more than half the size of the proprietary name).

### Conclusion:

The final CMC recommendation for NDA 21-817 (zoledronic acid) Injection is APPROVAL.

This recommendation does not cover the review of the proprietary name, graphics, and colors of the product labeling; refer to the recommendations from DMETS and DDMAC (Office of Drug Safety) on these non-CMC items.

3 Page(s) Withheld

       Trade Secret / Confidential

  X   Draft Labeling

       Deliberative Process

Withheld Track Number: Chemistry-   1

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/s/  
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Suong Tran  
3/19/2007 08:42:38 AM  
CHEMIST

labeling review; no issue

Blair Fraser  
3/19/2007 08:48:58 AM  
CHEMIST



**NDA 21-817**

**Aclasta® (zoledronic acid) Injection**

**Novartis**

**David B. Lewis, Ph.D.**

**Division of Metabolic and Endocrine Drug Products  
(DMEDP, HFD-510)**

27 Page(s) Withheld

X Trade Secret / Confidential

       Draft Labeling

       Deliberative Process

Withheld Track Number: Chemistry-2



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# Chemistry Review Data Sheet

1. NDA 21-817
2. REVIEW #: 1
3. REVIEW DATE: March 8<sup>th</sup>, 2005
4. REVIEWER: David B. Lewis, Ph.D.
5. PREVIOUS DOCUMENTS: None

Previous Documents

None

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

ORIGINAL NDA  
AMENDMENT  
AMENDMENT

Document Date

21/09/2004  
17/12/2004  
20/01/2005

- The amendment of December 17<sup>th</sup>, 2004 provided updated stability information for the drug product.
- The amendment of January 20<sup>th</sup>, 2005 provided a response to the items from the request for information communicated to the applicant on January 7<sup>th</sup> (method validation for the HPLC assay and identity of label adhesive and printing ink components).
- The amendment of January 21<sup>st</sup>, 2005 contained responses to a request for information drafted by the microbiology staff, and was addressed in the consult microbiology review. This amendment was not addressed in this (CMC) review.



## Chemistry Review Data Sheet

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Novartis Pharmaceuticals Corporation  
Address: One Health Plaza, East Hanover, NJ 07936-1080  
Representative: Lynn Mellor, Director Drug Regulatory Affairs  
Telephone: (862) 778-3665

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Aclasta®
- b) Non-Proprietary Name (USAN): Zoledronic acid
- c) Code Name/# (ONDC only): ZOL446
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 3
  - Submission Priority: P

## 9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: 3030400, Bone/Calcium-phosphorus metabolism.

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 5 mg per 100 mL

13. ROUTE OF ADMINISTRATION: Intravenous injection (IV)

14. Rx/OTC DISPENSED:  Rx  OTC

## 15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product



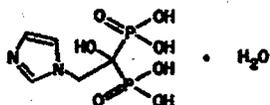
# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name (1) Phosphonic acid, [1-hydroxy-2-(1*H*-imidazol-1-yl)ethylidene]bis-, monohydrate; (2) (1-Hydroxy-2-imidazol-1-ylethylidene)diphosphonic acid, monohydrate.  
CAS Numbers CAS-165800-06-6.



Molecular Info

$C_5H_{10}N_2O_7P_2 \cdot H_2O$ . 290.10.

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE	STATUS	DATE REVIEW COMPLETED	COMMENTS
				3	Adequate	10/10/02	
				3	Adequate	08/07/98	

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Original NDA for Zometa®	NDA 21-233	Approved August 20 <sup>th</sup> , 2001
Zometa CMC Review # 1	NDA 21-233; Zometa® (zoledronic acid) for injection	Adequate (1 <sup>st</sup> review cycle) S. Markofsky
Request for Information	NDA 21-817	Communicated to the applicant on January 7 <sup>th</sup> (attached to end of the review)

### 18. STATUS:

#### ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	ACCEPTABLE	31/01/2005	J. D' Ambrogio
Pharm/Tox	pending		G. Kuijpers, Ph.D.
Biopharm	pending		S. W. "Johnny" Lau, Ph. D.
LNC	N/A		
Methods Validation	Adequate*		
ODS	NOT ACCEPTABLE	31/01/2005	Kristina C. Arnwine, PharmD
EA	Categorical exclusion per 21 CFR 25.31(b)		D. Lewis
Microbiology	APPROVAL	14/02/2005	J. Metcalfe, Ph.D.

\* The analytical method were found to be adequate for release and stability studies

### 19. ORDER OF REVIEW (OGD Only): N/A



# The Chemistry Review for NDA 21-817

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The application may be approved upon the submission of acceptable labeling (pending labeling review by all disciplines).

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

### II. Summary of Chemistry Assessments

NDA 21-817 provides CMC information for Aclasta® (zoledronic acid) injection, 5 mg/100 mL, which is closely related to NDA 21-233, Zometa® (zoledronic acid) for injection, from the same applicant. *CMC information regarding the drug substance was reviewed and found adequate for NDA 21-233, and remains adequate for this NDA (no changes in manufacture, controls, or facilities).* The manufacturing processes and release specifications for Aclasta® are essentially identical to those, which were approved for Zometa® and are acceptable for this NDA ( \_\_\_\_\_ )

\_\_\_\_\_ The application was reviewed by the microbiology staff and found acceptable on the basis of sterility assurance. The manufacturing and testing facilities for the drug substance and product were evaluated by the Office of Compliance (OC), and found acceptable to support this application.

#### A. Description of the Drug Product(s) and Drug Substance(s)

The drug product, Aclasta® (zoledronic acid) injection, is a \_\_\_\_\_ drug product providing 5 mg of zoledronic acid in a 100-mL injection, filled into a 100-mL plastic vial equipped with a rubber stopper and aluminum crimp. The proposed proprietary name, Aclasta® was reviewed, and found NOT ACCEPTABLE by the Division of Medication Errors and Technical Support (DMETS); the DMETS opinion was that the drug product should use the same proprietary name as the NDA 21-223 product, Zometa. *This opinion will be addressed in the final DMEDP labeling meeting.* The drug product is terminally sterilized, and is intended for use as a single injection for the treatment of Paget's disease of bone (one dose represents an entire round of treatment). There are two excipients in the drug product, citric acid \_\_\_\_\_ and mannitol \_\_\_\_\_



## Executive Summary Section

The drug substance, zoledronic acid (USAN) is utilized as the monohydrate in drug product formulation on the basis of adequate solid-state stability and high aqueous solubility. All CMC information regarding zoledronic acid is adequate to support this NDA by reference to the approved NDA 21-233, Zometa® (zoledronic acid) for injection. Zoledronic acid is prepared by \_\_\_\_\_ by the NDA applicant, and is processed for drug product formulation by a \_\_\_\_\_ Morphic forms are not relevant to this application, since the drug product exists as a relatively dilute aqueous solution and the drug substance is freely soluble in aqueous media. The retest date for zoledronic acid \_\_\_\_\_ is based on accumulated ICH stability data.

The drug product manufacturing process is



Three (3) different formulations were utilized in clinical trials for this NDA; these formulations include a 4 mg freeze-dried powder (approved drug product, Zometa®, NDA 21-223), a 5 mg per 5 mL concentrate for dilution & injection), and the 5 mg per 100 mL ready-to-use injection (the proposed commercial formulation for this NDA). A comparison between the 5 mg/5 mL concentrate and the 5 mg/100 mL infusion indicates the following: the concentrate utilized \_\_\_\_\_ while the proposed NDA 21-817 formulation utilizes mannitol. The target quantities of the active ingredient and of citric acid \_\_\_\_\_

**B. Description of How the Drug Product is Intended to be Used**

The drug product is intended for use as a single injection, to be administered by IV infusion once daily. *The drug is recommended for administration as a single dose (5 mg); clinical trials in support of this application monitored patients for six (6) months after the administration of this single dose.* The drug product provides 5.3 mg of zoledronic acid monohydrate (equivalent to 5 mg of anhydrous zoledronic acid) in 100 mL of \_\_\_\_\_. The drug product has been demonstrated to be compatible with the most commonly used dispensing apparatus (e.g., tubing and dispensing kits fabricated from various plastic materials).

The applicant has proposed an expiration dating period of 30 months with storage at controlled room temperature (25°C) with excursions permitted between 15 and 30°C. The expiry is supported by 18 months of acceptable ICH long-term and intermediate stability data for three exhibit batches accompanied by 6 months of acceptable ICH accelerated stability data on the same batches. The submitted stability data exhibited very little variability and change, allowing the expiry to be extrapolated to 30 months per the recommendations of ICH Q1E, *Evaluation of Stability Data*.



Executive Summary Section

The suitability of the proposed packaging for the drug product was addressed by the determination of extractables and leachables from the container closure for the exhibit batches via a validated HPLC analytical method. All container components are either detectable by the method, or are present in the container closure system at levels so low that even 100% migration into the contents would result in levels below the reporting threshold (e.g., trace components in the label adhesive and labeling inks).

**C. Basis for Approvability or Not-Approval Recommendation**

The application is recommended for approval from the standpoint of CMC on the basis of the following:

- Adequate CMC information for the drug substance (by reference to NDA 21-233)
- Adequate CMC information for the drug product (batch formula, controls, and analytical test results)
- Demonstration of container/closure suitability *via* determination of extractables and leachables in the drug product
- Submission of stability data that supports the proposed expiration date of 30 months
- Acceptable cGMP status for all manufacturing and testing facilities

**III. Administrative**

**A. Reviewer's Signature**

Electronically, in DFS

**B. Endorsement Block**

See DFS

ChemistName/Date: Same date as draft review  
ChemistryTeamLeaderName/Date  
ProjectManagerName/Date

**C. CC Block**

See DFS

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/s/  
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David Lewis

3/18/05 12:15:31 PM

CHEMIST

The application may be approved from the standpoint of CMC.

Mamta Gautam-Basak

3/18/05 12:29:45 PM

CHEMIST

Concur

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-817**

**PHARMACOLOGY REVIEW**

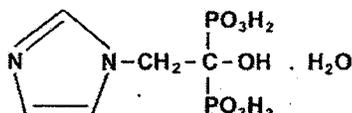
## PHARMACOLOGY/TOXICOLOGY COVER SHEET

**NDA number:** 21-817  
**Compound:** Zoledronic acid  
**Submission date:** September 21, 2004  
**Sequence number:** 000  
**Type of submission:** N  
**Information to Sponsor:** Yes (x) (Labeling comments)  
**Sponsor:** Novartis Pharmaceuticals Corporation, NJ, USA  
**Manufacturer for drug substance:** Novartis Pharma AG, Basel, and Novartis Pharma Stein AG, Stein, Switzerland

**Reviewer name:** Gemma Kuijpers  
**Division name:** Division of Metabolic and Endocrine Drug Products  
**HFD #:** 510  
**Review completion date:** February 22, 2005

**Drug:**  
**Trade name:** Aclasta® (zoledronic acid) Injection  
**Generic name:** Zoledronic acid monohydrate  
**USAN name:** zoledronic acid  
**Code name:** CGP 42446, ZOL446  
**Chemical name:** [1-hydroxy-2-imidazol-1-yl-phosphonoethyl] phosphonic acid monohydrate  
**CAS registry number:** 118072-93-8  
**Molecular formula:** C<sub>5</sub>H<sub>10</sub>N<sub>2</sub>O<sub>7</sub>P<sub>2</sub>·H<sub>2</sub>O  
**Molecular weight:** 290.1 g/mole

**Structure:**



formula: C<sub>5</sub>H<sub>10</sub>N<sub>2</sub>O<sub>7</sub>P<sub>2</sub>·H<sub>2</sub>O  
molecular weight: 290

**Relevant INDs/NDAs/DMFs:**  
IND 43,240  
IND \_\_\_\_\_  
IND \_\_\_\_\_  
NDA 21-223 (indication: \_\_\_\_\_ hypercalcemia  
\_\_\_\_\_ of malignancy)  
DMF \_\_\_\_\_

**Drug class:** Bisphosphonate (bone resorption inhibitor)

**Indication:** Treatment of Paget's disease of bone

**Clinical formulation:** Aclasta (zoledronic acid) Injection, solution for intravenous infusion, 5 mg/100 mL  
Solution: 5.33 mg zoledronic acid monohydrate (5 mg zoledronic acid), 4950 mg mannitol, 30 mg sodium citrate, 100 mL water for injection

**Route of administration:** I.V. (15-minute infusion)  
**Dose:** 5 mg (83 ug/kg)

Proposed use:

IV infusion over 15 minutes, one dose

Pivotal clinical studies:

Two 6-month trials in patients with Paget's disease  
(Study 2304 and Study 2305), active-controlled, with p.o.  
risedronate as comparator

Disclaimer:

Tables and Figures from the electronic NDA submission  
have been copied for use in this review

**Appears This Way  
On Original**

## Executive Summary

### I. Recommendations

#### A. Recommendation on Approvability Approval (AP)

Based on the results of nonclinical pharmacology and toxicology studies, Pharmacology/ Toxicology recommends approval of the NDA for zoledronic acid (Aclasta®), 5 mg as 15-minute infusion, for the indication of treatment of Paget's disease of bone.

The main toxicities identified in nonclinical studies are renal and GI toxicity. The safety margins for these toxicities suggest a low level of safety concern for the proposed 5 mg human IV dose. Clinical monitoring for the toxicities has been performed. The mechanism(s) underlying the serum Ca and P decreases were not clearly established and proper clinical management of these events is required.

#### B. Recommendation for Nonclinical Studies No additional nonclinical studies are required.

#### C. Recommendations on Labeling Recommended labeling changes have been appended to this Review.

1.

2.

3.

### II. Summary of Nonclinical Findings

The current application (NDA #21-817) was submitted on September 21, 2004, for the treatment of Paget's disease of bone. Studies submitted to the Division under NDA 21-223 (4 mg, iv, treatment of hypercalcemia) were cross referenced.

Zoledronic acid (or zoledronate) is a third generation nitrogen-containing bisphosphonate and a potent inhibitor of osteoclastic activity and bone resorption. The exact mechanism of action of zoledronate involved in the various cellular effects is unknown. In the osteoclast, zoledronate appears to reduce the level of farnesylated and geranylgeranylated proteins due to inhibition of isopentyl- and farnesyl-diphosphate synthases.

#### Pharmacology

Zoledronate inhibited in vitro osteoclastogenesis, induced rabbit osteoclast apoptosis and altered osteoblast production of OPG and RANKL. The ratio between the IC<sub>50</sub> for calcium incorporation and the IC<sub>50</sub> for calcium release in murine calvaria cultures was 15,000. This suggests that for bone resorption inhibition indications there is very high therapeutic margin with regard to inhibition of bone mineralization.

In vivo bone pharmacology studies in ovariectomized (OVX) rats (up to 12-months) and rhesus monkeys (16-month study) demonstrated a dose-dependent increase in bone mineral density and bone strength parameters in OVX animals. Bone turnover and bone remodeling activation frequency were markedly suppressed in trabecular and haversian bone. There were no clinical adverse effects in the studies. Bone

and bone marrow tissue and cells were normal, and there was no evidence of a mineralization defect, accumulation of osteoid or woven bone.

In the 8-month bone quality study in OVX rats, one single dose of 0.8, 4, 8, 20, 100, 500 ug/kg showed dose-dependent bone protective effects that were transient at the lower doses but persisted for the entire study duration at 100 and 500 ug/kg. There was complete inhibition at 100 and 500 ug/kg of the OVX-induced decreases in proximal tibial BMD and cortical thickness, vertebral compressive strength, and femoral diaphyseal and metaphyseal strength, but there was no significant effect on strength at the femoral neck. The significance of the decreased vertebral and femoral bone strength at the lowest dose of 0.8 ug/kg is unclear. At the 4 ug/kg and 20 ug/kg doses, proximal tibial BMD was increased as compared to OVX but femoral and vertebral strength were not affected. The cause of this apparent discrepancy is unclear.

Safety pharmacology studies indicated that there were no effects on CNS, cardiovascular or respiratory systems.

#### ADME

ADME studies showed a high affinity of zoledronic acid for bone tissue, rapid elimination via renal excretion, no evidence of metabolism and accumulation in bone proportional to cumulative dose. Compound is also retained in soft tissues such as thymus, kidney, lung, heart, liver, GI tract. Plasma AUC in rats was the same upon iv and sc dosing. Exposure in TK studies was dose-proportional and there was little accumulation in plasma.

Mannitol is unlikely to affect renal clearance and thus plasma levels of zoledronic acid in humans.

#### General toxicity

In acute i.v. toxicity studies, target organs were kidney, liver and GI tract in rats and dogs. In dogs, a short infusion time of 5 minutes was associated with kidney, GI tract and esophagus lesions while a 15-min infusion did not cause these effects. Serum Ca and P were decreased in dogs with 5- and 15-min infusions. Renal effects in acute infusion studies consisted of tubule basophilia, necrosis, vacuolation, urothelial hyperplasia, and focal inflammation, hemorrhage and congestion. GI findings were inflammation, hemorrhage and congestion in stomach and intestine.

Repeat dose iv studies in rats and dogs resulted in effects on kidney, liver, GI tract, and spleen, and irritation at the injection site. The renal toxicity is related to the fact that, like other bisphosphonates, zoledronate is excreted by and retained in the kidney. Most toxicities were at least partially reversible. Bone changes resulting from the intended pharmacological activity were observed in most repeat-dose studies at the lowest dose and below the NOAEL for other organ toxicity.

In intermittent (2- or 3-weekly) i.v. infusion studies of 2-wk, 13-week, 26-week duration in the dog, renal and GI tract lesions and irritation at the injection site were observed. The renal toxicity was recoverable and included tubular necrosis and degeneration, cortical debris mineralization, tubular regeneration, inflammation and dilatation, and papillary necrosis. Renal toxicity was exacerbated by repeat dosing with 3-weekly intervals. GI toxicity (congestion, erosion, hemorrhage, inflammation) was observed at higher doses than renal toxicity.

Ca and P were decreased in the single dose and 13-week intermittent infusion studies in dogs at doses below those causing microscopic renal toxicity. The exact mechanism of the disturbance of Ca and P metabolism is unclear but is probably related to the pharmacologic activity of the compound to suppress bone resorption and possibly an effect on kidney tubule function and direct Ca binding.

Safety margins based on NOAEL levels for renal toxicity and (cumulative) AUC or mg/m<sup>2</sup> comparison with the 5 mg clinical dose were derived from acute and repeat-dose i.v. (bolus and infusion) dose studies in rats and dogs. The most relevant safety margins for the microscopic renal toxicity based on AUC and single dose animal data were in the range of 1.5x-10x the intended 5 mg clinical dose. The lowest margins (1.5x) were from acute rat studies with bolus injection and large dose separation. In single dose and multiple intermittent dose infusion studies in rats and dogs, safety margins were larger and ranged

from 4x-13x. The safety margins are acceptable and support the use of the proposed human 5 mg dose for Paget's disease of bone. The effect on serum Ca and P in dogs was seen at <10 times human exposure (AUC) and these events if they occur need proper clinical management.

Genotoxicity, carcinogenicity, reprotoxicity

There was no evidence of mutagenicity in a standard battery of genotoxicity tests: Ames test, an in vitro Chinese Hamster cell V79 assay, an in vitro Chinese Hamster Ovary clastogenicity assay and an in vivo rat micronucleus assay.

Carcinogenicity studies of 2-year duration were carried out using the oral gavage route in mice and rats. In rats, there was no evidence of carcinogenicity. In mice, an increased incidence of Harderian gland adenomas/adenocarcinomas was observed in males at 0.1 and 1.0 mg/kg and in females at doses 0.3 and 1 mg/kg.

Reproductive toxicity studies were performed by the subcutaneous route in rats and rabbits. Dystocia and periparturient mortality were observed in the Segment I rat study probably resulting from drug-related hypocalcemia. The teratogenicity observed in the Segment II rat study may have been due to a decrease in serum calcium levels and/or binding to fetal bone.

Conclusion

Taken together, the nonclinical pharmacology and toxicology data submitted to NDA 21-817 support the safety of a single clinical dose of 5 mg zoledronic acid, i.v., for the treatment of Paget's disease of bone.

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## PHARMACOLOGY/TOXICOLOGY REVIEW

### INTRODUCTION

This NDA is for the treatment of Paget's disease with one dose of 5 mg zoledronic acid (15-minute IV infusion). Zometa® (zoledronic acid) was approved for marketing by the FDA (DMEDP, ODE II) on August 20, 2001, for the treatment of hypercalcemia of malignancy. The approved dose was 4 mg, given by  $\geq 15$ -minute IV infusion. Sponsor is developing the same compound under the name Aclasta™ for non-oncology indications.

### BACKGROUND

Zoledronic acid (ZOL446) is a nitrogen-containing hydroxy-bisphosphonate. Zoledronic acid has 2 nitrogen atoms in a heterocyclic imidazole ring attached to carbon atom 1, in contrast to other nitrogen-containing bisphosphonates that have a single nitrogen atom in an aliphatic side chain (e.g. pamidronate). Zoledronic acid is a potent inhibitor of osteoclastic bone resorption and skeletal calcium release. Bone resorption can be stimulated by a variety of stimuli (VitD<sub>3</sub>, PTH, PTHrP, PGE<sub>2</sub>). The compound has irritating properties at the site of application, especially when intravenous dosing is employed.

Zoledronate is approved for 2 conditions: (1) bone metastases resulting from primary tumors (AP February 22, 2002), and (2) hypercalcemia of malignancy (AP, August 20, 2001). Approved doses are: 4 mg i.v. infusion every 3-4 weeks for bone metastases (52-72 mg annually), and 4 mg i.v. infusion for hypercalcemia of malignancy. The 4 mg dose is to be given as a single dose infusion over no less than 15 minutes. For hypercalcemia, retreatment may be considered if serum calcium does not return to normal.

Paget's disease results from excessive bone resorption by abnormal osteoclasts, followed by excessive formation of disorganized and structurally unsound bone. Usual treatment is with anti-resorptives to slow down abnormal remodeling. The proposed dose for Paget's disease is 5 mg i.v., once, to induce a remission for several years.

Known adverse effects of bisphosphonates are GI and renal events. The renal toxicity is believed to be related to the renal excretion of these compounds and has been observed in animals and humans (e.g. oncology patients treated with zoledronate, 4 mg short infusion). GI events (esophageal, gastric, intestinal irritation, ulceration, perforation) have been observed in animals and humans. The mechanism of GI toxicity is unclear. In animal studies, both oral and IV dosing can cause GI lesions.

*In vitro* and *in vivo* nonclinical pharmacology, toxicology, and pharmacokinetic (ADME) studies were conducted for NDA #21-223. For the current NDA, the sponsor submitted additional pharmacology and toxicology studies. Studies relevant for bone and systemic safety of a single 5 mg dose were reviewed in detail.

**Table 1-1 Toxicology program and supporting studies**

Study type and duration	Route of administration	Species or in vitro test system
Single-dose toxicity	sc and iv, bolus + infusion	mouse, rat and dog
Repeat-dose toxicity		
2-week	iv infusion	Rat
4-week	sc and iv, bolus	rat and dog
3-month	sc and iv, bolus + infusion	rat and dog
26-week	iv infusion	Dog
26/52-week	sc and iv, bolus	rat and dog
Genotoxicity		
Ames test	in vitro	S. typhimurium
Cytogenetics test	in vitro	chinese hamster cells
Gene mutation test	in vivo	V79 Chinese hamster cells
Micronucleus test	oral	rat, bone marrow and liver
Carcinogenicity, 104-week	oral	mouse and rat
Reproductive & developmental toxicity		
Fertility & early embryonic	sc bolus	
Embryo-fetal development	sc bolus	Rat
Local tolerance	iv bolus	rat and rabbit
Sensitization	Dermal	rat and rabbit guinea pig

**CLINICAL STUDIES****Table 1-1 Summary of all studies in Paget's disease**

Study No.	Study objective, population	Patients	Study Duration	Medication, Dosing scheme	Type of control
<b>Large efficacy trials</b>					
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
<b>Large dose-ranging trial</b>					
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
<b>Small dose-ranging trial</b>					
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

**Clinical Pharmacology**

PK (AUC) was dose-proportional between 2 and 16 mg. Elimination is by renal excretion, and approximately 50% of the dose is retained by bone. AUC was increased 30-40% in patients with mild to moderate renal dysfunction. Sponsor recommends that dose adjustment is not needed for those patients.

Efficacy

Two 6-month comparative trials were performed of a single dose of zoledronate (5 mg) versus daily doses of 30 mg risedronate every 2 months. The 15-min infusion of zoledronate was efficacious in the treatment of Paget's disease with regard to reduction of SAP (serum alkaline phosphatase), changes in serum or urine CTx, changes in pain. Zoledronate was superior over risedronate since there was a faster onset and greater effect on bone resorption and formation, and it had a longer duration of action. Response rate was also better than with risedronate.

Safety

Zoledronate was associated with higher rates of influenza-like illness than risedronate. This is a class effect of bisphosphonates. Other potential effects are renal events, seen after fast (5-min) infusions in oncology patients, and transient hypocalcemia. Clinical data with the 5-mg dose (15-min infusion) in the Paget's indication did not show increase in renal dysfunction. Hypocalcemia was observed in phase III studies, more often than with risedronate. Bone biopsies (N=22) from Pagets' patients showed expected reduction in bone resorption but did not show mineralization defects or poor bone quality. Safety data from ongoing osteoporosis trials with 5 mg annually were also provided in the NDA. There were no ECG recordings in the Paget's trials, but ECG data are currently being collected in osteoporosis trials.

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## I. PHARMACOLOGY

Zoledronate is a third generation bisphosphonate and a potent inhibitor of osteoclastic bone resorption. Nonclinical data from several *in vitro* and *in vivo* pharmacological models demonstrate that the compound potently inhibits bone resorption.

*In vitro*, zoledronate inhibits bone resorption at concentrations of 0.3-30 nM, and *in vivo* it inhibits bone resorption at doses of 0.3-30 µg/kg. In cultures of murine calvaria the IC<sub>50</sub> value for inhibition of calcium release by zoledronate is approximately 1/100 (0.01x) times the value for pamidronate. In the calvarial cultures, zoledronate and other bisphosphonates also inhibit calcium incorporation. The ratio between the IC<sub>50</sub> for calcium incorporation and the IC<sub>50</sub> for calcium release varies largely, from approximately 3 for etidronate and 500 for pamidronate to 15,000 for zoledronate.

**Table 2-1 Inhibition by zoledronate and reference compounds of calcium release and calcium incorporation in murine calvarial cultures**

compound	Mean IC <sub>50</sub> value (µM) from (n) experiments		ratio (b/a)
	calcium release (a)	calcium incorporation (b)	
zoledronate	0.002 (5)	30 (3)	15000
etidronate	4.0 (3)	10 (2)	3
clodronate	0.4 (3)	50 (2)	125
pamidronate	0.2 (6)	100 (3)	500
alendronate	0.05 (2)	n.d.	n.d.
ibandronate	0.02 (3)	n.d.	n.d.

a: bone resorption stimulated with 20 nM 1,25(OH)<sub>2</sub>D<sub>3</sub> for 72 hr; b: bone mineralization stimulated with 2 mM calcium 1,2-glycerophosphate for 48 hr; n.d. = not determined.

The exact mechanism of action of zoledronate involved in the various cellular effects is unknown. In the osteoclast zoledronate appears to reduce the level of farnesylated and geranylgeranylated proteins, due to inhibition of isopentyl- and farnesyl-diphosphate synthases, possibly leading to inhibition of cell function and/or viability. Zoledronate inhibited *in vitro* osteoclastogenesis (RD-2001-00476) and induced rabbit osteoclast apoptosis (RD-1999-0390). Zoledronate also alters osteoblast production of OPG and RANKL, cytokines controlling osteoclast formation and activity (Pan et al, 2004, JBMR 19:147-154).

In the thyroparathyroidectomized rat zoledronate dose-dependently inhibits 1,25(OH)<sub>2</sub>D<sub>3</sub>-induced acute hypercalcemia with an ED<sub>50</sub> of ca. 0.07 µg/kg s.c., and is several orders of magnitude more potent than clodronate or etidronate. The inhibition of hypercalcemia in this model is presumably brought about by inhibition of osteoclastic bone resorption (Study 95/89 IBA).

In short term studies in ovariectomized rats, zoledronate can completely prevent the OVX-induced bone loss at a dose of 0.3 µg/kg given 5x/week for 3 weeks (Studies BS76/1996; 69/94; 86/93 IBA). Long term studies were carried out in ovariectomized rats (12 months) and rhesus monkeys (69 week, i.e., 16 months), of 0.3, 1.5, 7.5 µg/kg/week s.c. (rat) and 0.5, 2.5, 12.5 µg/kg/week, s.c. (monkey). The long term studies were submitted previously to NDA #21,223, but were not reviewed in detail. For the current NDA, Sponsor submitted and additional bone quality study with a single dose IV treatment in the OVX rat (RD 2002-04006).

Since there is no validated animal model of adult Paget's disease, the OVX rat and monkey bone studies can be used to demonstrate the compound's ability to suppress *in vivo* bone turnover.

**An intravenous dose of zoledronic acid exerts a long-term protective effect against cancellus and cortical bone loss in ovariectomized rats (ZOL446 H/K/L; RD-2002-04006)**

Mature, 7-month old Wistar rats (N=10/group), were given a single intravenous injection of zoledronic acid (trisodium salt, Mw 393), at 0 to 500 ug/kg, or alendronate at 200 ug/kg, 4 days before OVX. Necropsy was performed after 32 weeks of (single dose) treatment. Non-GLP study.

Study report authors: ~~et al, 2002~~

The following treatment groups were included:

SHAM OP	NaCl 0.9% i.v.
OVX	NaCl 0.9% i.v.
OVX + Zoledronic acid	0.8 µg/kg i.v.
OVX + Zoledronic acid	4.0 µg/kg i.v.
OVX + Zoledronic acid	20 µg/kg i.v.
OVX + Zoledronic acid	100 µg/kg i.v.
OVX + Zoledronic acid	500 µg/kg i.v.
OVX + Alendronate	200 µg/kg i.v.

**Assessments:**

- BMD (pQCT) (proximal tibia, cancellous and cortical bone), every 4 weeks
- Plasma osteocalcin (every 4 wks)
- Histomorphometry (microscopy) (wk 33) (left tibia, femur, lumbar vertebra)
- MicroCT (wk 33) (proximal tibia)
- Biomechanics (wk 33) (compression: distal femur metaphysis, L5, femoral neck; 3-pt bending: femoral shaft)

The tibia (proximal tibia metaphysis) was used for dynamic histomorphometry (left tibia), and structural cancellous bone parameters (microCT) and biomechanics (right tibia)

**RESULTS**

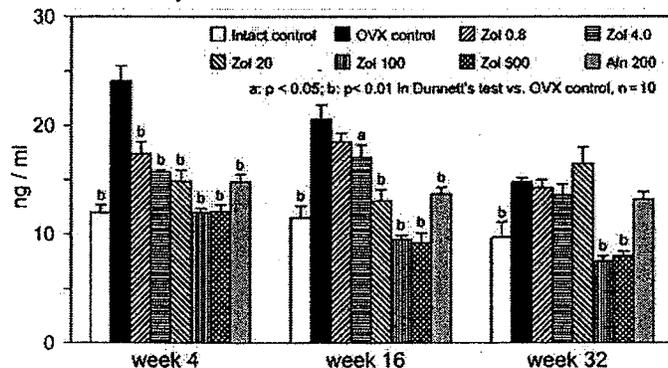
Body weight: No effect on OVX-induced gain

Plasma osteocalcin:

Increased in OVX, but increase was partially reversed over time

Dose-dependent suppression of increase by zoledronate, transient in lower dose groups.

**Figure 2-6 Effect of a single i.v. injection of zoledronate or alendronate on plasma osteocalcin levels**

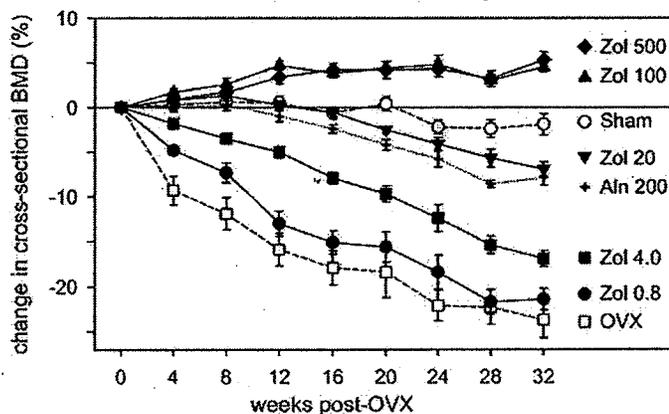


Bone mass (pQCT)

BMD tibia

- OVX: decrease, suppressed dose-dependently by zoledronate.
- Two highest dose groups increased BMD as compared to SHAM.

**Figure 2-7** Effect of a single i.v. injection of zoledronate or alendronate on cross-sectional BMD in the proximal tibia of the OVX adult rat

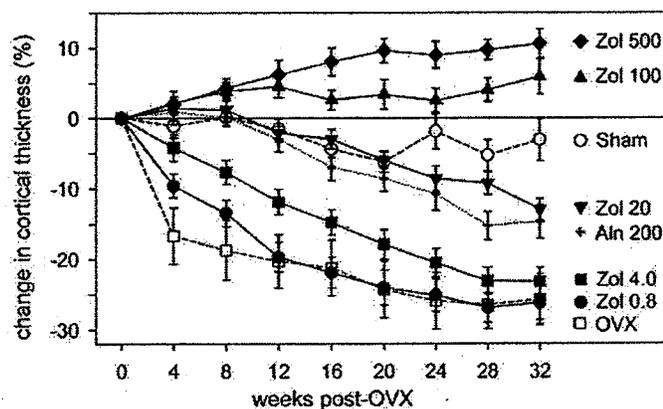


Mean ± sem, n = 10 rats per group. All points were significantly different from the OVX control ( $p < 0.05$  or lower) in Dunnett's test except for Zol 0.8 at weeks 20-32.

Cortical thickness tibia: similar effects as on BMD.

Cortical thinning in OVX was caused by endocortical bone loss, since OVX increased cancellous bone area and zoledronate suppressed this effect. Effect of 20 ug/kg was similar as 200 ug/kg alendronate.

**Figure 2-8** Effect of a single i.v. injection of zoledronate or alendronate on cortical thickness in the proximal tibia of the OVX adult rat



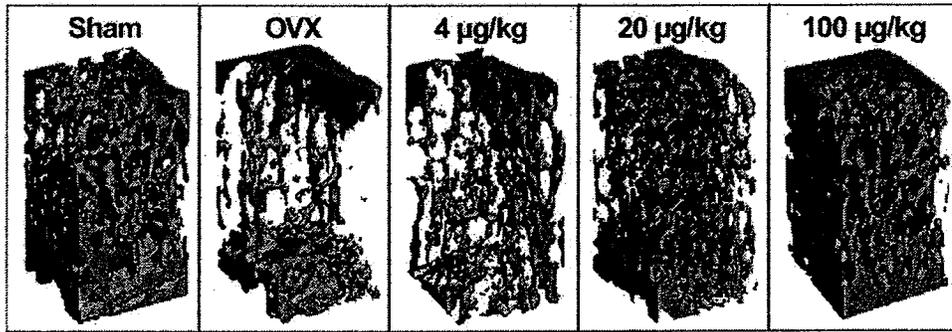
Mean ± sem, n = 10 rats per group. All points were significantly different from the OVX control ( $p < 0.05$  or lower) in Dunnett's test except for Zol 0.8 at weeks 8-32, and Zol 4.0 at weeks 16-32.

BMD of other bone sites was not measured (vertebrae, femur)

MicroCT (vivaCT20 scanner, SCANCO) of cancellous bone tibia:

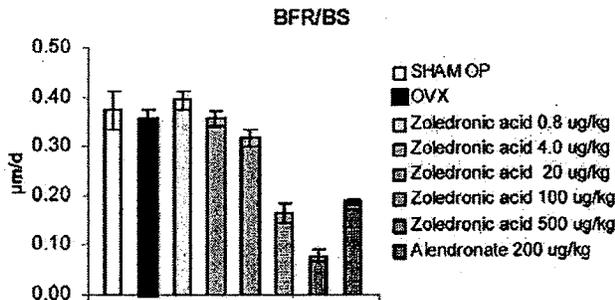
Zoledronate prevented decreases in Tb.BV, Tb.N, Tb.Sp, connectivity density, SMI. At the 100 and 500 ug/kg doses parameters were reversed up/down to levels above or below SHAM, particularly SMI. Data indicate thickened trabeculae with increased connectivity at higher doses.

**Figure 2-12 3-D micro-CT images of the proximal tibial at week 32 after a single i.v. injection of zoledronate in the OVX adult rat -**



Dynamic histomorphometry:

Surprisingly, there were no/minimal effects of OVX on bone formation rate parameters. Zoledronate suppressed formation parameters (e.g. BFR/BS) up to 60-80% at the high doses of 100-500 ug/kg. Results correlated with effect on plasma osteocalcin, which was suppressed up to 20%-50% at 100 and 500 ug/kg.



Biomechanics

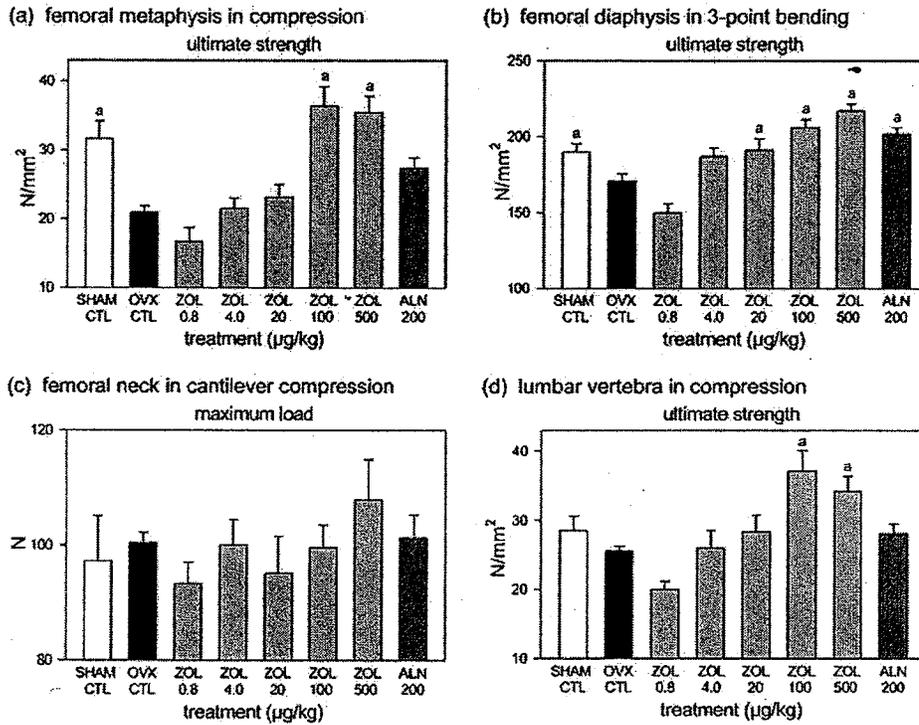
Vertebra and femur, compressive strength:

Vertebral body and distal femur metaphysis: Decreased extrinsic and intrinsic strength in OVX (load, N, and strength, N/mm<sup>2</sup>), protected by zoledronate at doses of 4 ug/kg and above. In vertebrae, load was larger than in SHAM animals at 500 ug/kg. Alendronate was ca. 10x less potent. There were no change in femoral neck (load, N) with OVX or treatment.

Femur, three point bending:

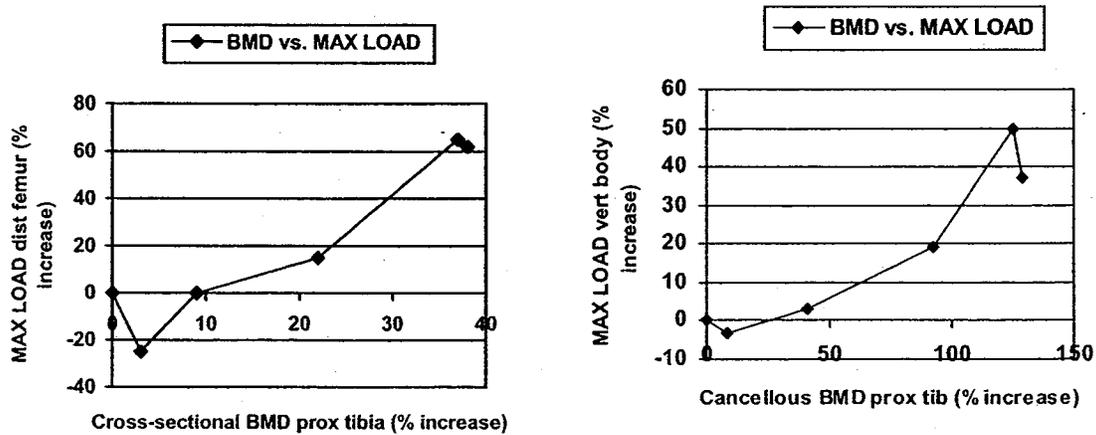
Femoral shaft had reduced strength in OVX, protected by zoledronate at doses 4 ug/kg and higher.

**Figure 2-13 Strength of vertebra and femur at 32 weeks after a single i.v. injection of zoledronate or alendronate in the OVX adult rat**



Mean ± sem, n = 10 rats per group. a: p < 0.05 in Dunnett's test vs. the OVX control.

Correlation BMD (cross-sectional BMD, mg/cm<sup>3</sup>, of proximal tibia) vs. maximal load (distal femur and vertebra). Correlation within bone site could not be calculated since BMD data were only available for tibia.



These graphs are based on data from Wk 33 (end of study) for both BMD and bone strength. Note that as compared to OVX, BMD at time of necropsy is increased at lower doses of 0.8 and 4 ug/kg, while strength (ultimate load) is decreased at 0.8 ug/kg and unaffected at 4 ug/kg. At higher doses of 20, 100 and 500 ug/kg strength is increased along with BMD.

It is unclear why femoral and vertebral strength is decreased at 0.8 ug/kg and whether this was biologically significant. No other parameters were adversely affected at 0.8 ug/kg. It is also unclear why BMD and strength parameters are not correlated in the lower dose range. It may be due to (1) the fact that BMD data are from different bone site than those for strength, or (2) the extended length of time after the single dose was given (since a similar phenomenon was not resolved for vertebral BMD and strength in the 12-month weekly sc dosing study, see below).

The latter could mean that BMD is protected for a longer time after ovariectomy than strength is. It is possible that the lack of effect on bone strength at the lower doses is related to the transient nature of the effect on bone turnover (resorption and formation), which at lower doses is no longer protected at end of study. However, this is speculative.

Strength was not adversely affected in the higher dose groups.

The other anomaly in the data is that histomorphometric formation parameters (wk 33) are not affected in the OVX group, while BMD and strength are clearly reduced. Possibly, this was due to earlier increase in bone turnover, which did not persist through end of study, while the BMD decrease did. Indeed, plasma osteocalcin was increased in OVX rats at all times, indicating increased turnover, and this was suppressed by treatment, particularly effectively at earlier time points of Wk4 and Wk16.

The unexplained data on BMD-strength correlation and histologic bone turnover have no immediate implications for the treatment of Paget's disease.

In conclusion, a single dose of zoledronate for the Paget's indication appears to be safe with regard to bone effects (suppression of turnover, increase of BMD, and maintenance or increase of strength).

**Effect of 12 months treatment with the bisphosphonate CGP 42'446 on bone mineral density, bone mechanical properties, and bone histomorphometric parameters in ovariectomised rats** (Report Nr -0591) 1994-1995

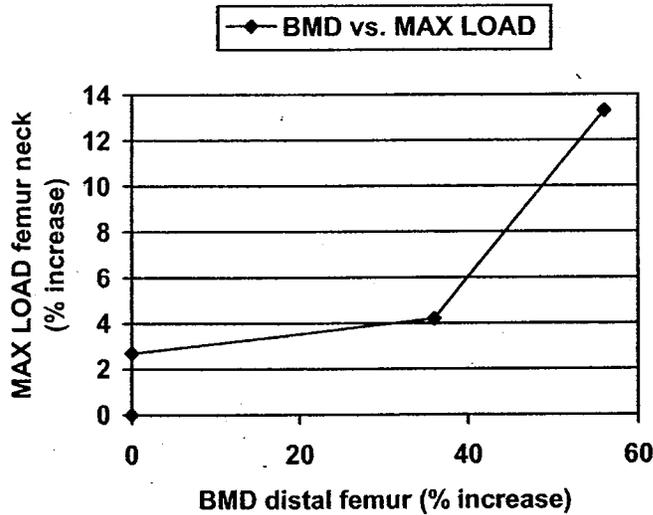
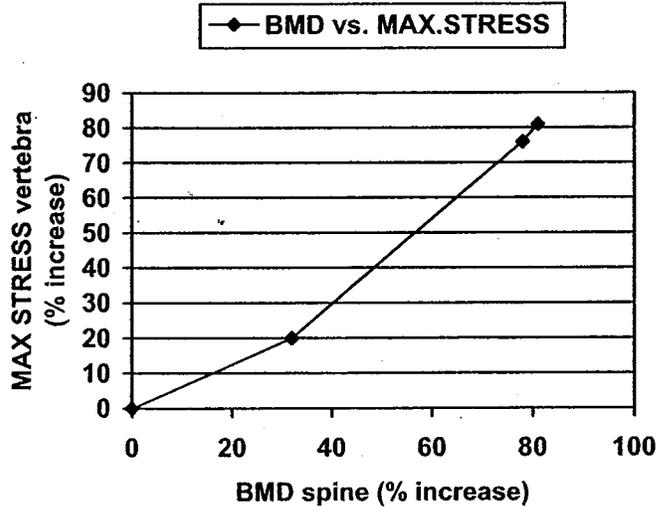
Sprague-Dawley rats (N=20/grp) were OVX'ed, and immediately thereafter dosed weekly, s.c., for 52 weeks, with CGP 42,446 (zoledronic acid). Groups included Sham, OVX, OVX + 0.3, or 1.5, or 7.5 ug/kg

Parameter		Sham	OVX	OVX + 0.3 ug/kg/wk	OVX + 1.5 ug/kg/wk	OVX + 7.5 ug/kg/wk	Treatment effect
BMD	Total body, spine, femur		D	=/I	I	I	I
Alk. Phos	Serum		I (wk 16, 51)				D (wk 16) = (Wk51)
Osteocalcin	Serum		I (wk 16)				D (wk 16)
DPD and PD	Urine		I	D	D	D	D
Tibia length			I			D	D
Strength	Vertebrae (max. stress, stiffness)		D	I	I	I	I
	Femoral neck (Fu)		D		I	I	I
	Femur shaft		D	I	I	I	I

	(Fu, J)						(biphasic)
HMM?	Formation		I?				D?

D=decrease  
 I=Increase  
 = no change  
 HMM = histomorphometry

Correlation BMD and strength (vertebrae and femur)



**Effects of 69 weeks treatment with the bisphosphonate CGP 42,446 on bone mineral density, bone mechanics, and bone cell function, in ovariectomized adult rhesus monkeys (Study Nr. 955041) (Novartis)**

Female rhesus monkeys (bred in captivity, skeletally mature, WRPRC colony) were sham-operated or ovariectomized (OVX'ed). OVX animals were treated immediately with weekly s.c. doses of 0, 0.5, 2.5, 12.5 ug/kg. Sham animals were given vehicle (saline) only.

OVX animals developed osteopenia in total body and spine. Effects were maximal at 39 weeks. After that, turnover declined towards baseline and there was no further bone loss in OVX monkeys. ZLN increased spine BMD and total body BMC until wk39.

Parameter		Sham	OVX	OVX + 0.5 ug/kg/wk	OVX + 2.5 ug/kg/wk	OVX + 12.5 ug/kg/wk	Treatment effect
BMC	total body		D (wk39)	=/I	I	I	I (wk39)
BMD	spine		D (wk39)	=	I	I	I (wk39)
BMD	Radius	D (I)	D	I	I	I	I
BMD	Femoral neck		D (wk26)	I	I	I	I(wk26)
BMD	Proximal femur		D (wk26)	=	I	I	I (wk26)
Osteocalcin	Serum		I (wk39)	D	D	D	D
NTx	Serum		I (wk39)	D	D	D	D
HMM	Iliac crest (activation frequency)		=	D	D	D	D
	Rib (haversian porosity)		I	D	D	D	D
Strength	Tibia (torsion shear modulus)		D	I	I	=	I
	Tibia (max bending stress)		D	=	I	=	=/I
	Tibia (elastic modulus)		D	=	I	=	=/I
	Femoral neck (stiffness)		D	=	I	I	I
	Whole vertebrae (Fu)		=	D	=	I	Unclear
	Vertebra core, compression stiffness		=	D/=	D/=	=	Not significant

D=decrease

I=Increase

= no change

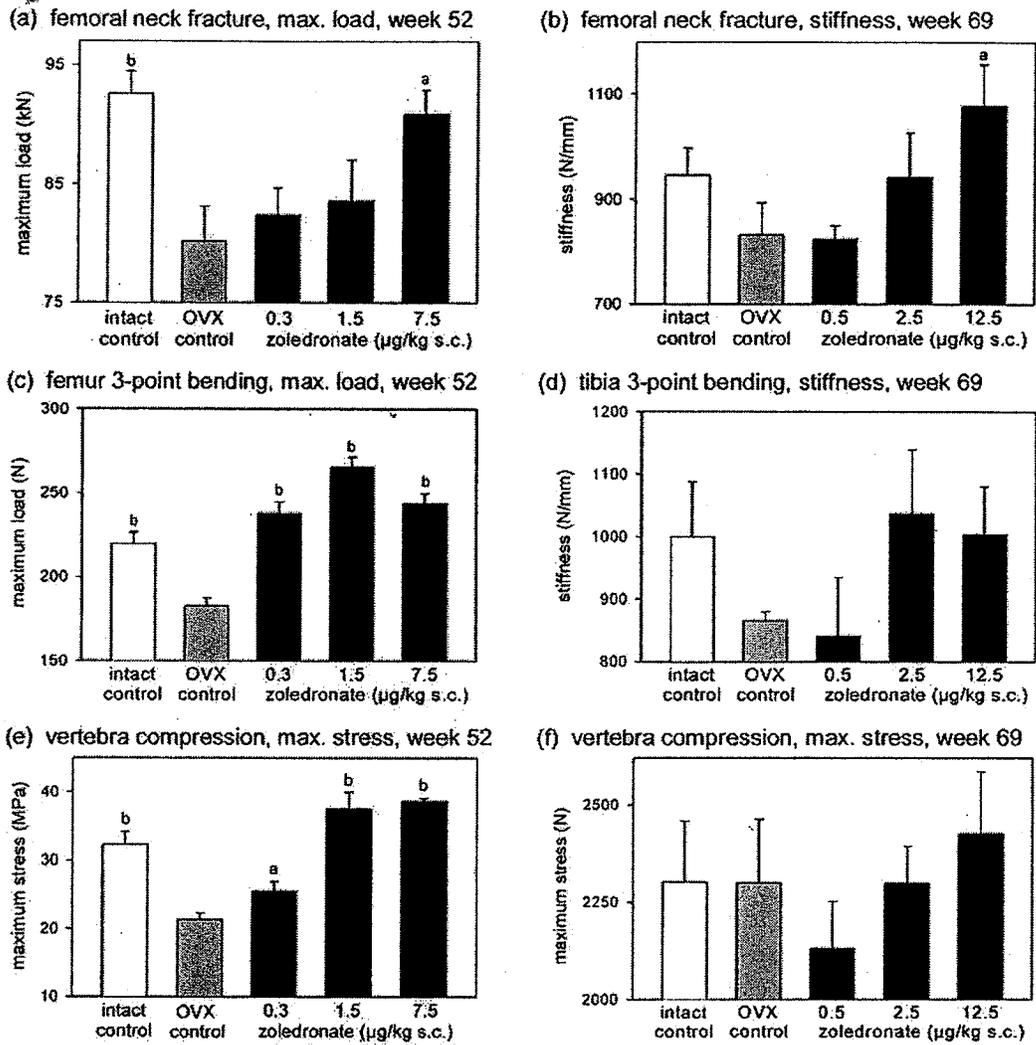
HMM = histomorphometry

There were no mineralization defects, no osteoid accumulation, no woven bone. No abnormalities in bone cells, tissue or marrow space in ZLN-treated monkeys.

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**Figure 2-16 Effect of long-term zoledronate treatment on bone mechanics in OVX rats (left) and OVX rhesus monkeys (right)**



Mean ± sem, n = 16-20 (rat), n = 7-8 (monkey). a: p < 0.05; b: p < 0.01 vs. the OVX control in Dunnett's test.

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**CONCLUSIONS**

- In the long term weekly repeat dose s.c. studies in OVX rats and monkeys, zoledronate dose-dependently prevents OVX-induced changes in bone mineral density (BMD), bone biomechanics and suppresses bone turnover.
- There was no indication of a deleterious effect on bone strength, or on bone cell morphology, osteoid deposition or mineralization. No woven bone was observed.

Sponsor's evaluation of doses used in bone studies

**Table 3-4 Comparison of the doses used in the long-term monkey and rat studies versus the human 5 mg iv dose / 60 kg body weight**

Experiment	Dose and dose ratios vs human 5 mg dose				
Monkey, dose µg/kg/week sc (a)			0.5	2.5	12.5
Total dose in 69 week study µg/kg			34.5	172.5	862.5
Equivalent dose mg/60 kg			2.1	10.4	51.8
Ratio: monkey/human 5 mg dose (a)			0.41	2.1	10.4
Rat, dose µg/kg/week sc (a)			0.3	1.5	7.5
Total dose in 52 week study µg/kg			15.6	78	390
Equivalent yearly mg dose/60 kg			0.94	4.7	23
Ratio: rat/human 5 mg dose (a)			0.19	0.94	4.6
Rat, single dose µg/kg iv (b)	0.8	4.0	20	100	500
Equivalent mg dose/60 kg	0.048	0.24	1.2	6.0	30
Ratio: rat/human 5 mg dose (a)	0.007	0.032	0.16	0.82	4.0
Molecular weight of test compound: (a) = 272.1, anhydrous free acid, (b) = 401.6, hydrated disodium salt					

Reviewer's evaluation

Multiples were based on mg/m2 comparison rather than dose (mg/kg) comparison, used by Sponsor.

Doses and dose multiples in monkey and rat bone studies

Monkey	Dose (weekly, s.c.) (ug/kg)			0.5	2.5	12.5
	Total dose in 69 weeks (ug/kg s.c.)			34.5	172.5	863
	Equivalent to human dose (per 60 kg), mg/m2 basis			0.69	3.45	17.3
	Multiple Monkey : Human 5 mg dose			<b>0.14x</b>	<b>0.7x</b>	<b>3.5x</b>
Rat	Dose (weekly, s.c.) (ug/kg)			0.3	1.5	7.5
	Total dose in 52 weeks (ug/kg s.c.)			15.6	78	390
	Equivalent to human dose (per 60 kg), mg/m2 basis			0.156	0.78	3.9
	Multiple Rat : Human 5 mg dose			<b>0.03x</b>	<b>0.16x</b>	<b>0.8x</b>
Rat	Total doses in 32 weeks (ug/kg s.c.)	0.8	4	20	100	500
	Total dose corrected for difference in Mw (free acid and disodium salt)	0.54	2.7	13.5	68	338
	Equivalent to human dose (per 60 kg), mg/m2 basis	0.005	0.027	0.14	0.68	3.38

	Multiple Rat : Human 5 mg dose	0.001x	0.005x	0.03x	0.13x	0.68x
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Cumulatively, the high dose in the 16-month s.c. weekly monkey bone study based on mg/m<sup>2</sup> dose comparison was 3.5x the human dose of 5 mg. However, the (cumulative) high doses in the 12-month s.c. weekly and 8-month single dose rat studies were equivalent to the human 5 mg dose and multiples were not attained.

Comparison of doses on the basis of AUC was not feasible, since PK data were not obtained in the bone studies. However, linear extrapolation from single dose rat PK study data (single dose, 600 ug/kg) yields that at 0.3, 1.5, 7.5 ug/kg, AUC is approximately 1.95, 9.75, 49 ngxh/ml. Thus, cumulative AUC over 1 year is  $52 \times 1.95 = 101, 507, 2535$  ngxh/mL. Thus, at the high dose of the 12-month study, a 4x multiple of the human dose in terms of AUC comparison is achieved. In the 32-week study, extrapolated AUC at the high dose of 500 ug/kg is 3250 ngxh/mL, and the AUC multiple is 5x. These multiples can be used in the description of these data in the label.

In conclusion, based on bone effects and AUC multiples the bone studies were performed at appropriate doses. Studies were adequate for bone efficacy and safety assessment of a 5 mg i.v. human dose. Results indicate safety for bone of a single 5mg i.v. dose for the treatment of Paget's disease.

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## **II. SAFETY PHARMACOLOGY**

It is well known that renal toxicity can occur upon treatment with relatively high doses of bisphosphonates. Renal toxicity is discussed in the toxicology section of this review.

Zoledronate had no significant CNS effects at doses up to 10 mg/kg i.v. in mice. It also has no significant effects on gastrointestinal transit time, drug-induced convulsions, or cardiac and smooth muscle contraction. There were no effects on in vivo respiration, hemodynamic and ECG parameters in anesthetized cats.

There were no ECG changes in a 4-week iv toxicity in dog up to 0.2 mg/kg/day, and in 3-month and 6-month iv toxicity studies in dog at doses up to 0.1 or 0.2 mg/kg/day (daily dose equivalent to human dose of 2.5-5 mg, based on mg/m<sup>2</sup>).

The acute phase response and increase of circulating cytokine levels that occurs in some patients treated with iv doses of bisphosphonates is probably related to stimulation of a  $\gamma\delta$ -T cell subset triggered by accumulation of intermediates in the mevalonate pathway following FPP synthase inhibition (, 2004).

In a fracture healing study, zoledronate (100 ug/kg, i.v.) increased the amount and strength of regenerate bone in tibial osteotomy.

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**III. PHARMACOKINETICS/TOXICOKINETICS**

Data from ADME (PK) and toxicokinetic studies:

**Table 4-1 Pharmacokinetic parameters**

Species	Dose (mg/kg)	Route	Day	Gender	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	AUC (ng·hr/mL)	CL (L/hr/kg)	Assay	Ref.
Rat	0.15	iv	1	m	1500	0.08	900	0.17	LSC	DM 1Z/1993
Rat	0.1	sc	1	m	400	0.25	550	0.18	LSC	DMET (EU) 8/1996
Rat	0.6	iv	1	m	4800	0.08	3900	0.15	RIA	DMPK (CH) R99-1978
	0.6	sc	1	m	2100	0.25	3900	0.15		
Dog	0.1	iv	1	m			2100	0.05	EI	BPK(CH) 1996/067
			1	f			1800	0.06		
	0.2	iv	87	m			2100	0.10		
			87	f			2000	0.10		
Dog	0.1	iv	1	m	670	0.08	1400	0.07	EI	DMPK (CH) 1997/304
			1	f	490	0.08	1400	0.07		
			190	m	710	0.08	1500	0.07		
			190	F	600	0.08	1300	0.08		
			352	M	810	0.08	1900	0.05		
			352	F	640	0.08	1500	0.07		
Dog	0.25	iv	1	M	1100	0.08	1600	0.16	RIA	BAPK(F) R0170102
			1	F	960	0.08	1300	0.19		
			85	M	940	0.08	1500	0.17		
			85	F	930	0.08	1300	0.19		
	1	iv	1	M	4600	0.08	7000	0.14		
			1	F	3500	0.08	5800	0.17		
			85	M	2400	0.08	6100	0.16		
			85	F	3700	0.08	7300	0.14		
Dog	0.25	iv	1	M	1000	0.08	1300	0.19	RIA	BAPK(F) R018037
			1	F	1200	0.08	1500	0.17		
			64	M	1100	0.08	1500	0.17		
			64	F	1200	0.08	1600	0.16		
			169	M	1300	0.08	1700	0.15		
			169	F	1200	0.08	1600	0.16		
	0.5	iv	1	M	2200	0.08	2800	0.18		
			1	F	2200	0.08	2900	0.17		
			64	M	2000	0.08	3000	0.17		
			64	F	2000	0.08	2900	0.17		
			169	M	2500	0.08	3700	0.14		
			169	F	2400	0.08	3400	0.15		
	1	iv	1	M	4600	0.08	6600	0.15		
			1	F	4700	0.08	6900	0.14		
			64	M	5400	0.08	8200	0.12		
			64	F	4300	0.08	7100	0.14		
			169	M	5200	0.08	8100	0.12		
			169	F	5300	0.08	9100	0.11		

Source: [Pharmacokinetics tabulated summary]

AUC data from i.v. studies in human (single doses, 2, 4, 8 mg) and dog

### 2.6.7.3 Overview of toxicokinetics data

Test article: Zoledronic acid

Steady-state AUC (ng·h/mL)

Daily dose: (mg/kg)	Mice		Rats		Dogs		Rabbits	Humans	Study Number	Location in Module 4 or 5
	m	f	m	f	m	f	f			
0.0377	-	-	-	-	-	-	-	344 <sup>a</sup>	ZOL J001	
0.0651	-	-	-	-	-	-	-	540 <sup>a</sup>	ZOL J001	
0.1	-	-	-	-	1464 <sup>a</sup>	1305 <sup>a</sup>	-	-	93-6193	
0.138	-	-	-	-	-	-	-	1133 <sup>a</sup>	ZOL J001	
0.2	-	-	-	-	2075 <sup>a</sup>	1982 <sup>a</sup>	-	-	92-6261	
0.25	-	-	-	-	1500 <sup>b</sup>	1300 <sup>b</sup>	-	-	0170102	
	-	-	-	-	1664 <sup>b</sup>	1614 <sup>b</sup>	-	-	018037	
0.5	-	-	-	-	3654 <sup>b</sup>	3447 <sup>b</sup>	-	-	018037	
1	-	-	-	-	8060 <sup>b</sup>	7270 <sup>b</sup>	-	-	0170102	
	-	-	-	-	8091 <sup>b</sup>	9144 <sup>b</sup>	-	-	018037	
3	-	-	-	-	35600 <sup>b</sup>	-	-	-	008189	

- = no data

<sup>a</sup> i.v. bolus

<sup>b</sup> i.v. infusion

#### Human PK/AUC

AUC in humans at the 5 mg dose = 650 ng·h/mL (Biopharmaceutics Review, NDA #21-817, Sandra Suarez-Sharp). PK evaluation was based on experimental human PK data with 2, 4, 8, 16 mg from bone cancer patients. The AUC value at 5 mg was calculated with a simulation program (WinNonlin) using initial estimates based on data from Study 1101.

#### Protein binding:

Binding:

Human: 62%-55%

Dog: 70%-44%

Rat 94%-85%

Unbound fraction:

Human 0.4

Rat 0.1

Dog 0.4-0.5

#### Clearance

The inclusion of mannitol in the dosing solution (4950 mg in 100 mL) could affect renal clearance through an diuresis and an effect on Cls and/or CL<sub>Ra</sub> (CL<sub>R</sub> = fp·GFR + Cls - CL<sub>Ra</sub>). However, animal data have shown that both Cls and Cra for zoledronic acid are likely to be very small (Barrett et al, 2004). Thus, mannitol is unlikely to affect renal clearance and thus plasma levels of zoledronic acid in humans.

#### Summary

- high affinity and slow elimination from bone tissue
- rapid elimination from circulation and soft tissues via renal excretion
- no evidence of biotransformation
- accumulation in bone proportional to cumulative dose.
- exposure dose-proportional in toxicokinetic studies (rat, dog)
- no or little accumulation in plasma
- no effect of gender on the PK/TK

**IV. GENERAL TOXICOLOGY**

Toxicology studies submitted to NDA #21,223:

- Single dose toxicity studies carried out in rat, dog and mouse by various dosing routes.
- Repeated dose studies by the intravenous route in rats and dogs, by the subcutaneous route in rats, and by the oral route in mice, rats and dogs.

**Single dose studies**

Species	Test No.	Study Title	Doses (mg/kg)
Rat	88-6126	Acute i.v. findings study in rats	0.6, 6, 30, 60, 80
	997049	A comparative acute i.v. findings study in rats (w, w/o dimer)	0, 1.6, 8, 16, 32
	96-8002	Acute oral findings study in rats	300, 1000
	230142	Assessment of acute oral findings with zoledronic acid	200, 2000
Dog	93-6084	Acute i.v. findings study in dogs	2, 10
Mouse	93-6085	Acute s.c. findings study in mice	10, 20, 50

**Repeated dose studies****Intravenous application**

Species	Test No.	Study Title	Doses (mg/kg/day)
Rat	89-6036	10-day i.v. range finding study in rats	0, 0.06, 0.6, 6
	1486	A 2-week i.v. findings study in Sprague Dawley rats	0, 0.06, 0.6, 3.2
Dog	90-6157	10-day i.v. range-finding study in dogs	0.1, 1
	90-6180	4-week i.v. findings study in dogs	0, 0.02, 0.06, 0.2
	92-6261	3-month i.v. findings study in dogs	0, 0.01, 0.03, 0.1-0.2
	93-6193	26/52 week i.v. findings study in mature dogs	0, 0.005, 0.03, 0.1
	94-4045	Bone analysis: 26/52 week i.v. findings study in mature dogs	0, 0.005, 0.03, 0.1

**Subcutaneous application**

Species	Test No.	Study Title	Doses (mg/kg/day)
Rat	90-6156	10-day s.c. range finding study in rats	0, 0.2, 0.6, 2.0
	90-6179	1-month s.c. findings study in rats	0, 0.02, 0.06, 0.2
	92-6259	3-month s.c. findings study in rats	0, 0.01, 0.03, 0.1
	93-6230	6/12-month s.c. findings study in rats	0, 0.001, 0.003, 0.01
	98-00873	Effect on tibial cancellous bone in a 6/12-month s.c. findings study in rats. Bone histomorphometry	0, 0.001, 0.003, 0.01

**Oral application**

Species	Test No.	Study Title	Doses (mg/kg/day)
Mouse	94-6024	Pilot 13-week oral toxicity study in mice	0, 0.3, 3, 10, 30-20
Rat	89-6306	10-day oral dose range-finding study in rats	0, 1, 10, 100
	90-6079	1-month oral findings study in rats	0, 6, 20, 60
	90-6191	6-month oral findings study in rats	0, 0.1, 1, 10
Dog	89-6307	10-day oral dose range-finding study in dogs	1-30, 10
	90-6080	1-month oral findings study in dogs	0, 3, 10, 30
	90-6190	6-month oral findings study in dogs	0, 0.01, 0.1, 1

These studies were reviewed for NDA #21,223 (Review date: August 1, 2000). Main target organs of toxicity identified in the animal studies were kidney, stomach, GI tract, liver, thymus, lung, and i.v. injection site. Zoledronate is concentrated and excreted by the kidney, and this is one of the most sensitive target organs for toxicity. Bone was the target organ for the compound's pharmacologic effect.

In the review of NDA #21-223, it was concluded that for single dose treatment renal and GI tract are the most relevant toxicities, and calculated NOAEL and LOAEL multiples for the highest proposed 8 mg human dose. For renal effects LOAEL multiples were lower (2-10x) than for GI

tract effects (10x-38x). Renal toxicity was concluded to be the main safety concerns. Pharmacology/Toxicology recommended approval (AP) of NDA#21-223 for the 4-8 mg i.v. dose (indication hypercalcemia of malignancy).

For the current NDA, Sponsor performed 2 new single dose iv studies in dog, 3 new repeat dose iv studies in dog (including TK), 1 local tolerance study in Wistar rats, a topical sensitization study in guinea pigs, a 2-week toxicity study with \_\_\_\_\_ (impurity) in rats, three <1-week oral studies in dogs. The single and repeat dose iv studies in the dog were performed to assess renal safety, its reversibility and dependence on infusion time.

Single dose

**Table 2-1 Single dose toxicity studies**

Species	Route	Doses (mg/kg)	Findings
Mouse [93-6085]	Sc	10, 50	LD <sub>50</sub> = 10-50 mg/kg in males; > 10 mg/kg in females
Rat [88-6126]	iv	0.6, 6, 30, 60, 80	LD <sub>50</sub> = approximately 13 mg/kg
Rat [997049]	iv	1.6, 8, 16, 32	≥ 8 mg/kg: mortality; clinical signs, kidney, liver, GI tract ≥ 1.6 mg/kg: ↓ BW/FC; injection site irritation maximum non lethal dose: 1.6 mg/kg minimum lethal dose: 8 mg/kg
Dog [0170119]	iv 5 & 15 min infusion	1.0	5 & 15 min infusion: clinical signs & moribund sacrifice, mainly due to infusion site leakage/irritation in 15 min grp; ↓ Ca & P in both groups considered pharmacol side-effect in absence of other renal effects (e.g. histopath) 5 min infusion: kidney, esophagus, GI tract lesions in 5 min grps but not 15 min group
Dog [0270126]	iv 15 min infusion	1.25	↓ Ca & P; kidney lesions
Dog [936084]	iv inj	2, 10	2 mg/kg: no clinical signs 10 mg/kg: mortality

Source: [Toxicology tabulated summary]

Repeat dose

RAT

**Table 3-1 Repeat-dose parenteral toxicity studies in rats and dogs**

Study Type	Species	Route	Doses (mg/kg)	Findings
10-Day range-finding [89-6036]	Rat	iv inj	0.06, 0.6, 6	0.06 mg/kg: well tolerated 0.6 mg/kg: clinical signs; kidneys, liver 6 mg/kg: sacrifice due to severe clinical signs; bone, kidneys, stomach, liver, thymus, spleen, lymph nodes NOAEL: 0.06 mg/kg
2-Week [998073]	Rat	iv 1-2 min infusion	0.06, 0.6, 3.2 (every third day for 18 days)	≥ 0.06 mg/kg: local irritation, bone changes ≥ 0.6 mg/kg: gastric lesions 3.2 mg/kg: mortality, clinical signs, ↓ BW/FC, clinical pathology, kidney, liver NOAEL: not established
10-Day range-finding [90-6156]	Rat	sc	0.2, 0.6, 2	≥ 0.2 mg/kg: injection site irritation ≥ 0.6 mg/kg: clinical signs 2 mg/kg: clinical signs; kidney, liver; spleen, thymus, lymph nodes, lung and adrenals NOAEL: not established
1-Month + 1 mo recovery [90-6179]	Rat	sc	0.02, 0.06, 0.2	≥ 0.06 mg/kg: clinical signs; inj. sites, spleen, muscle 0.2 mg/kg: liver, lymph nodes NOAEL: 0.02 mg/kg/day
3-Month + 1 mo recovery [92-6259]	Rat	sc	0.01, 0.03, 0.1	Tolerated without mortality at doses up to and including 0.1 mg/kg. Pharma bone changes at all doses. NOAEL 0.01 mg/kg/day
6/12-Month + 6 mo recovery [93-6230]	Rat	sc	0.001, 0.003, 0.01	≥ 0.001 mg/kg: clinical path, bone, bone marrow ≥ 0.003 mg/kg: kidney findings 0.01 mg/kg: equivocal changes in testes NOAEL: 0.001 mg/kg/day
6/12-Month bone analyses [93-6230]				Bone morphometry normal

Repeat dose**DOG****Table 3-1 Repeat-dose parenteral toxicity studies in rats and dogs**

Study Type	Species	Route	Doses (mg/kg)	Findings
10-Day range-finding [90-6157]	Dog	iv inj	0.1, 1	≥ 0.1 mg/kg: bone rib, inj. sites 1 mg/kg: clinical signs; GI, liver, lung, thymus NOAEL: 0.1 mg/kg
4-Week + 4wk recovery [90-6180]	Dog	iv inj	0.02, 0.06, 0.2	≥ 0.06 mg/kg: clinical signs 0.2 mg/kg: GI tract NOAEL: 0.02 mg/kg/day
3-Month + 4wk recovery [92-6261]	Dog	iv inj	0.01, 0.03, 0.1→0.2 (increased to 0.2 at 6 weeks)	≥ 0.01 mg/kg: genital tract (F); bone, spleen; lung, thymus ≥ 0.03 mg/kg: moribund sacrifice at 0.1→0.2 mg/kg due to inj. site irritation, ↓ BW/FC, clinical pathology; kidney, liver, genital tract (M), pancreas, urinary bladder, esophagus, stomach, inj site irritation NOAEL: not established
Renal Tox Pilot Study through 29 days [008189]	Dog	Intermittent inj or iv infusion, variable infusion times	0.2, 0.5, 0.75, 1.0, 3.0, 6.0	0.2 mg/kg: no effects 0.5 mg/kg: renal NOAEL when given at 2-wk intervals (3x) over 28 days as 5 or 15-minute infusion; kidney effects when infused over 60 min, same dosing regimen ≥ 0.75 mg/kg given 3x over 28 days: kidney effects regardless of infusion time ≥ 3 mg/kg: not tolerated
13-wk [0170102]	Dog	iv 15 min infusion once triweekly	0.25, 1	≥ 0.25 mg/kg: local irritation at infusion sites; ↓ Ca & P 1.0 mg/kg: kidney Renal NOAEL: 0.25 mg/kg
26-wk + 3 wk recovery [018037]	Dog	iv 15 min infusion once triweekly	0.25, 0.5, 1	0.25 mg/kg = Renal NOAEL after 1, 3 & 5 doses. Minimal renal effects after 9 doses in 2/8 dogs 1.0 mg/kg: clinical signs; 2 dogs sacrificed moribund; kidney, GI tract
26/52-wk + 6 mo recovery [93-6193] Bone analyses from 26/52-wk dog [93-6193]	Dog	iv inj <sup>a</sup>	0.005, 0.03, 0.1	All doses: inj site irritation; bone ≥0.03 mg/kg : kidney, GI tract; clinical pathology NOAEL: 0.005 mg/kg  All doses: ↑ mineralization at 12 mo No mineralization or structural defects at 6 or 12 mo.; ↓ bone formation at 6 & 12 mo (reversible). ↑ connectivity parameters with ↑ dose (reversible). Biomechanical parameters assessing bone quality showed either no deleterious effect or ↑ quality

Source: [Toxicology tabulated summary]

<sup>a</sup>Administered on alternating days for 16 weeks, then every third day through wk 52.

Previously reviewed toxicity studies

In the single dose studies, moderate to marked toxicity was seen at doses  $\geq 6$  mg/kg. In an acute IV study in rats with 1.6, 8, 16, 32 mg/kg, 1.6 mg/kg was tolerated with local irritation only. In another acute rat study, 0.6 mg/kg was the NOEL with renal changes at higher dose of 6 mg/kg and above. An acute IV study in the dog caused mortality at 10 mg/kg probably due to GI hemorrhage or cardiac arrest, and 2 mg/kg was the GI NOEL. Renal findings were not reported but a histopathology evaluation was not done in this study.

In the repeat dose iv dies, there were effects on body weight, red blood cells, kidney, liver, GI tract, spleen, lung, and injection site (local irritation). Target organ toxicity was evidenced by changes in serum parameters (e.g. liver enzymes, renal toxicity markers), changes in organ weight, and inflammatory changes, necrosis and hemorrhage. In rat, there were decreases in serum Ca and P. Bone changes and secondary effects thereof were due to the pharmacologic activity of the compound and were seen in most studies at the lowest doses used. Findings were partially or totally recoverable. Kidney toxicity included renal tubular necrosis/regeneration, vacuolation, dilatation, inflammation, with BUN and serum creatinine elevations.

Note that GI lesions were observed in rat and dog studies with the IV dosing route. In one intermittent 18-day iv study in rat, gastric necrosis in females was seen at a dose (0.6 mg/kg) lower than the renally toxic dose (3.2 mg/kg). The GI irritation may partly be due to local effects in the tissue but may also be due to systemic effects such as mast cell effects or serum electrolyte changes. Effects on the GI system with IV rather than oral on has also been observed with other bisphosphonates.

IV infusion studies in the dog

IV dog studies not reviewed previously included 2 single dose studies with 5-min and 15-min iv infusion (0170119 and 0270126), a 2-week interval renal pilot study (008109) with iv injection or infusion, a 13-week once 3-weekly 15-min infusion study (0170102), and a 6-month once 3-weekly 15-min infusion study with 3-week recovery.

Single dose iv studies

In a single dose i.v. dog study (#0170119) with **1 mg/kg (5- or 15-min infusions)**, a 5-min dose had renal and GI effects, but a 15-minute infusion did not. Dose-related decreases in Ca and P were seen in both groups that persisted for 6 days. Kidney effects in the 5-min infusion group included renal cortical tubular vacuolation, tubule basophilia, necrosis, urothelial hyperplasia, and focal inflammation, hemorrhage and congestion. GI findings included inflammation, hemorrhage, congestion in stomach and intestine.

In a single dose i.v. study (#0270126) with **0, 1.25 mg/kg (15-min infusion)** with 1-wk, 13-wk or 26-wk recovery period (2/grp controls, 3/grp treated), and clinical pathology on Days 4, 8, 22, there was hypocalcemia and hypophosphatemia on Days 4, 8, and 22. BUN was decreased ( $<10$  mg/dL) in 3 dogs on Day 8 and 1/3 dogs with low BUN was isothermic (low urine specific gravity). The low serum P was thought to be due to drug-related renal tubule damage and dysfunction. At 1 week recovery, 1/3 dogs had microscopic tubule necrosis and basophilia. After 13- or 26-wk recovery kidney findings had resolved. The low BUN was thought to be related to transient medullary washout secondary to a diuretic-like effect and/or tubular damage. It is unclear whether the low Ca and P were related to the medullary washout or renal tubule damage or due to an other drug-related effect.

Based on single dose iv studies, the renal NOEL was 1 mg/kg.

Intermittent dose iv studies

In a pilot 2-week repeat iv renal study in the male dog (008109), with doses of **0.2, 0.5, 0.75, 1, 3, 6 mg/kg (1 or 3 doses)**, and 5-, 15-, or 60-min infusions, 5-min and 60-min infusions appeared more toxic than a 15-min infusion. This was unexplained. There was no renal effect at 0.2 and 0.5

mg/kg (15-min), and a minimal microscopic effect at 0.5 mg/kg (60-min). Renal NOAEL was 0.5 mg/kg (15-min).

In the 13-week intermittent dog study (0170102) with **0.25 and 1 mg/kg (15-min infusions)**, once every 3 weeks, for 1, 3, or 5 doses, serum Ca and P were decreased in all treated, which recovered in females but not all males after 13 weeks. Urine specific gravity was decreased, probably due to tubular damage. Injection site irritation was present in all treated. Renal microscopic findings were seen at 1 mg/kg and included slight tubular cortical necrosis and debris mineralization, and slight tubular regeneration, inflammation and dilatation. PK data indicated dose proportional C<sub>max</sub> and no accumulation of compound. Renal NOAEL was 0.25 mg/kg (5 doses).

In the 26-week intermittent iv dose study in dogs (018037), with doses of **0.25, 5, 1 mg/kg, for 9 doses every 3 weeks**, 2/6 HD males died on D82 and D140 after clinical signs. These 2 dogs had increased BUN and creatinine, with kidney findings including degeneration/necrosis of tubule epithelial cells, mineralization in cortical tubules, inflammation, increased connective tissue, and papillary necrosis. 1 of the 2 dogs had GI lesions of congestion, erosion, hemorrhage and (sub)acute inflammation. Ca and P were decreased transiently at all doses. At interim sacrifice (Day 46, after 3 doses) there was minimal degeneration/ necrosis of kidney at 0.5 mg/kg. At terminal sacrifice (after 9 doses) there was kidney degeneration/necrosis of tubule epithelial cells, mineralization in cortical tubules, inflammation, increased connective tissue, and papillary necrosis, at 0.25, 0.5 and 1 mg/kg. At recovery (3 wks after 9 doses) there were kidney findings at 1 mg/kg, but no significant GI toxicity. PK: Exposure was dose-proportional and slight accumulation after 25 weeks. Renal NOAEL was 0.25 mg/kg after 3 doses, and <0.25 mg/kg after 9 doses. Mortality occurred at 3 or 6 doses of 1 mg/kg.

Note that hypocalcemia and hypophosphatemia occurred at doses lower than those causing microscopic renal damage. These events were likely to be related to the pharmacologic effect of the drug on bone resorption and possibly the ability of the compound to bind Ca. An effect of tubule function may also have contributed. The NOAEL for this effect was <1 mg/kg in single dose study 0170119 (<6.7x1.5=<10x human AUC), and <0.25 mg/kg (5 doses, 9 doses) in the 13-wk and 26-wk intermittent study, respectively (<10.8x human AUC)

In conclusion, in the iv studies (15-min infusions) with 2-3 week dosing intervals, renal NOAEL values were 0.5 mg/kg (3 doses), and 0.25 mg/kg (5 and 3 doses). At higher doses or more infusions, renal toxicity including tubule basophilia, necrosis, de- or regeneration, vacuolation, dilatation, inflammation, and papillary necrosis was observed. The data suggest a potential for accumulation of renal toxicity with multiple doses.

#### Impurities

Three main impurities in toxicology and clinical study batches:

- 1.
- 2.
- 3.

Qualification threshold for impurities in new drug substances is 0.15% (ICH Guidance Q3A). Specification limit in the drug product (for degradation products) is 0.2%.

The first 2 impurities were present in acute and repeat dose iv toxicity studies in rats and dogs, at percentages ranging from <1/10x – 1x the 0.2% values. However, the maximum tolerated dose (i.e. the dose that did not lead to mortality) in acute studies was 12x (rat) and 25x (dog), and in repeat dose studies of up to 26/52 week duration, it was 1x (dog)-5x (rat) the highest expected dose of 0.17 ng/kg in a 60 kg human, based on mg/kg dose comparison (NDA 21-817, Toxicology Written Summary, p.67). Based on mg/m<sup>2</sup> comparison these multiples are 2x (rat) and 12x (dog) for acute studies, and 0.5x (dog) and 1x (rat) for repeat dose studies. Therefore, these 2 impurities are adequately qualified for the proposed single dose treatment regimen.

Levels of \_\_\_\_\_ in the toxicology batches ranged from \_\_\_\_\_. Nevertheless, a separate 2-week repeat dose i.v. rat toxicity study was performed with 0.0005 and 0.005 mg/kg/day \_\_\_\_\_ (Study 0470043). The LOAEL for liver toxicity was 0.005 mg/kg. This is approximately 12x (based on mg/kg) and 2x (based on mg/m<sup>2</sup>) the expected human dose of 0.0004 mg/kg in a 5 mg clinical dose at a specification limit of \_\_\_\_\_. The NOAEL was 0.0005mg/kg (0.2x human dose, based on mg/m<sup>2</sup>; 14-day cumulative dose 2.8x human dose, based on mg/m<sup>2</sup>). Thus, \_\_\_\_\_ is adequately qualified.

### Safety margins (multiples)

Renal NOAEL values from acute and repeat dose bolus iv studies and from intermittent iv infusion studies (rat and dog) were used by Sponsor to calculate multiples of the human single 5 mg dose. Multiples, or safety margins, were based on NOAEL-dose or exposure (AUC)-at-NOAEL in animals as compared to the dose (mg/m<sup>2</sup>) or exposure (AUC) in humans. For repeat dose data, the multiples are of cumulative dose or AUC. Cumulative dose (or AUC) was the dose (or AUC) multiplied by the number of doses (e.g. 90x in a 3-month study).

The calculations are acceptable for evaluation of safety for a single dose human treatment such as proposed for the current NDA.

### 1. Based on mg/m<sup>2</sup> comparison

**Table 5-3 Renal NOAELs in rat and dog (parenteral bolus administration)**

Bolus dose		Rat				Dog			
Zoledronate		Cumulative NOAEL				Cumulative NOAEL			
Dosing	No. doses	NOAEL (mg/kg)	(mg/kg)	(mg/m <sup>2</sup> )	x single clinical 5 mg dose <sup>2</sup>	NOAEL (mg/kg)	(mg/kg)	(mg/m <sup>2</sup> )	x single clinical 5 mg dose <sup>2</sup>
Single [88-6126]	1	0.6	0.6	3.6	1.2	2 <sup>1</sup> [93-6084]	2	40	13.4
Single [997049]	1	1.6	1.6	9.4	3.2	-	-	-	-
Daily [90-6156]	10	0.06	0.6	3.6	1.2	0.1 [90-6157]	1	20	6.7
Daily [906179]	28	0.2	5.6	33.6	11.3	0.02 [90-6180]	.6	12	4
Daily [92-6259]	90	0.03	2.7	16	5.4	0.01 [92-6261]	0.9	18	6.0
Daily [93-6230]	365	0.01	3.7	22	7.4	-	-	-	-
Q2 d for 16 wk; then Q 3d to wk 52	141	-	-	-	-	0.005 [93-6193]	0.71	14.1	4.7

<sup>1</sup>Based on clinical signs and necropsy observations only; no clinical or histopathology

<sup>2</sup>Comparison based on mg/m<sup>2</sup> BSA (60 kg human) Source: [Toxicology tabulated summary]

**Table 5-4 Renal NOAELs in rat and dog (iv infusion)**

Dosing	No. doses	NOAEL (mg/kg)	Cumulative NOAEL (mg/kg)	(mg/m <sup>2</sup> )	x single clinical 5 mg dose <sup>1</sup>
Q 3 d Rat for 18 d [998073]	6	0.6 (1-2min)	3.6	21.6	7.3
Single Dog [0170119]	1	1.0 (15 min)	1.0	20	6.7
Q 2 wk 28 days Dog (pilot study) [008189]	3	0.5 (15 min)	1.5	30	10.1
Q 3 wk 13 wk Dog [0170102]	5	0.25 (15min)	1.3	25	8.7
Q 3 wk 26 wk Dog [018037]	3	0.25 (15 min)	0.8	16	5.4

<sup>1</sup> comparison based upon mg/m<sup>2</sup> BSA (60 kg human) Source: [Toxicology tabulated summary]

**2. Based on AUC comparison**

**Table 10-3 Comparative systemic exposure (AUC) at the animal renal NOAEL (parenteral bolus administration) versus 5 mg human equivalent**

Zoledronate	No. doses	NOAEL (mg/kg)	Rat			Dog			
			Cumulative NOAEL		X single clinical 5 mg dose <sup>4</sup>	Cumulative NOAEL			
			AUC <sup>2</sup> (ng·h/mL)	Cum. AUC (ng·h/mL)		AUC <sup>3</sup> (ng·h/mL)	Cum. AUC (ng·h/mL)	x single clinical 5 mg dose <sup>4</sup>	
Single [88-6126]	1	0.6	3917	3917	1.0	2 <sup>1</sup> [93-6084]	12820	12820	12.8
Single [997049]	1	1.6	10445	10445	2.6	-	-	-	-
Daily [90-6156]	10	0.06	392	3920	1.0	0.1 [90-6157]	641	6410	6.4
Daily [906179]	28	0.2	1306	36568	9.1	0.02 [90-6180]	128	3584	3.6
Daily [92-6259]	90	0.03	196	17640	4.4	0.01 [92-6261]	64	5760	5.8
Daily [93-6259]	365	0.01	65	23725	5.9	-	-	-	-
Q2 d for 16 wk; then Q 3d to wk 52	141	-	-	-	-	0.005 [93-6193]	32	4512	4.5

Source: [Toxicology tabulated summary]

<sup>1</sup>Based on clinical signs and necropsy observations only; no clinical or histopathology

<sup>2</sup>Rat AUC based on 3917 after 0.6 mg/kg sc [R99-1978]

<sup>3</sup>Dog AUC based on 6410 (day 1 average male/female) Day 1 after 1 mg/kg [R0170102]

<sup>4</sup>Human AUC based on AUC<sub>(0-∞)</sub> = 1601 after 8 mg [Clinical Study J001] ≈ 1001 for 5 mg

**Table 10-4 Comparative systemic exposure (AUC) at the animal renal NOAEL (infusion studies) versus 5 mg human equivalent**

Dosing	No. doses	NOAEL (mg/kg)	AUC <sub>(0-48hrs)</sub> (ng·h/mL)	Cum AUC (ng·h/mL)	x single clinical 5 mg dose
Q 3 d Rat for 18 d [998073]	6	0.6 (1-2min)	3936	23616	5.9
Single Dog [0170119]	1	1.0 (15 min)	6410	6410	6.4
Q 2 wk 28 days Dog (pilot study) [008189]	3	0.5 (15 min)	2848	8544	8.5
Q 3 wk 13 wks Dog [0170102]	5	0.25 (15min)	1440	7200	7.2
Q 3 wk 26 wks Dog [018037]	3	0.25 (15 min)	1405	4215	4.2

Source: [Toxicology tabulated summary]

Rat AUC based on 3936 after 0.6 mg/kg iv [R99-1978]

Single dog AUC based on 6410 (day 1 average male/female) after 1 mg/kg [R0170102]

28d dog AUC based on 2848 (day 1 average male/female) after 0.5 mg/kg [R018037]

13w dog AUC based on 1440 (day 1 average male/female) after 0.25 mg/kg [R0170102]

26w dog AUC based on 1405 (day 1 average male/female) after 0.25 mg/kg [R018037]

Human AUC based on AUC<sub>(0-∞)</sub> = 1601 after 8 mg [Clinical Study J001] ≈ 1001 for 5 mg

For the AUC exposure multiple calculation, Sponsor used an AUC value of 1001ngxh/mL for humans dosed with 5 mg. This was extrapolated from the AUC value of 1601 ngxh/mL at 8 mg i.v. (Study J001). However, based on data from Study 1101, the AUC at a 5 mg single iv dose was calculated to be 650 ngxh/mL (simulation by Biopharmaceutics Reviewer NDA #21-817).

Thus, this reviewer believes that sponsor's AUC multiples were underestimated by a factor 0.67x, and real values are 1.5x higher.

For AUC exposure multiples, the ratio of rat: human AUC was corrected by a factor 4x, since the unbound fraction in rat plasma (0.1) is about 4-fold lower than in human (0.4). The unbound fraction in dog and human plasma is approximately the same (0.4) and no correction was needed. This is acceptable.

The sponsor concluded that based on both single and repeat dose rat and dog toxicity studies, the safety margin for renal toxicity is adequate for the 5 mg single dose. The sponsor also stated that the fact that margins were based on multiple doses in several animal studies while intended human dose is single dose adds to the calculated safety margins. This reviewer does not agree since the use of cumulative dose or exposure values takes this into consideration. Therefore, reviewer concludes margins can be directly evaluated (after correction by a factor 1.5x for AUC exposure multiples).

#### Safety evaluation

Multiples calculated by Sponsor are appropriate to serve as basis for safety evaluation. The multiples are based on renal NOAEL dose levels for rat and dog derived from both single dose, intermittent dose, and daily dose IV studies. GI toxicity was the other main safety concern and occurred at similar or higher doses than renal effects. Toxicities in other organ systems were observed at higher doses with higher NOAEL's. In the review of NDA#21-223, it was concluded that based on acute studies in rats and dogs renal toxicity is the main safety concern for a clinical iv dose regimen.

Safety margins (AUC multiples, based on NOAEL) for renal toxicity

Study type	IV dose	RAT		DOG	
		Study #	AUC multiple	Study #	AUC multiple
Single dose	Bolus	88-6126; 997049	1.5x-4x	0170119	9.6x
10-day repeat dose	Bolus	90-6156	1.5x	90-6157	9.6x
≥1-month repeat dose	Bolus	90-6179; 92-6259; 936259	6.6x-14x	90-6180; 92-6261	5.4x-8.7x
Intermittent doses	Infusion, 1-2 min	998073	9.1x	-	-
	Infusion, 15 min	-	-	008189; 0170102; 018037	6.3x-13x

AUC multiples, after a 1.5x adjustment (based on human AUC of 650 ngxh/mL), are 1.5-4x (rat, single dose, and 10-day repeat dose) and 9.6x (dog, single dose). Values are higher based on ≥1-month daily studies in both species. Based on intermittent dose studies, adjusted multiples are 9.1x (rat, every 3 days for 18 days) and 6.3x-13x (dog, bi- or triweekly intermittent dose). All multiples can be considered for safety evaluation. The lowest multiples from rat studies (1.5x) were from an acute study with no histopathology evaluation and with mortality at the next 10x-higher dose of 6 mg/kg (15x multiple), and from a 10-day study with kidney and liver effects at the next 10x higher dose of 0.6 mg/kg (15x).

Serum Ca and P decreases were seen at levels below the NOAEL and the safety margin for this was <9.6x and <10.8x based on AUC comparison (<1 mg/kg in single dose study 0170119, and <0.25 mg/kg, 5 doses, in the 13-wk intermittent study 0170102). It is unclear whether this finding is due to a direct drug Ca-binding effect or related to suppression of bone resorption or an effect on tubule function. Since the effect persisted for up to ca. 3 weeks and occurred in association with tubule dysfunction or damage (single dose study #0270126, 1.25 mg/kg) it may have a renal component.

The reviewer concludes that safety margins for the main toxicities (renal, GI) are adequate to support the proposed clinical treatment with a 5 mg iv dose, given as a 15-minute infusion. The reviewer also concludes that hypocalcemia and hypophosphatemia are potential adverse events

that may be associated with the compounds pharmacologic activity, but their cause (bone and/or kidney effect, Ca-chelation) has not clearly been elucidated.

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**V. GENETIC TOXICOLOGY**

There was no evidence of mutagenicity in three Ames tests, an in vitro Chinese Hamster cell V79 assay, an in vitro Chinese Hamster Ovary clastogenicity assay and an in vivo rat micronucleus assay.

## **VI. CARCINOGENICITY**

Carcinogenicity studies of 2-year duration were carried out using the oral gavage route in mice and rats, and were submitted and reviewed for NDA #21-223. Animals were fasted before dosing to facilitate oral absorption.

There was no evidence of carcinogenic in rats. In mice an increased incidence of Harderian gland adenomas/adenocarcinomas was observed in males at 0.1 and 1.0 mg/kg and in females at doses 0.3 and 1 mg/kg. Although there was no dose response, the incidence exceeded the historical control range in some groups, and it was concluded that the finding was biologically significant but its relevance is unclear (Executive CAC meeting minutes, May 23, 2000, NDA 21-223).

In the current label (Zometa), multiples of human dose are expressed as multiples based on mg/m<sup>2</sup> (dose/body surface area) comparison. The multiples are very low (<<1) since the doses in the long term carcinogenicity studies were given daily for lifetime duration, while the clinical dose is a relatively high single or infrequently repeated dose. Based on AUC, multiples in rats dosed by the s.c. route have been found to be larger than based on mg/m<sup>2</sup>. However, TK data for the oral carcinogenicity studies were not available. Therefore multiples are based on mg/m<sup>2</sup> comparison.

In the previous review of NDA #21-223, multiples were based on the assumption of 1% bioavailability, However, for the label sponsor and Division agreed that bioavailability in rats and mice can be assumed to be 2%.

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## **VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY**

Reproductive toxicity studies were carried out by the subcutaneous route in rats and rabbits, and were reviewed for NDA (#21-223). Due to the dystocia and periparturient mortality observed in the Segment I study probably resulting from drug-related hypocalcemia, a Segment III study was not performed. The dystocia was probably due to lowered serum calcium causing interference with the mobilization of calcium and contraction of uterine muscle.

Bisphosphonates cross the placental barrier and are taken up into the developing fetal skeleton. The teratogenicity observed in the rat Segment II study may be due to a decrease in serum calcium levels and binding to fetal bone.

For the rat Segment I and II studies, multiples were based on AUC comparison, based on data available from single dose s.c. studies at 0.1 and 0.6 mg/kg, and the finding from a 3-month toxicity study that  $C_{pl}$  (plasma concentration) does not change upon repeated daily dosing with 0.1 mg/kg. For the rabbit study Segment II study, multiples were based on a mg/m<sup>2</sup> comparison.

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**VIII. SPECIAL TOXICOLOGY**

In an i.v. irritation study in rabbits, there were dose-dependent local inflammatory changes at the site of i.v. injection (ear) (Study 93-6282). A single sc injection of zoledronate in rats at doses of 0.2, 0.4, 2 and 4 mg/kg (concentrations 0.4, 0.8, 4 or 8 mg/ml) was not tolerated due to dose-dependent local irritation at the site of injection (edema, erythema, skin thickening, ulceration) in all dose groups (Study 007062). In a guinea pig sensitization study, zoledronate was considered a weak sensitizer in female guinea pigs. Zoledronate is irritating at the site of administration.

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**OVERALL SUMMARY AND EVALUATION**

See Executive Summary

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**IX. APPENDIX**

LABEL (with Reviewers corrections)

Sections relevant for Pharmacology/Toxicology are appended.

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-817**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Pharmacoepidemiology and Statistical Science  
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA/Serial Number:** 21-817

**Drug Name:** Zometa (zoledronic acid) injection

**Indication(s):** Paget's disease of bone

**Applicant:** Novartis

**Date(s):** Submitted 9/21/04  
6-month goal date 3/21/05

**Review Priority:** Priority

**Biometrics Division:** HFD-715

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**Keywords:** NDA review, clinical studies

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# 1. EXECUTIVE SUMMARY

## 1.1 Conclusions and Recommendations

The sponsor submitted two randomized, double-blind, active-controlled, multi-center clinical trials (2304 and 2305) as primary evidence of the efficacy of Zometa (zoledronic acid) in reducing serum alkaline phosphatase (SAP) levels in patients with Paget's disease of bone. The trials were identically designed. The primary endpoint was therapeutic response, defined as (1) a reduction of at least 75% from baseline in SAP excess (difference between measured level and midpoint of the normal range) or (2) normalization of SAP. In both trials, a significantly greater proportion of Zometa patients experienced therapeutic response than did patients receiving the active control, risedronate ( $p < .001$ ).

Table 1 shows results on the primary endpoint for the individual studies and the pooled data.

**Table 1. Therapeutic response (6 months)**

	Aclastia	Risedronate	Trt difference (95% CI, p-value) <sup>1</sup>
<u>Trial 2304</u> No. (%) patients with therapeutic response	85/88 97%	60/82 73%	24% (12%, 35%) p<.0001
<u>Trial 2305</u> No. (%) patients with therapeutic response	84/88 95%	67/89 75%	20% (9%, 31%) p=.0002
<u>Pooled studies</u> No. (%) patients with therapeutic response	169/176 96%	127/171 74%	22% (14%, 30%) p<.0001

<sup>1</sup> CI based on Fleiss' normal approximation to the binomial. P-value from Fisher's Exact test.

Zometa was associated with significantly lower calcium and phosphorus levels early in the trial. The relative risk of hypocalcemia at Day 10 for Zometa compared to risedronate in the combined studies was 8.27 ( $p < .0001$ ). The relative risk of hypophosphatemia at Day 10 was 14.18 ( $p < .0001$ ). Calcium and phosphorus levels returned to normal by the next scheduled measurement, Day 63.