

There was a nominally significant interaction ($p = 0.10$) between treatment and last Paget's therapy (oral bisphosphonate, IV bisphosphonate, clodronate, others, none). The nominally significant interaction was driven by the 70% treatment difference in patients previously treated with risedronate. Zometa was still significantly more effective than risedronate by an analysis of the pooled data that excluded patients with previous risedronate treatment.

Other issues are discussed in Section 5.2 which addresses the sponsor's proposed label.

1.2 Brief Overview of Clinical Studies

Paget's disease of bone is characterized by excessive bone re-modeling. SAP is a marker of bone formation and is typically elevated in patients with Paget's. Trials 2304 and 2305 were submitted as the primary evidence of the efficacy of Zometa in reducing SAP levels in patients with Paget's disease of bone. Patients were enrolled with moderate to severe Paget's disease characterized by SAP levels $\geq 2 \times$ ULN based on an age-specific normal reference range. The studies were 6 months in duration and compared a single 15-minute infusion of Zometa 5 mg to oral daily doses of risedronate 30 mg over 2 months which is the recommended regimen for Paget's disease.

Table 2. Major study characteristics

Trial # Centers Dates	Patients	# randomized	Design Primary endpoint	Duration
Study 2304 33 centers (International) 1/02 – 3/04	M and F age ≥ 30 yrs with confirmed Paget's disease SAP ≥ 2 ULN	Zometa n=90 Risedronate n=82	R, DB, AC, therapeutic response (Y/N) ¹	6 months
Study 2305 45 centers (International) 4/02 – 12/03	M and F age ≥ 30 yrs with confirmed Paget's disease SAP ≥ 2 ULN	Zometa n=92 Risedronate n=93	R, DB, AC, therapeutic response (Y/N) ¹	6 months

¹ A positive therapeutic response was defined as a reduction of at least 75% from baseline in serum alkaline phosphatase (SAP) excess (difference between measured level and midpoint of the normal range) or normalization of SAP.

Abbreviations

R = randomized
DB = double-blind (double-dummy)
AC = active-controlled
|| = parallel groups
SAP = serum alkaline phosphatase
ULN = upper limit of normal

Phase 2 Study 002 (n=176) compared four Zometa doses (50, 100, 200 and 400 µg single infusion) to placebo over 3 months on two endpoints, the maximum % changes from baseline in SAP and urine hydroxyproline/creatinine ratio. The study was not reviewed here since none of the Zometa doses was 5 mg, the to-be-marketed dose.

1.3 Statistical Issues and Findings

- The primary objective of the trials was to show the non-inferiority of Zometa to risedronate with respect to the proportion of patients achieving therapeutic response. The pre-defined non-inferiority margin was -16% based on preserving 75% of the treatment effect of risedronate relative to etidronate (65%). A technical statistical issue involved the sponsor's claim of superiority based on statistically significant p-values computed under a null hypothesis that was not pre-specified, namely that of equal effectiveness¹. Nevertheless, a claim of superiority is fully justified on statistical grounds even without pre-specification of the superiority hypothesis. The required elements for claiming superiority, all of which hold in these trials, are pre-specification of the NI margin, nested null hypotheses for NI and superiority, and the use of a common statistical procedure for both hypotheses. The additional test for superiority can be conducted at the nominal 5% level while still maintaining an overall 5% type I error rate.

The preceding argument is largely a technicality; the p-values in the trial are significant under even the most conservative multiple comparison adjustment method.

- The primary endpoint consisted of two components, a 75% reduction from baseline in SAP excess and normalization of SAP. Therapeutic response was achieved if a patient satisfied either component. In both trials, all patients who achieved a 75% reduction in excess SAP did so with or without normalizing SAP. No patient in either trial achieved therapeutic response solely by normalizing SAP.
- Percent (%) change in SAP has been used to evaluate several standard treatments for Paget's disease. Percent change in SAP is numerically different than % change in SAP excess, the primary endpoint. Percent change in SAP is defined mathematically as:

¹ The Protocol did not explicitly mention testing for superiority. The Statistical Analysis Plan mentioned prospective testing for superiority but did not precisely say how the additional analyses fit into the overall hypothesis testing framework:

"Non-inferiority of zoledronic acid relative to risedronate will be concluded if the lower limit of the one-sided 97.5% confidence interval (or the 2-sided 95% confidence interval) for the difference in proportions (zoledronic acid minus risedronate) is greater than -0.16. If the lower limit is also above zero, the statistical significance of the between-treatment difference on the proportions will be provided using a logistic regression model."

$$(1) \quad \% \text{ change in SAP} = 100 \times (T - B) / B$$

where B = baseline SAP and T = on-treatment SAP. % change from baseline in SAP excess is defined as:

$$(2) \quad \% \text{ change in SAP excess} = 100 \times ((T - M) - (B - M)) / (B - M) \\ = 100 \times (T - B) / (B - M)$$

where M = midpoint of the normal range for SAP. The absolute value of (2) is always larger than the absolute value of (1) since $(B - M) < B$. Therefore, (2) is smaller than (1) when $T < B$ and greater than (1) when $T > B$. Stated another way, % reductions are greater for (2) than for (1) when SAP decreases from baseline, and % increases are greater for (2) than for (1) when SAP increases from baseline. A drug that lowers SAP will appear to be more impressive clinically if the reduction is measured in terms of SAP excess rather than SAP alone. See section 5.1 for data comparing % changes in SAP and SAP excess.

2. INTRODUCTION

2.1 Overview

Five bisphosphonates are currently approved for the treatment of Paget's disease: pamidronate, which is given intravenously, and etidronate, tiludronate, alendronate and risedronate which are taken orally. The Division assigned priority review status to this submission for Zometa due to the apparent superiority of Zometa to risedronate, on face at the time of filing the application, on the primary efficacy endpoint in Trials 2304 and 2305.

2.2 Data Sources

Links to the raw data, Final Reports and final proposed label in the EDR are shown below

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3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Aspects of Trials 2304 and 2305 will be discussed together, not in separate sections, since the trials had identical designs.

Design

Patients were screened for eligibility 16 to 20 days before randomization (Day 1). The double-blind period was 6 months in duration with patient visits at Days 10, 28, 63, 91 and 182. SAP and secondary variables CTX, urine α -CTX and P1NP were measured at Screening and each visit after randomization. Serum chemistries, including calcium and phosphate, were measured at Screening and Days 10, 63 and 182. Vitamin D was measured at Screening only.

Percent changes from baseline for all variables were calculated using the Screening value as the baseline.

Patients received 500mg of calcium twice daily and 400-1000 IU of vitamin D as part of multiple vitamin supplements.

The sample size calculation specified that 89 patients per group would provide 80% power to demonstrate the non-inferiority of Zometa to risedronate on the primary endpoint. The calculation assumed a margin of -0.16, response rates in each group of 0.85 and a 10% dropout rate. The margin was based on preserving 75% of the treatment difference between risedronate and etidronate (0.65).

Methods

The therapeutic response rates in the two groups were compared using a 2-sided 95% CI for the difference in proportions based on Fleiss, an asymptotic method with continuity correction.

Seven secondary endpoints were evaluated as part of a prospective closed testing procedure. The endpoints were tested in the order below, with significance required in both studies at the 5% level before moving to the next test in the sequence:

- CTx at Day 10 (% change)
- urine α -CTx at Day 10 (% change)
- SAP at Day 28 (% change)
- Pain severity (change over time)

- Pain interference (change over time)
- SAP normalization (% of subjects)
- Time to onset of therapeutic effect

CTX, urine α -CTX, SAP and P1NP levels were analyzed using the following model:

$$\log(\text{endpoint/baseline}) = \text{treatment country} \log(\text{baseline}).$$

Pain severity and interference scores over time were analyzed using a mixed model with change from baseline as the response variable and an unstructured covariance matrix:

$$\text{Change} = \text{baseline} + \text{treatment} \times \text{time}.$$

A fixed effect for study was added to the model for the pooled studies.

Time to onset of therapeutic effect was analyzed using a Cox proportional hazards model.

Demographic variables

Table 3 shows demographic and disease characteristics separately for Studies 2304 and 2305. All variables shown were balanced between groups except for a nominal difference in age in Study 2305 ($p=.047$). Zometa patients in Study 2305 were on average 3 years older than risedronate patients.

Table 3a. Study 2304 demographic and disease characteristics

	Zometa N=90	Risedronate N=82	Total N=172
Sex			
Male	62 (69%)	61 (74%)	123 (72%)
Female	28 (31%)	21 (26%)	49 (28%)
Race			
Caucasian	84 (93%)	80 (98%)	164 (95%)
Black	6 (7%)	2 (2%)	8 (5%)
Mean age (SD)	70 (10)	72 (10)	71 (10)
Min, max	42, 94	44, 87	42, 94
< 65 years	25 (28%)	17 (21%)	42 (24%)
≥ 65 years	65 (72%)	65 (79%)	130 (76%)
Baseline disease severity			
Normal (<2 x ULN)	1 (1%)	2 (2%)	3 (2%)
Mild (≥ 2 and < 3 x ULN)	46 (51%)	43 (52%)	49 (52%)
Moderate (≥ 3 and < 7 x ULN)	36 (40%)	30 (37%)	66 (38%)
Severe (≥ 7 x ULN)	7 (8%)	7 (9%)	14 (8%)

<u>Previous Paget's treatment</u>			
Oral bisphosphonates	23 (26%)	28 (34%)	51 (30%)
IV bisphosphonates	13 (14%)	10 (12%)	23 (13%)
Clodronate	3 (3%)	1 (1%)	4 (2%)
Other	2 (2%)	2 (2%)	4 (2%)
None	49 (54%)	41 (50%)	90 (52%)

Table 3b. Study 2305 demographic and disease characteristics

	Zometa N=92	Risedronate N=93	Total N=185
<u>Sex</u>			
Male	62 (67%)	57 (61%)	119 (64%)
Female	30 (33%)	36 (39%)	66 (36%)
<u>Race</u>			
Caucasian	84 (91%)	84 (90%)	168 (91%)
Black	3 (3%)	3 (3%)	6 (3%)
Other	5 (5%)	6 (6%)	11 (6%)
<u>Mean age (SD)</u>	71 (9)	68 (11)	70 (10)
Min, max	45, 92	34, 88	34, 92
< 65 years	68 (74%)	61 (66%)	129 (70%)
≥ 65 years	24 (26%)	32 (34%)	56 (30%)
<u>Baseline disease severity</u>			
Normal (<2 x ULN)	0	2 (2%)	2 (1%)
Mild (≥ 2 and < 3 x ULN)	46 (50%)	55 (59%)	101 (55%)
Moderate (≥ 3 and < 7 x ULN)	39 (42%)	28 (30%)	67 (36%)
Severe (≥ 7 x ULN)	7 (8%)	8 (9%)	15 (8%)
<u>Previous Paget's treatment</u>			
Oral bisphosphonates	33 (36%)	35 (38%)	68 (37%)
IV bisphosphonates	14 (15%)	16 (17%)	30 (16%)
Clodronate	3 (3%)	1 (12%)	4 (2%)
Other	6 (7%)	5 (5%)	11 (6%)
None	36 (39%)	36 (39%)	72 (39%)

The studies had non-overlapping centers.

Table 4 shows enrollment by country. In study 2304, 75% of patients were from Great Britain, Australia or Canada. Study 2305 involved a larger number of countries with Spain having the largest enrollment (30%).

Table 4a. Study 2304 patient enrollment by country

	Zometa N=90	Risedronate N=82	Total N=172
United States	13 (14%)	16 (20%)	29 (17%)
Great Britain	24 (27%)	20 (24%)	44 (26%)
Spain	1 (1%)	0	1 (1%)
Australia	21 (23%)	23 (28%)	44 (26%)

New Zealand	8 (9%)	6 (7%)	14 (8%)
Canada	23 (26%)	17 (21%)	40 (23%)

Table 4b. Study 2305 patient enrollment by country

	Zometa N=92	Risedronate N=93	Total N=185
United States	9 (10%)	13 (14%)	22 (12%)
Great Britain	12 (13%)	9 (10%)	21 (11%)
Spain	29 (32%)	27 (29%)	56 (30%)
Australia	10 (11%)	9 (10%)	19 (10%)
New Zealand	6 (7%)	5 (5%)	11 (6%)
Canada	6 (7%)	5 (5%)	11 (6%)
France	8 (9%)	10 (11%)	18 (10%)
South Africa	5 (5%)	6 (6%)	11(6%)
Germany	3 (3%)	3 (3%)	6 (3%)
Belgium	4 (4%)	6 (6%)	10 (5%)

Disposition

Completion rates were high, 94% for each study (Table 5). Patients were withdrawn from treatment early due to AE (5 patients pooled studies), protocol violation (6), withdrawn consent (8) and lost to F/U (2).

Table 5a. Study 2304 patient disposition

# patients	Zometa	Risedronate	Total
Randomized	90 (100%)	82 (100%)	172 (100%)
Study completers	86 (96%)	76 (93%)	162 (94%)
Withdrawn	4 (4%)	6 (7%)	10 (6%)
ITT	88 (98%)	82 (100%)	170 (99%)

Table 5b. Study 2305 patient disposition

# patients	Zometa	Risedronate	Total
Randomized	92 (100%)	93 (100%)	185 (100%)
Study completers	85 (92%)	89 (96%)	174 (94%)
Withdrawn	7 (8%)	4 (4%)	11 (6%)
ITT	88 (96%)	89 (96%)	177 (96%)

SAP Results

Table 6 shows results on the primary endpoint, therapeutic response, for Studies 2304 and 2305 and the pooled data. In both trials, a significantly greater proportion of Zometa patients had a therapeutic response ($p < .001$).

Table 6. Therapeutic response (6 months LOCF)

	Zometa	Risedronate	Trt difference (95% CI, p-value) ¹
<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

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

Percent (%) change in SAP has been used to evaluate several standard treatments for Paget's disease. Percent change in SAP is numerically different than % change in SAP excess, the primary endpoint. Percent change in SAP is defined mathematically as:

$$(1) \quad \% \text{ change in SAP} = 100 \times (T - B) / B$$

where B = baseline SAP and T = on-treatment SAP. % change in SAP excess is defined as:

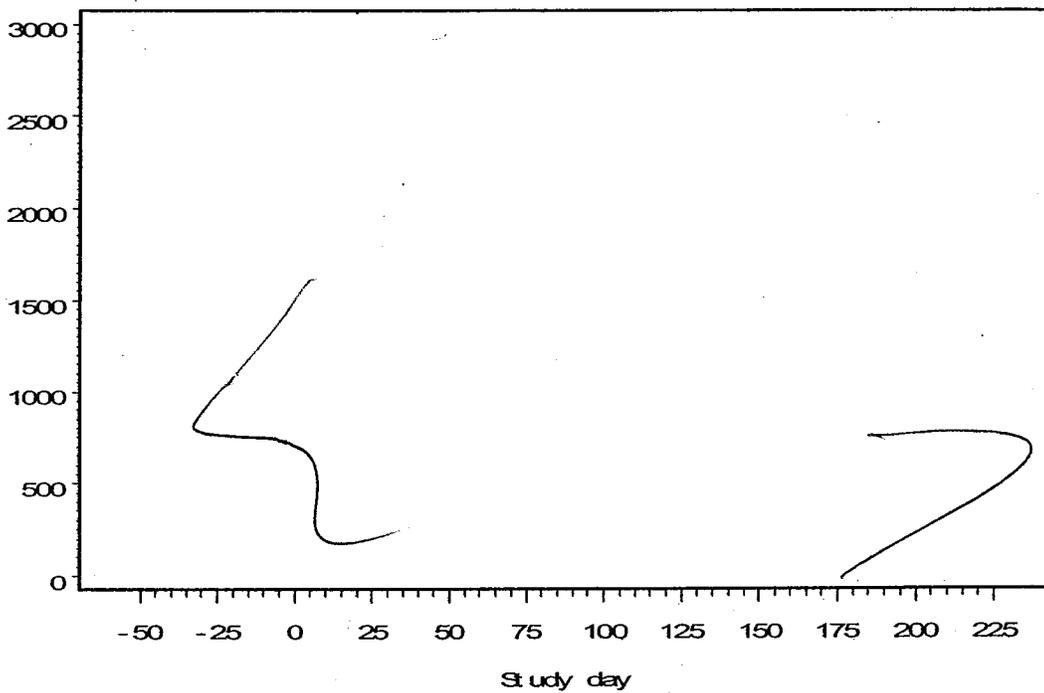
$$(2) \quad \% \text{ change in SAP excess} = 100 \times ((T - M) - (B - M)) / (B - M) \\ = 100 \times (T - B) / (B - M)$$

where M = midpoint of the normal range for SAP. The absolute value of (2) is always larger than the absolute value of (1) since $(B - M) < B$. Therefore, (2) is smaller than (1) when $T < B$ and greater than (1) when $T > B$. Stated another way, % reductions are greater for (2) than for (1) when SAP decreases from baseline, and % increases are greater for (2) than for (1) when SAP increases from baseline. A drug that lowers SAP will appear to be more impressive

clinically if the reduction is measured in terms of SAP excess rather than SAP alone. See section 5.1 for data comparing % changes in SAP and SAP excess.

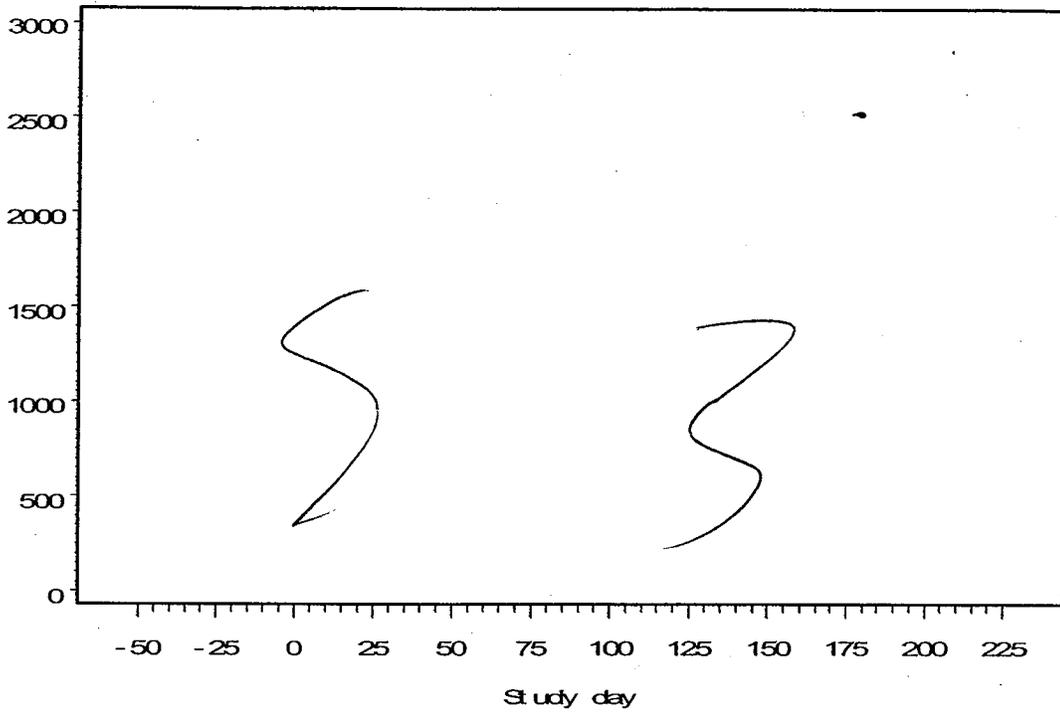
Figures 1 and 2 (Study 2304, Zometa and risedronate, respectively) and Figures 3 and 4 (Study 2305) show the raw SAP data over time.

Figure 1
Study 2304
SAP levels for Zometa patients



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Figure 2
Study 2304
SAP levels for risedronate patients



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Figure 3
Study 2305
SAP levels for Zometa patients

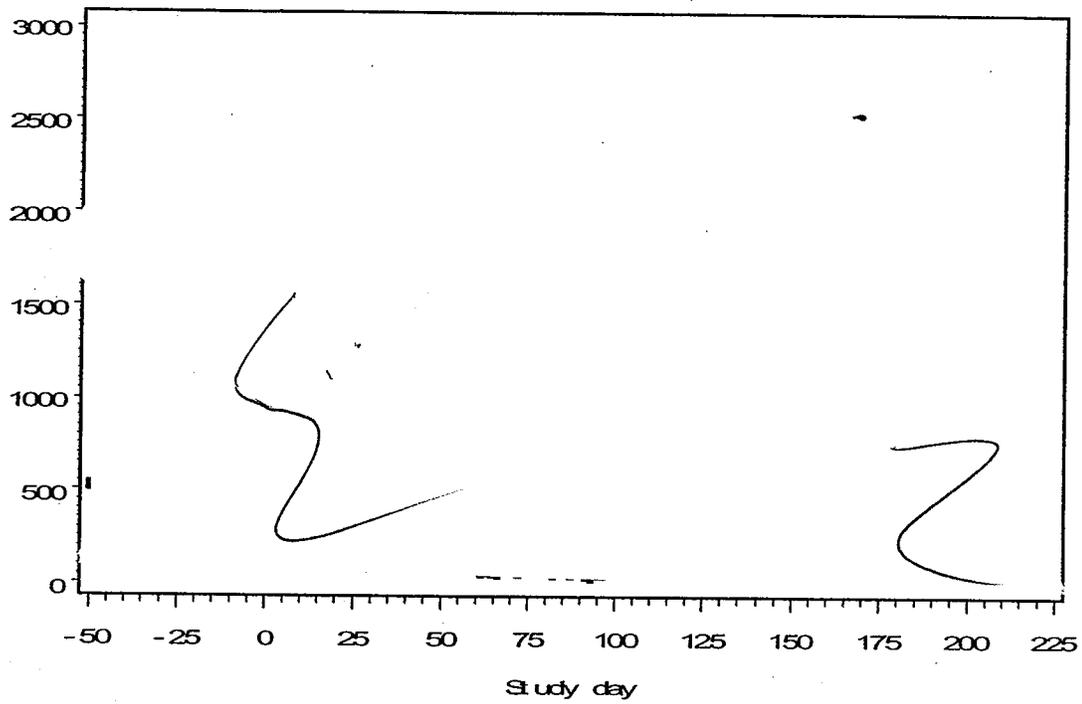
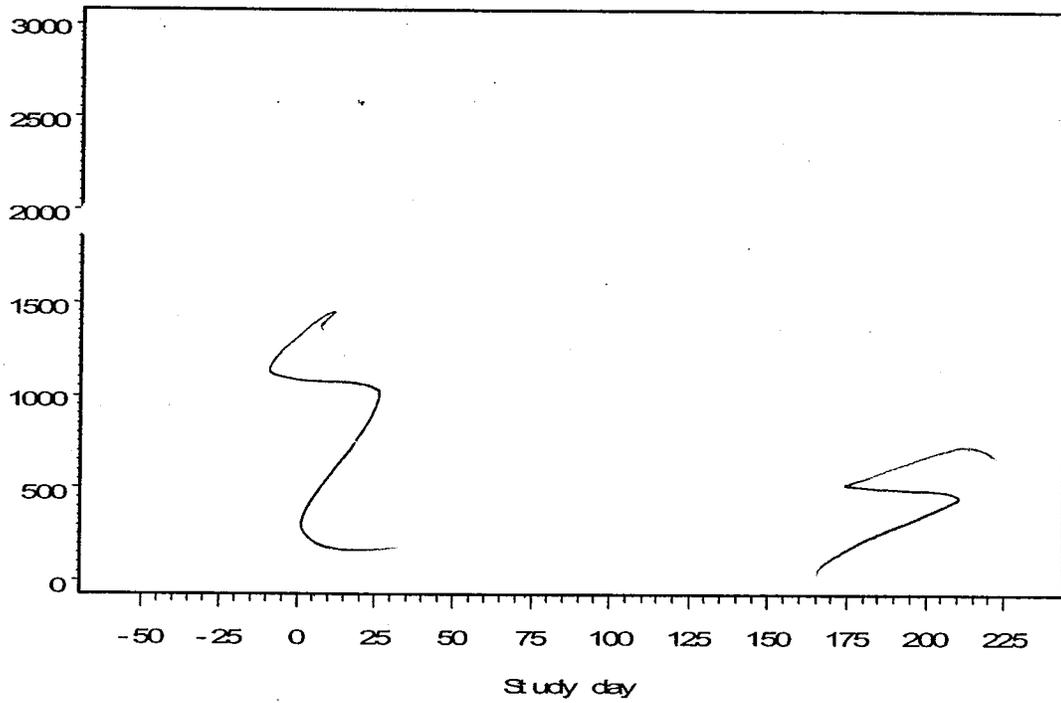
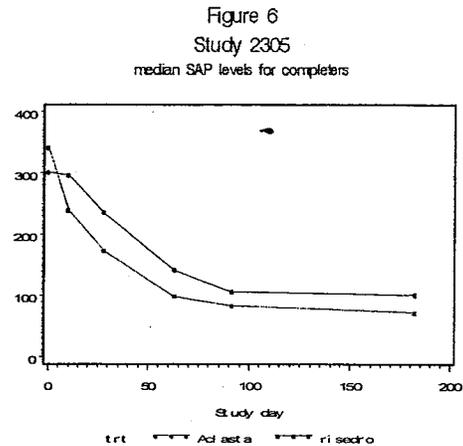
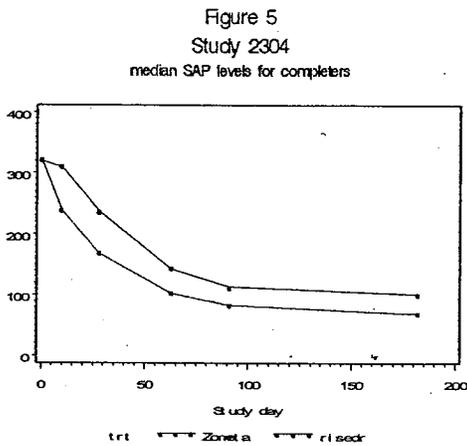


Figure 4
Study 2305
SAP levels for risedronate patients



Figures 5 (2304) and 6 (2305) show median SAP levels over time for completers.



Pooled study data for % change in SAP, time to therapeutic response, response rates for the normalization component of primary endpoint, CTX, urine α -CTX, P1NP and pain severity and interference are analyzed in Section 5.1 (Statistical Issues and Collective Evidence)

3.2 Evaluation of Safety

Calcium and phosphorus

This reviewer examined the incidence of hypocalcemia (calcium < LLN = 2.1 mmol/L) and hypophosphatemia (phos < LLN = 0.71 mmol/L) for each trial and for the pooled data. Table 7 shows rates of hypocalcemia at scheduled visits on Days 10, 63 and 182. Table 8 shows the corresponding data for phosphorus. For the pooled data, the relative risk of hypocalcemia at Day 10 for Zometa compared to risedronate 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 Day 63.

Table 7. Incidence of hypocalcemia for patients with normal calcium levels at baseline

No (%) of patients	Zometa	Risedronate	Relative risk (A/R) (exact 95% CI)
<u>Trial 2304</u>			
Day 10	21/78 (27%)	3/75 (4%)	6.73 (2.31, 30.87)
Day 63	4/81 (5%)	6/77 (8%)	0.63 (0.14, 2.32)
Day 182	0/77	0/72	NA
<u>Trial 2305</u>			
Day 10	11/73 (15%)	1/81 (1%)	12.21 (2.19, 322.4)
Day 63	0/79	2/86 (2%)	0
Day 182	0/79	0/84	NA
<u>Pooled studies</u>			
Day 10	32/151 (21%)	4/156 (3%)	8.27 (3.23, 27.94)
Day 63	4/160 (3%)	8/163 (5%)	0.51 (0.07, 1.66)
Day 182	0/156	0/156	NA

Table 8. Incidence of hypophosphatemia for patients with normal phosphorus levels at baseline

No (%) of patients	Zometa	Risedronate	Relative risk (exact 95% CI)
<u>Trial 2304</u>			
Day 10	17/81 (21%)	0/77	NA
Day 63	1/84 (1%)	0/79	NA
Day 182	1/83 (1%)	0/74	NA
<u>Trial 2305</u>			
Day 10	11/76 (14%)	2/82 (2%)	5.93 (1.56, 58.65)
Day 63	0/83	0/87	NA
Day 182	0/83	0/85	NA
<u>Pooled studies</u>			
Day 10	28/157 (18%)	2/159 (1%)	14.18 (4.06, 108.6)
Day 63	1/167 (1%)	0/166	NA
Day 182	1/166 (1%)	0/159	NA

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4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Data from Studies 2304 and 2305 were combined for the analysis of subgroups.

4.1 Gender, Race and Age

There were no statistically significant interactions between treatment and age (< 65 yrs, ≥ 65 yrs) and between treatment and sex (Table 9).

93% of patients were Caucasian. The significant interaction p-value (p=.0069) is a consequence of very large differences in treatment effects between the race subgroups. Despite the significance of this p-value, the small sample sizes in the non-Caucasian subgroups make the result difficult to interpret.

Table 9. Therapeutic response rates by age, sex and race

	Zometa n=176	Risedronate n=171	Difference		Interaction p-value
			%	p-value	
Age category					
< 65 years	45/45 (100%)	37/45 (82%)	18%	0.0039	0.49
≥ 65 years	124/131 (95%)	90/126 (71%)	24%		
Sex					
Male	117/121 (97%)	86/116 (74%)	23%	<0.001	0.53
Female	52/55 (95%)	41/55 (75%)	20%	0.0034	
Race					
Caucasian	158/163 (97%)	120/161 (75%)	22%	<0.001	0.0069
Black	7/8 (88%)	1/4 (25%)	63%	NS	
Other	4/5 (80%)	6/6 (100%)	-20%	NS	

4.2 Other Special/Subgroup Populations

There were no statistically significant interactions between treatment and the following variables (Table 10):

- Baseline SAP (< 3ULN, ≥ 3ULN)
- Washout period for last bisphosphonate treatment (< 180 days, 180-365 days, > 365 days)
- Baseline disease severity (normal, mild, moderate, severe)
- Symptomatic pain at screening (Y/N)

There was a nominally significant interaction ($p = 0.10$) between treatment and last Paget's therapy (oral bisphosphonate, IV bisphosphonate, clodronate, others, none). The nominally significant interaction was driven by the low 55% response rate (bolded in Table) in risedronate patients whose previous Paget's treatment was an oral bisphosphonate.

Table 10. Therapeutic response by various disease factors

	Zometa n=176	Risedronate N=171	Treatment difference
<u>Baseline disease severity</u>			
Normal (<2 x ULN)	1/1 (100%)	0/2 (0%)	100%
Mild (≥ 2 and < 3 x ULN)	86/89 (97%)	74/97 (76%)	21%
Moderate (≥ 3 and < 7 x ULN)	70/73 (96%)	41/57 (72%)	24%
Severe (≥ 7 x ULN)	12/13 (92%)	12/15 (80%)	12%
<u>Previous Paget's treatment</u>			
Oral bisphosphonates	53/55 (96%)	33/60 (55%)	41%
IV bisphosphonates	22/25 (88%)	21/26 (81%)	7%
Clodronate	6/6 (100%)	2/2 (100%)	0%
Other	8/8 (100%)	6/7 (86%)	14%
None	80/82 (98%)	65/76 (86%)	12%
<u>Symptomatic pain at screening</u>			
No	60/60 (100%)	54/66 (82%)	18%
Yes	109/116 (94%)	73/105 (70%)	24%

Previous oral bisphosphonate treatment in Table 10 was further categorized in Table 11. Patients randomized to risedronate who were previously treated with risedronate experienced a poor response rate, only 30% (bolded in Table). See also Section 5.2 (labeling)

Table 11. Therapeutic response by previous oral bisphosphonate treatment

Oral bisphosphonate	Zometa n=176	Risedronate N=171	Treatment difference
Alendronate	16/17 (94%)	9/13 (69%)	25%
Risedronate	13/13 (100%)	7/23 (30%)	70%
Tiludronate ¹	17/17 (100%)	10/14 (71%)	29%
Other oral bisphosphonates	7/8 (88%)	7/10 (70%)	18%
Total	53/55 (96%)	33/60 (55%)	42%

¹ Tiludronate sodium and tiludronic acid

An analysis of the pooled data was conducted excluding the 36 patients in both groups with previous risedronate treatment. The response rate in the risedronate group improved from 74% to 81% when the 23 patients previously treated with risedronate were excluded. The response rate for Zometa was unchanged (96%) when the 13 patients previously treated with risedronate were excluded. The treatment difference was smaller (15%) but still statistically significant ($p < .001$).

Table 12. Analysis of therapeutic response excluding 36 patients with prior risedronate therapy

	Aclastia	Risedronate	Trt difference (95% CI, p-value) ¹
No. (%) patients with therapeutic response	156/163 96%	120/148 81%	15% (7%, 22%) $p < .0001$

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

Table 13 shows response rates on the primary endpoint by country in order of decreasing sample size. The biggest treatment differences among the 5 largest countries were in North America (US, CAN) due primarily to lower risedronate response rates. The lower rates may be attributed to the fact that the US and Canada had 12 of the 23 risedronate patients who received prior risedronate treatment.

Table 13. Pooled primary endpoint results by country

Country	N	Zometa N=176	Risedronate N=171	Treatment difference
Australia	63	30/31 (97%)	26/32 (81%)	16%
Great Britain	62	32/33 (97%)	24/29 (83%)	14%
Spain	55	30/30 (100%)	21/25 (84%)	16%
Canada	51	27/29 (93%)	13/22 (59%)	34%
United States	47	20/20 (100%)	19/27 (70%)	30%
New Zealand	25	14/14 (100%)	9/11 (81%)	19%
France	17	7/7 (100%)	6/10 (60%)	40%
South Africa	11	4/5 (80%)	6/6 (100%)	-20%
Belgium	10	3/4 (75%)	1/6 (17%)	58%
Germany	6	2/3 (67%)	2/3 (67%)	0%

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The analyses in this section primarily address labeling issues for the pooled data.

Table 14 shows results on the normalization component of the primary endpoint for the combined studies.

Table 14. Normalization of response for pooled studies

	Aclastia	Risedronate	Trt difference (95% CI, p-value) ¹
No. (%) patients with normalization of SAP	156/176 ² 89%	99/171 58%	31% (21%, 40%) p<.0001

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

² Includes 3 patients below SAP normal range lower limit

Table 15 shows time to therapeutic response for the combined data. The medians (64, 89) correspond closely to scheduled visit days (63, 91) as would be expected when the event times are not observed in continuous time (See Section 5.2).

Table 15. Time to first therapeutic response

	Zometa n=182	Risedronate N=175
Number of events	169	131
Number censored	13	44
<u># days to response</u>		
Median	64	89
Mean	63	107
	p < .001 ¹	

¹ Cox proportional hazards model comparing medians

Table 16 shows mean % changes in SAP and SAP excess. Percent reductions were always greater for Zometa compared to risedronate (see discussion in Section 3.1). For both drugs, % reductions for SAP excess exceeded those for SAP alone.

Table 16. % change from baseline in SAP and SAP excess (completers) ¹

	Zometa n=171	Risedronate N=165
<u>Mean % change in SAP excess</u>		
Day 10	-36	-10
Day 28	-62	-33
Day 63	-90	-68
Day 91	-96	-80
Day 182	-101	-82
<u>Mean % change in SAP</u>		
Day 10	-28	-8
Day 28	-49	-26
Day 63	-70	-53
Day 91	-74	-62
Day 182	-79	-64

¹ Sample sizes varied slightly over time due to missed visits.

CTX, urine α -CTX, P1NP and SAP

Table 17 shows this reviewer's results for secondary variables CTX, urine α -CTX, P1NP and SAP. These analyses differ from the sponsor's analyses in several respects: (1) only completers were analyzed; (2) visit windows were widened to include all data irrespective of when they were collected; (3) outliers were not deleted; (4) fasting values were included; and (5) multiple observations occurring in a visit window were averaged instead of selecting the observation closest to the scheduled visit day. These analyses clearly included additional data the sponsor's analysis did not and were meant to be a test of the robustness of the sponsor's results.

Analyses were conducted on the log scale and transformed back. The entries in the Table are geometric LS means. Despite the differences in the two approaches, the results here were similar to the sponsor's, namely that Zometa significantly reduced levels of each parameter relative to risedronate at each visit. See also Section 5.2 (labeling).

Table 17. Reviewer's results for CTX, urine α -CTX, P1NP and SAP (completers)

	Ratio of post-baseline to baseline levels ¹		Relative treatment effect ² (95% CI)
	Aclastia	Risedronate	
<u>CTX</u>			
Day 10	0.10	0.48	0.21 (0.17, 0.25)
Day 28	0.17	0.40	0.43 (0.37, 0.52)
Day 63	0.26	0.34	0.77 (0.65, 0.91)
Day 91	0.26	0.50	0.52 (0.45, 0.61)
Day 182	0.23	0.51	0.46 (0.40, 0.52)
<u>Urine CTX</u>			
Day 10	0.05	0.53	0.09 (0.08, 0.12)

Day 28	0.07	0.29	0.23 (0.19, 0.29)
Day 63	0.09	0.19	0.50 (0.40, 0.62)
Day 91	0.10	0.23	0.44 (0.37, 0.52)
Day 182	0.10	0.26	0.41 (0.34, 0.49)
P1NP			
Day 10	0.55	0.85	0.64 (0.58, 0.71)
Day 28	0.34	0.56	0.62 (0.55, 0.69)
Day 63	0.15	0.27	0.56 (0.49, 0.63)
Day 91	0.11	0.20	0.53 (0.46, 0.62)
Day 182	0.09	0.21	0.45 (0.39, 0.52)
SAP			
Day 10	0.71	0.91	0.77 (0.75, 0.81)
Day 28	0.49	0.71	0.69 (0.66, 0.73)
Day 63	0.28	0.43	0.66 (0.61, 0.71)
Day 91	0.24	0.35	0.70 (0.64, 0.75)
Day 182	0.20	0.31	0.64 (0.58, 0.69)

- 1 Exponential of LS means on the log scale equivalent to the geometric LS mean on the original scale.
2 Exponential of the difference in LS means on the log scale equivalent to the geometric LS mean on the original scale, and equals the ratio of the preceding 2 columns. An upper limit < 1 indicates nominal statistical significance ($p < .05$) favoring Zometa.

Pain interference and severity

The Figures below from the sponsor's submission show mean interference and severity scores over time.

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Figure 3-5 Change in BPI-SF pain severity score by visit – combined active-controlled studies (MITT population)

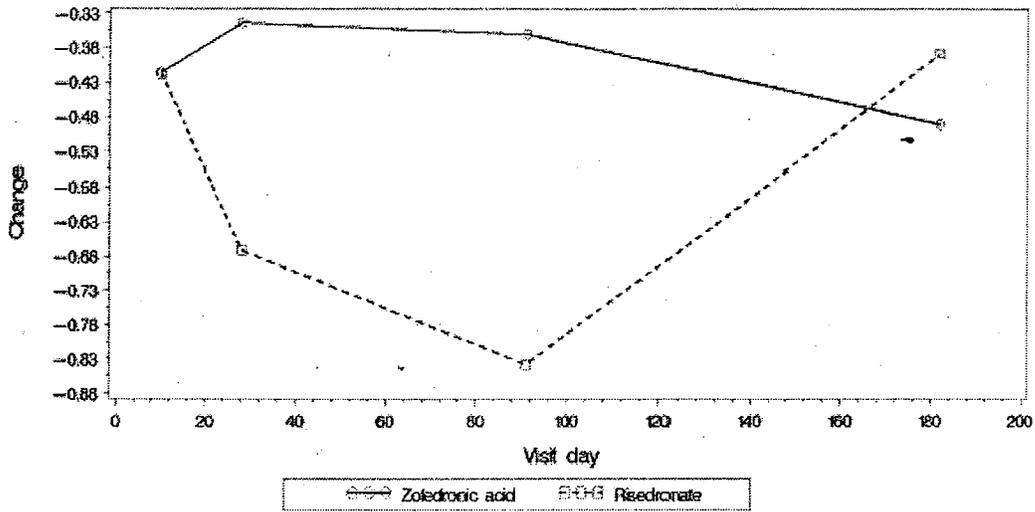
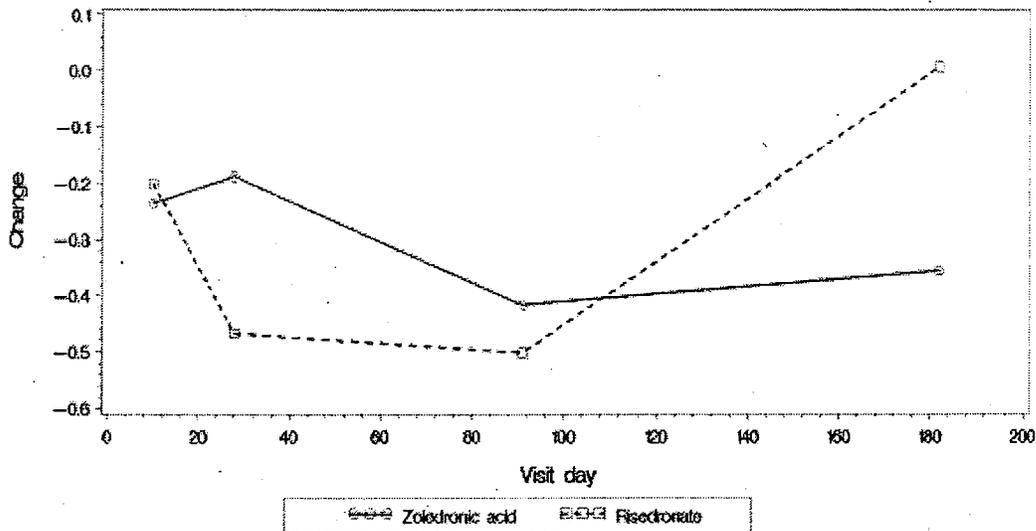


Figure 3-6 Change in BPI-SF pain interference score by visit – combined active-controlled studies (MITT population)



This reviewer analyzed average pain interference and severity scores over Days 91 and 182. These visits were chosen in consultation with the Medical Officer and were thought to represent the most relevant data since they were subsequent to the total dosing of

both drugs by Day 60. The sponsor's analysis averaged the data across Days 28, 91 and 182.

Statistical results were consistent with the sponsor's results. Treatments were not significantly different for either intensity or severity scores (Table 18, $p \geq 0.27$). Study effects were not significant in either analysis. Treatment differences for both endpoints favored risedronate at Day 91 and Zometa at Day 182. The treatment-by-time interaction was significant for pain severity ($p=.035$) and marginally significant for interference ($p=.11$). See also Section 5.2 (labeling).

Table 18. Pain interference and severity (average of Days 91 and 182)

	Zometa	Risedronate
Pain interference	N=110	N=99
Baseline mean (SD)	2.83 (2.67)	2.76 (2.21)
Mean change from baseline (SD)	-0.37 (1.76)	-0.27 (1.55)
LS mean change from baseline	-0.37	-0.29
LS mean treatment difference (SE)	-0.09 (0.21)	
p-value	p=0.68	
95% CI	(-0.50, +0.33)	
Pain severity	N=111	N=102
Baseline mean (SD)	3.48 (2.30)	3.38 (2.03)
Mean change from baseline (SD)	-0.41 (1.78)	-0.63 (1.97)
LS mean change from baseline	-0.40	-0.65
LS mean treatment difference (SE)	0.26 (0.23)	
p-value	p=0.27	
95% CI	(-0.20, +0.71)	

5.2 Labeling comments

This section addresses the sponsor's updated label in the Jan. 19, 2005 submission.

1.

2.



3. F

4.



sentences referring to the mediator should be deleted.

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this page is the manifestation of the electronic signature.**

/s/

Todd Sahlroot
3/2/05 04:14:46 PM
BIOMETRICS

S. Edward Nevius
3/8/05 11:43:48 AM
BIOMETRICS
Concur with review.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-817

MICROBIOLOGY REVIEW

Product Quality Microbiology Review

Review for HFD-510

08 Feb 2005

NDA: 21-817

Drug Product Name

Proprietary: Aclasta®
Non-proprietary: Zoledronic Acid
Drug Product Classification: 3

Review Number: 1

Subject of this Review

Submission Date: September 21, 2004
Receipt Date: September 22, 2004
Consult Date: November 29, 2004
Date Assigned for Review: December 1, 2004

Submission History (for amendments only)

Date(s) of Previous Submission(s): Not applicable.
Date(s) of Previous Micro Review(s): Not applicable.

Applicant/Sponsor

Name: Novartis Pharmaceuticals Corp.
Address: One Health Plaza
East Hanover, NJ 07936-1080
Representative: Joan Materna
Telephone: 862-778-3379

Name of Reviewer: John W. Metcalfe, Ph.D.

Conclusion: Recommended for Approval.

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Original NDA.
 2. **SUBMISSION PROVIDES FOR:** New drug product.
 3. **MANUFACTURING SITE:**
Novartis Pharma Stein AG
Schaffhauserstrasse
4332-Stein
Switzerland
 4. **DOSE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - 100 mL solution in clear plastic _____ vials.
 - Intravenous Infusion.
 - 5 mg/100 mL.
 5. **METHOD(S) OF STERILIZATION:** _____
 6. **PHARMACOLOGICAL CATEGORY:** Treatment of Paget's disease of bone.
- B. **SUPPORTING/RELATED DOCUMENTS:** None

C. **REMARKS:**

The subject NDA was submitted electronically.

A phone call was placed by this reviewer on January 4, 2005 to Ms. Joan Materna (applicant representative) to pose the following questions/comments.



A written response was forwarded by Ms. Materna to this reviewer by FAX on January 7, 2004. Following are the responses provided:



A phone call was placed on January 26, 2005 by this reviewer to Ms. Materna to ask the following question regarding the stability protocol.

Regarding the post approval stability protocol for the annual batches, are sterility and bacterial endotoxin testing planned? There is no mention of these tests in the annual batch stability protocol provided in section 3.2.P.8.2 of the submission.

Ms. Materna stated that

An additional phone call was placed on January 26, 2005 by this reviewer to Ms. Materna informing her that the Product Microbiology team would not support approval of the application with an annual stability protocol which lacks sterility and endotoxin testing. Reference was made to the FDA stability guidance which states that annual stability testing of parenteral drugs should include both sterility and bacterial endotoxin testing. This information was left as a voice mail message for Ms. Materna since she was not in the office at the time of the call. On January 28, 2005, Ms. Materna phoned this reviewer to discuss the rationale for requiring microbiological testing to be performed as part of the annual stability protocol. She will discuss the issue with her colleagues in Switzerland next week, and inform this reviewer of the applicant's response.

On February 7, 2005, this reviewer received a facsimile which provided a written response to the concerns described above regarding the annual stability protocol. Following is a summary taken from the cover page of the 11 page fax:

"Novartis agrees to revise the Aclasta Stability Protocol for Annual Batches to include sterility and BET testing at the initial time point and at expiry. An updated stability protocol for annual batches reflecting this change is provided as separate attachment (document 3769387_P82_M_840_2)".

Further, the written response contained copies of both the revised Post-Approval Stability Protocol and Stability Commitment and the Drug Product Stability Protocol for Annual Batches. The applicant will amend the subject NDA to include these revised documents.

Satisfactory

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Executive Summary**I. Recommendations**

- A. Recommendation on Approvability** – NDA 21-817 is recommended for approval from the standpoint of drug product microbiological quality.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – Not Applicable.

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -**



- B. Brief Description of Microbiology Deficiencies** – There are no microbiology deficiencies.
- C. Assessment of Risk Due to Microbiology Deficiencies** – Not applicable.

III. Administrative

- A. Reviewer's Signature** _____
John W. Metcalfe, Ph.D.
- B. Endorsement Block**
David Hussong, Ph.D.
- C. CC Block**
In DFS

8 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

Withheld Track Number: Microbiology- /

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

John Metcalfe
2/14/05 10:01:37 AM
MICROBIOLOGIST

David Hussong
2/17/05 01:52:45 PM
MICROBIOLOGIST

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-817

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-817
Proprietary Drug Name:	ACLASTA®
Generic Name:	Zoledronic Acid
Indication:	Treatment of Paget's Disease of Bone
Dosage Form:	Solution for Injection
Strength:	5 mg/100 mL
Route of Administration:	Intravenous
Applicant:	Novartis Pharmaceuticals Corporation
Clinical Division:	DMEDP (HFD-510)
Submission Dates:	September 21, 2004; November 16, 2004; January 5 th , 2005; January 14, 2005.
Reviewer:	Sandra Suarez-Sharp, Ph.D.
Team Leader:	Hae-Young Ahn, Ph. D.

TABLE OF CONTENTS

ITEM	PAGE NUMBER
1. Executive Summary	3
1.1 Recommendation	3
1.2 Comment	3
1.3 Phase IV Commitments	3
1.4 Summary of Clinical Pharmacology and Biopharmaceuticals Findings	3
2. Question-Based Review	6
2.1 General Attributes	7
2.2 General Clinical Pharmacology	8
• Exposure-Response	9
○ ER for Efficacy	10
○ ER for Safety	11
• PK Characteristics of Drug	13
• Metabolism and Excretion	15
2.3 Intrinsic Factors	17
• Effect of Age, Race, Gender	17
• Renal Impairment	18
• Hepatic Impairment	19
2.4 Extrinsic Factors	19
• DDI	19
• Inhibition	19
2.5 General Biopharmaceutics	20
2.6 Analytical Section	22
3. Labeling Recommendations	23
4. Appendices	40
4.1 Individual Study Reviews	
• Study 1101 (single PK)	40
• Study 001 (Dose-response)	44
• Study 002 (Dose-response)	48
4.2 CPB Filing/Review Form	57

1. EXECUTIVE SUMMARY

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/ Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed NDA 21-817 submitted on September 21, 2004. We found this NDA acceptable from a CPB standpoint provided that the sponsor agrees with the Agency's labeling recommendations. Please convey recommendation, comment and labeling recommendation as appropriate.

1.2 Comment

- It appears that mannitol in the amount of 5 g in the Aclasta formulation most likely will not affect the pharmacokinetics of zoledronic acid. The 5 mg/100 mL final formulation of Aclasta is now being used in the ongoing pivotal fracture trial (Study 2301) in post-menopausal osteoporotic women and future clinical studies. Therefore, if there is a safety signal, you should conduct a cross study comparison of the PK of zoledronic acid in osteoporotic women vs. that in bone cancer patients to confirm the lack of effect of mannitol on the PK of zoledronic acid.

1.3 Phase IV Commitments

None

1.4 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Aclasta® solution for injection contains zoledronic acid, a bisphosphonate that inhibits osteoclast-mediated bone resorption. Aclasta is proposed for the treatment of Paget's disease of bone, a chronic, focal skeletal disorder characterized by greatly increased and disorderly bone remodeling resulting in a weakened bone structure. The proposed dose in men and women is a single 5 mg of Aclasta® in 100 mL aqueous solution infused over no less than 15 minutes. Retreatment with Aclasta may be considered 12 months after the initial dose in patients who have relapsed.

Zoledronic acid is approved in many countries, including the USA for the treatment of 2 conditions: 1. Bone myeloma and bone metastases (NDA 21-386) and 2. Hypercalcemia of malignancy (NDA 22-223). The dose approved for hypercalcemia of malignancy is a single 4 mg infused over no less than 15 minutes. Retreatment may be considered at a minimum of 7 days elapse before retreatment with renal function monitoring. For bone myeloma and bone metastasis, 4 mg infused over 15 min every 3 or 4 weeks is recommended. The brand name of zoledronic acid for these indications is Zometa®.

The efficacy and safety of Aclasta in patients with Paget's disease of bone was assessed in two identical double-blind active-controlled, non-inferiority trials of 6-months duration in patients with Paget's disease of bone receiving a single 5 mg dose of zoledronic acid infused over 15 minutes. The efficacy and specially the safety of this dose are not fully supported by the dose-response studies conducted in patients with Paget's disease of bone. In addition, based on population PK analysis conducted by the Agency under NDA 21-386 review, the time to onset and degree of renal function deterioration were correlated with exposure. Furthermore, post-marketing experience with Zometa indicated that renal deterioration, progression to renal failure and dialysis, have occurred in patients including those treated with the dose of 4 mg infused over 15 minutes.

The clinical pharmacology of zoledronic acid solution for injection was assessed in 6 studies including two dose-response studies. The PK studies were single/multiple doses in nature all conducted in cancer patients. Three of these studies were previously submitted and reviewed under NDA 21-386. These studies included the effect of renal impairment on the PK of the drug, dose-response and population PK analysis of all the data. In the present submission, one additional single/multiple PK study in cancer patients was included as well as two dose-response studies conducted in patients with Paget's disease of bone. The doses tested in the PK studies range from 2- to 16 mg infused over 5- or 15 min. No PK studies were conducted with the 5 mg dose. The dose ranging studies evaluated doses of 50- to 400 mcg infused over 60 minutes. The to-be marketed formulation (containing ~~of~~ mannitol) was not used in the PK or pivotal clinical trials. However, it appears that the presence of mannitol in the amount of ~~in~~ the Aclasta to-be marketed formulation most likely will not affect the pharmacokinetics of zoledronic acid. According to the sponsor, mannitol in high doses (50-200 grams) can promote diuresis through increased sodium excretion and not through significant changes in GFR. Thus, the ~~of~~ mannitol in this presentation is not associated with any significant effect on the renal elimination of zoledronic acid. Nevertheless, since the to-be marketed of Aclasta is now being used in the ongoing pivotal fracture trial in post-menopausal osteoporotic women and future clinical studies the sponsor should conduct a cross study comparison of the PK of zoledronic acid in osteoporotic women vs. that in bone cancer patients to confirm the lack of effect of mannitol on the PK of zoledronic acid if there is a safety signal.

In summary, a key clinical pharmacology issue is the renal toxicity of the drug which appears to be correlated with zoledronic acid AUC. The efficacy and safety of the proposed single 5 mg dose of zoledronic acid infused over 15 minutes are not supported by the dose-response studies conducted in patients with Paget's disease of bone (doses tested ranged from 50- to 400 mcg). Therefore, the renal safety of a single dose of 5 mg zoledronic acid should be determined by the medical reviewer based on the safety data reported from the clinical trials. A dose- adjustment in patients with moderate renal impairment is suggested for labeling, contrary to the sponsor's recommendation.

Below is a summary of the pharmacokinetics of zoledronic acid, much of which has previously been reported under NDA 21-386 (Zometa for the treatment of bone metastases).

Pharmacokinetics in Bone Cancer Patients

Single Dose

Following a single 4 mg iv infused over 15 minutes of Aclasta solution, the mean C_{max} and AUC_{0-24hr} of zoledronic acid were 416.5 ng/mL (range 178- to 919 ng/mL) and 486.1 ng*hr/mL (range 202- to 772 ng*hr/mL), respectively. Prolonging infusion time from 5 to 15 minutes produced an expected decline in peak zoledronic acid levels by 30%, with no significant effect on AUC. The AUC of zoledronic acid was linear and dose-proportional in the range of 2 to 16 mg. The AUC and C_{max} of zoledronic acid 5 mg infused over 15 min were 650 ng*hr/mL and 519 ng/mL, respectively based on computer simulation using WinNonlin.

Repeat Dose

Zoledronic acid is to be administered as a single dose for Paget's disease; therefore no systemic accumulation of drug would be expected. Nevertheless, the accumulation of zoledronic

acid following a repetitive 28-day dosing schedule was low and the AUC_{0-24h} for subsequent doses was approximately 1.13-fold higher relative to the first dose.

Distribution

After infusion, the time course of zoledronic acid in plasma follows a three-compartment disposition pattern that is characterized by an α - $t_{1/2}$ of 0.24 hrs, a β - $t_{1/2}$ of 1.87 hours and a γ - $t_{1/2}$ of 146 hours. The observed plasma zoledronic acid concentrations decreased to <1% of the observed peak concentrations by 24-hours post-dose. It is believed that zoledronic acid is slowly released back into the circulation following initial rapid sequestration in the bone. Total plasma clearance is about 5 to 7 L/h and appears to be dependent upon creatinine clearance alone. Zoledronic acid plasma protein binding is about 56% bound. The V_d was about 6.78 L.

Elimination

Zoledronic acid is not metabolized and is mainly eliminated by renal excretion. On average (\pm s.d.) a total of $39 \pm 16\%$ of the administered dose is excreted in urine within 24 hours. The remainder is retained in the body, subject to slow release from bone governed by the rate of bone remodeling. The zoledronic acid renal clearance shows strong association with creatinine clearance.

Pharmacokinetics in Special Populations

Age, Gender, Race

Based on population PK analysis, gender, race and age (42 to 92 year olds) did not affect the PK of zoledronic acid. Pharmacokinetic data in pediatric patients are not available.

Renal Impairment

Compared to patients with normal renal function ($n=37$), patients with mild renal impairment ($N=15$) showed an average increase in plasma AUC of 15%, whereas patients with moderate renal impairment ($n=11$) showed an average increase in plasma AUC of 43%. Limited pharmacokinetic data (data available for only one patient) are available for zoledronic acid in patients with severe renal impairment (creatinine clearance <30 mL/min).

Population PK modeling and PK/PD correlations conducted by the agency showed that the risk of a renal deterioration doubled for a patient with the upper limit of moderate renal impairment ($Cl_{cr} = 30$ ml/min) compared to a patient with normal creatinine clearance (average 100 ml/min) when 4 mg of zoledronic acid was administered. This risk tripled at a creatinine clearance of 10 ml/min. In addition, the Zometa label states that in the trials and in post-marketing experience, renal deterioration, progression to renal failure and dialysis, have occurred in patients, including those treated with a single dose of 4 mg infused over 15 minutes. Therefore, zoledronic acid should not be recommended for patients with severe renal impairment (creatinine clearance <30 mL/min). In addition, dose reductions in patients with moderate renal impairment should be made, contrary to the applicant's conclusion that no action is required. The recommended dose (normalized to the zoledronic acid AUC observed in normal renal function) in patients with moderate renal function ($CrCl$ between > 30- and < 60 mL/min) should be 3 mg infused over no less than 15 minutes.

Hepatic Impairment

The effect of hepatic impairment on the PK of zoledronic acid has not been addressed. Since zoledronic acid appears not be metabolized, it is unlikely that hepatic impairment will affect the PK of this drug.

Drug/Drug Interactions (DDI)

DDI studies have not been conducted with zoledronic acid. Zoledronic acid is not systemically metabolized and does not affect human cytochrome P450 enzymes in vitro. Zoledronic acid in plasma protein binding is low (22%); therefore, interactions resulting from displacement of highly protein-bound drugs are unlikely. No DDI were conducted with drugs eliminated by renal excretion.

Dose-Response (Efficacy and Safety) Relationships

The applicant did not attempt to correlate the efficacy and safety markers in patients with Paget's disease to plasma concentrations or exposure. A dose-response was observed in the range of 50- to 400 mcg, with the 50- and 100 mcg doses showing superiority to placebo, but with clinically unimpressive effects on the primary key bone markers serum alkaline phosphatase (SAP) and urinary hydroxyproline/creatinine ratio (UOHP/CR). Since the percentage of patients with normalization in SAP or UOHP/CR levels was low even at the highest dose tested (20% and 43% for SAP and UOHP/CR, respectively), the minimum effective dose could not be defined. The most frequently reported drug-related adverse experiences, by $\geq 10\%$ of patients in any treatment group were fatigue, fever, arthralgia, back pain, and skeletal pain. Fever, back and skeletal pain showed a dose-dependency trend.

The selection of 5 mg of zoledronic acid infused over at least 15 minutes as the proposed dose in the treatment of Paget's disease of bone is not supported by the dose-response studies which evaluated doses of zoledronic acid from 50- to 400 mcg infused over 60-minutes. The effect of zoledronic acid on QT/QTc was not reported.

Reviewer

Sandra Suarez-Sharp, Ph.D. _____
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Final version signed by Hae-Young Ahn Ph.D., Team leader _____

cc

NDA 21-817 : Division File
HFD-870: Malinowski, Hunt
HFD-510: Ahn, Colman, Hedin, Suarez-Sharp

2. QUESTION BASED REVIEW

2.1 General Attributes

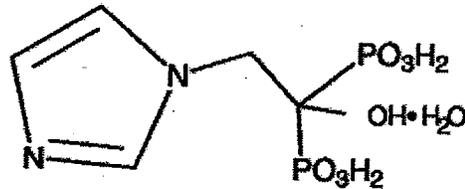
2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

The active component of Aclasta[®] solution for i.v. injection is zoledronic acid, a third generation bisphosphonate. Zoledronic acid in solution is available as zoledronate at physiological pH.

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Chemical name:

The parent compound from which zoledronate is prepared is zoledronic acid monohydrate which is designated chemically as (1-hydroxy-2-imidazol-1-yl-phosphonoethyl) phosphonic acid monohydrate and its structural formula is:



Molecular formula: C₅H₁₀N₂O₇P₂ · H₂O

Molecular weight: 290.1g/Mol

Zoledronic acid monohydrate is highly soluble in 0.1N sodium hydroxide solution, sparingly soluble in water and 0.1N hydrochloric acid, and practically insoluble in organic solvents. The pH of a 0.7% solution of zoledronic acid in water is approximately 2.0.

FORMULATION

Aclasta® 5 mg/100 ml solution for infusion is a clear, colorless aqueous solution packaged in colorless 100 ml plastic vials. Aclasta® injection is available as a sterile solution in bottles for intravenous infusion. One bottle with 100 ml solution contains 5.330 mg of zoledronic acid monohydrate, equivalent to 5 mg zoledronic acid anhydrous basis and the following inactive ingredients: mannitol, _____ and sodium citrate, _____ water for injection (Table 1). Zoledronic acid is marketed for oncology indications and tumor induced hypercalcemia under the brand name Zometa® (zoledronic acid) Injection 4 mg concentrate for intravenous infusion.

Table 1. Composition in mg/100 ml vial

Name of Ingredient	Theoretical amount	Function	Reference to standards
Zoledronic acid monohydrate	5.330 ¹	Drug substance	Novartis
Mannitol		Tonicity agent	Ph. Eur., USP
Sodium citrate		pH adjustment	Ph. Eur., USP
Water for injection		Solvent	Ph. Eur., USP

¹ corresponds to 5.0 mg of zoledronic acid anhydrous

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Mechanism of Action:

Aclasta[®] acts primarily on the bone. It is an inhibitor of osteoclast-mediated bone resorption. The selective action of bisphosphonates on bone is based on their high affinity for mineralized bone. The main molecular target of zoledronic acid in the osteoclast is the enzyme farnesyl pyrophosphate synthase, but this does not exclude other inhibitory mechanisms. In long-term animal studies, zoledronic acid inhibits bone resorption without adversely affecting bone formation, mineralization or mechanical properties of bone.

INDICATION (as per proposed label)

Aclasta[®] solution for intravenous infusion is indicated for the treatment of Paget's disease of bone in men and women. Treatment is indicated in patients with Paget's disease of bone with elevations in serum alkaline phosphatase of two times or higher than the upper limit of the age-specific normal reference range, or those who are symptomatic, or those at risk for complications from their disease.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed route of administration is by intravenous infusion.

DOSAGE AND ADMINISTRATION (as per proposed label)

The recommended dose is 5mg of Aclasta[®] in 100mL aqueous solution administered intravenously via a vented infusion line. The infusion time must not be less than 15 minutes.

2.2 General Clinical Pharmacology

2.2.1 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology and biopharmaceutics study data?

Efficacy and safety were evaluated in two identical phase III international, randomized, double-blind trials of intravenous zoledronic acid for the treatment of Paget's disease of bone using oral risedronate as a comparator. Treatment consisted of a single intravenous infusion of 5 mg zoledronic acid in 100 ml of fluid over 15 min (or placebo infusion) or 30 mg oral risedronate o.d. for 2 months (or placebo capsules). Observation continued for 6 months after baseline measurements were taken.

Serum alkaline phosphatase (SAP) and urinary hydroxyproline/creatinine ratio were the primary efficacy variables. Standard markers of bone turnover were used to assess treatment response. These were SAP and amino-terminal propeptide of type I collagen (PINP) for bone formation and serum C-telopeptide (CTx) and urinary α -CTx for bone resorption.

2.2.2 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

Serum alkaline phosphatase was chosen as the primary efficacy variable, because it is the standard measure of disease activity, it is routinely used to diagnose and monitor Paget's disease, and it formed the basis of the registration claim for risedronate.

The primary efficacy variable was the proportion of patients achieving therapeutic response, defined as either normalization of SAP or $\geq 75\%$ decrease in serum alkaline phosphatase excess (difference between measured level and midpoint to the normal range) at 6 months.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Zoledronic acid was analyzed in plasma and urine using a specific RIA method with an LOQ of --- ng/mL for 25 μL plasma and urine, respectively. Precision, as measured by CV (%), was generally $\leq 20\%$ for both plasma and urine samples. Accuracy was generally within 20% for both plasma and urine samples. No metabolites were formed.

2.2.4 Exposure Response

2.2.4.1 What are the characteristics of the dose-systemic exposure relationships for efficacy?

The efficacy and safety markers in patients with Paget's disease were not correlated to plasma concentrations by the applicant.

The sponsor attempted to establish a dose-response relationship for efficacy using doses of Aclasta (50 to 400 mcg/infused over 60 minutes) which were far below the dose used in the clinical trials in patients with Paget's disease (5mg infused over 15 min). Therefore, the use of the 5 mg dose in the pivotal clinical trials is not fully supported by the dose-response studies.

A dose-response was observed in the range of 50 to 400 mcg, with the 50- and 100 mcg doses showing superiority to placebo, but with clinically unimpressive effects on the key bone markers SAP and UOHP/CR (Figures 1 and 2). Since the percentage of patients with normalization in SAP or UOHP/CR levels was low even at the highest dose tested (20% and 43% for SAP and UOHP/CR, respectively), the minimum effective dose could not be defined (Table 2).

These results came from Study 002, a multicenter double-blind parallel group, randomized, placebo-controlled trial using a single one-hour intravenous infusion of 50, 100, 200, or 400 μg of zoledronic acid administered in 5% dextrose in water. Male and female patients (35 patients per treatment) were 30 years of age or older, with a SAP of at least two times the upper limit of normal, and x-ray confirmation of Paget's disease. The primary criteria for effectiveness was that the maximum percent reduction in SAP and UOHP/C ratio over the entire three month trial be statistically significantly greater for zoledronic acid as compared with placebo. Therapeutic response for SAP or UOHP/C was defined as follows:

- An $\geq 80\%$ reduction in these biomarkers.
- The proportion of patients who normalized their SAP and their UOHP/CR. SAP levels less than or equal to 117 were considered normalized. UOHP/CR levels less than 0.04 were considered normalized.

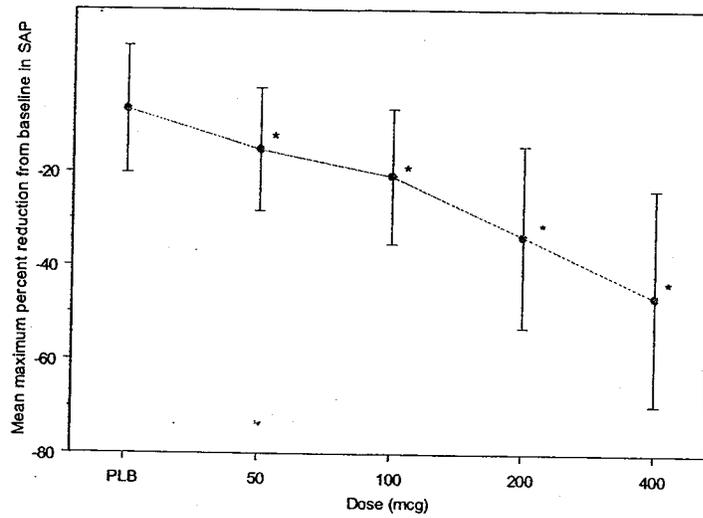


Figure 1. Mean (SD) for maximum percent reduction from baseline in SAP (ITP) following single one-hour intravenous infusion of 50, 100, 200, or 400 μ g of zoledronic acid administered in 5% dextrose in water. N=35 patients per treatment group. * statistically significant at the 0.05 level compared to placebo.

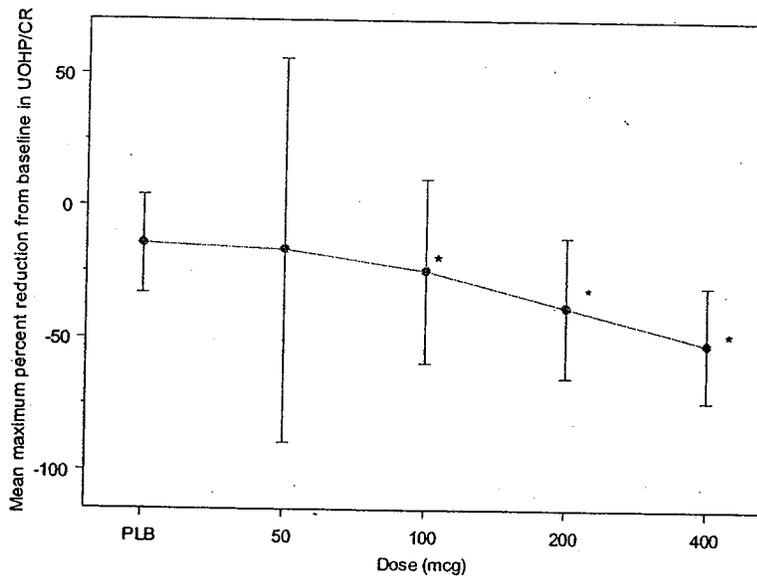


Figure 2. Mean (SD) for maximum percent reduction from baseline in UOHP/CR (ITP) following single one-hour intravenous infusion of 50, 100, 200, or 400 μ g of zoledronic acid administered in 5% dextrose in water. N=35 patients per treatment group. * statistically significant at the 0.05 level compared to placebo.

Table 2. Therapeutic responders for SAP: $\geq 80\%$ decreased or normalization at any time (ITP)

Response	Stratum	50 μg	100 μg	200 μg	400 μg	Placebo
		N (%)	N (%)	N (%)	N (%)	N (%)
$\geq 80\%$ Decrease From Baseline	SAP $\leq 3 \times \text{ULN}$	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	SAP $> 3 \times \text{ULN}$	0 (0)	0 (0)	1 (5)	1 (5)	0 (0)
	All Patients	0 (0)	0 (0)	1 (3)	1 (3)	0 (0)
Normalization	SAP $\leq 3 \times \text{ULN}$	0 (0)	1 (8)	1 (8)	4 (27)	0 (0)
	SAP $> 3 \times \text{ULN}$	0 (0)	0 (0)	1 (5)	3 (15)	0 (0)
	All Patients	0 (0)	1 (3)	2 (6)	7 (20)	0 (0)
$\geq 80\%$ Decrease From Baseline or Normalization	SAP $\leq 3 \times \text{ULN}$	0 (0)	1 (8)	1 (8)	4 (27)	0 (0)
	SAP $> 3 \times \text{ULN}$	0 (0)	0 (0)	1 (5)	4 (20)	0 (0)
	All Patients	0 (0)	1 (3)	2 (6)	8 (23)	0 (0)

2.2.4.2 What are the characteristics of the dose-systemic exposure relationships for safety?

Exposure-response for safety was not attempted by the applicant. In Study 002 (dose-response) the most frequently reported drug-related adverse experiences, by $\geq 10\%$ of patients in any treatment group, were fatigue, fever, arthralgia, back pain, and skeletal pain. This study showed that fever had a trend towards drug dose-dependency. Back and skeletal pain also showed a dose-dependency trend (Figure 3). According to the sponsor, these events and arthralgia are commonly related to Paget's disease and their reporting probably represents an exacerbation of pre-existing symptoms.

A higher incidence of $> 25\%$ decreases from baseline in creatinine clearance was seen in the 200 mcg treatment group, than in the other treatment groups, including 400 mcg and placebo: 9 (28.1%) and 3 (8.6%) in the 200 mcg and placebo treatment groups, respectively (Table 3).

Table 3. Renal safety parameters; patients with $> 25\%$ change from baseline in creatinine clearance by treatment group

	50 μg		100 μg		200 μg		400 μg		PL	
	N	%	N	%	N	%	N	%	N	%
Total Patients	33		35		32		32		35	
$> 25\%$ Incr	6	18.2	7	20.0	1	3.1	7	21.9	6	14.3
$> 25\%$ Decr	3	9.1	4	11.4	9	28.1	4	12.5	3	8.6

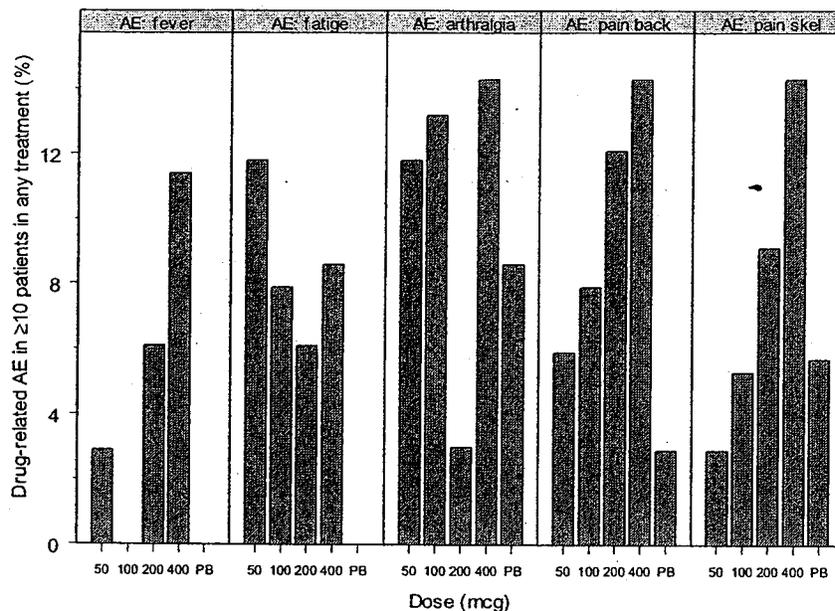


Figure 3. Most frequently reported drug-related adverse experiences in $\geq 10\%$ of patients in any treatment group. N= 35 patients per group. Data from Study 002.

In the previous submitted NDA for Zometa (NDA 21-386), the CPB reviewer analyzed the relationship between exposure and renal side effects of zoledronic acid. The pivotal clinical trials (three trials) that contain renal safety information did not include any Zometa plasma concentration measurements. However, since the population PK analysis of data collected from studies J001, 503 and 506 predicted the plasma concentration very well, the pop PK model and its parameters were used to predict the typical AUC values given the dosing regimen (4- or 8/4 mg infused over 15 min) in the clinical studies. The AUC represented the average overall exposure in these patients.

Time to onset of renal function deterioration was found to be correlated with each of the exposure measures – Cmax, AUC, Zometa dose and treatment. It was hypothesized that cumulative exposure, rather than acute increases in concentration of circulating Zometa might result in a gradual deterioration of the kidney function. A separate analysis of the 3 clinical trials consistently indicated that AUC and baseline creatinine clearance (Base CLcr) were important predictors of renal deterioration. According to the CPB reviewer of NDA 21-386, if the patient is dosed with 4 mg of Zometa, the risk of renal deterioration increases two-fold at the upper limit of severe renal impairment compared to normal Clcr, and three-fold at a Clcr of 10 ml/min.

2.2.4.3 Does this drug prolong the QT or QTc interval?

The effect of zoledronic acid on QT or QTc interval was not reported by the sponsor. The sponsor was requested to provide evidence that 5 mg zoledronic acid intravenously administered over 15 minutes does not cause QT prolongation at NDA filing. The Sponsor believes that, based on the mechanism of action of bisphosphonates, the pre-clinical data available on zoledronic acid (in vitro guinea pig atria, ECG effects in cats, and no observed cardiac effects

in the mouse, rat or dog pre-clinical safety studies), and the lack of a signal in clinical trials with other bisphosphonates and with zoledronic acid to date, the likelihood of observing changes in ECG parameters is low. The sponsor stated that this appraisal is supported by the postmarketing experience on zoledronic acid received by Novartis to date. ECG data is planned to be submitted with the application for the treatment of postmenopausal osteoporosis.

2.2.5 What are the PK characteristics of the drug?

2.2.5.1 What are the single dose PK parameters? What are the characteristics of drug distribution?

How do the PK parameters change with time following chronic dosing?

The pharmacokinetics of zoledronic acid were studied in four separate clinical trials all carried out in cancer patients. In Studies J001, 503, 506 and 1101, single and/or multiple infusions of zoledronic acid in the dose range 2 – 16 mg were administered to a total of 74 cancer patients with bone metastases. Pharmacokinetic parameters were derived using non-compartmental and compartmental methods.

Studies J001, 503 and 506 were submitted to NDA 21-386 and were resubmitted by the sponsor to the present NDA. Study 1101 had a similar design to that for study J001 and it did not contribute any additional PK information to what was already reported in NDA 21-386. *Therefore, the PK characteristics of the drug, including excretion and metabolism, described below and throughout this review were taken from the CPB review by Dr. Brian Booth for NDA 21-386.*

After the i.v. infusion, the time course of zoledronic acid in plasma was characterized by a triphasic disposition pattern, with rapid initial drop in zoledronic acid plasma concentrations during the 24-hour post-infusion period, followed by a prolonged terminal distribution/elimination phase. Average population estimates of volume of distribution and half-lives corresponding to each of the three disposition phases are $V_d = 6.78$ L; $t_{1/2\alpha} = 0.24$ h, $t_{1/2\beta} = 1.87$ h and $t_{1/2\gamma} = 146$ h. Total plasma clearance was about 5 L/h.

Table 4 summarizes the PK of zoledronic acid following single administration of zoledronic acid 4 mg i.v. infusion over 15 minutes.

Table 4. Mean (SD) non-compartmental pharmacokinetic parameters of zoledronic acid following single administration of zoledronic acid 4 mg i.v. infusion over 15 minutes. Data from Study 1101; n= 9-10 patients

PK parameter	Mean	SD
C _{max} (ng/mL)	426	101
T _{max} (hr)	0.362	0.035
T _{1/2} (hrs)	67.8	37.6
AUC (0-24hr) (ng*hr/mL)	576	130
AUC (0-inf) (ng*hr/mL)	882	297
CL (L/hr)	5.29	2.63
Ae(0-24hr)	1304	449
Ae(0-24hr) (% of dose)	32.6	11.2
CL _r	2.33	0.98
CL _r /CL	0.497	0.17

The AUC_{0-24h} following 4 mg of zoledronic acid was approximately the same across all four studies (400 to 600 ng*h/ml).

The PK of zoledronic acid following a 5 mg dose were not characterized. However, this reviewer ran simulations to estimate the AUC and C_{max} of zoledronic acid following single

infusion over 15 min at the dose of 5 mg using WinNonlin. Initial estimates were taken from PK parameters reported in study 1101. The simulated plasma concentration-time profile is shown in Figure 4. The estimated AUC and C_{max} were 650 ng*hr/mL and 519 ng/mL, respectively.

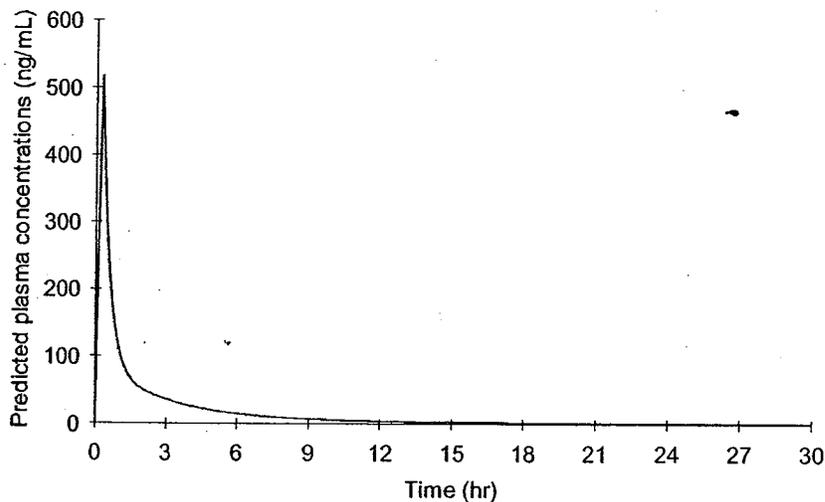


Figure 4. Simulated plasma concentration-time profile of zoledronic acid following single 5 mg dose infused over 15 minutes.

Generally, Aclasta is to be administered as a single dose. However, additional doses may be administered in patients if needed. The accumulation of zoledronic acid following the repetitive 28-day dosing schedule was low and the AUC_(0-24h) for subsequent doses was 1.13-fold higher relative to the first dose. At the 4 mg dose level, changing the infusion time from 5 min to 15 min resulted in an approximately 30% decrease in C_{end}.

Binding of zoledronic acid to plasma proteins is unclear since two different values have been reported (22% and 56% bound). Nevertheless, the interactions resulting from displacement of highly protein-bound drugs are unlikely due to the low binding.

2.2.5.2 Are the PK of zoledronic acid linear and dose-proportional?

A power analysis indicated that doubling the dose lead to a 2.32 fold increase in AUC_{0-24h}, suggesting dose proportionality. The data from study J001 were linearly regressed, and the correlation coefficients were 0.99 and 0.87 for AUC and C_{max} respectively, indicating that the PK of zoledronic acid were linear, apparently over the range of 2 to 16 mg (Figure 5).

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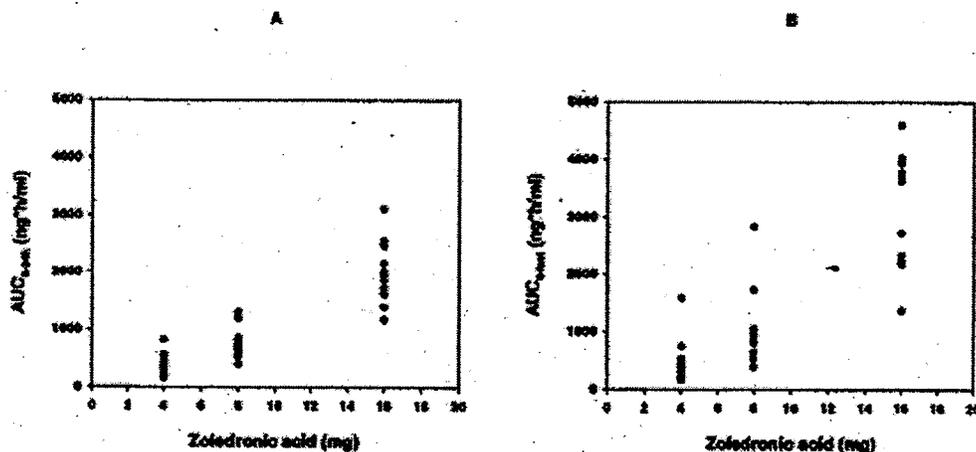


Figure 5. AUC vs. dose from applicant Study 503/503E. A: AUC_{0-24h} vs. dose; B: AUC_{0-last} vs. dose. Data taken from Dr. Brian Booth's review of NDA 21-386.

2.2.5.3 What are the mass balance characteristics of the drug?

The plasma and urine measurements of radioactivity have shown that the majority of radioactivity was recovered within the first 24 hours post-dose and the residual concentrations on days 29 and 85 were largely below the detection limit. The urinary excretion of ¹⁴C-labeled zoledronic acid was 29% of administered dose after 24 hours and 32% after 72 hours postdose. In addition, the distribution study of radiolabeled zoledronic acid between whole blood and plasma indicated no major affinity of ¹⁴C-radioactivity for red blood cells. Fecal recovery of Zometa was not reported.

2.2.5.5 What are the characteristics of drug metabolism and excretion?

Metabolism

No in-vitro metabolism studies using CYP P450 enzymes were reported by the sponsor. In general, it is known that bisphosphonates are not metabolized in humans. According to Dr. Booth's review for NDA 21-386, evidence that zoledronic acid itself is not metabolized in vivo was derived from the study of ¹⁴C-Zometa in Study 506/506E. The plasma and urine samples indicated that only a single ¹⁴C-containing peak was obtained, suggesting that no other metabolites are formed.

According to the sponsor, the urinary analysis of ¹⁴C-labeled zoledronic acid by accelerator mass spectrometry (AMS) demonstrated the presence of only unchanged zoledronic acid, showing the metabolic stability of this drug indicating that zoledronic acid is not metabolized. Similarly, the concordance between the ¹⁴C-labeled and unlabeled zoledronic acid indicated comparable drug levels, suggesting lack of metabolism of zoledronic acid. The plasma and urine measurements of radioactivity have also shown that the majority of radioactivity was captured within the first 24 hours post-dose and the residual concentrations on days 29 and 85 were largely below the detection limit.

Excretion

Zoledronic acid is excreted primarily in the urine as the parent molecule. Urinary excretion was measured in three studies using both labeled and unlabeled compound. Approximately 40% of the dose is recovered in the urine within 24 hours of administration (Table 5, Figure 6).

Complete urinary excretion of zoledronic acid was estimated to reach 48 to 67% in Study J001, which underscores the avid binding of zoledronic acid to bone.

Table 5. Urinary excretion of zoledronic acid (data taken from Dr. Booth's review of NDA 21-386)

Study	Dose/Renal Impairment	Urinary Excretion, 24 hrs (% Dose Administered)
Study 503/503E	4 mg/normal (n=12)	38 ± 13
	8 mg/normal (n=12)	41.3 ± 14.3*
	16 mg/normal (n=12)	37.2 ± 16.5
Study J001	2 mg/normal (n=3)	48.2 ± 12.2*
	4 mg/normal (n=3)	67.2 ± 43.8*
	8 mg/normal (n=3)	60.9 ± 19.6*
Study 506/506E	4 mg/normal (n=9)	36.2 ± 15.1
	4 mg/mild (n=7)	40.4 ± 18.8
	4 mg/moderate (n=3)	27.9 ± 10.2

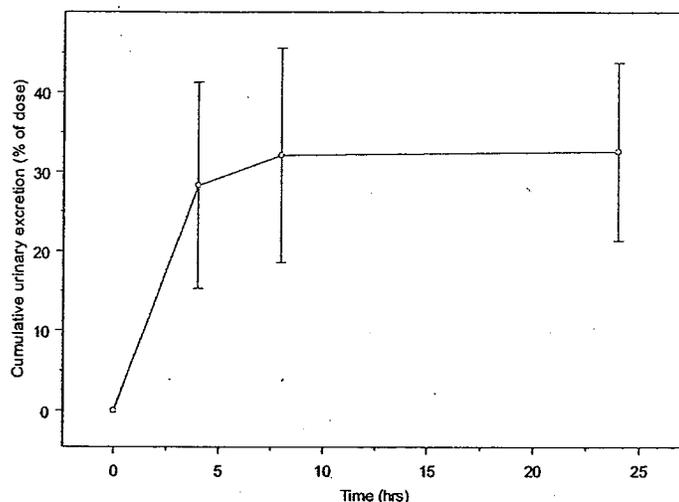


Figure 6. Mean cumulative urinary excretion of zoledronic acid following single administration of zoledronic acid 4 mg i.v. infusion over 15 minutes. Data taken from Study 1101. N=10 patients

2.2.5.4 What is the inter- and intra-subject variability of PK parameters?

A population pharmacokinetic analysis was performed using the pooled data from three clinical pharmacokinetic studies involving a total of 64 patients. The inter-subject variation for plasma clearance was 36% and the intra-subject variation for zoledronic acid concentration was 34%. The CV% (intersubject variability) for the C_{max} and AUC of zoledronic acid was around 25%.

2.3 Intrinsic Factors

2.3.1 Does age, gender or race affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

Based on population PK analysis previously reported and reviewed (see Dr. Booth review for NDA 21-386), race, gender and age did not affect the PK of zoledronic acid (see Figure 7). Therefore, no dose adjustment is necessary in these subgroups. Pharmacokinetic data in pediatric patients are not available. In the phase III clinical trial in patients with Paget's disease of bone the age ranged from 42 to 92 years.

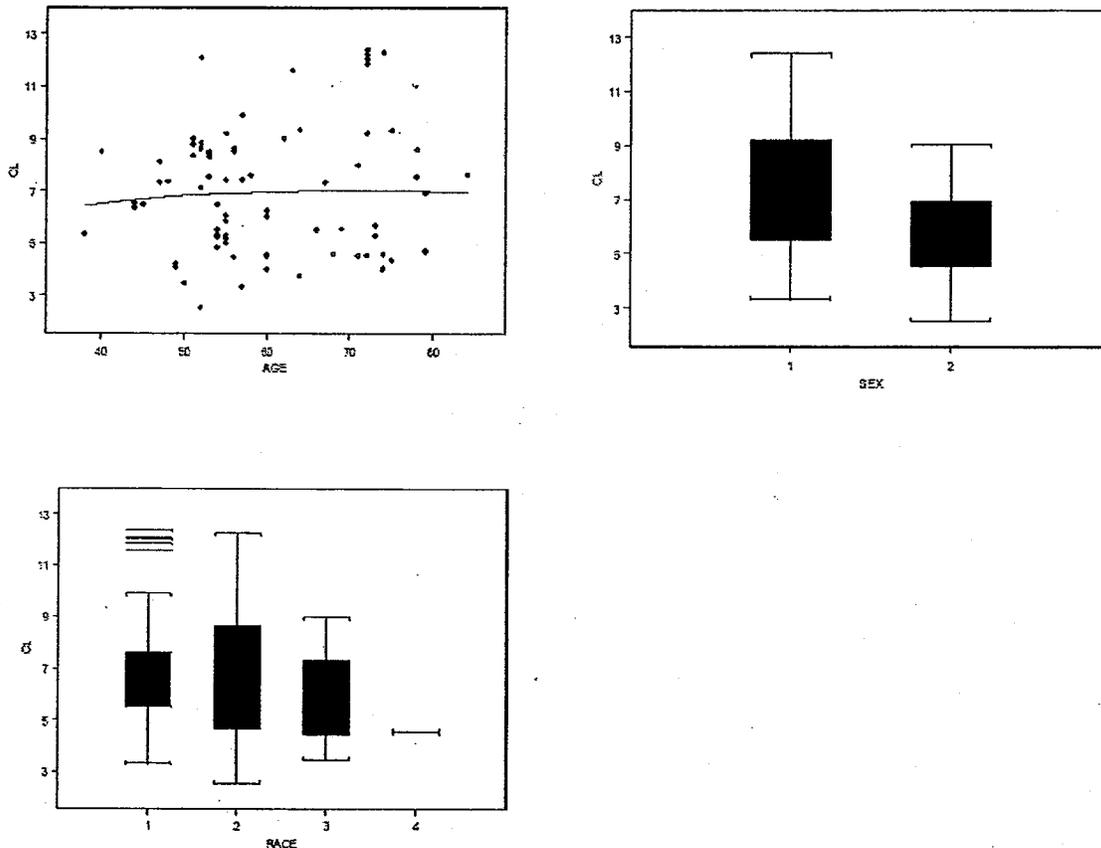
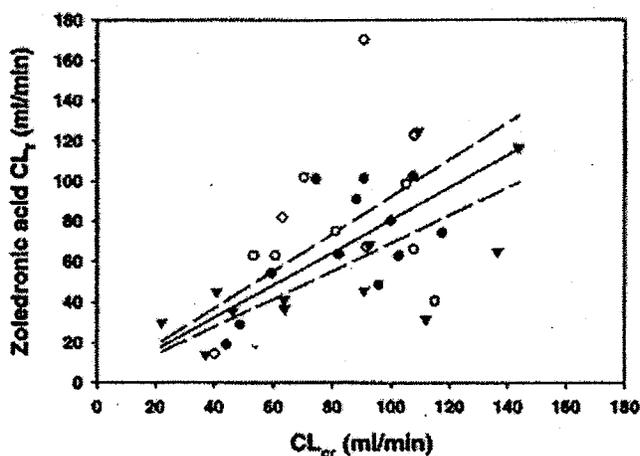


Figure 7. Effect of age, gender and race on zoledronic acid CL from FDA analysis (Taken from Dr. Booth's review for NDA 21-386).

2.3.1.4. Does renal impairment affect the PK of the drug? Is dosage regimen adjustment recommended?

Studies 506/506E and 503/503E were conducted in 64 cancer patients with normal to moderately impaired renal function. These studies showed that zoledronic acid AUC_{0-24h} tends to increase with increasing renal impairment (Figure 8), suggesting that renal impairment would be an important consideration for zoledronic acid dosing.

The applicant plotted the Zometa AUC_{0-24h} vs. creatinine clearance for all cycles of treatment and derived a linear relationship that allows for a prediction of the increase in Zometa AUC_{0-24h} as summarized in Table 5.



Symbols and lines: ● (4 mg), ○ (8 mg), and ▼ (16 mg), — (regression line, $y=0.81x$, $p<0.0001$), --- (95% confidence interval).

Figure 8. Creatinine clearance vs. renal clearance in from Applicant Study 503/503E (Taken from Dr. Booth's review of NDA 21-386).

Compared to patients with normal renal function (N=37), patients with mild renal impairment (N=15) showed an average increase in plasma AUC of 15%, whereas patients with moderate renal impairment (N=11) showed an average increase in plasma AUC of 43% (Table 6). Limited pharmacokinetic data (data available for only one patient) are available for zoledronic acid in patients with severe renal impairment (creatinine clearance <30 mL/min).

Table 6. Effect of renal Impairment on Zometa Exposure (Taken from Dr. Booth's review of NDA 21-386).

Renal Impairment	% increase in Zometa AUC_{0-24h}
Mild	20-40
Moderate	40-50
Severe	50-60

According to the CPB reviewer for NDA 21-386, one could expect zoledronic acid exposures following single 4 mg infusion in severe renal impairment to approximate those of the 8 mg dose. Patients treated with 8 mg of zoledronic acid are at risk for renal deterioration and renal failure. In the database submitted, one patient developed severe renal impairment (CLcr decreased from 46.6 to 9.08 ml/min, cycle 1 to cycle 2, respectively). In this individual, AUC_{0-24h} increased from 2758 ng*h/ml to 4435 ng*h/ml, a 60% increase.

As mentioned in section 2.2.4.2, the FDA population pharmacokinetic modeling and PK/PD correlations showed that the risk of a renal deterioration doubled for a patient with the upper limit of moderate renal impairment (CLcr = 30 ml/min) compared to a patient with normal

creatinine clearance (average 100 ml/min) when 4 mg of zoledronic acid was administered. This risk tripled at a creatinine clearance of 10 ml/min. Therefore, dose reductions in patients with moderate renal impairment should be made, contrary to the applicant's conclusion that no action is required.

The recommended dose (normalized to the zoledronic acid AUC observed in normal renal function) in patients with moderate renal function should be 3 mg infused over no less than 15 minutes.

2.3.1.5 Does liver impairment affect the PK of the drug? Is dosage adjustment recommended?

The effect of hepatic impairment on the PK of zoledronic acid has not been addressed. Since zoledronic acid appears not be metabolized, it is unlikely that hepatic impairment will affect the PK of this drug.

2.3.1.6 What pregnancy and lactation use information is there in the application? There are no studies in pregnant women using zoledronic acid.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

The effects of herbal products, diet, smoking and alcohol use were not evaluated.

2.4.2 Drug-Drug Interactions (DDI)

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Drug-drug interaction studies have not been conducted with zoledronic acid. Zoledronic acid is not systemically metabolized and does not affect human cytochrome P450 enzymes in vitro (see section 2.4.2.4). Zoledronic acid in plasma protein binding is low (22%); therefore, interactions resulting from displacement of highly protein-bound drugs are unlikely.

Zoledronic acid is eliminated by renal excretion. No DDI were conducted with drugs eliminated by renal excretion.

2.4.2.2 Is the drug a substrate of CYP enzymes?

No in-vitro metabolism studies using CYP P450 enzymes were reported by the sponsor.

2.4.2.4 Is the drug an inhibitor and/or an inducer of CYP enzymes?

According to Dr. Booth (see CPB review for NDA 21-386), the sponsor investigated the ability of zoledronic to inhibit CYP 450 isozymes. No significant inhibition occurred following 15-minute incubations of zoledronic acid with any CYP 450 isozyme. Studies also indicated that zoledronic acid did not induce any irreversible CYP450 inhibition.

2.4.2.5 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

This was not evaluated by the sponsor.

2.4.2.6. Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

The label states that since zoledronic acid is eliminated by renal excretion, caution is indicated when Aclasta is administered in conjunction with drugs that can significantly impact renal function (e.g. aminoglycosides, or diuretics leading to dehydration). This interaction potential has not been evaluated in humans.

2.4.2.7 What is the effect of zoledronic acid on the PK of other drugs? What is the effect of other drugs on the PK of zoledronic acid?

No studies have been conducted to evaluate these effects.

2.4.2.8 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

Binding of zoledronic acid to plasma proteins is unclear since two different values have been reported (22% and 56% bound). Nevertheless, the interactions resulting from displacement of highly protein-bound drugs are unlikely due to the low binding.

2.4.2.9 What issues related to dose, dosing regimens or administration are unresolved, and represent significant omissions?

The selection of 5 mg of zoledronic acid infused over at least 15 minutes as the proposed dose in the treatment of Paget's disease of bone is not supported by the dose-response (50- to 400 mcg infused over 60-minutes) study conducted. As mentioned before, time to onset of renal function deterioration was found to be correlated with exposure measures and dose of zoledronic acid. In addition, analysis of the 3 clinical trials in bone cancer patients consistently indicated that AUC and baseline creatinine clearance were important predictors of renal deterioration. Furthermore, post-marketing experience with Zometa, a drug approved for bone cancer indicated that renal deterioration, progression to renal failure and dialysis, have occurred in patients, including those treated with the dose of 4 mg infused over 15 minutes. *Therefore, the safety of a single dose of 5 mg zoledronic acid infused over 15 min should be determined by the medical reviewer based on the renal safety reported in the clinical trials.*

The formulation used in the PK and pivotal clinical trials is different than the to-be marketed formulation. The to-be marketed formulation contains mannitol as an ~~excipient~~. Although, strictly speaking no BE studies are required for an IV formulation, the effect of mannitol on renal excretion and therefore the systemic exposure of zoledronic acid is unknown. The sponsor claims that the presence of mannitol in the formulation (approx. ~~100 mg~~) is not expected to influence the renal excretion of zoledronic acid, as osmotic diuresis does not increase glomerular filtration rate, the main mechanism for renal excretion, and will not be induced by such small amounts of ~~mannitol~~ mannitol (see section 2.5.2 for discussion on this issue).

2.5 General Biopharmaceutics

2.5.1 What is the BCS Class classification for zoledronic acid?

This information was not provided by the sponsor. Also, this information may not be relevant since this is not a solid dosage form.

2.5.2 Was the to-be-marketed formulation used in the PK/clinical trials?

No. The formulation used in the Clinical Pharmacology studies was 4 mg zoledronic acid as a lyophilized powder reconstituted with 5 mL isotonic saline. Appropriate volumes of the reconstituted solution were then diluted to 50 or 100 mL with isotonic saline. The formulation used in the clinical studies of Paget's disease patients was 5 mg zoledronic acid in a solution of 5 mL. The solution was diluted to 100 mL with isotonic saline for i.v. infusion over 15 minutes. The final formulation intended for marketing is 5 mg zoledronic acid in 100 mL of solution, containing mannitol as an _____

According to the sponsor, the use of mannitol as an _____ should have no biopharmaceutical effect. The sponsor stated that the presence of mannitol in the formulation (approx. _____) is not expected to influence the renal excretion of zoledronic acid, as osmotic diuresis does not increase glomerular filtration rate, the main mechanism for renal excretion, and will not be induced by such small amounts of _____ mannitol.

The following comment was conveyed to the sponsor on November 08, 2004 regarding the use of mannitol:

- Please reference the appropriate section(s) of the NDA that contain data to substantiate the above claims, or provide the Division with evidence to substantiate that:
 - An osmotic diuretic does not change glomerular filtration rate
 - The amount of mannitol in the to-be-marketed zoledronic acid injection does not change the glomerular filtration rate.

The sponsor replied that the renal clearance of zoledronic acid is mainly governed by GFR. The diuretic action of mannitol is attributed to an increase in renal medullary blood flow through a prostaglandin-mediated mechanism. This results in a partial washout of the normal medullary hypertonicity, with a consequent decrease in net reabsorption of Na in the thin ascending limb of Henle's loop. Mannitol in high doses (50-200 grams) can promote diuresis through increased sodium excretion and not through significant changes in GFR. Therefore the _____ of mannitol in this presentation is not associated with any significant effect on the renal elimination of zoledronic acid. In addition, the majority of parenteral toxicology studies were performed using mannitol in the formulation with no attributable untoward effects.

Reviewer's Remark

It appears then that mannitol in the amount of _____ in the Aclasta formulation most likely will not affect the pharmacokinetics of zoledronic acid. The 5mg/100ml final formulation of Aclasta is now being used in the ongoing pivotal fracture trial (Study 2301) in post-menopausal osteoporotic women and future clinical studies. A cross study comparison of the PK of zoledronic acid in osteoporotic women vs. that in bone cancer patients may confirm the lack of effect of mannitol on the PK of zoledronic acid.

2.5.3 Are the method and dissolution specifications supported by the data provided by the sponsor?

This does not apply for this drug. No in vitro dissolution studies were necessary, as zoledronic acid is administered i.v. as a solution.

2.5.4 What is the effect of food on the BA of the drug?

As zoledronic acid is administered i.v., the effect of food was not studied.

2.5.5 If different-strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product

This does not apply.

2.6 Analytical Section

2.6.1 Was the suitability of the analytical method supported by the submitted information?

Concentrations of zoledronic acid in the plasma and urine from patients receiving zoledronic acid were determined by a radioimmunoassay (RIA) method. The radioimmunoassay utilizes a polyclonal rabbit anti-zoledronic acid antibody, and a radioactive zoledronic acid derivative, in a competitive format for the direct quantification of zoledronic acid. The antibody adheres to a sheep antirabbit IgG antibody that is chemically precoated to the wells of a commercial microtiter plate. Solutions of ¹²⁵I-labelled zoledronic acid derivative (tracer) and unlabelled zoledronic acid are added. After equilibration of zoledronic acid and tracer with the antibody, unbound reagents are removed by aspiration and washing, and the bound fraction of tracer in the well of the microtiter plate is determined by gamma counting.

The lower and upper limit of quantification of zoledronic acid in plasma were 1 ng/mL and 10 ng/mL, respectively. The lower and upper limit of quantification of zoledronic acid in urine were 1 ng/mL and 10 ng/mL, respectively. Zoledronic acid concentrations > 4 ng/mL in plasma or >100 ng/mL in urine could be determined after dilution with blank (zoledronic acid free) biological fluid.

Precision, as measured by CV (%), was generally $\leq 20\%$ for both plasma and urine samples. Accuracy was generally within 20% for both plasma and urine samples.

Zoledronic acid aqueous stock solution was stable for at least 4 months storage at 4°C. Zoledronic acid in plasma stored frozen was stable for at least two freeze-thaw cycles over a 2-week period. Selectivity was not reported.

Dr. Booth review for NDA 21-386 contains the following comment regarding the analytical method. This comment was conveyed to the sponsor at that time.

- The applicant used Accelerator Mass Spectrometry (AMS) to measure radiolabeled Zometa. This assay was not properly validated. The data generated was deemed acceptable because it was in agreement with data generated by a validated assay. However, for future use, the AMS assay should be validated according to the FDA Guidance for Industry entitled "Bioanalytical Method Validation".

17 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

4. APPENDIX

4.1 Individual Study Reports

" Clinical Pharmacology Study of CGP42446 Injection in Patients with Metastatic Bone Malignancies "

Name of Sponsor: _____
Included Protocols: 1101
Development Phase of Study: I
Study Initiation Date: August 7, 2001
Study Completion Date: March 11, 2002

OBJECTIVE

- To perform a pharmacokinetic (PK) analysis of plasma and urine concentrations of unchanged drug and calculate the pharmacokinetic parameters following administration of a single intravenous 4 mg dose of CGP42446 (Z0L446) over a period of 15 min to patients with metastatic bone malignancies.
- To correlate PK with efficacy and to evaluate safety

SUBJECTS

Ten patients with metastatic bone malignancies

STUDY DESIGN

Using an uncontrolled study design, PK, the correlation between efficacy and PK, and safety were investigated when a single intravenous dose of CGP42446 was administered over a period of 15 min to patients with metastatic bone malignancies. In the study, up to 2 additional administrations (total of 3 including initial administration) were permitted if a decrease in the level of a marker of bone metabolism or improvement in a symptom resulting from bone metastasis was seen. Plasma and urine drug concentrations were measured during the period following the initial dosing.

Investigational product dosage and administration

One 4 mg vial of CGP42446 was dissolved in the 5 mL of water for injection included with the vial, and the solution was mixed with 100 mL of physiologic saline. The resulting solution was then administered intravenously over 15 min (see Appendix I for the actual infusion time for each subject).

PHARMACOKINETIC MEASUREMENTS

Blood collection time points: Before and 5, 15, and 30 min; 1, 2, 4, 6, 8, and 24 hr; and 8, 15, and 29 days after the initial administration.

Cumulative urine time points: Urine was collected immediately before the initial dosing, and cumulative urine was collected for the intervals from the time of dosing to 4 hr after dosing, from 4 to 8 hr after dosing, and from 8 to 24 hr after dosing.

SAFETY MEASUREMENTS

Safety was assessed by monitoring adverse events, laboratory safety tests (CBC, blood chemistries and urinalysis).

EFFICACY MEASUREMENTS

Efficacy was assessed by measurement of bone metabolism markers. The response of calcium regulating hormones to the drug was also assessed.

DATA ANALYSIS

Pharmacokinetic Data Analysis

Non-compartmental and compartmental pharmacokinetic analyses of plasma and urine concentrations of unchanged drug were performed. In the compartmental analysis, a 3-compartment model was used for the analysis of first-order elimination from the central compartment, and the data were fitted to the model using the non-linear least squares method using WinNonlin software.

RESULTS

Analytical Method

Zoledronic acid was determined in plasma and urine using a specific radioimmunoassay. The assay is a competitive radioimmunoassay performed on a special μ microtiterplate. The limits of quantitation were \sim ng/mL in plasma and \sim ng/mL in urine.

In study Validation Results

Table 1. In-study validation information for zoledronic acid

Linearity	Satisfactory: Standard curve range from 0.004 ng/ml to 40 ng/mL in plasma and 1 to 1000 ng/mL in urine
Accuracy	Satisfactory: % Bias less than \sim in plasma and \sim % in urine at the / QC concentration tested
Precision	Satisfactory: %CV less than \sim in plasma and < than \sim in urine at the / QC concentrations tested.
Specificity	Sample chromatograms were not submitted

Pharmacokinetic Results

The mean plasma concentration-time profiles for zoledronic acid following single administration of zoledronic acid 4 mg i.v. infusion over 15 minutes is shown in Figure 1. Figure 2 shows the mean cumulative urinary excretion of zoledronic acid following single administration of zoledronic acid 4 mg i.v. infusion over 15 minutes.

The mean non-compartmental and compartmental pharmacokinetic parameters for zoledronic acid are summarized in Table 2 and 3, respectively.

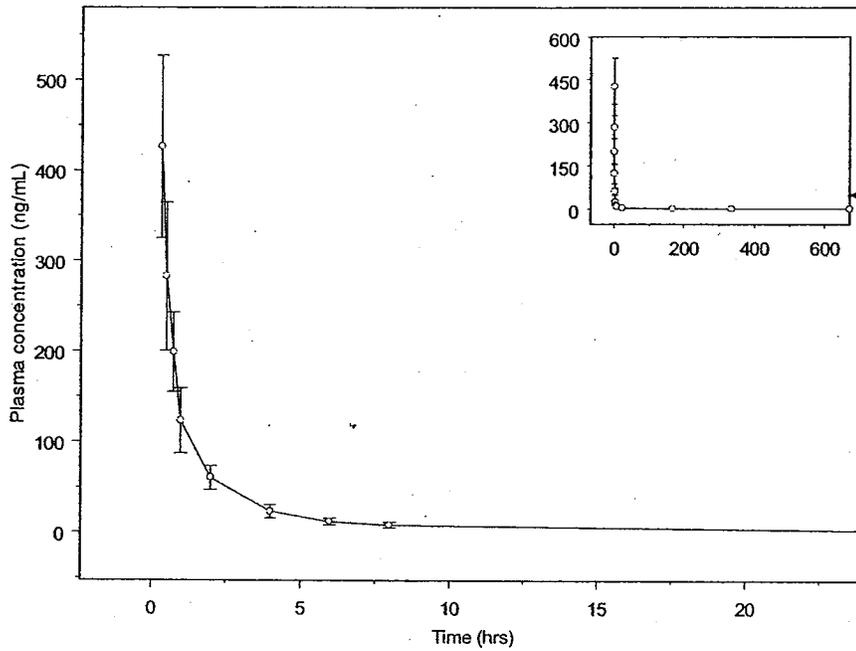


Figure 1. Mean (SD) plasma concentration-time profiles of zoledronic acid following single administration of zoledronic acid 4 mg i.v. infusion over 15 minutes.

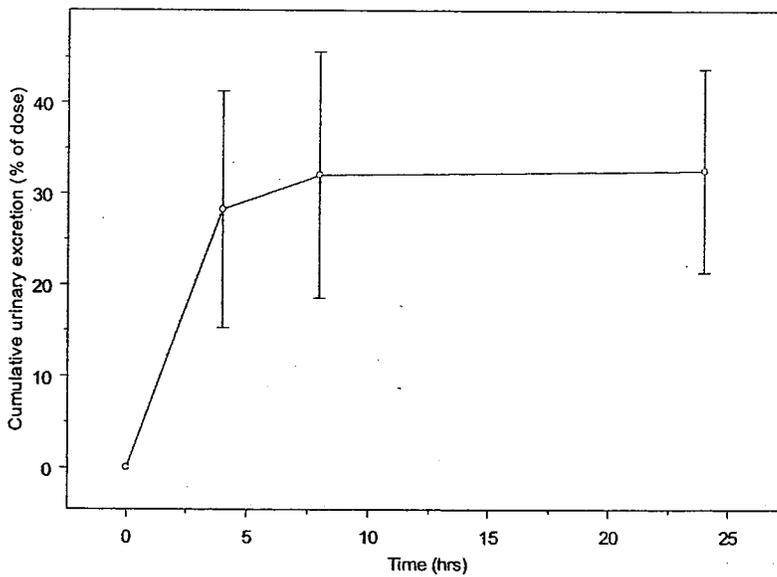


Figure 2. Mean cumulative urinary excretion of zoledronic acid following single administration of zoledronic acid 4 mg i.v. infusion over 15 minutes.

Table 2. Mean (SD) non-compartmental pharmacokinetic parameters of zoledronic acid following single administration of zoledronic acid 4 mg i.v. infusion over 15 minutes.

PK parameter	N	Mean	SD
C _{max} (ng/mL)	10	426	101
T _{max} (hr)	10	0.362	0.035
T _{1/2} (hrs)	10	67.8	37.6
AUC (0-24hr) (ng*hr/mL)	10	576	130
AUC (0-inf) (ng*hr/mL)	10	882	297
CL (L/hr)	10	5.29	2.63
V _{ss} (L)	10	217	97
Ae(0-24hr)	9	1304	449
Ae(0-24hr) (% of dose)	9	32.6	11.2
CL _r	9	2.33	0.98
CL _r /CL	9	0.497	0.17

Table 3. Mean (SD) compartmental pharmacokinetic parameters of zoledronic acid following single administration of zoledronic acid 4 mg i.v. infusion over 15 minutes.

PK parameter	N	Mean	SD
α (h ⁻¹)	10	3.12	3.6
β (h ⁻¹)	10	0.33	0.23
γ (h ⁻¹)	10	0.0167	0.0226
T _{1/2} (hrs)	10	198	255
AUC (0-t) (ng*hr/mL)	10	811	230
AUC (0-inf) (ng*hr/mL)	10	938	289
V _{ss} (L)	10	480	610
Ae _{inf}	10	2179	918
Ae inf (% of dose)	10	54.5	23
CL _r (L/h)	10	2.44	1.06
CL _r /CL	10	0.54	0.229

CONCLUSIONS

- The mean plasma drug concentration decreased to < 1/100 of the value immediate postdosing by 24 hrs and it was followed by more gradual elimination.
- The mean C_{max} was 426±101 ng/mL and the AUC_{0-24h} was 576±130 ng*hr/mL. These values are comparable to previous reported data in Japanese patients receiving the same dose (Study J001; C_{max}=668±251 ng/mL and AUC_{0-24h}=540 ± 232 ng*hr/mL). Although the C_{max} values in Japanese patients appears to be higher compared to than observed in Caucasian patients receiving the same dose (C_{max} 264 ±86 ng/mL from study 503), population PK analysis showed that gender did not altered the PK of the drug.
- The cumulative percentage of drug excreted in the urine by 24 hours postdosing was 32.6% and is in agreement with that reported in previous studies.

"Open-Label, Fixed Ascending, Dose-Ranging Study of Intravenous CGP-42446 in Patients with Paget's Disease of Bone"

Study No.: 001

Trial Phase: I/II

Investigator and Centre:

Study Dates: From 10/6/93 to 3/28/94

Objectives

Primary Objective

- To assess the safety and tolerability of a single infusion of either 24, 72, 216 or 400 mcg of CGP-42446 in patients with Paget's disease of bone

Secondary Objective

- to assess the effect of a single infusion of CGP-42446 in lowering urinary hydroxyproline/creatinine ratio in this patient population

Study Design

This was a two-center, open-label, fixed-ascending dose-ranging safety and tolerability trial using a single 60-minute intravenous infusion of either 24, 72, 216 or 400 µg of zoledronic acid (four patients in each dose group). Patients were male or female (postmenopausal), 30 years of age or older, with a serum alkaline phosphatase of at least two times the upper limit of normal, and an x-ray diagnosis of Paget's disease. Patients were followed for 14 days.

Test Drug

Dosage and Administration

CGP-42446 was available in vials of 100 mcg of lyophilized drug. Initial reconstitution of each vial was done with 5 ml of sterile water. Dilution of the final infusion solution was done accordingly with 5% dextrose. The infusion was given at a constant rate of 1 mL/mm over 60 minutes.

Efficacy Variables

As a secondary objective, efficacy was to be assessed by evaluating the following variables:

Primary Variable

- Urinary hydroxyproline/creatinine ratio (UOHP/C) was measured at all visits (Visits 1-6). The measurement at Visit I (Day 4 to -3) was considered baseline.

Secondary Variable

- Urinary calcium/creatinine ratio (UCaIQ: The urinary calcium/creatinine ratio was measured at all visits (Visits 1-6). The measurement at Visit I (Day -5 to -3) was considered baseline.

- Serum Alkaline Phosphatase: Serum Alkaline Phosphatase (SAP) was measured at all visits (Visit 1-6). The measurement at Visit 1 (Day -5 to -3) was considered baseline.

RESULTS

Groups were well balanced for demographic characteristics at baseline. There were no protocol violations, or discontinuations from the study.

There was no evidence of a dose-dependent effect for SAP (Figure 1), which according to the sponsor this was probably because of the length of the trial being only 14 days. However, at the 216 and 400 mcg dose level, the calcium/creatinine ratio (Figure 2) and hydroxyproline/creatinine ratio (Figure 3) data was suggestive of a dose dependent response with the 400 mcg demonstrating a more dramatic decline than the 216 mcg dose.

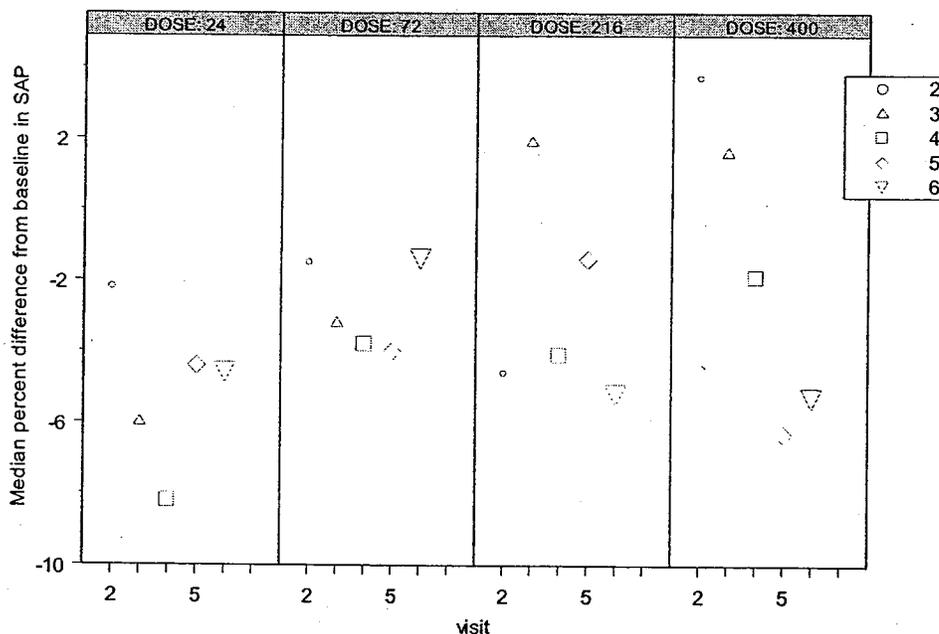


Figure 1. Median percent difference from baseline in serum alkaline phosphatase following single 60-minute infusion of either 24, 72, 216 or 400 mcg of CGP-42446 in patients with Paget's disease of bone (N=4 per treatment).

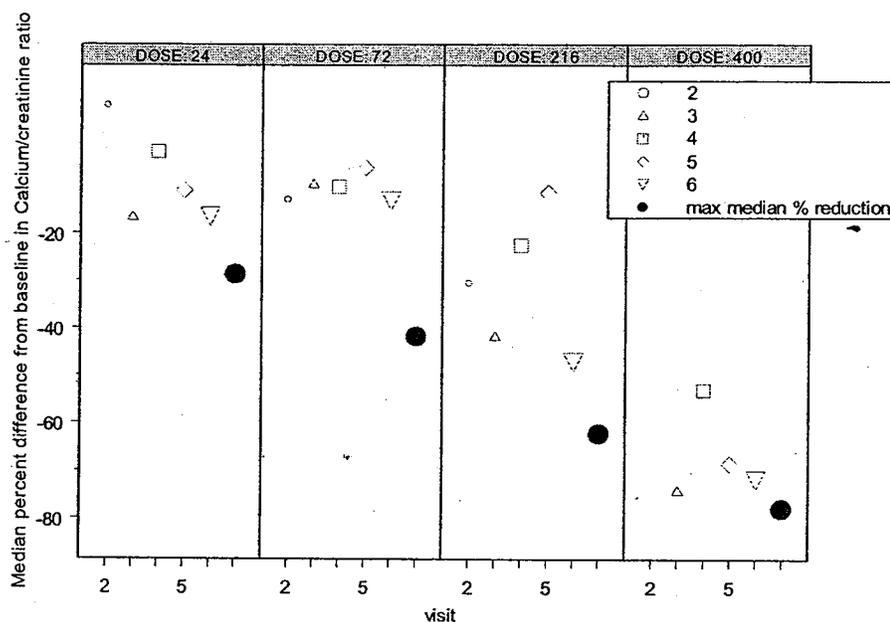


Figure 2. Median percent difference from baseline in Calcium/Creatinine ratio following single 60minute infusion of either 24, 72, 216 or 400 mcg of CGP-42446 in patients with Paget' s disease of bone (N=4 per treatment).

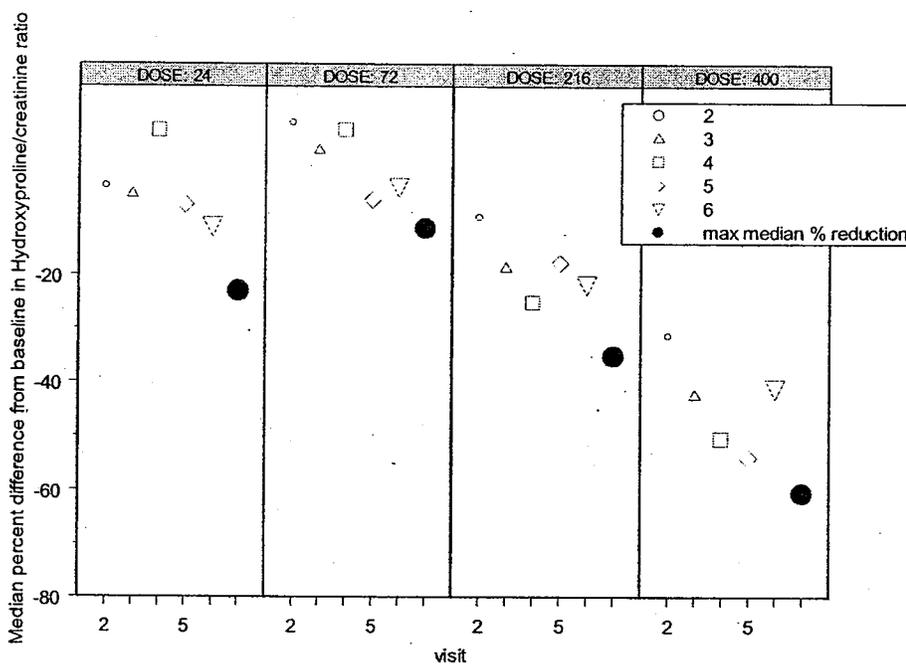


Figure 3. Median percent difference from baseline in Hydroxyproline/Creatinine ratio following single 60minute infusion of either 24, 72, 216 or 400 mcg of CGP-42446 in patients with Paget' s disease of bone (N=4 per treatment).

CONCLUSIONS

- The single 60-minute infusion of zoledronic acid at the doses of 24- and 72 mcg was essentially non-effective (the median percent difference from baseline based on the three endpoint tested was less than -20%).
- A dose-dependent effect for the calcium/creatinine ratio and hydroxyproline/creatinine ratio SAP was observed at the 216 and 400 mcg dose level (the maximum median % reduction range from -60- to -78%). No dose response was observed based on SAP.
- There was a rebound effect for both UOHP/C and UCa/C; these parameters achieved their nadir between 5 and 11 days post-infusion, but then slowly began to rise.
- Although dose-response effect was observed for both UOHP/C and UCa/C at the 216 and 400 mcg dose level, the minimum effective dose should be evaluated by the medical reviewer, since the conclusions made in here are based on only 4 patients.

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"A Double-Blind Placebo-Controlled Parallel, Randomized, Dose-Ranging Trial Using Intravenous Zoledronic Acid in Patients with Paget's Disease of Bone"

Study No.: 002
Trial Phase: II
Investigator and Centre: _____
Study Dates: From 3/21/94 to 4/10/95.

Objectives

Primary Objective

- To assess the effects of 50, 100, 200, or 400 mcg of CGP 42446 administered as an intravenous infusion in comparison to placebo in lowering serum alkaline phosphatase, urinary hydroxyproline/creatinine ratio in patients with Paget's disease of bone.
- To ascertain the maximum and minimum effective dose.

Secondary Objective

- To assess the effects of CGP 42446 in lowering urinary pyridinium/creatinine ratio, u deoxypyridinium/creatinine ratio, and urinary calcium/creatinine ratio.
- To evaluate tolerability and safety.

Study Design and Population

This was an international multicenter double-blind parallel group, randomized, placebo-controlled trial using a single one-hour intravenous infusion of 50, 100, 200, or 400 µg of zoledronic acid administered in 5% dextrose in water. Patients (35 patients per treatment group planned) were male or female of non-child-bearing potential, 30 years of age or older, with a serum alkaline phosphatase of at least two times the upper limit of normal, and x-ray confirmation of Paget's disease. Patients were followed for 3 months.

Test Drug

Dosage and Administration

CGP-42446 was available in vials of 100 mcg of lyophilized drug. Dilution of infusion solution was done accordingly with 5% dextrose. The infusion was given at a constant rate of 1 mL/mm over 60 minutes.

Efficacy Variables

Primary Variable

- Urinary hydroxyproline/creatinine ratio (UOHP/C) was measured at all visits (Visits 1-8). The measurement at Visit I (Day -30 to -2) was considered baseline.
- Serum Alkaline Phosphatase: Serum Alkaline Phosphatase (SAP) was measured at all visits (Visit 1-8). The measurement at Visit I (Day -30 to -2) was considered baseline

The primary analysis endpoint was the comparison of the maximum percent decrease over the entire trial of the drug 50, 100, 200 or 400 mcg versus placebo.

Secondary Variables

- urine calcium/creatinine ratio
- urine pyridinoline/creatinine ratio
- urine deoxypyridinoline/creatinine ratio
- excess serum alkaline phosphatase (defined as the number of units above the upper limit of normal for SAP (i.e., number of units above '117')).
- bone alkaline phosphatase

All secondary efficacy variables were measured at Visits 1-8, and the maximum percent reduction from baseline over the entire trial was also calculated for each variable. The measurement at Visit 1 was considered the baseline.

Criteria for efficacy

The primary criteria for effectiveness was that the maximum percent reduction in SAP and UOHP/C ratio over the entire three month trial be statistically significantly greater for CGP 42446 as compared with placebo. Therapeutic response for SAP or UOHP/C was defined as follows:

- An $\geq 80\%$ reduction in these biomarkers.
- The proportion of patients who normalized their SAP and the proportion of patients who normalized their UOHP/CR. Patients who normalized their SAP (or their UOHP/CR) were considered responders for SAP (or for UOHP/CR) even *if* the prescribed decrease of 80% did not occur. SAP levels less than or equal to 117 were considered normalized. UOHP/CR levels less than 0.04 were considered normalized.
- Additionally, similar comparisons based on a prescribed decrease of at least 50% from baseline in SAP (or UOHP/CR), instead of 80%, were also examined.

RESULTS

Groups were well balanced for demographic and disease characteristics at baseline. There were no protocol violations. Four patients discontinued from the study: two due to death, one due to loss to follow-up, and one due to unsatisfactory therapeutic effect (Table 1).

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Table 1. Distribution of patients by treatment group

Number of Patients	50 µg	100 µg	200 µg	400 µg	Placebo	Total
Randomized	35	38	33	35	35	176
Included in Intent-To-Treat Analysis	35	38	33	35	35	176
Stratum 1 (Baseline SAP ≤ 3 × ULN)	11	12	13	15	13	64
Stratum 2 (Baseline SAP > 3 × ULN)	24	26	20	20	22	112
Discontinued Prematurely	1	1	0	2	0	4
For death	0	1	0	1	0	2
Lost to follow-up	1	0	0	0	0	1
For unsatisfactory therapeutic effect	0	0	0	1	0	1
Included in Laboratory Report	35	38	33	35	35	176
Included in Safety Analyses	34	38	33	35	35	175

Statistically significant differences were seen between each of the zoledronic acid dose groups and placebo for the maximum percent reduction in serum alkaline phosphatase (Figure 1). A dose response relationship was seen (Figure 1, Tables 2-3). Percent reduction from baseline was maximal by Day 60 for SAP (46.6%) which was achieved by the 400 mcg dose (Figure 1). However, the percentage of patients with SAP normalization was low (20%) (Tables 2-3).

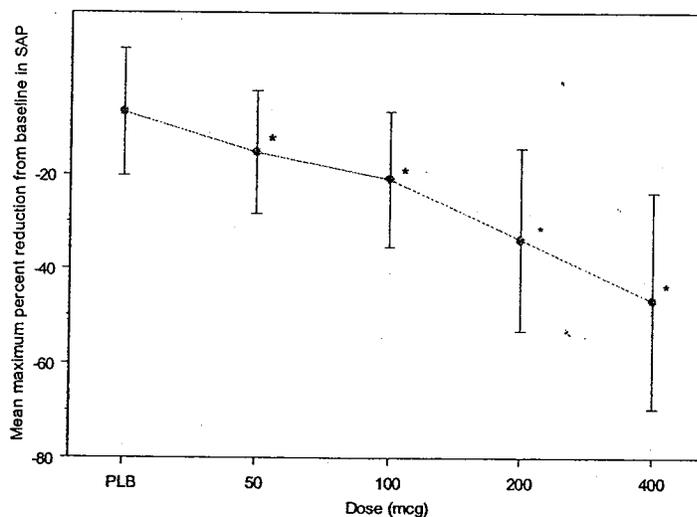


Figure 1. Mean (SD) for maximum percent reduction from baseline in SAP (ITP) following single one-hour intravenous infusion of 50, 100, 200, or 400 µg of zoledronic acid administered in 5% dextrose in water. N=35 patients per treatment group. * statistically significant at the 0.05 level compared to placebo.

The following is a summary of the analysis results at Visits 2-8 for SAP:

- For the pairwise comparisons of each CGP 42446 dose versus placebo, there were statistically significant greater percent decreases from baseline, in favor of the active treatment, at Visits 3-8, after a Bonferroni adjustment to the α -level (with the exception of the non significant difference between the 50 mcg treatment versus placebo at Visit 4 (Day 10) ($p=0.025$)).
- For most of the pairwise comparisons between active doses of CGP 42446, there were

statistically significant greater percent decreases from baseline, in favor of the higher dose, for the given pair of treatments beginning at Visit 5 (Day 30). The 400 mcg treatment group was statistically significantly favored over the 50 mcg and 100 mcg treatment group by Visit 4 (Day 10).

The following is a summary of the results from the between-treatment comparisons of the proportion of therapeutic responders for SAP:

- No statistically significant differences were detected between the treatment groups for the proportion of patients with a $\geq 80\%$ decrease in SAP at any time.
- Statistically significant between-treatment differences, in favor of the 400 mcg treatment group over placebo and the 50 mcg and 100 mcg treatment groups were detected for the proportion of patients with either a $\geq 50\%$ decrease from baseline or normalization at any time during the trial.
- Statistically significant between-treatment differences, in favor of the 400 mcg treatment over placebo, 50-, 100-, and 200 mcg, were detected for the proportion of patients with a $\geq 50\%$ decrease from baseline and the proportion of patients with either a $\geq 50\%$ decrease from baseline or normalization at any time during the trial.

Table 2. Therapeutic responders for SAP: $\geq 80\%$ decreased or normalization at any time (ITP)

Response	Stratum	50 µg	100 µg	200 µg	400 µg	Placebo
		N (%)	N (%)	N (%)	N (%)	N (%)
$\geq 80\%$ Decrease From Baseline	SAP \leq 3xULN	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	SAP > 3xULN	0 (0)	0 (0)	1 (5)	1 (5)	0 (0)
	All Patients	0 (0)	0 (0)	1 (3)	1 (3)	0 (0)
Normalization	SAP \leq 3xULN	0 (0)	1 (8)	1 (8)	4 (27)	0 (0)
	SAP > 3xULN	0 (0)	0 (0)	1 (5)	3 (15)	0 (0)
	All Patients	0 (0)	1 (3)	2 (6)	7 (20)	0 (0)
$\geq 80\%$ Decrease From Baseline or Normalization	SAP \leq 3xULN	0 (0)	1 (8)	1 (8)	4 (27)	0 (0)
	SAP > 3xULN	0 (0)	0 (0)	1 (5)	4 (20)	0 (0)
	All Patients	0 (0)	1 (3)	2 (6)	8 (23)	0 (0)

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Table 3. Therapeutic responders for SAP: \geq 50% decreased or normalization at any time (ITP)

Response	Stratum	50 μ g	100 μ g	200 μ g	400 μ g	Placebo
		N (%)	N (%)	N (%)	N (%)	N (%)
\geq 50% Decrease From Baseline	SAP \leq 3xULN	0 (0)	1 (8)	3 (23)	5 (33)	0 (0)
	SAP > 3xULN	0 (0)	1 (4)	3 (15)	11 (55)	1 (5)
	All Patients	0 (0)	2 (5)	6 (18)	16 (46)	1 (3)
Normalization	SAP \leq 3xULN	0 (0)	1 (8)	1 (8)	4 (27)	0 (0)
	SAP > 3xULN	0 (0)	0 (0)	1 (5)	3 (15)	0 (0)
	All Patients	0 (0)	1 (3)	2 (6)	7 (20)	0 (0)
\geq 50% Decrease From Baseline or Normalization	SAP \leq 3xULN	0 (0)	1 (8)	3 (23)	5 (33)	0 (0)
	SAP > 3xULN	0 (0)	1 (4)	3 (15)	11 (55)	1 (5)
	All Patients	0 (0)	2 (5)	6 (18)	16 (46)	1 (3)

Table 4. Time to response for SAP (Days) (ITP)

Response	50 μ g	100 μ g	200 μ g	400 μ g	Placebo
\geq 80% Decrease From Baseline					
N	0	0	1	1	0
Median	-	-	96	62	-
\geq 80% Decrease From Baseline or Normalization					
N	0	1	2	8	0
Median	-	44	49	62	-
\geq 50% Decrease From Baseline					
N	0	2	6	16	1
Median	-	18	41	47	48
\geq 50% Decrease From Baseline or Normalization					
N	0	2	6	16	1
Median	-	18	41	47	48

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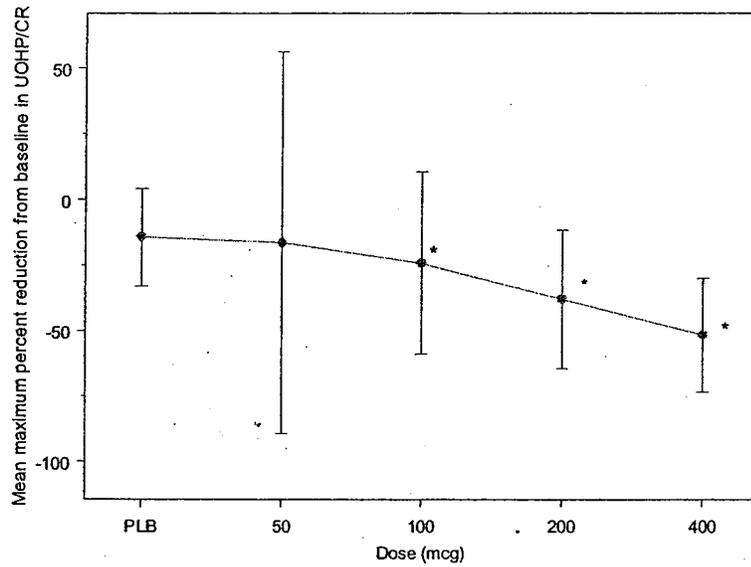


Figure 2. Mean (SD) for maximum percent reduction from baseline in UOHP/CR (ITP) following single one-hour intravenous infusion of 50, 100, 200, or 400 µg of zoledronic acid administered in 5% dextrose in water. N=35 patients per treatment group. * statistically significant at the 0.05 level compared to placebo.

Table 5. Therapeutic responders for UOHP/CR; ≥80% decreased or normalization at any time (ITP)

Response	Stratum	50 µg	100 µg	200 µg	400 µg	Placebo
		N (%)	N (%)	N (%)	N (%)	N (%)
≥ 80% Decrease From Baseline	SAP ≤ 3xULN	0 (0)	0 (0)	0 (0)	1 (7)	0 (0)
	SAP > 3xULN	0 (0)	0 (0)	2 (10)	0 (0)	0 (0)
	All Patients	0 (0)	0 (0)	2 (6)	1 (3)	0 (0)
Normalization	SAP ≤ 3xULN	5 (45)	4 (33)	5 (38)	8 (53)	5 (38)
	SAP > 3xULN	2 (9)	3 (12)	7 (35)	7 (35)	1 (5)
	All Patients	7 (21)	7 (18)	12 (36)	15 (43)	6 (17)
≥ 80% Decrease From Baseline or Normalization	SAP ≤ 3xULN	5 (45)	4 (33)	5 (38)	8 (53)	5 (38)
	SAP > 3xULN	2 (9)	3 (12)	8 (40)	7 (35)	1 (5)
	All Patients	7 (21)	7 (18)	13 (39)	15 (43)	6 (17)

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Table 6. Therapeutic responders for UOJHP/CR: $\geq 50\%$ decreased or normalization at any time (ITP)

Response	Stratum	50 μg	100 μg	200 μg	400 μg	Placebo
		N (%)	N (%)	N (%)	N (%)	N (%)
$\geq 50\%$ Decrease From Baseline	SAP $\leq 3 \times \text{ULN}$	4 (36)	3 (25)	5 (38)	9 (60)	0 (0)
	SAP $> 3 \times \text{ULN}$	2 (9)	5 (19)	3 (15)	11 (55)	1 (5)
	All Patients	6 (18)	8 (21)	8 (24)	20 (57)	1 (3)
Normalization	SAP $\leq 3 \times \text{ULN}$	5 (45)	4 (33)	5 (38)	8 (53)	5 (38)
	SAP $> 3 \times \text{ULN}$	2 (9)	3 (12)	7 (35)	7 (35)	1 (5)
	All Patients	7 (21)	7 (18)	12 (36)	15 (43)	6 (17)
$\geq 50\%$ Decrease From Baseline or Normalization	SAP $\leq 3 \times \text{ULN}$	6 (56)	5 (42)	7 (54)	11 (73)	5 (38)
	SAP $> 3 \times \text{ULN}$	3 (13)	7 (27)	8 (40)	12 (60)	1 (5)
	All Patients	9 (26)	12 (32)	15 (45)	23 (66)	6 (17)

SAFETY RESULTS

Renal Safety

Blood urea nitrogen, serum creatinine and creatinine clearance were examined as renal safety parameters. These parameters were assessed based on comparison of post-dose values against baseline values. Individual patient measurements were examined, and were also assessed based on post-dose values above or below a previously specified value or percent change from baseline.

There were no treatment related abnormalities in any of the safety parameters examined. For the renal safety parameters, the number of patients with post-baseline BUN above the specified value was comparable among all treatment groups, including the placebo treatment group. No patient had post-baseline serum creatinine value above the specified value of 2.0 mg/dL.

Table 7. Blood chemistry safety measurements; patients with post-baseline values above/below specified value in BUN, Calcium, Phosphate, total bilirubin, SGPT and SGPT

	50 μg		100 μg		200 μg		400 μg		PL	
	N	%	N	%	N	%	N	%	N	%
Total patients	35	100	38	100	33	100	35	100	35	100
BUN > 22 mg/dl	7	20.0	8	21.1	14	42.4	12	34.3	12	34.3
Calcium < 8 mg/ml	0	0	0	0	0	0	3	8.6	0	0
Phosphate < 2 mg/dl	0	0	1	2.6	0	0	3	8.6	0	0
Total Billi > 1.5 mg/dl	0	0	0	0	0	0	0	0	2	6.4
SGOT > 80 U/L	0	0	1	2.7	0	0	0	0	0	0
SGPT > 90 U/L	0	0	1	2.7	0	0	0	0	1	3.2

Creatinine clearance values were obtained at baseline (Visit 1) and at Visit 8. The original protocol was amended to include patients with creatinine clearance values below 60 mL/minute,

but with serum creatinine within normal range. Most patients in this population with a median age ≥ 70 years had baseline creatinine clearance values below the lower limit of the normal laboratory range.

The number of patients per treatment group with $> 25\%$ increases or decreases from baseline in creatinine clearance, for all patients with a baseline value and at least one post-baseline value, was examined and is given below (Table 8). The mean percent change from baseline in CrCl at visit 8 as a function of treatment is shown in Figure 3.

Table 8. Renal safety parameters; patients with $>25\%$ change from baseline in creatinine clearance, by treatment group.

	50 μg		100 μg		200 μg		400 μg		PL	
	N	%	N	%	N	%	N	%	N	%
Total Patients	33		35		32		32		35	
$> 25\%$ Incr	6	18.2	7	20.0	1	3.1	7	21.9	5	14.3
$> 25\%$ Decr	3	9.1	4	11.4	9	28.1	4	12.5	3	8.6

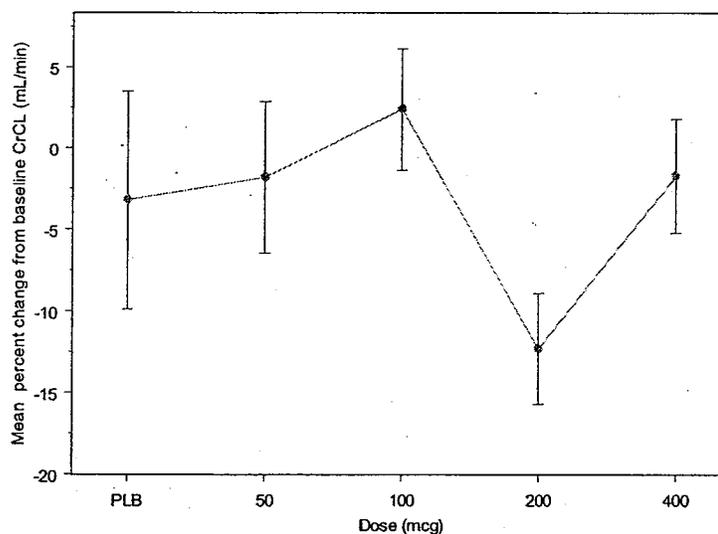


Figure 3. Mean percent change from baseline in CrCl at visit 8 as a function of treatment

SUMMARY OF RESULTS

- The maximum median percent reductions from baseline in SAP were 10.8, 16.8, 32.7 and 46.9 for the 50-, 100 -, 200- and 400 mcg of CGP 42446, respectively, versus a median percent reduction of 6.2 for the placebo group.
- The maximum median percent reductions from baseline in UOHP/CR observed were 27.6, 28.0, 37.0, and 58.0 for the 50-, 100 -, 200- and 400 mcg of CGP 42446 respectively, versus a median percent reduction of 16.7 for the placebo group.
- In all cases, these reductions were significantly greater on active treatment than on

placebo, except for the 50 mcg versus placebo comparison for the UOHP/CR reduction from baseline.

- The largest proportion of patients who reached SAP normalization at any time during the Trial was at the 400 mcg dose with 7 (20%) patients reaching SAP normalization in the 400 mcg dose compared to 2 (5%) and 1 (3%) at the 200 and 100 mcg doses.
- UOHP/CR nadir (maximum reduction) seemed to have occurred by Visit 4 (Day 10), while SAP nadir was seen by Visit 7 (Day 60).
- A higher incidence of > 25% decreases from baseline in creatinine clearance was seen in the 200 mcg treatment group, than in the other treatment groups, including 400 mcg and placebo: 9 (28.1%) and 3 (8.6%) in the 200 mcg and placebo treatment groups, respectively.

CONCLUSIONS

- There seemed to be a dose-response relationship, with the 50- and 100 mcg doses showing superiority to placebo, but clinically unimpressive effects on the key bone markers SAP and UOHP/CR.
- Since the percentage of patients with normalization was low (20% and 43% for SAP and UOHP/CR, respectively), the minimum effective dose cannot be defined

Appears This Way
On Original

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission				
	Information	Brand Name	Information	
NDA	21-817		ACLASTA®	
OCBP Division	2	Generic Name	Zoledronic acid	
Medical Division	DMEDP, HFD-510	Drug Class	Bisphosphonate	
OCBP Reviewer	S.W. Johnny Lau	Indication(s)	Treat Paget's disease of bone	
OCBP Team Leader	Hae-Young Ahn	Dosage Form	Solution for injection	
Date of Submission	21-SEPT-2004	Dosing Regimen	5 mg/100 mL over 15 minutes	
Estimated Due Date of OCPB Review	14-FEB-2005	Route of Administration	Intravenous	
Division Due Date	28-FEB-2005	Sponsor	Novartis Pharmaceuticals Corp.	
PDUFA Due Date	21-MAR-2005	Priority Classification	Priority	
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers -				
single dose:				
multiple dose:				
Cancer Patients -				
single dose:	X	3		Studies J001, 503, & 1101
multiple dose:	X	2		Studies 503 & 1101
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	X	1		Study 506
hepatic impairment:				
Achlorhydria:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	2		Studies 001 & 002 (dose-ranging)
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	X	3		Studies J001, 503, & 506
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				

Relative bioavailability -				
Bioequivalence studies -				
traditional design; multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
iii. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	■	6		Studies 001, 002, J001, 503, 506, & 1101
Fileability and QBR comments				
	"X" if yes	Comments		
Application fileable ?	X			
Comments sent to firm ?	X	<p>Reference the appropriate NDA section(s) that contain the following, or provide the Division with the following:</p> <ul style="list-style-type: none"> • evidence that 5 mg zoledronic acid intravenously administered over 15 minutes does not cause QT prolongation • files (model building, model validation, control file for the final model, and data sets) for the population pharmacokinetic covariate analyses in SAS transport files 		
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

Filing Memo

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

NDA: 21-817
Compound: Zoledronic acid (ACLASTA[®])
Sponsor: Novartis Pharmaceuticals Corporation
Submission Date: September 21, 2004
From: S.W. Johnny Lau, R.Ph., Ph.D.

Background

The sponsor markets 4 mg zoledronic acid/5 mL (dilute to 100 mL and infuse over 15 minutes) to treat hypercalcemia of malignancy, multiple myeloma, and bone metastases of solid tumors. The sponsor is seeking 5 mg zoledronic acid/100 mL's approval to treat Paget's disease of bone in men and women via NDA 21-817.

Findings

To support NDA 21-817, the sponsor conducted the following studies or provided the following information:

- 2 Phase III clinical efficacy and safety studies (2304 and 2305; see Attachment)
- a large (002) and a small (001) dose-ranging studies (see Attachment)
- 3 clinical pharmacology studies' results in cancer patients (J001, 503, and 506 that supported previous submissions). See Attachment for study description.
- a new clinical pharmacology study (1101) in cancer patients for confirmation
- justification for the formulation change and lack of zoledronic acid-mannitol interaction via NDA 21-817-N-000-BC on November 16, 2004. The clinical study's formulation contains _____ g glucose and _____ mg NaCl and the to-be-marketed formulation contains _____ g mannitol _____ (see Attachment).
- population pharmacokinetic covariate analysis from Studies J001, 503, and 506's data
- Study 1101's bioanalytical report for review
- proposed labeling for review

The sponsor did not conduct pharmacokinetic study for the 5 mg zoledronic acid infused over 15 minutes. However, zoledronic acid pharmacokinetics was dose proportional from 2 to 16 mg based on C_{max} and AUC_{24h} (*Clin Cancer Res* 9:2394 (2003)).

The filing meeting was on November 17, 2004.

Attachment starts here.

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

Study No.	Study Objective, Population	No. of Patients	Treatment	Medication i.v. dose / infusion time	Parameters
cancer patients					
J001	Single dose PK and safety of zoledronic acid, effect on bone markers	9	1 dose	2 mg zol / 5 min 4 mg zol / 5 min 8 mg zol / 5 min	C _{max} , AUC, A _{e(0-24h)} bone markers
503 (503E)	Single and multiple dose PK and safety, effects of single dose on bone resorption markers	36 (27)	1 dose (+2 doses, 4 wks apart)	4 mg zol / 5 min 4 mg zol / 15 min 8 mg zol / 15 min 16 mg zol / 15 min	C _{max} , AUC, A _{e(0-24h)} bone markers
506 (506E)	Effects of renal function on single and multiple dose PK and bone resorption markers, ADME study	19 (19)	3 x 1dose, (4 wks apart)	4 mg zol / 15 min	C _{max} , AUC, A _{e(0-24h)} bone markers
1101	Single dose PK, multiple dose safety, effects on bone resorption	10	1 dose (+2 doses, 4 wks apart)	4 mg zol / 15 min	C _{max} , AUC, A _{e(0-24h)} bone markers

The clinically tested formulation was 5 mg zoledronic acid/5 mL solution and the to-be-marketed formulation was 5 mg zoledronic acid/100 mL solution.

Ingredient	ZOL446K 5 mg/5 ml Concentrate for solution for infusion *	ZOL446K 5 mg/100 ml Solution for infusion *	Compendial status
Zoledronic acid	5.0 mg	5.0 mg	Internal monograph
Sodium citrate			Ph. Eur. / USP
Mannitol			Ph. Eur. / USP
Water for injection			Ph. Eur. / USP

* To facilitate the comparison, the composition of ZOL446K 5 mg/5 ml is reported as mg/100 ml after dilution to 100ml with

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sandra Suarez
3/11/05 01:50:56 PM
BIOPHARMACEUTICS

Hae-Young Ahn
3/15/05 03:41:57 PM
BIOPHARMACEUTICS

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-817

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 21-817

SUPPL #

HFD # 510

Trade Name Reclast

Generic Name zoledronic acid

Applicant Name Injection

Approval Date, If Known April 16, 2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1), SE2

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# NDA 21-223

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, ~~the~~ investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies 2304 & 2305

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Studies 2304 & 2305

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 43,240 YES ! NO
! Explain:

Investigation #2
IND # 43,240 YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Randy Hedin
Title: Senior Regulatory Management Officer
Date: April 11, 2007

Name of Office/Division Director signing form: Eric Colman, M.D.
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Eric Colman
4/16/2007 05:48:30 PM
Eric Colman for Mary Parks

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: NDA 21-817 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: September 21, 2004 PDUFA Goal Date: April 16, 2007

HFD 510 Trade and generic names/dosage form: Reclast (zoledronic acid) Injection

Applicant: Novartis Pharmaceuticals, Inc. Therapeutic Class: Bisphosphonate

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next question.
 No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: Treatment of Paget's Disease of Bone

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
 No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
 No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
 Disease/condition does not exist in children
 Too few children with disease to study
 There are safety concerns+
 Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

NDA 21-817

Page 3

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH
STAFF at 301-796-0700**

(Revised: 10/10/2006)