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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-223 /SE5-016
Drug Name:	Zometa (zoledronic acid) intravaneous injection (i.v.) 4 mg lyophilized powder
Indication(s):	Treatment of children with Osteogenesis Imperfecta (OI)
Applicant:	Novartis
Date(s):	Submitted September 21, 2007
	User fee date March 24, 2008
Review Priority:	Priority
Biometrics Division:	Division of Biometrics II (HFD-715)
Statistical Reviewer:	Lee-Ping Pian, Ph.D.
Concurring Reviewers:	Todd Sahlroot, Ph.D.
Medical Division:	Division of Metabolic and Endocrine Products (HFD-510)
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Keywords: NDA, clinical studies, pediatric exclusivity, active control/non-inferiority

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EXECUTIVE SUMMARY

Zometa (zoledronic acid) injection was initially approved on August 20, 2001 for treatment for hypercalcemia of malignancy and treatment of patients with multiple myeloma and documented bone metastases from solid tumors. The Pediatric Written Request Letter was issued on August 19, 2002 and subsequently amended on November 19, 2002 and August 30, 2006.

This submission includes a pediatric study for the fulfillment of the Pediatric Written Request (WR). The sponsor is proposing to include the study in the label only if the potential benefit outweighs the potential risk.

The Written Request stated that the study should be a randomized, parallel-group study to compare the safety and efficacy of intravenous zoledronic acid to intravenous pamidronate in the treatment of children with moderate-to-severe Osteogenesis imperfecta (OI). The WR stated that patients should be 1 to 17 years of age with at least 1/3 of the patients 12 months through 8 years of age.

The primary endpoint was a comparison of the percent change in lumbar spine bone mineral density (BMD) from baseline to month 12 in zoledronic acid-treated patients versus pamidronate-treated patients. Secondary endpoints included the number of clinical fractures over a one-year period. In addition, bone pain, height or supine length, and biochemical markers of bone turnover were secondary endpoints. Biochemical marker data were not collected in patients <3 years of age.

The non-inferiority treatment group comparisons for percent change from baseline to month 12 percent change in lumbar spine BMD applied a margin of -13%. The WR stated that the ultimate selection of the NI margin was a review issue based on available data at the time of the review. With 66 patients per treatment group, the trial had 80% power to rule out a -13% NI margin assuming zoledronic acid was 2% superior to pamidronate in lumbar spine BMD. The calculation was based on a one-sided 2.5% level of significance, standard deviation of 29% and a 10% dropout rate.

The Data Safety Monitoring Board recommended patients with type I OI should receive no further study drug, regardless of study drug assignment based on the conclusion that there was an increased incidence of femoral fracture in Type I OI patients during the course of the evaluation period. No type I OI patient had been treated after December 13, 2006. The study completed on May 9, 2007.

1.1 Conclusions and Recommendations

Zoledronic acid was noninferior to Pamidronate in percent change from baseline in lumbar spine BMD at month 12. The lower bound of the 95% confidence interval for the treatment difference was -1% and fell within the -13% non-inferiority margin (Table 1).

Table 1 Percent change from baseline to Month 12 in lumbar spine BMD by treatment - ITT, LOCF

Treatment	n	Baseline BMD	% change LSM,12-M	LSM Difference* (95% CI) 12-M (LOCF)
Zoledronic acid	63	0.41	46%	5% (-1, 12)

		(0.14)		p=0.1
Pamidronate	68	0.44 (0.17)	41%	

*analysis of covariance on percent change from baseline with baseline BMD value as covariate and treatment, region, gender, and puberty stage as fixed effects

1.2 Brief Overview of Clinical Studies

Study 2202-A was an open-label, multicenter, randomized, parallel-group study to compare the safety and efficacy of zoledronic acid (0.025 mg/kg or 0.05 mg/kg, dependent upon age) to intravenous pamidronate (1.5 mg/kg, 2.25 mg/kg, or 3.0 mg/kg – total dose over three days, dependent upon age) in pediatric patients who were 1 to 17 years of age with severe osteogenesis imperfecta for 12 months. The definition for severe phenotypic OI are OI type III or IV, or OI type I and ≥3 minimal trauma fractures (including vertebral fractures) in the previous 2 years or with a history of limb deformity requiring surgery.

The primary objective was to demonstrate that zoledronic acid is non-inferior to pamidronate with respect to the percentage change from baseline in lumbar spine bone mineral density (LS BMD) at month 12. The noninferiority margin was proposed at -13%. Secondary efficacy variables included change from baseline in lumbar spine Z-score at month 12, change from baseline infemoral neck BMC at month 6 and 12, and number of clinical fractures over a year (frequency and time to first fracture).

Twenty centers in 9 countries randomized a total of 155 patients of which 152 contributed to safety analyses (zoledronic acid 74, pamidronate 78) and 131 patients (zoledronic acid 63, pamidronate 68) were in the ITT population for the primary efficacy analysis. Of these patients, 107 contributed to the completer analysis (zoledronic acid 51 and pamidronate 56). The percentages of patients distributed by OI phenotype were 49%, 22%, 29%, respectively for types 1, 3 and 4.

The doses and regimen for each of the treatment groups were weight and age dependent, which is outlined in Table 2.

Table 2 Treatment regimen

Treatment	Age group	Dose	Infusion duration	Infusion frequency
Zoledronic acid	1 - <3 years	0.025 mg/kg	30-45 mins	Every 3 months
	3 - 17 years	0.05 mg/kg	30 mins	Every 3 months
Pamidronate	1 - <2 years	0.5 mg/kg/day x 3 days	Over 4 hours	Every 2 months
	2 - <3years	0.75mg/kg/day x 3 days	Over 4 hours	Every 3 months
	3 -17 years	1.0 mg/kg/day x 3 days	Over 4 hours	Every 3 months

1.3 Statistical Issues and Findings

The primary analysis (t-test) and the supporting analysis ANCOVA with baseline lumbar spine BMD as a covariate and treatment, region (North America and rest of the world), gender and

pubertal stage as fixed effects produced the same non-inferiority results. However, the 97.5% lower bound of the confidence interval was above 0 for the t-test (Zometa superior) and less than zero for ANCOVA (Zometa not superior to Pamidronate). The results, therefore, were not robust with respect to the superiority claim.

2. INTRODUCTION

2.1 Overview

Osteogenesis imperfecta (OI) comprises a group of disorders principally (but not always) affecting type I collagen which result in increased bone fragility; hence the common name for the condition "brittle bone disease". The clinical classification of the disease divides the condition into the Sillence classification of Types I-IV.
Type I patients have mild non-deforming disease. Type III is the most severe form of OI in affected children who survive infancy, whereas patients with type IV have mild to moderate bone deformities and can include all individuals who are not clearly a part of the type I, II or III classification groups

This randomized, open-label study was designed to evaluate the efficacy and safety of intravenous zoledronic acid compared to intravenous pamidronate in children with severe osteogenesis imperfecta. One hundred and fifty five patients, who were between 1 to 17 years of age, all inclusive, were randomized to either zoledronic acid or pamidronate in a 1:1 ratio.

2.2 Data Sources

The following are links to the study report and the electronic data, respectively.
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\\Cdsesub1\N21223\S_016\2007-11-20\crt\datasets

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The patient population for the primary efficacy analysis on percent change from baseline was the ITT population with patients who had available data at both baseline and at least one post-baseline visit. Missing values were imputed using the last post-treatment observation carried forward (LOCF). If a patient did not have a baseline measurement or was lost to follow-up without any post-baseline measurements, he/she was not included in the analysis.

Countries were pooled into two regions to assess any geographical differences in most of the statistical models:
1. North America: Canada (center # 201) and USA (center # 501, 502, 503, 504, 506,

507, 508, 512, 514, 515)
2. ROW (Rest Of World): Belgium (101), France (302), South Africa (601), Hungary (801), Poland (850), Finland (901), Great Britain (401, 402, 403)

Patient Disposition, Demographic and Baseline Characteristics

A total of 155 patients were randomized. Table 3 summarizes patient disposition for the ITT population. Ninety-one percent of patients completed the study.

Table 3 Patient disposition (ITT)

	Zoledronic acid	Pamidronate	Total
	N=74	N=76	N=150
Patient Status	**n (%)**	**n (%)**	**n (%)**
Completed	68 (91.9)	69 (90.8)	137 (91.3)
Discontinued	6 (8.1)	7 (9.2)	13 (8.7)
Subject withdrew consent	3 (4.1)	3 (3.9)	6 (4.0)
Adverse Event(s)	2 (2.7)	2 (2.6)	4 (2.7)
Lost to follow-up	1 (1.4)	2 (2.6)	3 (2.0)

Baseline demographics are summarized in Table 4 (from sponsor table 11-2). Approximately 50% of patients were between 12 months and 8 years of age which exceeded the 33% proportion specified in the WR.

Table 4 Baseline demographics (ITT)

		Zoledronic acid	Pamidronate	Total
		N=74	N=76	N=150
Age (years)	n	74	76	150
	Mean (SD)	8.6 (4.25)	8.5 (4.20)	8.5 (4.21)
	Median	8.5	9.0	9.0
	Min - max	1 - 16	1 - 17	1 - 17
Age group – n (%)	1 - <2 years	1 (1.4)	1 (1.3)	2 (1.3)
	2 - <3 years	6 (8.1)	5 (6.6)	11 (7.3)
	3 - <9 years	30 (40.5)	31 (40.8)	61 (40.7)
	≥9 years	37 (50.0)	39 (51.3)	76 (50.7)
Sex – n (%)	Female	36 (48.6)	31 (40.8)	67 (44.7)
	Male	38 (51.4)	45 (59.2)	83 (55.3)
Race – n (%)	Caucasian	63 (85.1)	63 (82.9)	126 (84.0)
	Black	6 (8.1)	7 (9.2)	13 (8.7)
	Oriental	3 (4.1)	1 (1.3)	4 (2.7)
	Other	2 (2.7)	5 (6.6)	7 (4.7)
Weight (kg)	n	74	76	150
	Mean (SD)	25.6 (14.9)	28.3 (16.0)	27.0 (15.5)
	Median	20.7	24.4	23.5
	Min - max	7.4 - 90.0	6.3 - 97.0	6.3 - 97.0
Height/supine length (cm)	n	73	74	147
	Mean (SD)	112.8 (24.1)	116.7 (24.9)	114.8 (24.5)
	Median	114.0	117.0	116.0
	Min - max	63.0 - 174.0	51.0 - 164.0	51.0 - 174.0
BMI (kg/m2)	n	73	74	147
	Mean (SD)	19.0 (5.9)	19.9 (6.9)	19.5 (6.4)
	Median	17.40	17.95	17.7
	Min - max	12.6 - 44.2	10.9 - 53.8	10.9 - 53.8
Pubertal stage - n(%)	Pre-adolescence	22 (29.7)	20 (26.3)	42 (28.0)
	Early adolescence	38 (51.4)	44 (57.9)	82 (54.7)
	Middle adolescence	6 (8.1)	7 (9.2)	13 (8.7)
	Late adolescence	8 (10.8)	5 (6.6)	13 (8.7)

Table 5 is from the sponsor's Table 11-3 which displays the baseline disease characteristics.

Table 5 Disease background and baseline characteristics (ITT)

		Zoledronic acid	Pamidronate	Total
		N=74	N=76	N=150
OI phenotype - n (%)	I	38 (50.7)	35 (46.1)	73 (48.7)
	III	18 (24.3)	15 (19.7)	33 (22.0)
	IV	18 (24.0)	26 (34.2)	44 (29.3)
Age at OI diagnosis	n	74	76	150
(years)	Mean (SD)	2.2 (2.99)	2.0 (3.28)	2.1 (3.13)
	Median	1.0	1.0	1.0
	Min - max	0 - 11	0 - 14	0 - 14
Lumbar spine BMD	n	64	68	132
(g/cm2)	Mean (SD)	0.42 (0.14)	0.44 (0.17)	0.43 (0.16)
	Median	0.41	0.40	0.41
	Min - max	0.13 - 0.76	0.16 - 0.94	0.13 - 0.94
Lumbar spine Z-score†	n	44	49	93
	Mean (SD)	-2.80 (1.25)	-2.53 (1.52)	-2.66 (1.40)
	Median	-2.70	-2.70	-2.70
	Min - max	-5.9 - -0.1	-7.1 - 0.7	-7.1 - 0.7
Femoral neck BMC	n	43	49	92
(g)	Mean (SD)	1.36 (0.78)	2.13 (4.00)	1.77 (2.97)
	Median	1.12	1.39	1.32
	Min - max	0.27 - 3.31	0.19 - 28.74‡	0.19 - 28.74‡
History of fracture	Yes	73 (98.6)	73 (96.1)	146 (97.3)
n (%)	No	1 (1.4)	3 (3.9)	4 (2.7)
No. of patients with fractures in the last 12 months - prior to first infusion				
n (%)		57 (77.0)	60 (78.9)	117 (78.0)
No. of fractures per patient in the last 12 months - prior to first infusion				
	n	74	74	148
	Mean (SD)	3.0 (3.28)	2.3 (1.74)	2.6 (2.64)
	Median	2.5	2.0	2.0
	Min - max	0 - 20	0 - 7	0 - 20
No. of fractures per patient in lifetime - prior to first infusion				
	n	74	76	150
	Mean (SD)	18.9 (24.25)	16.5 (26.54)	17.7 (25.38)
	Median	10.5	9.5	10.0
	Min - max	0 - 115	0 - 200	0 - 200

† Lumbar spine Z-score data includes only patients aged ≥3 years who were imaged on the Hologic equipment and patients aged ≥5 years imaged on the Lunar equipment which have manufacturer validated normative ranges.
‡ Patient POL/0850/00015: femoral neck BMC noted as "abnormally high" on eCRF.

Statistical Methodologies

The protocol proposed t-test for the primary analysis and analysis of covariance (ANCOVA) for the supportive analysis. In addition, the non-parametric ANCOVA was performed to the ranked score of BMD percent change from baseline in lumbar spine. All three methods showed non-inferiority of zoledronic acid to pamidronate in the primary efficacy variable.

Results and Conclusions

The objective of non-inferiority of zoledronic acid to pamidronate in lumbar spine BMD percent change from baseline was achieved. Superiority was also demonstrated by the sponsor's primary analysis using a t-test (Table 5) as evidenced by the lower bound of the confidence interval was greater than 0 (0.4%). However, the sponsor's supportive analysis using ANCOVA demonstrated non-inferiority only (Table 1). Figure 1 displays the percent change in BMD over time (at 6 months and 12 months) by treatment group and Figure 2 the cumulative distribution of the BMD percent change from baseline to month 12. Figure 3 displays the BMD percent change by OI phenotype.

Table 6 Percentage change from baseline in lumbar spine BMD at month 12: treatment comparisons by population

Population	Treatment	N	Mean (SE)*	Mean difference*	95% CI (1)
ITT (LOCF)	Zoledronic acid	63	42.7 (2.8)	8.01	0.4, 15.7
	Pamidronate	68	34.7 (2.7)		
Per-protocol	Zoledronic acid	51	45.6 (3.0)	10.0	1.5, 18.6
	Pamidronate	55	35.6 (3.1)		
Completers	Zoledronic acid	51	45.6 (3.0)	9.8	1.3, 18.3
	Pamidronate	56	35.8 (3.0)		

*Mean, mean difference (zoledronic acid minus pamidronate) and 95% CI of mean difference are based on t-distribution.

Figure 1 BMD percent change from baseline by treatment group

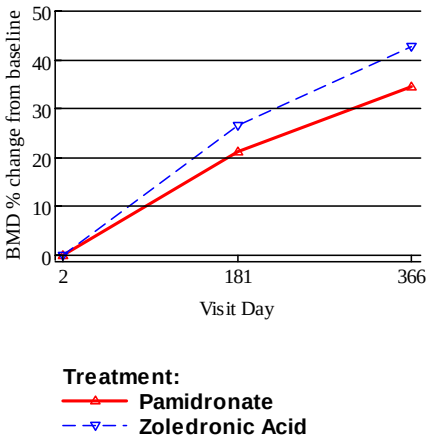


Figure 2 Cumulative distribution of BMD % change from baseline by treatment

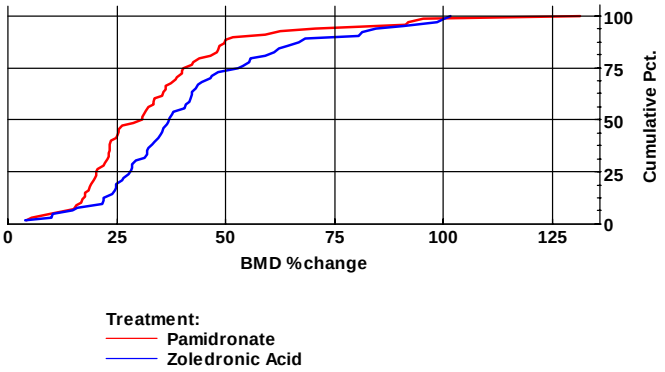
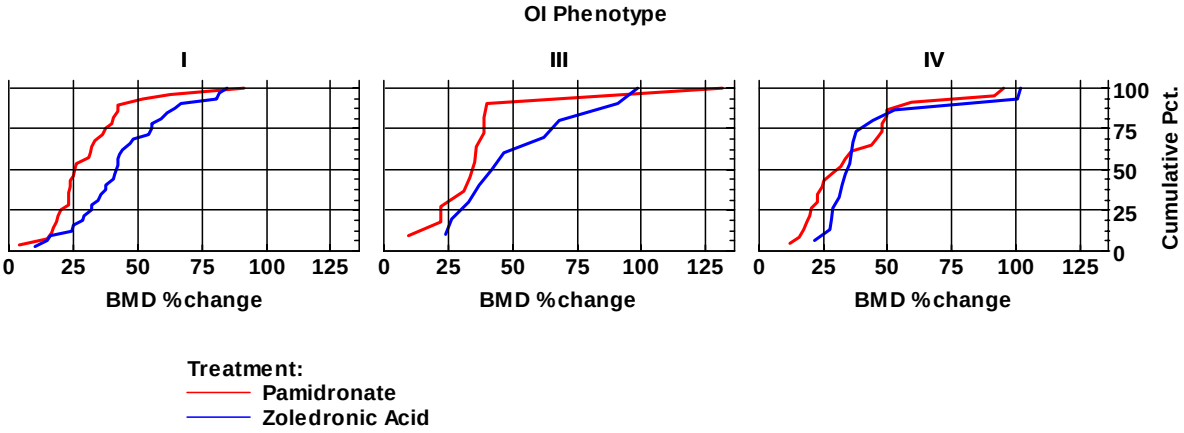


Figure 3 Cumulative distribution of BMD % change from baseline by treatment and OI phenotype



3.2 Evaluation of Safety

The medical Reviewer, William Lubas, M.D. requested a between group comparison of the change from baseline in number of fractures per year. Table 7 is a summary of the analysis. The sample size is not sufficient to detect the difference as indicated by p values of 0.4 and 1.0. Figure 4 and 5 displays the cumulative distribution of the change from baseline in clinical fracture by treatment group overall and by OI phenotype, respectively.

Table 7 Changes in numbers of clinical fractures per year by treatment group and OI type

	Overall		OI Type I		OI Type III or IV	
	Zoledronic	**Pamidronate**	**Zoledronic**	**Pamidronate**	**Zoledronic**	**Pamidronate**
Baseline: fractures per patient that occurred in the 12 months prior to first infusion						
n	68	67	33	31	35	36
Mean (SD)	3.00 (3.37)	2.22 (1.75)	2.88 (2.62)	2.61 (1.61)	3.11 (3.99)	1.89 (1.82)
Median	3	2	3	3	2	2
P	0.1		0.6		0.1	
Post-baseline: fractures per patient that occurred in the 12 months after first infusion						
n	68	67	33	31	35	36

	Overall		OI Type I		OI Type III or IV	
	Zoledronic	**Pamidronate**	**Zoledronic**	**Pamidronate**	**Zoledronic**	**Pamidronate**
Mean (SD)	1.04 (3.00)	0.67 (1.21)	0.67 (0.74)	0.39 (0.72)	1.40 (4.12)	0.92 (1.48)
Median	0	0	1	0	0	0
P	0.3		0.1		0.5	
Change in numbers of fractures per patient from baseline: post-baseline - baseline						
n	68	67	33	31	35	36
Mean (SD)	-1.96 (3.84)	-1.55 (2.08)	-2.21 (2.77)	-2.23 (1.69)	-1.71 (4.66)	-0.97 (2.22)
Median	1	1	2	2	1	1
Mean difference (95% CI) Z - P	-0.4 (-1.5, 0.6)		0.01 (-1.14, 1.17)		-0.74 (-2.46, 0.98)	
p-value	0.4		1.0		0.4	

Z: Zoledronic acid, P: Pamidronate

Figure 4 Cumulative distribution of change from baseline in # of clinical fractures/patient/year by treatment

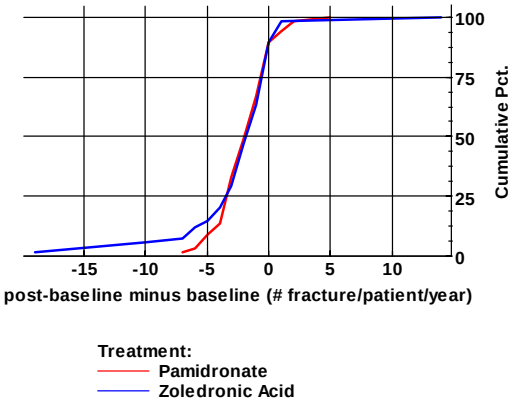


Figure 5 Cumulative distribution of change from baseline in # of clinical fractures/patient/year by treatment and OI phenotype

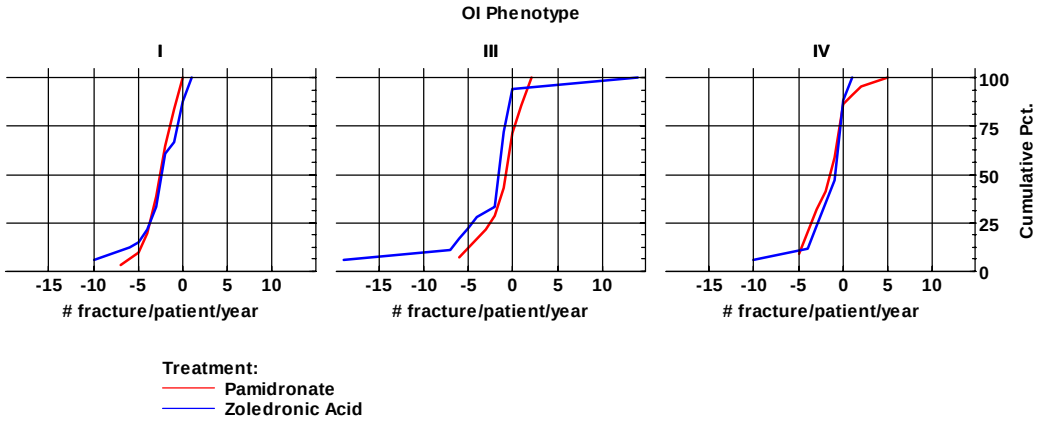


Figure 6 displays the change from baseline in the number of clinical fractures/patient/year by the BMD change at Month 12 for all patients. Figure 7 shows the same data by OI phenotype.

Figure 6 Change from baseline in # of clinical fractures by percent change in BMD

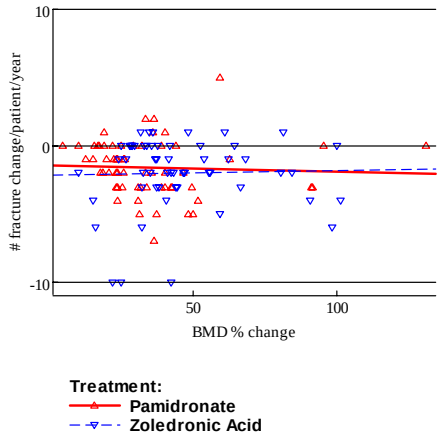
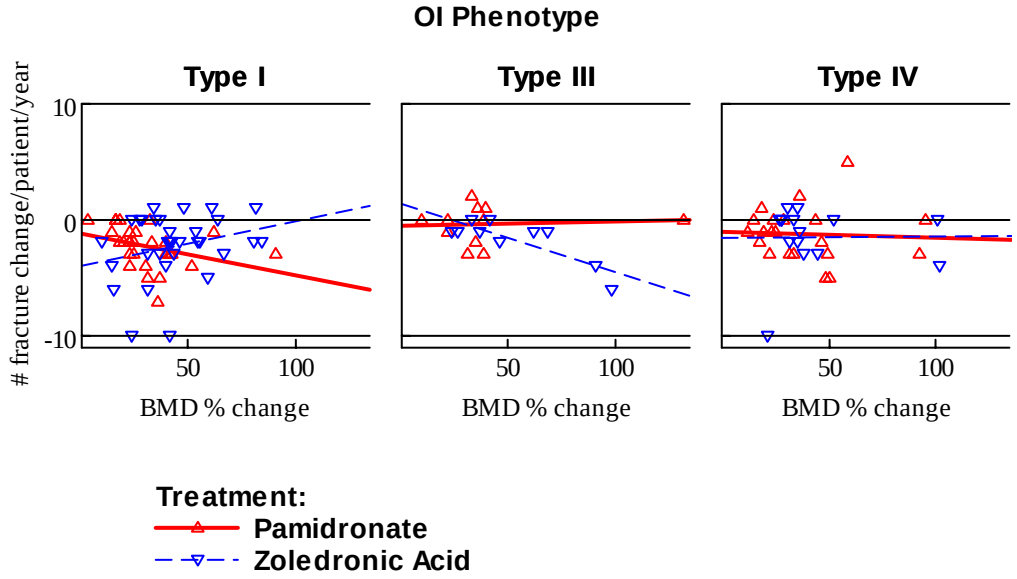


Figure 7 Change from baseline in # of clinical fractures by % change in BMD



4. SUMMARY AND CONCLUSIONS

The sponsor provided no label information for this study in pediatric patients. The study demonstrated Zoledronic acid was non-inferior to Pamidronate in the primary efficacy variable, lumbar spine BMD percent change from baseline to Month 12. However, superiority of Zoledronic to pamidronate was not consistently demonstrated; the primary efficacy analysis using the t-test showed superiority while the prespecified supportive analysis of covariance did not.

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