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STATISTICAL REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIostatISTICS

STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

NDA/Serial Number: 22-080/N-000
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Applicant: Novartis Pharmaceuticals Corporation
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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Data from the ZOL446H2301 pivotal fracture trial have demonstrated that Reclast[®] (zoledronic acid) 5 mg once yearly injection was effective in lowering the proportion of patients with new morphometric vertebral fractures and in delaying the time to first hip fracture over 3 years when compared with placebo. Significant effects were also seen at Years 1 and 2 for the new morphometric vertebral fracture parameter, but not for the hip fracture parameter. Reclast[®] also exhibited greater reductions than placebo in both parameters at 3 years regardless of age (< 70, 70 – 74, ≥ 75 years), race (Caucasian, Hispanic, and other Asian and Pacific Islander), geographic region (North America/Oceania, Latin America, Western Europe, Eastern Europe, and Asia), femoral neck bone mineral density (BMD) T-score at baseline (≤ -2.5 and > -2.5), body mass index (BMI) at baseline (< 19, 19 – 25, > 25 kg/m²), and number of prevalent vertebral fractures at baseline (0, 1, ≥ 2). However, the effect in hip was not seen for subjects who were previously treated with bisphosphonates.

Data from the ZOL446H2301 trial also showed that Reclast[®] was effective in improving BMDs of total hip, femoral neck, and lumbar spine and biochemical bone markers of C-telopeptides (b-CTx), bone specific alkaline phosphatase (BSAP), and N-terminal propeptide of type I collagen (PINP) after 36 months of treatment when compared with placebo. Although mean reductions in height were seen in both treatment groups at 3 years, the decrease was significantly less in the zoledronic acid group than in the placebo group. In addition, treatment with Reclast[®] resulted in significantly fewer days with limited activity and/or bed rest due to back pain when compared with placebo.

Labeling Comments: The 2 primary _____ all showed superiority of zoledronic acid over placebo in the closed testing procedure at $p < 0.05$. In fact, except for disability due to back pain parameter (a subjective measure), the statistical results for those _____ were all highly significant ($p < 0.001$), effectively ruling out chance as an explanation for the observed treatment differences. Therefore, whether to include those _____ in the labeling would be up to the medical reviewer's discretion.

1.2 Brief Overview of Clinical Studies

Novartis Pharmaceuticals Corporation has submitted an original New Drug Application for 5 mg zoledronic acid injection (solution for intravenous infusion) for treatment of postmenopausal osteoporosis under the trade name of Reclast[®]. According to the sponsor, zoledronic acid is approved for several oncology related indications such as tumor-induced hypercalcemia, treatment of multiple myeloma, and bone metastases from solid tumors under

the trade name of Zometa[®] in at least 96 countries. In addition, zoledronic acid is also approved for Paget's disease of bone, a non-oncology indication, under the trade name of Aclasta[®] in at least 50 countries.

This submission contains a large clinical fracture trial (Protocol CZOL446H2301) that was still ongoing at the time of submission. Protocol CZOL446H2301 was a Phase III, 36-month, randomized, double-blind, 2-parallel-group, placebo-controlled, multi-center, international trial, conducted in 7736 postmenopausal women between 64 and 89 years old with osteoporosis documented by either (1) a femoral neck BMD T-score ≤ -2.5 with or without evidence of an existing vertebral fracture or (2) a femoral neck BMD T-score ≤ -1.5 and radiological evidence of at least 2 mild or 1 moderate existing vertebral fracture(s). Caucasian (79%), other Asian and Pacific Islander (14%), and Hispanic (6%) constituted the majority of the population. Approximately 63% had at least 1 prevalent vertebral fracture, 85% were naïve to bisphosphonate use, and 72% had a baseline femoral neck T-score ≤ -2.5 .

The first patient enrolled in the study on 01/22/2002 and the last patient completed the study on 06/01/2006. However, the results presented in this submission were based on the data collected up to 03/31/2006, at which point all patients had completed 2 years of treatment and received the 3rd annual dose. Specifically, by 03/31/2006, 66.1% of the 7736 ITT subjects completed the study, 14.7% were discontinued, and 19.2% were still ongoing. This registration strategy was agreed to by the Agency and other health authorities. Therefore, although the submitted efficacy analysis was, technically speaking, an interim analysis, it was considered **final** and used for the labeling claims.

There were 2 primary efficacy variables for the study: (1) proportion of patients with at least 1 new vertebral fracture over 36 months in Stratum I and (2) time to first hip fracture over time in all patients (Stratum I + II). Stratum I consisted of women assigned to zoledronic acid or placebo for whom usual care involves taking calcium and vitamin D only but no additional concomitant osteoporosis medications. Stratum II consisted of women assigned to zoledronic acid or placebo for whom usual care involves taking calcium and vitamin D plus additional osteoporosis therapies, either starting or continuing at randomization. Among the 7736 ITT subjects, 79% of them were in Stratum I and 21% in Stratum II.

—They were evaluated at $p < 0.05$ each in a closed testing procedure to preserve the overall Type I error rate.

1.3 Statistical Issues and Findings

In general, this reviewer did not find any serious statistical issues. Since there was only one, but fairly large, pivotal clinical trial in this submission, the collective evidence is summarized based on the results from the primary and secondary efficacy variables. To facilitate the report writing, 'Year 3' or similar texts are used interchangeably to represent the data collected up to 03/31/2006.

After Year 3, the proportion of zoledronic acid-treated patients with at least 1 new morphometric vertebral fracture or hip fracture was significantly lower than that of placebo-treated patients (Text Table 1). In addition, the time to first hip fracture over a 3-year period was significantly longer in the zoledronic acid group than in the placebo group ($p = 0.0032$). The risk of having at least 1 new morphometric vertebral fracture or hip fracture over 3 years was 70% or 40% less, respectively, in the zoledronic acid group relative to the placebo group.

On 07/03/2007 when this review report was first finished, the EDR received final efficacy data sets from the sponsor, which contained 3-year data for all patients (including the data collected after 03/31/2006). This reviewer re-analyzed the 2 primary variables using the most up-to-date data sets and found similar significant findings (Text Table 1).

Text Table 1 – Summary Results for the Primary Efficacy Variables

Year 3	Zoledronic acid	Placebo	p-value	Relative Risk / Hazard Ratio	95% CI
Using Data Sets Submitted on 10/16/2006 (with 03/31/2006 data cut-off date)					
New vertebral fracture (Stratum I)	87 / 2260 (3.8%)	300 / 2352 (12.8%)	<0.0001	0.30	(0.24, 0.38)
Time to first hip fracture (Stratum I + II)	52 / 3875 (1.3%) Kaplan-Meier = 1.5%	87 / 3861 (2.3%) Kaplan-Meier = 2.5%	0.0032	0.60	(0.43, 0.85)
Using Data Sets Submitted on 07/03/2007 (including data collected after 03/31/2006)					
New vertebral fracture (Stratum I)	92 / 2822 (3.3%)	310 / 2853 (10.9%)	<0.0001	0.30	(0.24, 0.38)
Time to first hip fracture (Stratum I + II)	52 / 3875 (1.3%) Kaplan-Meier = 1.4%	88 / 3861 (2.3%) Kaplan-Meier = 2.5%	0.0024	0.59	(0.42, 0.83)

Note that the risk of developing a hip fracture after 1 or 2 years could be actually higher in the zoledronic acid group than in the placebo group, as suggested by the 95% upper confidence limit of hazard ratio (Text Table 2).

Text Table 2 -- Results for Time to First Hip Fracture at Year 1 and Year 2

	Zoledronic acid	Placebo	p-value	Hazard Ratio	95% CI
Year 1	23 / 3875 (0.6%) Kaplan-Meier = 0.6%	33 / 3861 (0.9%) Kaplan-Meier = 0.9%	0.1828	0.70	(0.41, 1.19)
Year 2	39 / 3875 (1.0%) Kaplan-Meier = 1.1%	56 / 3861 (1.5%) Kaplan-Meier = 1.5%	0.0834	0.70	(0.46, 1.05)

The zoledronic acid group also showed smaller incidence rates after 3 years in new/worsening vertebral fractures, new vertebral fractures with moderate/severe grade, new vertebral fractures in patients ≥ 75 years old, new vertebral fractures in patients with 0 baseline vertebral fracture, new vertebral fractures in patients with 1 baseline vertebral fracture, new vertebral fractures in patients with ≥ 2 baseline vertebral fractures, clinical vertebral fracture, non-vertebral fracture, and clinical fracture when compared to the placebo group. The risks of having these events over 3 years were all significantly lower for the zoledronic acid-treated patients than the placebo-treated patients (Text Table 3).

Text Table 3 -- Summary Results for Key Secondary Variables

Variable No. and Name		Zoledronic acid	Placebo	p-value	RR / HR	95% CI
1	New vertebral fracture at Year 1	42 / 2814 (1.5%)	106 / 2847 (3.7%)	<0.0001	0.40	(0.28, 0.57)
3	New and/or worsening vertebral fracture at Year 3	102 / 2260 (4.5%)	323 / 2352 (13.7%)	<0.0001	0.33	(0.27, 0.41)
15	New vertebral fracture with moderate/severe grade at Year 3	74 / 2260 (3.3%)	257 / 2352 (10.9%)	<0.0001	0.30	(0.23, 0.39)
16	New vertebral fracture for age ≥ 75 years at Year 3	48 / 880 (5.5%)	122 / 880 (13.9%)	<0.0001	0.39	(0.29, 0.54)
17	New vertebral fracture with 0 prevalent vertebral fracture at Year 3	19 / 815 (2.3%)	58 / 825 (7.0%)	<0.0001	0.33	(0.20, 0.55)
18	New vertebral fracture with 1 prevalent vertebral fracture at Year 3	19 / 653 (2.9%)	58 / 659 (8.8%)	<0.0001	0.33	(0.20, 0.55)
19	New vertebral fracture with ≥ 2 prevalent vertebral fractures at Year 3	49 / 792 (6.2%)	184 / 868 (21.2%)	<0.0001	0.29	(0.22, 0.39)
4	Time to first clinical vertebral fracture ¹ at Year 3	20 / 3875 (0.5%) KM = 0.6%	81 / 3861 (2.1%) KM = 2.6%	<0.0001	0.25	(0.15, 0.40)
10	Time to first non-vertebral fracture ² at Year 3	289 / 3875 (7.5%) KM = 9.5%	384 / 3861 (9.9%) KM = 10.7%	0.0002	0.75	(0.64, 0.87)

11	Time to clinical fracture ² at Year 3	306 / 3875 (7.9%) KM = 10.0%	451 / 3861 (11.7%) KM = 12.9%	<0.0001	0.67	(0.58, 0.78)
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¹ Including thoracic spine and lumbar spine fractures

² Excluding finger, toe, and facial bone fractures

RR = Relative Risk; HR = Hazard Ratio; KM = Kaplan-Meier

As shown in Text Table 4, after 3 years of treatment, the mean % changes from baseline in the cases of total hip BMD, femoral neck BMD, lumbar spine BMD, b-CTx, BSAP, PINP, and height were all significantly better in the zoledronic acid group than in the placebo group. In addition, for the zoledronic acid-treated patients, there were significantly fewer days with limited activity or bed rest due to back pain when compared with placebo-treated patients (the key secondary efficacy variable No. 20, p = 0.0028 and 0.0111, respectively).

Text Table 4 – Summary Results for Key Secondary Variables (Continued)

Variable No., Name, and Month			LS Mean % Change from Baseline ± SE (N)		Treatment Difference	p-value	95% CI
			Zoledronic acid	Placebo			
5	Total Hip	36	4.1 ± 0.1 (2350)	-1.9 ± 0.1 (2408)	6.0	<0.0001	(5.7, 6.3)
6	Femoral Neck	36	3.9 ± 0.1 (2356)	-1.1 ± 0.1 (2414)	5.0	<0.0001	(4.7, 5.3)
7	Total Hip	6	2.2 ± 0.1 (3516)	0.3 ± 0.1 (3544)	1.9	<0.0001	(1.8, 2.1)
8	Femoral Neck	6	2.2 ± 0.1 (3523)	0.6 ± 0.1 (3550)	1.6	<0.0001	(1.4, 1.8)
9	Lumbar Spine	36	6.8 ± 0.5 (181)	-0.1 ± 0.5 (170)	6.9	<0.0001	(5.7, 8.0)
12	Serum b-CTx	36	-26.7 ± 9.7 (111) Median = -47.3	47.0 ± 10.0 (115) Median = 23.0	-73.7	<0.0001	(-93.7, -53.6)
13	Serum BSAP	36	-16.2 ± 7.2 (113) Median = -30.2	9.0 ± 7.4 (119) Median = 3.4	-25.2	0.0009	(-40.0, -10.5)
14	Serum PINP	36	-21.2 ± 9.5 (192) Median = -48.1	35.2 ± 9.4 (215) Median = 1.5	-56.4	<0.0001	(-76.7, -36.1)
2.	Height (mm)	36	-4.2 ± 0.4 (1287)	-6.7 ± 0.4 (1290)	2.5	<0.0001	(1.6, 3.4)

Superiority of zoledronic acid over placebo was demonstrated for all the pre-specified key secondary variables in the closed testing procedure at p < 0.05.

Treatment effects on reducing the incidence of new morphometric vertebral fractures and hip fractures at 3 years (primary efficacy variables) were consistent across the subgroups defined by age (< 70, 70 – 74, ≥ 75 years), race (Caucasian, Hispanic, and other Asian and Pacific Islander), geographic regions (North America/Oceania, Latin America, Western Europe, Eastern Europe, and Asia), baseline femoral neck BMD T-score (≤ -2.5 and > -2.5), baseline BMI (< 19, 19 – 25, > 25 kg/m²), prevalent vertebral fractures (0, 1, ≥ 2), and baseline creatinine clearance level (< 60 and ≥ 60 mL/min), as no significant treatment-by-subgroup

interactions were observed ($p > 0.10$ in most cases). Within these subgroups, the risk of developing at least 1 new morphometric vertebral fracture or hip fracture over 3 years was lower in the zoledronic acid group than in the placebo group. Note that no such finding in hip was observed for subjects who were previously treated with bisphosphonates, as their risk of having a hip fracture over 3 years was greater in the zoledronic acid group than in the placebo group (12/565 vs. 8/557, hazard ratio = 1.50, p-value = 0.3727).

In general, this reviewer's findings agree with the sponsor's results.

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2. INTRODUCTION

2.1 Overview

Zoledronic acid is a third-generation nitrogen-containing bisphosphonate. According to the sponsor, an intravenous formulation of zoledronic acid has been approved in over 96 countries worldwide under the trade name of Zometa[®] for several oncology related indications such as tumor-induced hypercalcemia, treatment of multiple myeloma, and bone metastases from solid tumors. Zoledronic acid is also approved for a non-oncology indication under the trade name of Aclasta[®] for Paget's disease of bone in 50 countries as of 04/30/2006, not including the US and Australia. The current submission is to seek approval for another non-oncology indication of zoledronic acid for treatment of postmenopausal osteoporosis (PMO) under the trade name of Reclast[®].

The efficacy and safety of Reclast[®] was studied in the CZOL446H2301 trial (see the study highlights below) that was still ongoing at the time of submission. The first patient enrolled in the study on 01/22/2002 and the last patient completed the study on 06/01/2006. However, the results presented in this submission were based on the data collected up to 03/31/2006, at which point all patients had completed 2 years of treatment and received the 3rd annual dose. This registration strategy was agreed to by the Agency and other health authorities. Therefore, although the submitted efficacy analysis was, technically speaking, an interim analysis, it was considered **final** and used for the labeling claims.

Study Design	Dose (Randomized)	Age/Gender/Race	Primary Endpoints
Phase III, 3-year, randomized, double-blind, placebo-controlled, parallel-group, multicenter (239 centers), international (27 countries) study	Administered once a year for 3 consecutive years	64 – 89 years (mean = 73 years)	1. Proportion of patients with at least 1 new vertebral fracture over 36 months in Stratum I
% of patients in USA/Canada centers: 16.6%	5 mg zoledronic acid (3875)	F: 7736 (100%) White: 6109 (79.0%) Black: 32 (0.4%) Hispanic: 441 (5.7%) Other Asian & Pacific Islander: 1100 (14.2%) Others: 54 (0.7%)	2. Time to first hip fracture over time in Stratum I and II
% of patients in other centers: 83.4%	Placebo (3861)		

2.2 Data Sources

The clinical study report is located in the EDR, the folder of \\Cdsub1\22080\N_000\2006-10-16\clinstat\controlled. The electronic data files this reviewer used are located in the folder of \\Cdsub1\22080\N_000\2006-10-16\crt\datasets\2301\derived. In general, those data files (a_base.xpt, a_bp.xpt, a_dby.xpt, a_dxadr.xpt, a_dxahip.xpt, a_dxals.xpt, a_fra2.xpt, a_lrsc.xpt, a_lrsp1n.xpt, a_mmt.xpt, and a_xylocf.xpt) were not difficult to work with and information was sufficient. On 07/03/2007, the sponsor submitted final efficacy data sets to the EDR.

(\\Cdsesub1\nonectd\N22080\N_000\2007-07-03\crt\datasets\2301\derived), which included the data collected after the 03/31/2006 data cut-off date. **Unless otherwise noted, all the results in this review report are based on the data sets with the 03/31/2006 data cut-off date (submitted to the EDR on 10/16/2006).**

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

Protocol CZOL446H2301 was a Phase III, 36-month, randomized, double-blind, 2-parallel-group, placebo-controlled, multicenter, international study, to evaluate the effect of 5-mg zoledronic acid in reducing the incidence of vertebral and hip fractures in postmenopausal women with osteoporosis documented by either (1) a femoral neck bone mineral density (BMD) T-score ≤ -2.5 with or without evidence of an existing vertebral fracture or (2) a femoral neck BMD T-score ≤ -1.5 and radiological evidence of at least 2 mild or 1 moderate existing vertebral fracture(s). The study medication was given intravenously to each patient once a year (on Day 0 and at Months 12 and 24) as a slow infusion over 15 minutes through a peripheral site. Recruitment was done in 240 centers across 27 countries, with randomization stratified by the following strata.

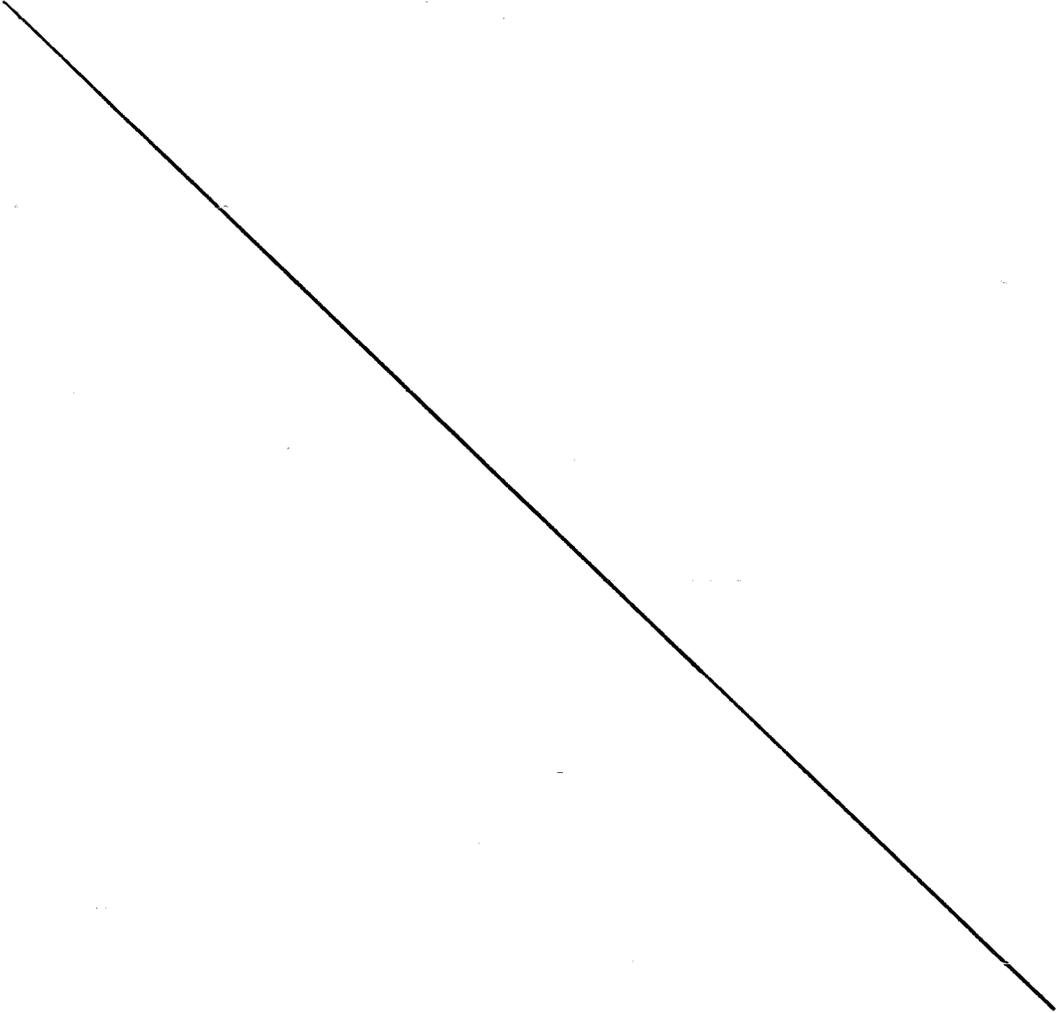
Stratum I: Women assigned to zoledronic acid or placebo for whom usual care involves taking calcium and vitamin D only but no additional concomitant osteoporosis medications.

Stratum II: Women assigned to zoledronic acid or placebo for whom usual care involves taking calcium and vitamin D plus additional osteoporosis therapies, either starting or continuing at randomization.

The additional osteoporosis therapies included hormone replacement therapy (HRT), selective estrogen receptor modulators (SERM, e.g., raloxifene), calcitonin, tibolone, tamoxifen, dehydroepiandrosterone(s), ipriflavone, and medroxyprogesterone, and excluded any non-study bisphosphonates. All patients were provided with 1000 to 1500 mg of elemental calcium and 400 to 1200 IU of vitamin D daily, depending on site and country.

Efficacy assessments included morphometric vertebral fractures, clinical fractures, dual x-ray absorptiometry (DXA) measurements, bone marker measurements, height measurements, and disability measurements. DXA measurements of the spine and distal radius, bone markers of C-telopeptides (b-CTx) and bone specific alkaline phosphatase (BSAP), and bone marker of PINP were performed on a subset of 549, 605, and 1246 patients, respectively.

There were 2 primary efficacy variables: (1) proportion of patients with at least 1 new vertebral fracture over 36 months in Stratum I and (2) time to first hip fracture over time in all patients (Stratum I + II).



The sponsor terminated Center 0196 (29 patients) in Mexico on 10/28/2005 because the data collection was done without properly obtaining informed consent and the timing of data collection for some patients was questionable (e.g., data was collected on Sundays when the site was closed).

3.1.2 Statistical Methods

Primary Efficacy Variables – The analysis of proportion of patients with at least 1 new morphometric vertebral fracture at 3 years was performed using a logistic regression model with treatment and baseline vertebral fracture status (i.e., number of prevalent vertebral

fracture categorized as 0, 1, or ≥ 2) as explanatory variables. The analysis of time to first hip fracture over 3 years was performed using a log-rank test stratified by stratum to compare the time-to-event curves. The hazard ratio and its 95% confidence interval were obtained using a Cox proportional hazards regression model stratified by stratum. Kaplan-Meier life table technique was also used to estimate the cumulative incidence at 3 years.

Approximately 7400 patients were to be enrolled in this study, which would provide 90% power to detect a difference in a zoledronic acid proportion of patients without hip fractures at 3 years of 0.991 and a placebo proportion without hip fractures at 3 years of 0.982 (a constant hazard ratio of 2.009) with a 15% loss to follow up prior to 3 years. A 2-sided log-rank test for equality of survival curves at 5% level was used for the sample size calculation. As stated in the protocol, the estimate of power was based on 1000 simulations using nQuery Advisor 4.0 software.

Secondary Efficacy Variables – For the variables related to morphometric vertebral fractures and clinical fractures, the analysis methods were the same as the ones used for the primary vertebral fracture variable and time to first hip fracture variable, respectively.

Percentage change from baseline in BMD of total hip, femoral neck, and lumbar spine were analyzed using an ANOVA model with treatment, stratum, and region (or center) as the factors by the sponsor. This reviewer also analyzed the data by adding baseline BMD to the model as the covariate. Similar analyses were also conducted for biochemical bone markers and height measurements. All BMD, biochemical marker, and height data were analyzed based on the observed data.

Days of disability due to back pain were evaluated by means of 2 components: total number of days with limited activity and total number of days with bed rest. Between-treatment difference in each of the 2 components were assessed using a Wilcoxon rank-sum test by the sponsor, where the patient with the greatest number of days received the highest ranked value and the patient with the smallest number of days received the lowest ranked value.

A closed testing procedure was implemented for the 2 primary and 20 secondary efficacy variables with a pre-specified order to maintain the overall Type I error rate at 0.05. There were 2 interim analyses performed prior to the analysis with the 03/31/2006 data cut-off date. According to the sponsor, the first interim analysis was performed when all Stratum I patients had their Year 1 x-ray evaluated (08/06/2004 data cut-off date) and the second interim analysis was performed when all patients had completed their Month 24 visits (08/06/2005 data cut-off date). Since the purpose of Year 1 analysis was for determining futility, no adjustment to the alpha (significance) level was made. Since the current analysis

with the 03/31/2006 data cut-off date is serving as the “final” efficacy analysis, the Year 2 analysis was, therefore, considered to be the “interim” analysis that required adjustment to the significance level. Table 1 below shows the adjusted significance levels due to the interim and final analyses for the 2 primary efficacy variables (copied from page 198 of the sponsor’s report).

Table 1 – Adjusted Alpha (Significance) Level for the Interim (Year 2) and Final Analyses

Analysis	Vertebral			Hip		
	Assumed Information Fraction	Critical Z-value	Significance Level	Assumed Information Fraction	Critical Z-value	Significance Level
Interim	66.7%	3	0.0027	88%	2.123	0.0338
Final	100%	1.963	0.0496	100%	2.048	0.0406

The intention-to-treat (ITT) population comprised all randomized subjects excluding Center 0196. The modified intention-to-treat (mITT) population comprised all the ITT subjects in Stratum I who were evaluable for incident vertebral fractures over the period being analyzed for at least 1 vertebra. For example, for the Year 3 time point, the mITT population consisted of the ITT subjects in Stratum I who were evaluable for incident fractures over 36 months for at least 1 vertebra, with the exclusion of the ongoing patients who neither had a confirmed new/worsening vertebral fracture, nor had their 3rd year x-ray evaluated as of the 03/31/2006 data cut-off date. The mITT population was used for efficacy variables related to morphometric vertebral fractures and the ITT population was used for all other efficacy variables, unless otherwise specified.

For subjects who did not provide data for morphometric vertebral fracture assessment at an annual visit, the last result of fracture status prior to that visit was used (last-observation-carried-forward, LOCF). The sponsor also performed four sensitivity analyses to evaluate the impact of such a missing data handling on the primary morphometric vertebral fracture endpoint (see Appendix I).

To avoid sparseness problem, the countries were grouped into the following 6 regions by the sponsor to assess any geographic differences that may exist between treatments:

North America/Oceania:	USA, Canada, Australia, New Zealand
Latin America:	Brazil, Argentina, Columbia, Mexico
Western Europe:	Sweden, Belgium, France, Germany, Israel, Italy, Norway, Switzerland, UK, Austria, Finland
Eastern Europe:	Poland, Russia, Hungary

Asia: Korea, Taiwan, Thailand, China, Hong-Kong

3.1.3 Subject Disposition

A total of 7765 subjects were randomized. Excluding all the 29 subjects in Center 0196 due to data reliability issues identified during monitoring visits and data review, 7736 subjects were included in the ITT population: 3875 and 3861 subjects for the zoledronic acid and placebo groups, respectively. Of those randomized, 66.1% completed the study, 14.7% were discontinued, and 19.2% were still ongoing by the data cut-off date, 03/31/2006. The reasons for discontinuation were similar between the 2 treatment groups (see Table 2 below copied from page 200 of the sponsor's report). Withdrawn consent was the most common recorded reason for discontinuation in this trial.

Table 2 – Subject Disposition – ITT Population

Patient Status	Zoledronic acid N=3875 n (%)	Placebo N=3861 n (%)	Total N=7736 n (%)
Ongoing	762 (19.66)	724 (18.75)	1486 (19.21)
Completed	2527 (65.21)	2588 (67.03)	5115 (66.12)
Discontinued			
- Total	586 (15.12)	549 (14.22)	1135 (14.67)
Subject withdrew consent	275 (7.10)	257 (6.66)	532 (6.88)
Death	129 (3.33)	109 (2.82)	238 (3.08)
Adverse event(s)	75 (1.94)	69 (1.79)	144 (1.86)
Lost to follow-up	72 (1.86)	60 (1.55)	132 (1.71)
Administrative problems	18 (0.46)	22 (0.57)	40 (0.52)
Protocol violation	11 (0.28)	16 (0.41)	27 (0.35)
Abnormal laboratory value(s)	3 (0.08)	5 (0.13)	8 (0.10)
Unsatisfactory therapeutic effect	2 (0.05)	7 (0.18)	9 (0.12)
Abnormal test procedure result(s)	1 (0.03)	1 (0.03)	2 (0.03)
Subject's condition no longer requires study drug	0 (0.00)	1 (0.03)	1 (0.01)
Missing	0 (0.00)	2 (0.05)	2 (0.03)

3.1.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics of all the ITT subjects are shown in Table 3 below (copied from pages 204 – 206 of the sponsor's report). Among the 7736 ITT subjects, 79% of them were in Stratum I and 21% in Stratum II. The overall mean age at entry was 73 years and 62% of the subjects were between 65 and 74 years old. Caucasian (79%), other Asian and Pacific Islander (14%), and Hispanic (6%) constituted the majority of the ITT population. The mean body mass index (BMI) at entry was about 25 kg/m². Of the patients in the ITT population, 85% were naïve to bisphosphonate use prior to entry, 50% were from Western and Eastern Europe, 78% were 5 to 30 years postmenopausal, and 72% had a baseline femoral neck T-score ≤ -2.5. Approximately 63% of the ITT subjects had at least 1 prevalent vertebral fracture. Based on visual examination, the subjects' demographic and baseline characteristics were similar between the 2 treatment groups.

Table 3 – Demographic and Baseline Characteristics – ITT Population

Demographic variables	Zoledronic acid N=3875	Placebo N=3861	Total N=7736
Race, n (%)			
Caucasian	3054 (78.81%)	3055 (79.12%)	6109 (78.97%)
Black	15 (0.39%)	17 (0.44%)	32 (0.41%)
Hispanic	226 (5.83%)	215 (5.57%)	441 (5.70%)
Japanese	9 (0.23%)	12 (0.31%)	21 (0.27%)
Other Asian and Pacific Islander	553 (14.27%)	547 (14.17%)	1100 (14.22%)
Other	18 (0.46%)	15 (0.39%)	33 (0.43%)
Age group (year), n (%)			
< 65	7 (0.18%)	8 (0.21%)	15 (0.19%)
65 – 74	2371 (61.19%)	2401 (62.19%)	4772 (61.69%)
75 – 84	1405 (36.26%)	1356 (35.12%)	2761 (35.69%)
≥ 85	92 (2.37%)	96 (2.49%)	188 (2.43%)
Age (year)			
n	3875	3861	7736
Mean (SD)	73.1 (5.34)	73.0 (5.40)	73.1 (5.37)
Min, Median, Max	64, 73.0, 89	64, 73.0, 89	64, 73.0, 89
Weight (kg)			
n	3872	3860	7732
Mean (SD)	59.9 (11.12)	60.6 (11.33)	60.3 (11.23)
Min, Median, Max	32, 59.0, 119	26, 60.0, 129	26, 59.5, 129
Height (cm) – Non-Stadiometer			
n	1890	1890	3780
Mean (SD)	153.4 (7.19)	153.6 (7.09)	153.5 (7.14)
Min, Median, Max	126, 153.0, 178	115, 153.0, 177	115, 153.0, 178
Height (mm) – Stadiometer			
n	2179	2165	4344
Mean (SD)	1551.1 (70.73)	1550.9 (69.42)	1551.0 (70.07)
Min, Median, Max	1295, 1550.5, 1790	1330, 1551.0, 1791	1295, 1550.5, 1791
Stratum, n (%)			
I	3045(78.58%)	3039(78.71%)	6084(78.65%)
II	830(21.42%)	822(21.29%)	1652(21.35%)
Region, n (%)			
North America/ Oceania	766(19.77%)	765(19.81%)	1531(19.79%)
Latin America	625(16.13%)	622(16.11%)	1247(16.12%)
Western Europe	1160(29.94%)	1162(30.10%)	2322(30.02%)
Asia	550(14.19%)	540(13.99%)	1090(14.09%)
Eastern Europe	774(19.97%)	772(19.99%)	1546(19.98%)
Prior BP use, n (%)			
No	3293(84.98%)	3282(85.00%)	6575(84.99%)
Yes	565(14.58%)	557(14.43%)	1122(14.50%)
Unknown/Missing	17(0.44%)	22(0.57%)	39(0.50%)

Table 3 – Demographic and Baseline Characteristics – ITT Population (Continued)

Demographic variables	Zoledronic acid N=3875	Placebo N=3861	Total N=7736
# of yrs postmenopausal, n (%)			
≤ 5	1(0.03%)	3(0.08%)	4(0.05%)
>5 - 30	3005(77.55%)	3011(77.98%)	6016(77.77%)
> 30	858(22.14%)	833(21.57%)	1691(21.86%)
Missing	11(0.28%)	14(0.36%)	25(0.32%)
BMI (kg/m²)			
n	3868	3856	7724
Mean (SD)	25.132 (4.3328)	25.377 (4.3093)	25.255 (4.3225)
Min, Median, Max	13.355, 24.671, 54.770	12.726, 24.990, 48.225	12.726, 24.806, 54.770
Femoral neck BMD (g/cm²)			
n	3852	3846	7698
Mean (SD)	0.533 (0.0624)	0.534 (0.0644)	0.533 (0.0634)
Min, Median, Max	0.281, 0.537, 0.842	0.211, 0.539, 0.958	0.211, 0.538, 0.958
Total hip BMD (g/cm²)			
n	3845	3840	7685
Mean (SD)	0.647 (0.0897)	0.648 (0.0908)	0.648 (0.0903)
Min, Median, Max	0.231, 0.648, 1.100	0.251, 0.651, 1.324	0.231, 0.650, 1.324
Femoral neck T-score, n (%)			
≤ -2.5	2815(72.65%)	2735(70.84%)	5550(71.74%)
>-2.5 - -1.5	1002(25.86%)	1073(27.79%)	2075(26.82%)
> -1.5	35(0.90%)	38(0.98%)	73(0.94%)
Missing	23(0.59%)	15(0.39%)	38(0.49%)
Prevalent vertebral fracture, n (%)			
0	1455(37.55%)	1380(35.74%)	2835(36.65%)
1	1090(28.13%)	1074(27.82%)	2164(27.97%)
≥ 2	1323(34.14%)	1400(36.26%)	2723(35.20%)
Missing	7(0.18%)	7(0.18%)	14(0.18%)
Alcohol (drinks/day) n (%)			
<1	3622(93.47%)	3606(93.40%)	7228(93.43%)
1-2	237(6.12%)	240(6.22%)	477(6.17%)
≥ 3	16(0.41%)	14(0.36%)	30(0.39%)
Missing	0(0.00%)	1(0.03%)	1(0.01%)
Current smoker - n(%)			
Yes	344(8.88%)	316(8.18%)	660(8.53%)
No	3531(91.12%)	3544(91.79%)	7075(91.46%)
Missing	0(0.00%)	1(0.03%)	1(0.01%)

3.1.5 Efficacy Results and Discussion

To facilitate the following report writing, 'Year 3' or similar wordings are used interchangeably to represent the data cut-off date, 03/31/2006, at which point about 20% and

19% of the ITT subjects in the zoledronic acid and placebo groups, respectively, were still ongoing.

Morphometric Vertebral Fractures. At Year 3, the proportion of zoledronic acid-treated patients with at least 1 new morphometric vertebral fracture (3.8%) was significantly lower than that of placebo-treated patients (12.8%). The associated relative risk of zoledronic acid to placebo was 0.30, meaning that the risk of developing at least 1 new morphometric vertebral fracture over 3 years in the zoledronic acid group was 70% less than that in the placebo group. Similar positive findings were also observed at Year 1 (the key secondary efficacy variable No. 1) and Year 2 (Table 4).

Table 4 – Results for Proportion of Patients with New Morphometric Vertebral Fractures (mITT, Stratum I)

	Zoledronic acid	Placebo	p-value	Relative Risk	95% CI
Year 1	42 / 2814 (1.5%)	106 / 2847 (3.7%)	<0.0001	0.40	(0.28, 0.57)
Year 2	63 / 2814 (2.2%)	218 / 2847 (7.7%)	<0.0001	0.29	(0.22, 0.39)
Year 3	87 / 2260 (3.8%)	300 / 2352 (12.8%)	<0.0001	0.30	(0.24, 0.38)

231 and 192 subjects in the zoledronic acid and placebo groups, respectively, did not have any post-baseline radiographic vertebral fractures and thus were excluded from the mITT population.

The sensitivity analyses performed by the sponsor and confirmed by this reviewer all showed superiority of zoledronic acid over placebo in reducing the incidence of new morphometric vertebral fractures after 3 years ($p < 0.0001$).

When compared to the placebo group, a significantly lower proportion of new/worsening vertebral fractures, new vertebral fractures with moderate/severe grade, new vertebral fractures in patients ≥ 75 years old, new vertebral fractures in patients with 0 baseline vertebral fracture, new vertebral fractures in patients with 1 baseline vertebral fracture, and new vertebral fractures in patients with ≥ 2 baseline vertebral fractures over 3 years were also observed in the zoledronic acid group (corresponding to the key secondary efficacy variable Nos. 3, 15, 16, 17, 18, and 19, all $p < 0.0001$). Moreover, relative to placebo, zoledronic acid consistently showed more than 60% risk reduction in these cases (Table 5).

Table 5 – Results for Key Secondary Variables Related to Morphometric Vertebral Fractures (mITT, Stratum I)

Year 3	Zoledronic acid	Placebo	p-value	Relative Risk	95% CI
New and/or worsening vertebral fracture	102 / 2260 (4.5%)	323 / 2352 (13.7%)	<0.0001	0.33	(0.27, 0.41)
New vertebral fracture with Moderate/severe grade	74 / 2260 (3.3%)	257 / 2352 (10.9%)	<0.0001	0.30	(0.23, 0.39)

New vertebral fracture for age \geq 75 years	48 / 880 (5.5%)	122 / 880 (13.9%)	<0.0001	0.39	(0.29, 0.54)
New vertebral fracture with 0 prevalent vertebral fracture	19 / 815 (2.3%)	58 / 825 (7.0%)	<0.0001	0.33	(0.20, 0.55)
New vertebral fracture with 1 prevalent vertebral fracture	19 / 653 (2.9%)	58 / 659 (8.8%)	<0.0001	0.33	(0.20, 0.55)
New vertebral fracture with \geq 2 prevalent vertebral fractures	49 / 792 (6.2%)	184 / 868 (21.2%)	<0.0001	0.29	(0.22, 0.39)

Clinical Fractures. Approximately 1.3% of the zoledronic acid-treated patients and 2.3% of the placebo-treated patients developed a new hip fracture over a 3-year period. The incidence rates adjusted for onset time (Kaplan-Meier estimates) were 1.5% and 2.5% for the zoledronic acid and placebo groups, respectively. Based on long-rank test and Kaplan-Meier survival curves (Figure 1, copied from page 216 of the sponsor's report), the time to first hip fracture was significantly longer in the zoledronic acid group than in the placebo group ($p = 0.0032$). The associated relative risk of zoledronic acid to placebo was 0.60, meaning that the risk of developing a hip fracture over 3 years in the zoledronic acid group was 40% less than that in the placebo group (Table 6).

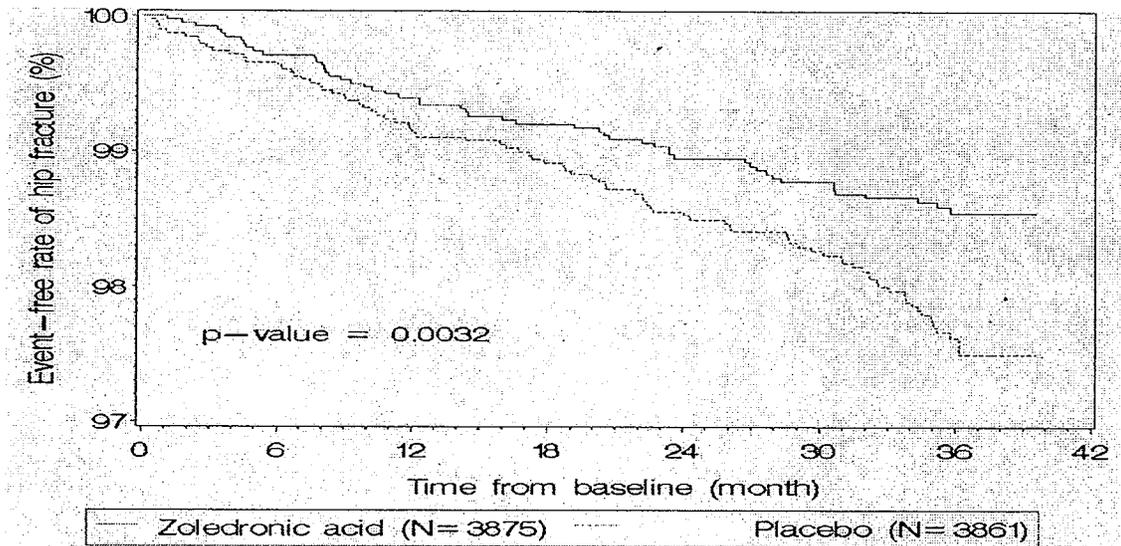
However, although the Year 1 and Year 2 incidence rates in the zoledronic acid group were smaller than those in the placebo group, the time-to-event curves were not statistically different ($p > 0.05$) and the risk of having a hip fracture at both years could be actually higher in the zoledronic acid group than in the placebo group, as suggested by the 95% upper confidence limit of hazard ratio (Table 6).

Table 6 – Results for Time to First Hip Fracture (ITT, Stratum I + II)

	Zoledronic acid	Placebo	p-value	Hazard Ratio	95% CI
Year 1	23 / 3875 (0.6%) Kaplan-Meier = 0.6%	33 / 3861 (0.9%) Kaplan-Meier = 0.9%	0.1828	0.70	(0.41, 1.19)
Year 2	39 / 3875 (1.0%) Kaplan-Meier = 1.1%	56 / 3861 (1.5%) Kaplan-Meier = 1.5%	0.0834	0.70	(0.46, 1.05)
Year 3	52 / 3875 (1.3%) Kaplan-Meier = 1.5%	87 / 3861 (2.3%) Kaplan-Meier = 2.5%	0.0032	0.60	(0.43, 0.85)

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Figure 1 – Kaplan Meier Curves of Time to First Hip Fracture (ITT, Stratum I + II)



In Stratum I (no concomitant osteoporosis therapy allowed) and Stratum II (with concomitant osteoporosis therapy taken), a 40% and 42% risk reduction, respectively, in hip fractures at 3 years was observed for the zoledronic acid-treated patients when compared to the placebo-treated patients. However, in Stratum II, the difference in time to first hip fracture between the 2 treatment groups was not statistically significant ($p = 0.1707$), which might be due to the smaller sample sizes in each group (Table 7).

Table 7 – Results for Time to First Hip Fracture at Year 3 by Stratum (ITT)

	Zoledronic acid	Placebo	p-value	Hazard Ratio	95% CI
Stratum I	42 / 3045 (1.4%) Kaplan-Meier = 1.5%	70 / 3039 (2.3%) Kaplan-Meier = 2.6%	0.0089	0.60	(0.41, 0.88)
Stratum II	10 / 830 (1.2%) Kaplan-Meier = 1.3%	17 / 822 (2.1%) Kaplan-Meier = 2.3%	0.1707	0.58	(0.27, 1.27)

Zoledronic acid also showed smaller incidence rates at 3 years in clinical vertebral fracture, non-vertebral fracture, and clinical fracture when compared to placebo (corresponding to the key secondary efficacy variable Nos. 4, 10, and 11). The times to these events were all significantly longer in the zoledronic acid group than in the placebo group ($p < 0.0005$). In addition, the risks of having these events over 3 years were also significantly lower for the zoledronic acid-treated patients than the placebo-treated patients (Table 8).

Table 8 – Results for Key Secondary Variables Related to Clinical Fractures (ITT, Stratum I + II)

Year 3	Zoledronic acid	Placebo	p-value	Hazard Ratio	95% CI
Clinical vertebral Fracture ¹	20 / 3875 (0.5%) Kaplan-Meier = 0.6%	81 / 3861 (2.1%) Kaplan-Meier = 2.6%	<0.0001	0.25	(0.15, 0.40)
Non-vertebral Fracture ²	289 / 3875 (7.5%) Kaplan-Meier = 9.5%	384 / 3861 (9.9%) Kaplan-Meier = 10.7%	0.0002	0.75	(0.64, 0.87)
Clinical fracture ²	306 / 3875 (7.9%) Kaplan-Meier = 10.0%	451 / 3861 (11.7%) Kaplan-Meier = 12.9%	<0.0001	0.67	(0.58, 0.78)

¹ Including thoracic spine and lumbar spine fractures

² Excluding finger, toe, and facial bone fractures

Note that the Kaplan-Meier estimates of non-vertebral fracture and clinical fracture for the zoledronic acid group shown in the sponsor's clinical report were the cumulative event rates at Month 36 (Day 1095) in the study (7.91% and 8.39%, respectively, Table 9-7, page 223), not the rates based on all events that occurred in the study (9.5% and 10.0%, respectively, in this reviewer's Table 8 above). In other words, patients who did not have a non-vertebral or clinical fracture by Day 1095 were censored in the sponsor's analyses (Appendix II).

DXA Measurements. After 3 years of treatment, the zoledronic acid group exhibited positive mean % changes from baseline in BMD of total hip, femoral neck, and lumbar spine, while the placebo group showed negative mean % changes in these cases (Table 9). The treatment differences between the 2 study groups were all highly significant, favoring the treatment of zoledronic acid (corresponding to the key secondary efficacy variable Nos. 5, 6, and 9). Significantly greater mean % increases from baseline in BMD of total hip and femoral neck at Month 6 were also observed in the zoledronic acid group when compared with the placebo group (corresponding to the key secondary efficacy variable Nos. 7 and 8). In fact, significant findings favoring zoledronic acid were also observed for Year 1 and Year 2 of total hip, femoral neck, and lumbar spine BMD, and all time points of trochanter BMD (Figures 2-5, copied from pages 5233-5236 of the sponsor's report, different sample sizes over time).

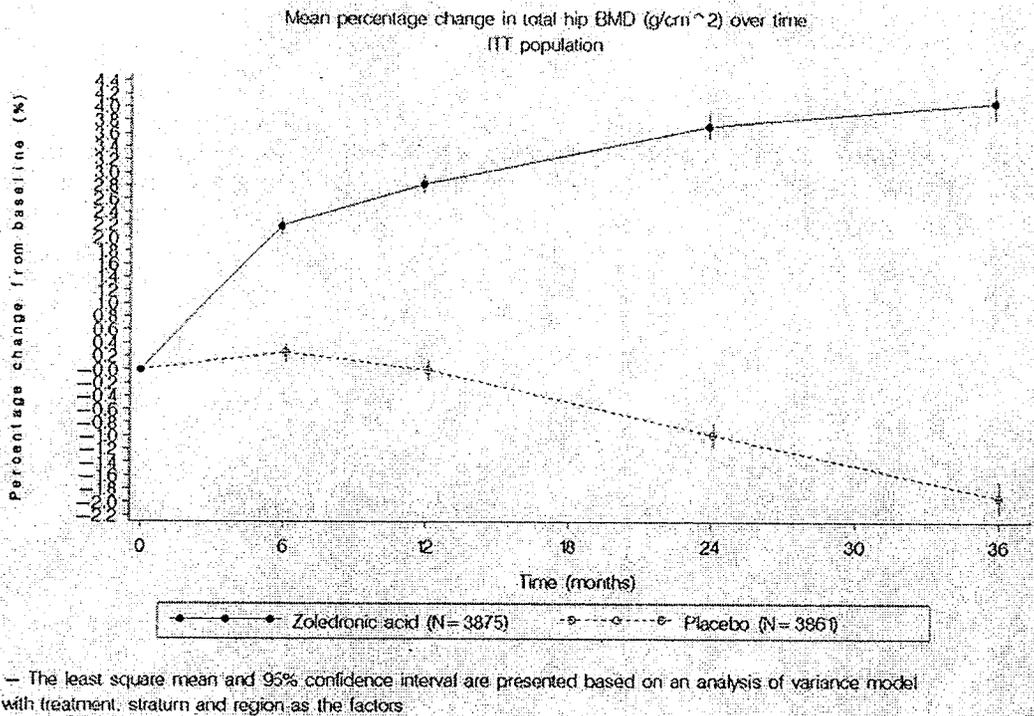
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Table 9 – Results for Key Secondary Variables Related to DXA Measurements (ITT)

	Month	LS Mean % Change from Baseline ± SE (N)		Treatment Difference	p-value	95% CI
		Zoledronic acid	Placebo			
Total Hip	6	2.2 ± 0.1 (3516)	0.3 ± 0.1 (3544)	1.9	<0.0001	(1.8, 2.1)
Total Hip	36	4.1 ± 0.1 (2350)	-1.9 ± 0.1 (2408)	6.0	<0.0001	(5.7, 6.3)
Femoral Neck	6	2.2 ± 0.1 (3523)	0.6 ± 0.1 (3550)	1.6	<0.0001	(1.4, 1.8)
Femoral Neck	36	3.9 ± 0.1 (2356)	-1.1 ± 0.1 (2414)	5.0	<0.0001	(4.7, 5.3)
Lumbar Spine	36	6.8 ± 0.5 (181)	-0.1 ± 0.5 (170)	6.9	<0.0001	(5.7, 8.0)

The LS (least-squares) mean % change from baseline ± SE, treatment difference, p-value, and 95% CI were obtained using the sponsor's 3-way ANOVA model with treatment, stratum, and region (or center for lumbar spine variable) as the factors.

Figure 2



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Figure 3

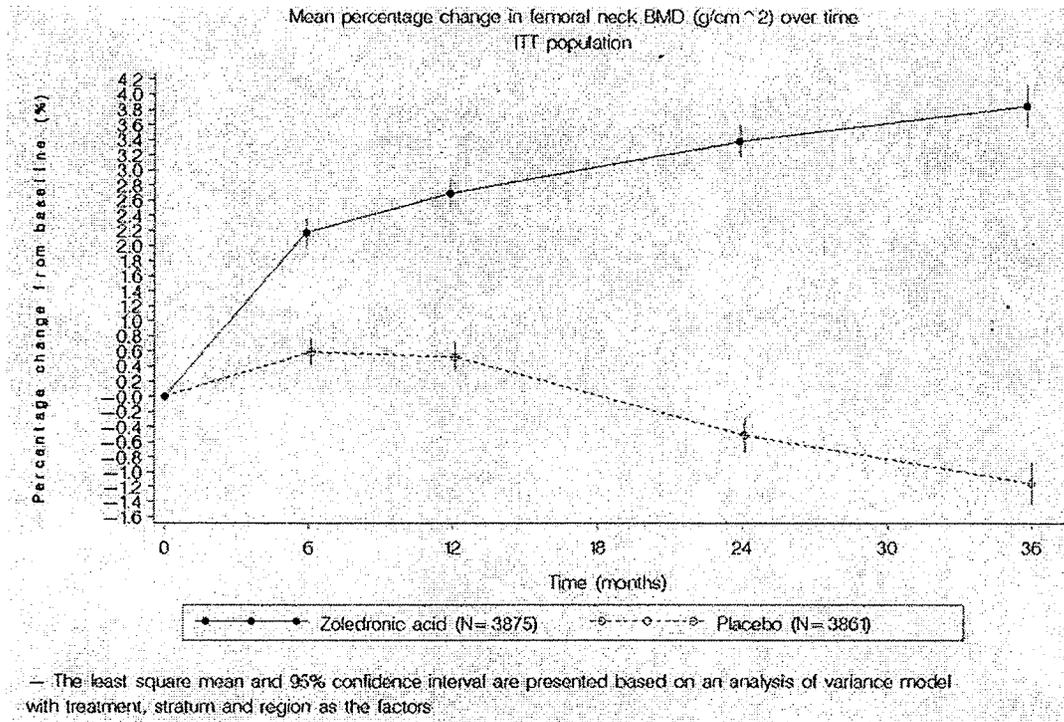


Figure 4

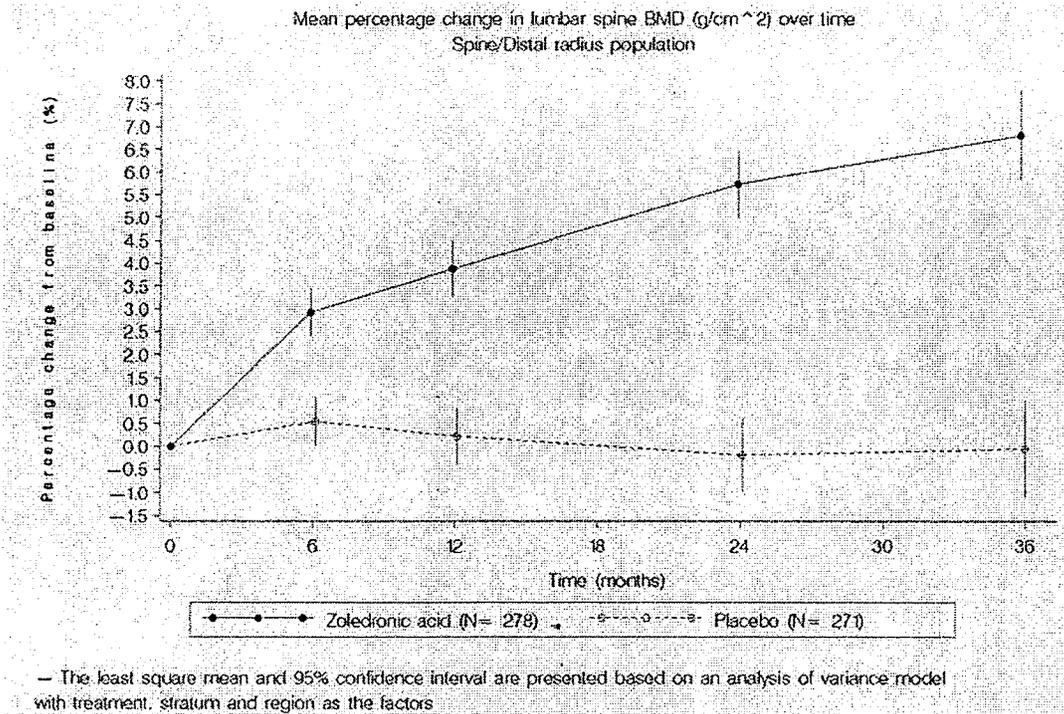
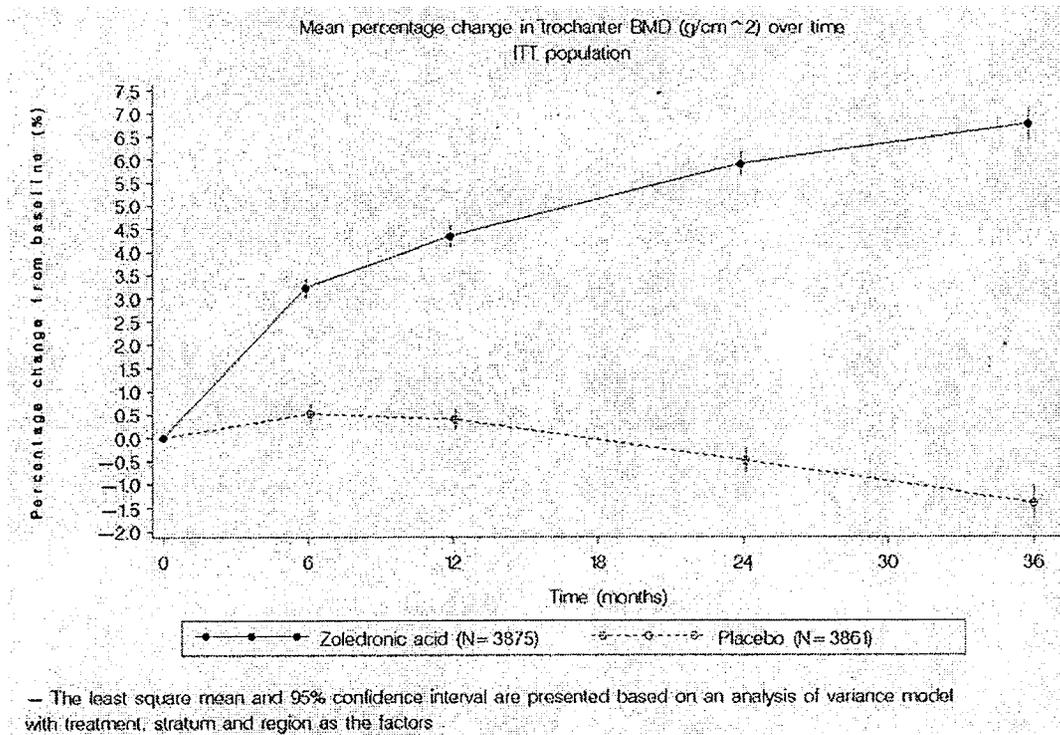


Figure 5



Similar results were also found when baseline BMD was added to the model as the covariate.

Biochemical Bone Markers. After 3 years of treatment, the means and medians of the biochemical markers of bone resorption (b-CTx) and bone formation (BSAP and PINP) were decreased over baseline in the zoledronic acid group, but were increased in the placebo group (Table 10). The treatment differences between the 2 study groups were all highly significant, favoring the treatment of zoledronic acid (corresponding to the key secondary efficacy variable Nos. 12, 13, and 14). In fact, significant findings favoring zoledronic acid were seen at all time points. As depicted in Figures 6-8 (copied from pages 5238-5240 of the sponsor's report, different sample sizes over time), greater mean reductions in the biochemical bone markers of interest were shown by Month 6 in the zoledronic acid group when compared with the placebo group. Afterwards, the mean values in both groups were generally sustained throughout the rest of the 3-year treatment period.

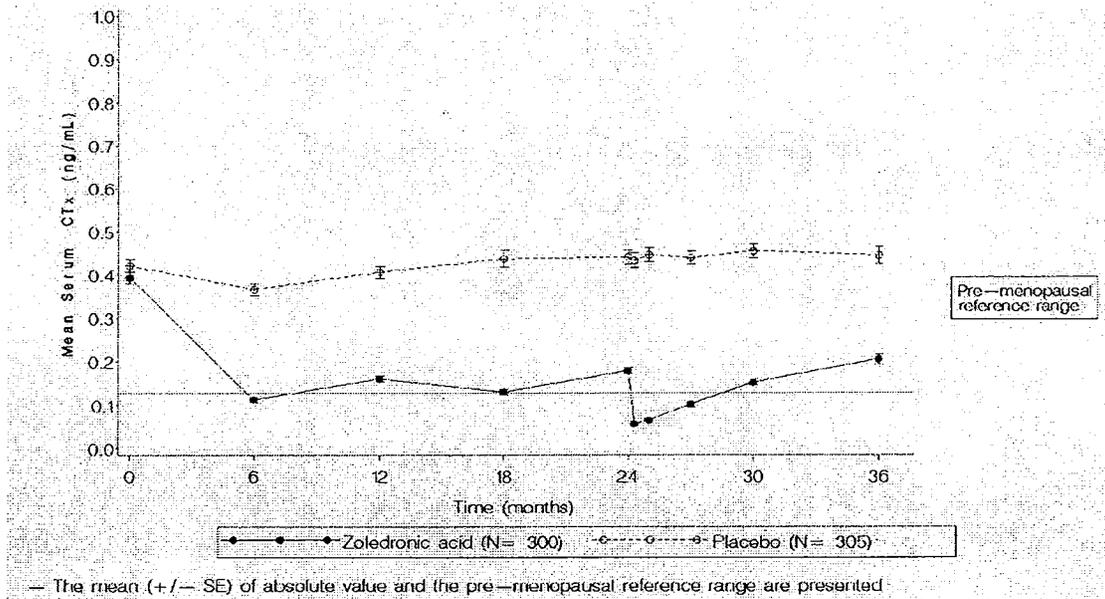
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Table 10 – Results for Key Secondary Variables Related to Biochemical Bone Markers (ITT)

	Month	LS Mean % Change from Baseline ± SE (N)		Treatment Difference	p-value	95% CI
		Zoledronic acid	Placebo			
Serum b-CTX	36	-26.7 ± 9.7 (111) Median = -47.3	47.0 ± 10.0 (115) Median = 23.0	-73.7	<0.0001	(-93.7, -53.6)
Serum BSAP	36	-16.2 ± 7.2 (113) Median = -30.2	9.0 ± 7.4 (119) Median = 3.4	-25.2	0.0009	(-40.0, -10.5)
Serum PINP	36	-21.2 ± 9.5 (192) Median = -48.1	35.2 ± 9.4 (215) Median = 1.5	-56.4	<0.0001	(-76.7, -36.1)

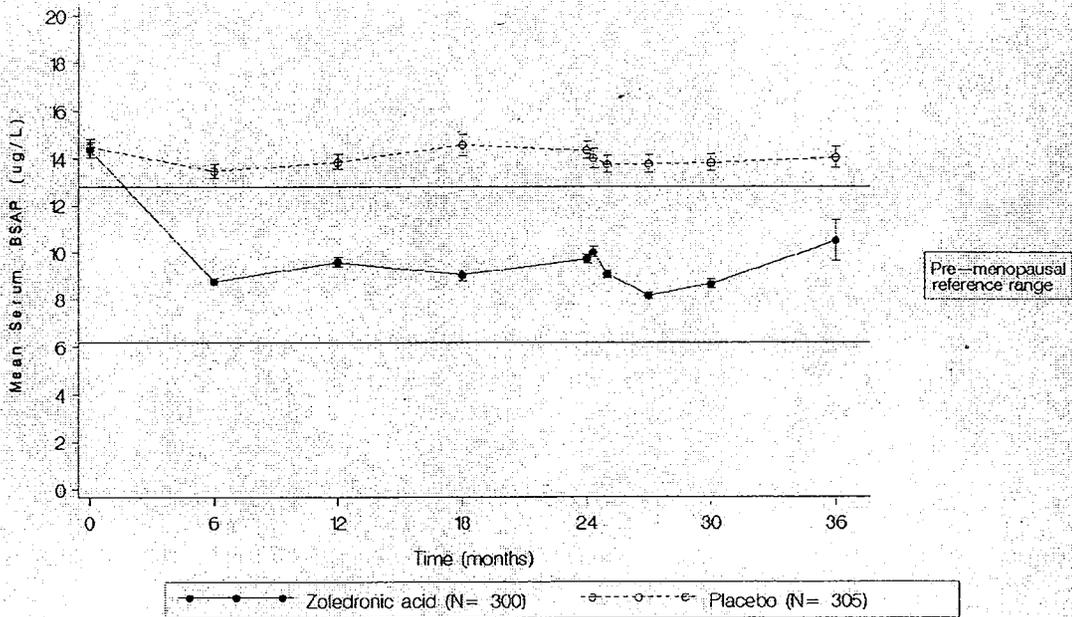
The LS (least-squares) mean % change from baseline ± SE, treatment difference, p-value, and 95% CI were obtained using an ANCOVA model with treatment, stratum, and center as the factors and baseline as the covariate.

Figure 6 – Mean serum b-CTX over time



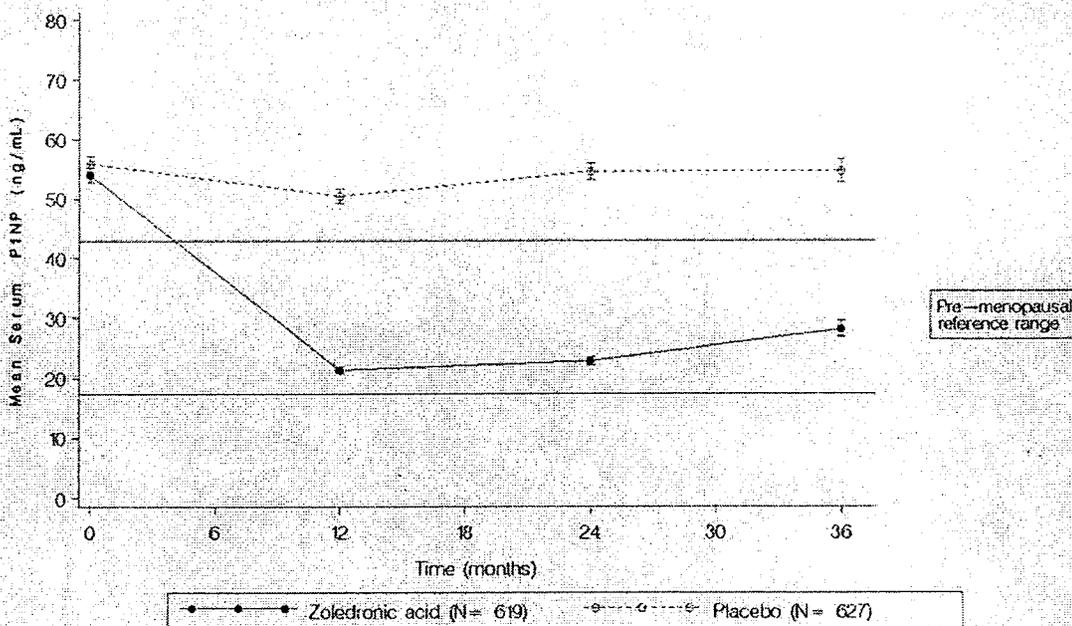
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Figure 7 – Mean serum BSAP over time



- The mean (+/- SE) of absolute value and the pre-menopausal reference range are presented.

Figure 8 – Mean serum PINP over time



- The mean (+/- SE) of absolute value and the pre-menopausal reference range are presented

The sponsor's analyses on the \log_e ratio of post-baseline value to baseline (dependent variable) also showed similar significant findings, so did the Wilcoxon-Mann-Whitney test (a non-parametric test).

Standing Height. According to the sponsor, Subject 0579_00001 in the zoledronic acid group had a stadiometer height recorded as 157.0 mm (= 15.7 cm) at Month 36 which resulted in an extremely skewed distribution. It was confirmed to be in error since the subject's baseline, Month 12, and Month 24 height values were 1582, 1582, and 1576 mm, respectively. Therefore, that data point was excluded from the analysis.

After 3 years of treatment, both the zoledronic acid and placebo groups showed a mean reduction in height from baseline. However, the decrease was significantly less in the zoledronic acid group than in the placebo group (the key secondary efficacy variable No. 2, Table 11). Figure 9 (copied from page 5242 of the sponsor's report) depicts that the differences in height between the 2 study groups became more apparent as the treatment continued.

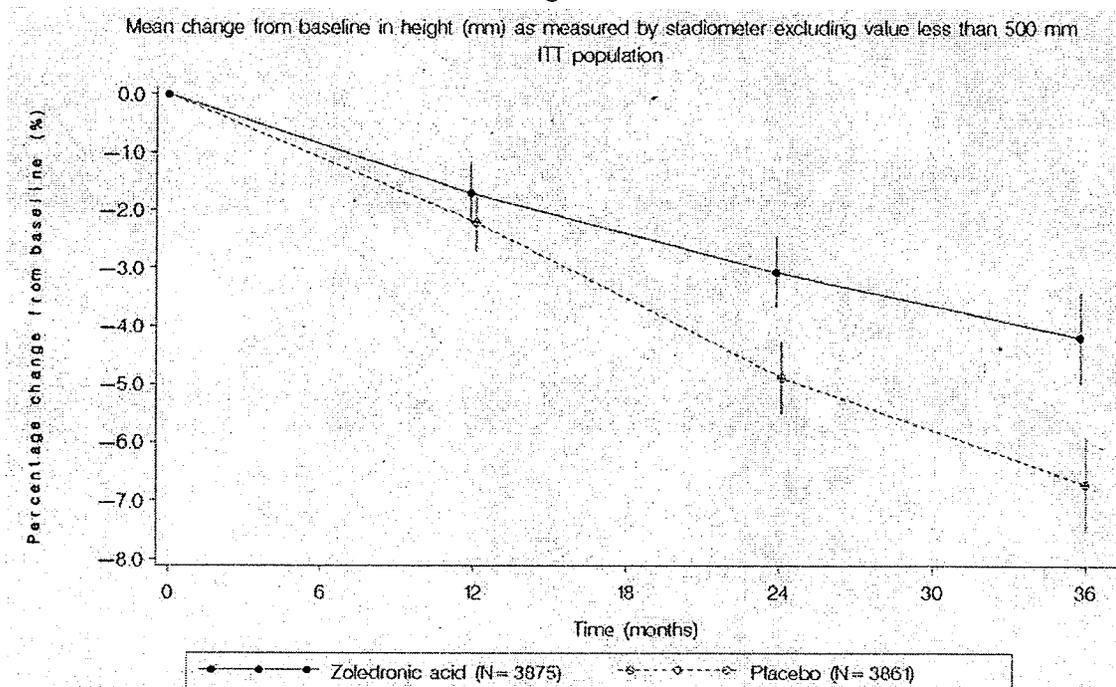
Table 11 – Results for Key Secondary Variables Related to Height Measurements (ITT)

	Month	LS Mean Change from Baseline \pm SE (N)		Treatment Difference	p-value	95% CI
		Zoledronic acid	Placebo			
Height (mm)	36	-4.2 \pm 0.4 (1287)	-6.7 \pm 0.4 (1290)	2.5	<0.0001	(1.6, 3.4)

The LS (least-squares) mean change from baseline \pm SE, treatment difference, p-value, and 95% CI were obtained using the sponsor's 3-way ANCOVA model with treatment, stratum, and region as the factors and baseline as the covariate.

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Figure 9



— The least square mean and 95% confidence interval are presented based on an analysis of covariance model with treatment, stratum, region and baseline height as the factors

Disability Measurements. As shown in Table 12, the total number of days with limited activity or bed rest due to back pain was significantly less in the zoledronic acid group than in the placebo group (the key secondary efficacy variable No. 20). Significant findings favoring the zoledronic acid treatment were also observed for days of disability due to fracture.

Table 12 – Results for Key Secondary Variables Related to Disability Measurements (ITT)

	Treatment	N	Mean	Median	Min, Max	p-value
Total number of days with limited activity due to back pain	Zoledronic acid	2210	105.0	25	0, 1095	0.0028
	Placebo	2244	122.9	30	0, 1086	
Total number of days with bed rest due to back pain	Zoledronic acid	2205	14.3	0	0, 998	0.0111
	Placebo	2244	15.9	0	0, 936	

3.2 Evaluation of Safety

In consultation with the reviewing medical officer, there were no aspects of safety that required review by a statistician. See Dr. Bill Lubas’s report for safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

Treatment effects on reducing the incidence of new morphometric vertebral fractures and hip fractures at 3 years were consistent across the subgroups of age (< 70, 70 – 74, ≥ 75 years) and race (Caucasian, Hispanic, and other Asian and Pacific Islander), as no significant treatment-by-subgroup interactions were observed ($p > 0.09$ in all cases). Within these subgroups, the risk of developing at least 1 new morphometric vertebral fracture or hip fracture over 3 years was lower in the zoledronic acid group than in the placebo group. Note that Black, Japanese, and the subjects categorized under Other were not in the analyses because the sample sizes were very small (< 0.5% each, see Table 3 above under Section 3.1.4) and most of them did not have any vertebral or hip fractures.

Since all the study subjects were females, no subgroup analysis for gender was performed.

4.2 Other Special/Subgroup Populations

Treatment effects on reducing the incidence of new morphometric vertebral fractures and hip fractures at 3 years were consistent across the subgroups defined by geographic regions, baseline femoral neck BMD T-score (≤ -2.5 and > -2.5), baseline BMI (< 19, 19 – 25, > 25 kg/m²), prevalent vertebral fractures (0, 1, ≥ 2), and baseline creatinine clearance level (< 60 and ≥ 60 mL/min), as no significant treatment-by-subgroup interactions were observed ($p > 0.10$ in most cases). Within these subgroups, the risk of developing at least 1 new morphometric vertebral fracture or hip fracture over 3 years was lower in the zoledronic acid group than in the placebo group.

For the subgroups defined by prior use of bisphosphonates (yes/no), a significant interaction was observed for hip fracture parameter ($p = 0.0262$), but not for morphometric vertebral fracture parameter ($p = 0.8419$). As shown in Table 13, for subjects who were previously treated with bisphosphonates, the risk of having a hip fracture over 3 years was numerically greater in the zoledronic acid group than in the placebo group (12/565 vs. 8/557). For subjects who were bisphosphonate-naïve, a 51% risk reduction in hip fractures at 3 years was observed for the zoledronic acid group relative to the placebo group.

Table 13 – Results for Time to First Hip Fracture at Year 3 by Previous Bisphosphonate Use (ITT)

	Zoledronic acid	Placebo	p-value	Hazard Ratio	95% CI
Yes	12 / 565 (2.1%)	8 / 557 (1.4%)	0.3727	1.50	(0.61, 3.66)
No	39 / 3293 (1.2%)	79 / 3282 (2.4%)	0.0002	0.49	(0.34, 0.73)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

In general, this reviewer did not find any serious statistical issues. Since there was only one, but fairly large, pivotal clinical trial in this submission, the collective evidence is summarized based on the results from the primary and secondary efficacy variables.

After Year 3 (based on the data with 03/31/2006 cut-off date), the proportion of zoledronic acid-treated patients with at least 1 new morphometric vertebral fracture or hip fracture was significantly lower than that of placebo-treated patients (Table 14). In addition, the time to first hip fracture over a 3-year period was significantly longer in the zoledronic acid group than in the placebo group ($p = 0.0032$). The risk of having at least 1 new morphometric vertebral fracture or hip fracture over 3 years was 70% or 40% less, respectively, in the zoledronic acid group relative to the placebo group. Similar significant findings were also observed when the final data sets were analyzed (including data collected after 03/31/2006).

Note that the risk of developing a hip fracture after 1 or 2 years could be actually higher in the zoledronic acid group than in the placebo group, as suggested by the 95% upper confidence limit of hazard ratio (see Table 6 in the 3.1.5 Section).

Table 14 – Summary Results for the Primary Efficacy Variables

Year 3	Zoledronic acid	Placebo	p-value	Relative Risk / Hazard Ratio	95% CI
Using Data Sets Submitted on 10/16/2006 (with 03/31/2006 data cut-off date)					
New vertebral fracture (Stratum I)	87 / 2260 (3.8%)	300 / 2352 (12.8%)	<0.0001	0.30	(0.24, 0.38)
Time to first hip fracture (Stratum I + II)	52 / 3875 (1.3%) Kaplan-Meier = 1.5%	87 / 3861 (2.3%) Kaplan-Meier = 2.5%	0.0032	0.60	(0.43, 0.85)
Using Data Sets Submitted on 07/03/2007 (including data collected after 03/31/2006)					
New vertebral fracture (Stratum I)	92 / 2822 (3.3%)	310 / 2853 (10.9%)	<0.0001	0.30	(0.24, 0.38)
Time to first hip fracture (Stratum I + II)	52 / 3875 (1.3%) Kaplan-Meier = 1.4%	88 / 3861 (2.3%) Kaplan-Meier = 2.5%	0.0024	0.59	(0.42, 0.83)

The zoledronic acid group also showed smaller incidence rates after 3 years in new/worsening vertebral fractures, new vertebral fractures with moderate/severe grade, new vertebral fractures in patients ≥ 75 years old, new vertebral fractures in patients with 0 baseline vertebral fracture, new vertebral fractures in patients with 1 baseline vertebral fracture, new vertebral fractures in patients with ≥ 2 baseline vertebral fractures, clinical vertebral fracture, non-vertebral fracture, and clinical fracture when compared to the placebo

group. The risks of having these events over 3 years were all significantly lower for the zoledronic acid-treated patients than the placebo-treated patients (Table 15).

Table 15 – Summary Results for Key Secondary Variables

Variable No. and Name		Zoledronic acid	Placebo	p-value	RR / HR	95% CI
1	New vertebral fracture at Year 1	42 / 2814 (1.5%)	106 / 2847 (3.7%)	<0.0001	0.40	(0.28, 0.57)
3	New and/or worsening vertebral fracture at Year 3	102 / 2260 (4.5%)	323 / 2352 (13.7%)	<0.0001	0.33	(0.27, 0.41)
15	New vertebral fracture with moderate/severe grade at Year 3	74 / 2260 (3.3%)	257 / 2352 (10.9%)	<0.0001	0.30	(0.23, 0.39)
16	New vertebral fracture for age \geq 75 years at Year 3	48 / 880 (5.5%)	122 / 880 (13.9%)	<0.0001	0.39	(0.29, 0.54)
17	New vertebral fracture with 0 prevalent vertebral fracture at Year 3	19 / 815 (2.3%)	58 / 825 (7.0%)	<0.0001	0.33	(0.20, 0.55)
18	New vertebral fracture with 1 prevalent vertebral fracture at Year 3	19 / 653 (2.9%)	58 / 659 (8.8%)	<0.0001	0.33	(0.20, 0.55)
19	New vertebral fracture with \geq 2 prevalent vertebral fractures at Year 3	49 / 792 (6.2%)	184 / 868 (21.2%)	<0.0001	0.29	(0.22, 0.39)
4	Time to first clinical vertebral fracture ¹ at Year 3	20 / 3875 (0.5%) KM = 0.6%	81 / 3861 (2.1%) KM = 2.6%	<0.0001	0.25	(0.15, 0.40)
10	Time to first non-vertebral fracture ² at Year 3	289 / 3875 (7.5%) KM = 9.5%	384 / 3861 (9.9%) KM = 10.7%	0.0002	0.75	(0.64, 0.87)
11	Time to clinical fracture ² at Year 3	306 / 3875 (7.9%) KM = 10.0%	451 / 3861 (11.7%) KM = 12.9%	<0.0001	0.67	(0.58, 0.78)

¹ Including thoracic spine and lumbar spine fractures

² Excluding finger, toe, and facial bone fractures

RR = Relative Risk; HR = Hazard Ratio; KM = Kaplan-Meier

As shown in Table 16, after 3 years of treatment, the mean % changes from baseline in the cases of total hip BMD, femoral neck BMD, lumbar spine BMD, b-CTx, BSAP, PINP, and height were all significantly better in the zoledronic acid group than in the placebo group. In addition, for the zoledronic acid-treated patients, there were significantly fewer days with limited activity or bed rest due to back pain when compared with placebo-treated patients (the key secondary efficacy variable No. 20, $p = 0.0028$ and 0.0111 , respectively).

Table 16 – Summary Results for Key Secondary Variables (Continued)

Variable No., Name, and Month			LS Mean % Change from Baseline ± SE (N)		Treatment Difference	p-value	95% CI
			Zoledronic acid	Placebo			
5	Total Hip	36	4.1 ± 0.1 (2350)	-1.9 ± 0.1 (2408)	6.0	<0.0001	(5.7, 6.3)
6	Femoral Neck	36	3.9 ± 0.1 (2356)	-1.1 ± 0.1 (2414)	5.0	<0.0001	(4.7, 5.3)
7	Total Hip	6	2.2 ± 0.1 (3516)	0.3 ± 0.1 (3544)	1.9	<0.0001	(1.8, 2.1)
8	Femoral Neck	6	2.2 ± 0.1 (3523)	0.6 ± 0.1 (3550)	1.6	<0.0001	(1.4, 1.8)
9	Lumbar Spine	36	6.8 ± 0.5 (181)	-0.1 ± 0.5 (170)	6.9	<0.0001	(5.7, 8.0)
12	Serum b-CTx	36	-26.7 ± 9.7 (111) Median = -47.3	47.0 ± 10.0 (115) Median = 23.0	-73.7	<0.0001	(-93.7, -53.6)
13	Serum BSAP	36	-16.2 ± 7.2 (113) Median = -30.2	9.0 ± 7.4 (119) Median = 3.4	-25.2	0.0009	(-40.0, -10.5)
14	Serum PINP	36	-21.2 ± 9.5 (192) Median = -48.1	35.2 ± 9.4 (215) Median = 1.5	-56.4	<0.0001	(-76.7, -36.1)
2	Height (mm)	36	-4.2 ± 0.4 (1287)	-6.7 ± 0.4 (1290)	2.5	<0.0001	(1.6, 3.4)

Superiority of zoledronic acid over placebo was demonstrated for all the pre-specified key secondary variables in the closed testing procedure at $p < 0.05$.

In general, this reviewer's findings agree with the sponsor's results.

5.2 Conclusions and Recommendations

Data from the ZOL446H2301 pivotal fracture trial have demonstrated that Reclast[®] (zoledronic acid) 5 mg once yearly injection was effective in lowering the proportion of patients with new morphometric vertebral fractures and in delaying the time to first hip fracture over 3 years when compared with placebo. Significant effects were also seen at Years 1 and 2 for the new morphometric vertebral fracture parameter, but not for the hip fracture parameter. Reclast[®] also exhibited greater reductions than placebo in both parameters at 3 years regardless of age (< 70 , $70 - 74$, ≥ 75 years), race (Caucasian, Hispanic, and other Asian and Pacific Islander), geographic region (North America/Oceania, Latin America, Western Europe, Eastern Europe, and Asia), femoral neck BMD T-score at baseline (≤ -2.5 and > -2.5), BMI at baseline (< 19 , $19 - 25$, > 25 kg/m²), and number of prevalent vertebral fractures at baseline (0, 1, ≥ 2). However, the effect in hip was not seen for subjects who were previously treated with bisphosphonates.

Data from the ZOL446H2301 trial also showed that Reclast[®] was effective in improving BMDs of total hip, femoral neck, and lumbar spine and biochemical bone markers of b-CTx, BSAP, and PINP after 36 months of treatment when compared with placebo. Although

mean reductions in height were seen in both treatment groups at 3 years, the decrease was significantly less in the zoledronic acid group than in the placebo group. In addition, treatment with Reclast[®] resulted in significantly fewer days with limited activity and/or bed rest due to back pain when compared with placebo.

5.3 Labeling Comments

The 2 primary and _____
_____ showed superiority of zoledronic acid over placebo in the closed testing procedure at $p < 0.05$. In fact, except for disability due to back pain parameter (a subjective measure), the statistical results for those _____ were all highly significant ($p < 0.001$), effectively ruling out chance as an explanation for the observed treatment differences. Therefore, whether to include those _____ in the labeling would be up to the medical reviewer's discretion.

Primary Statistical Reviewer: Cynthia Liu, MA

Concurring Reviewer: Todd Sahlroot, Ph.D., Statistical Team Leader
Tom Permutt, Ph.D., Division Director

CC: HFD-510/JMarchick, TKehoe, WLubas
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HFD-700/ENevius, LPatrician

6. APPENDIX I

To evaluate the robustness of the primary logistic regression analysis with LOCF techniques for missing data for the primary vertebral endpoint, the sponsor performed 4 sensitivity analyses as described below (copied from page 187 of the sponsor's report).

1. Multiple imputation under "Missing at Random" assumption for the ITT patients in Stratum I with incomplete data
 - The ITT patients in Stratum I who did not provide complete information for baseline fracture status, year 1, year 2, and year 3 fracture outcomes had their missing data imputed using the multiple imputation method. These imputation schemes for missing data were based on the assumption that patient data is missing at random (MAR). The details are described in Appendix 5.1. This method produces simulated estimates of treatment effect for each replicate of the data by combining the vertebral fracture outcome that was actually observed with vertebral fracture outcome that was imputed through simulation. The multiple imputation method combines the treatment effect estimates so that a single p-value for the treatment effect can be obtained. This imputation scheme was included in the final statistical analysis plan and developed prior to unblinding. — 1996, — 1999.
2. Completer analysis
 - The completer analysis was performed based on the mITT patients who had actual data presented at the 3rd annual visit.
3. Single imputation for the cITT patients in Stratum I being excluded from mITT at Year 3.
 - The fracture status for the cITT patients in Stratum I being excluded from the mITT population at year 3 were imputed as "no vertebral fracture" at any time point including baseline and the analysis of the primary efficacy endpoint was performed by including all the Stratum I patients in the cITT population.
4. Mixture models for non-ignorable dropouts
 - Additional sensitivity analyses were performed to evaluate the validity of the missing at random assumptions. It was assumed that the fracture outcome for the patients with missing values was distributed differently from what was defined by the patients with observed data. The sensitivity analyses were carried out under several scenarios of difference in the treatment benefits between the patients with actual data and the patients with missing data. The analyses were performed using the ITT, cITT, and mITT populations at Year 3. The detailed statistical methodology is described in Appendix 5.1. — 1996 and 1978, — 1997, — 2000.

7. APPENDIX II

The sponsor's e-mail on 06/04/2007 in response to this reviewer's question sent on 05/31/2007.

Question:

The event rates (Kaplan-Meier estimates) of non-vertebral fracture and clinical fracture shown in your clinical report were 7.91% (for 285/3875) and 8.39% (for 302/3875), respectively, on page 223, Table 9-7. However, this reviewer's findings were 9.5% (for 289/3875) and 10.0% (for 306/3875), respectively, in these cases. Please explain the differences.

Response:

In the footnote to Table 9-7 on page 223 of the interim clinical study report for Study CZOL446H2301 it states the following: "The event rate is from Kaplan-Meier estimate at Month 36 (the approximate median duration of follow-up)." The Kaplan-Meier estimates provided in Table 9-7 reflect the cumulative event rate at Month 36 (Day 1095) in the study.

The Kaplan-Meier estimates calculated by the Agency are based on all events that occurred in the study. The final statistical analysis plan states that Month 36 Kaplan-Meier estimate will be presented for all time-to-event clinical fracture endpoints because this point in time represents the median duration of follow-up for patients in the study. These estimates should only be viewed as a descriptive statistic of the cumulative event rate over time for clinical fracture rates in the same way that one would report mean, median or inter-quartile range for other continuous endpoints. The number of patients at risk for a fracture event after Month 36 declines rapidly after this timepoint from 2250 patients at risk in zoledronic acid group at Day 1071 to 123 patients at risk when the last event occurred at Day 1120. This rapid decline occurs since it was specified in the protocol that all patients should return by Month 36 for their final visit assessment with a visit window of only -1 month (Month 35). Thus, any events that occur after Month 36 would substantially impact the cumulative event rate and potentially cause misinterpretation of the differences between treatment groups. However, it should be made clear that all test statistics (log-rank tests and hazard ratios computed from the Cox proportional hazards regression model) included all events that occurred up to Month 39 (Day 1186) as part of the analysis visit window for clinical fractures described in the final statistical analysis plan. This window for calculating the formal test statistics for the clinical fracture endpoints was all encompassing for all clinical fractures that were confirmed in the study.

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/s/

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