CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-817

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-817
Drug Name:	Zometa (zoledronic acid) injection
Indication(s):	Paget's disease of bone
Applicant:	Novartis
Date(s):	Submitted 9/21/04 6-month goal date 3/21/05
Review Priority:	Priority
Biometrics Division:	HFD-715
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Keywords: NDA review, clinical studies

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

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

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

Table 1. Therapeutic response (6 months)

	Aclastia	Risedronate	Trt difference (95% CI, p-value)[1]
Trial 2304			
No. (%) patients with therapeutic response	85/88 97%	60/82 73%	24% (12%, 35%) p<.0001
Trial 2305			
No. (%) patients with therapeutic response	84/88 95%	67/89 75%	20% (9%, 31%) p=.0002
Pooled studies			
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.

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

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 ≥ 2 x 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 effectiveness [1]. 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:

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[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 zolendronic 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 then -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) % change in SAP = 100 x (T - B) / B

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

(2) % change in SAP excess = 100 x ((T - M) - (B - M)) / (B – M)
= 100 x (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(endpoint/baseline) = treatment country log(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:

Change = baseline treatment time treatment*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%)

Previous Paget's treatment			
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
Sex			
Male	62 (67%)	57 (61%)	119 (64%)
Female	30 (33%)	36 (39%)	66 (36%)
Race			
Caucasian	84 (91%)	84 (90%)	168 (91%)
Black	3 (3%)	3 (3%)	6 (3%)
Other	5 (5%)	6 (6%)	11 (6%)
Mean age (SD)	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%)
Baseline disease severity			
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%)
Previous Paget's treatment			
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]
Trial 2304 No. (%) patients with therapeutic response	85/88 97%	60/82 73%	24% (12%, 35%) p<.0001
Trial 2305 No. (%) patients with therapeutic response	84/88 95%	67/89 75%	20% (9%, 31%) p=.0002
Pooled studies 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) $$\% \text{ change in SAP} = 100 \times (T - B) / B$$

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

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

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

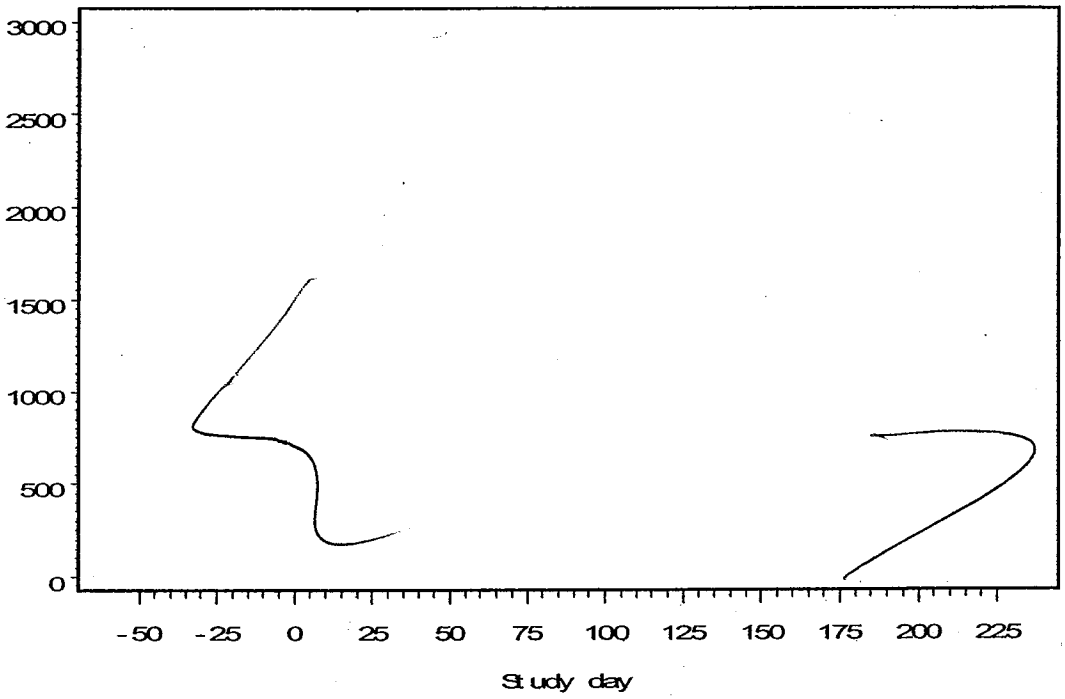

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Figure 2

Study 2304

SAP levels for risedronate patients

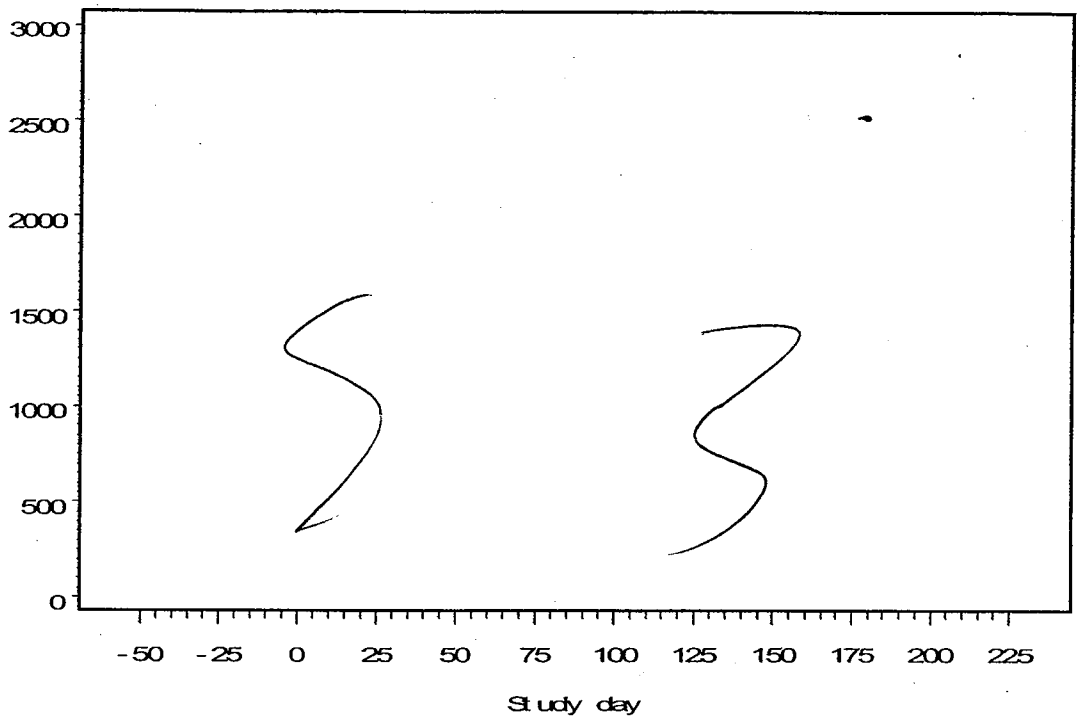

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Figure 3

Study 2305

SAP levels for Zometa patients

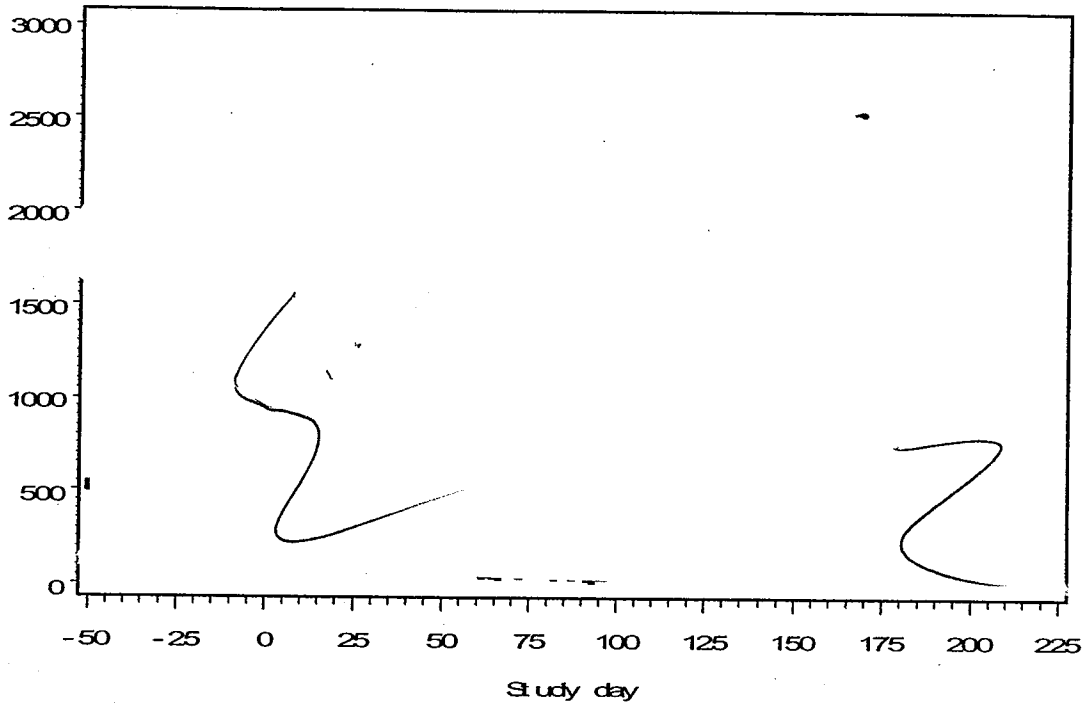
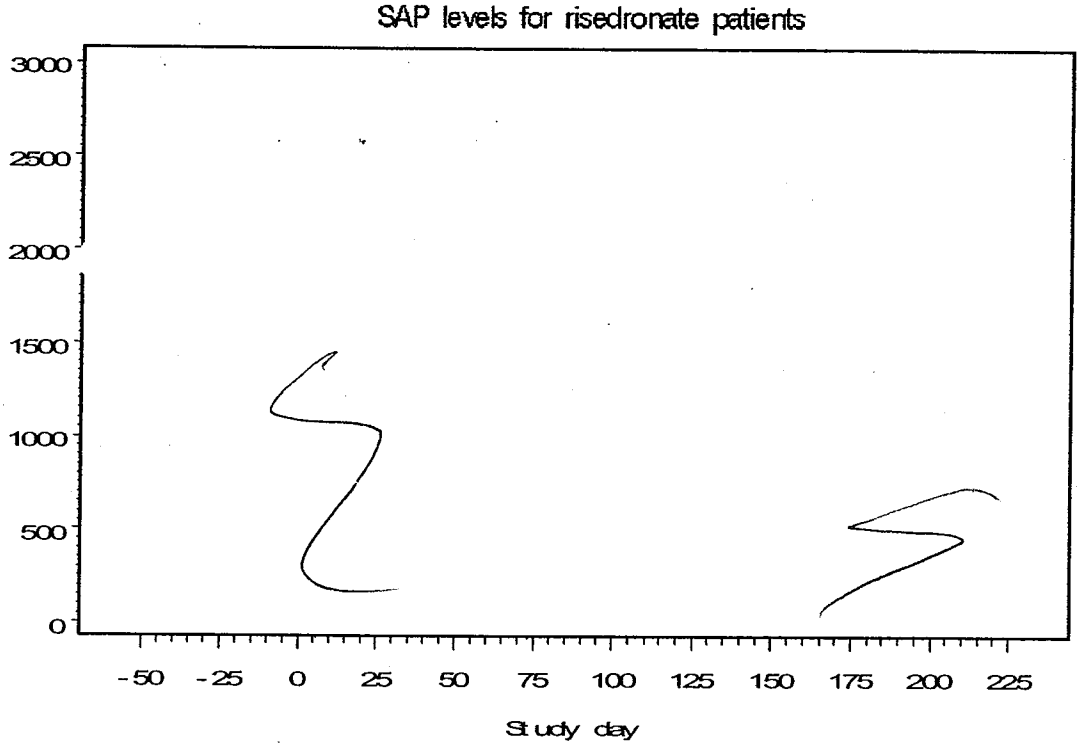


Figure 4

Study 2305



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

Figure 5
Study 2304
median SAP levels for completers

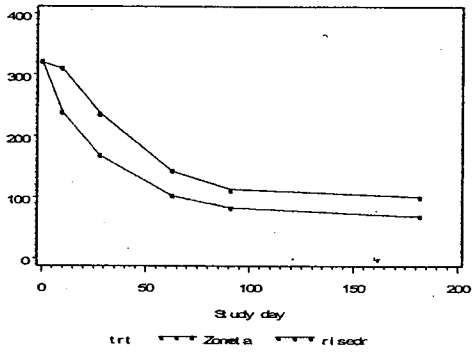
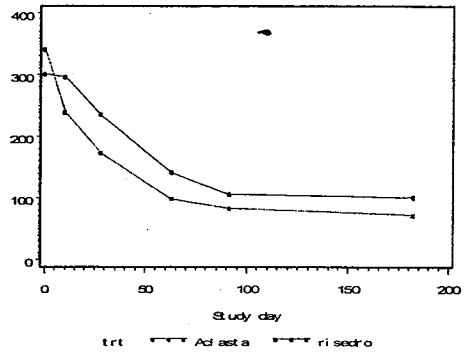


Figure 6
Study 2305
median SAP levels for completers



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)
Trial 2304			
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
Trial 2305			
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
Pooled studies			
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)
Trial 2304			
Day 10	17/81 (21%)	0/77	NA
Day 63	1/84 (1%)	0/79	NA
Day 182	1/83 (1%)	0/74	NA
Trial 2305			
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
Pooled studies			
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

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
Baseline disease severity			
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%
Previous Paget's treatment			
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%
Symptomatic pain at screening			
No	60/60 (100%)	54/66 (82%)	18%
Yes	109/116 (94%)	73/105 (70%)	24%

Previous oral bishosphonate 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 bishosphonate 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	¾ (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
# days to response		
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
Mean % change in SAP excess		
Day 10	-36	-10
Day 28	-62	-33
Day 63	-90	-68
Day 91	-96	-80
Day 182	-101	-82
Mean % change in SAP		
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 sponsors 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	
CTX			
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)
Urine CTX			
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.

Appears This Way
On Original

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

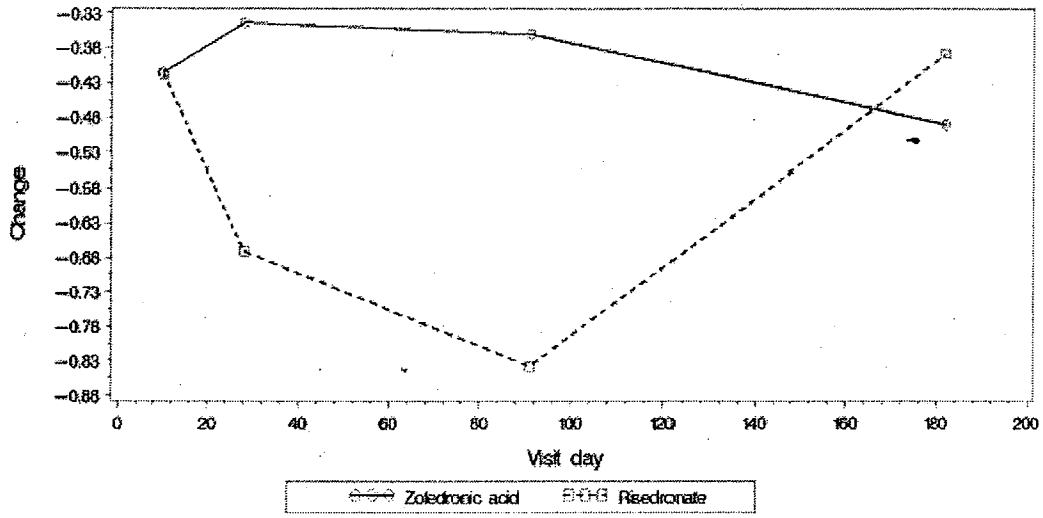
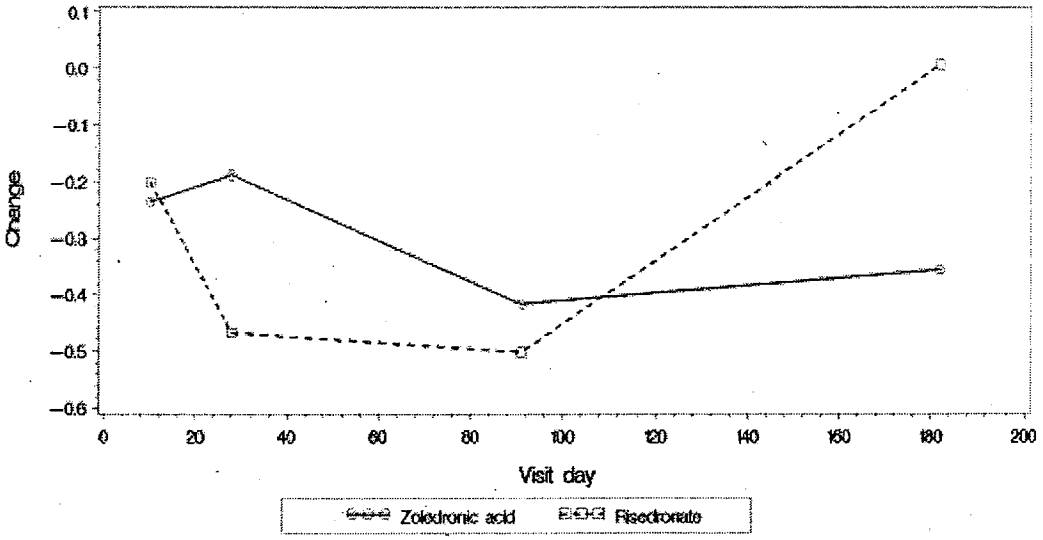


Figure 3-6 Change in BPI-SF pain interference score by visit – combined active-controlled studies (MITT population)



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.

sentence reforming to the modians should be [illegible]

This is a representation of an electronic record that was signed electronically and 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.