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:	20-835 / SE-035
Drug Name:	ACTONEL® (risedronate sodium) 30mg tablets
Indication(s):	Treatment and prevention of postmenopausal osteoporosis
Applicant:	Proctor & Gamble Pharmaceuticals, Inc.
Date(s):	Submission Date: 1/26/2009
	PDUFA Due Date: 7/26/2009
Review Priority:	Priority
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Keywords: NDA review, clinical studies

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1.1 Conclusions and Recommendations

The results support the efficacy of risedronate sodium in improving bone mineral density (BMD) in pediatric patients with osteogenesis imperfecta compared to placebo patients. However, the results also demonstrated statistically significant increase in the incidence of new morphometric vertebral fractures in risedronate sodium treated patients compared to placebo treated patients.

From a statistical perspective, although we agree that treatment with risedronate sodium improves bone mineral density, but this improvement appeared to outweigh the increased risk of new fractures in pediatric patients with osteogenesis imperfecta.

1.2 Background

Osteogenesis imperfecta (OI) is a disease associated with very low bone mass. Children with OI suffer recurrent fractures resulting in pain, deformity, and disability. ACTONEL® (risedronate sodium) is a biphosphonate currently approved for the prevention and treatment of postmenopausal osteoporosis, treatment to increase bone mass in men with osteoporosis, treatment and prevention of glucocorticoid-induced osteoporosis and treatment of Paget's disease.

This efficacy supplement was submitted to support the changes to the ACTONEL labeling regarding use in pediatric patients to fulfill the Pediatric Written Request (PWR) issued by FDA on January 8, 2004 and to determine the exclusivity extension.

1.3 Statistical Issues and Findings

The sponsor's statistical plan included testing for secondary endpoints in a hierarchical order, putting one of the key secondary endpoint: the incidence of new vertebral fractures, last in the order. Therefore, if the preceding secondary endpoints are not statistically significant, this endpoint would not be tested. While this closed testing procedure was appropriate method for controlling type I error rate, but the ordering of the hypothesis in such a situation are based on clinical justification. As per clinical team, the incidence of new vertebral fracture is one of the important endpoint to evaluate. Although, the sponsor performed analysis of this endpoint, but they used Fisher's Exact Test instead of the pre-specified Cochran-Mantel-Haenszel (CMH) test to control for two strata: age group (4 through 9 and 10 through 15) and pooled country. To address the issue, we performed analysis on fracture data using the CMH test. Our results showed that there was a statistically significant difference in new fracture (31.9% and 16.7, p-value = 0.0448) between risedronate and placebo group, respectively, while the sponsor's showed no statistically significant difference between the treatments. Also there are higher rate of vertebral fractures in 4 to 9 age group than that of 10 to 15 years age group.

From a statistical perspective, although we agree that risedronate sodium is efficacious in improving BMD, but the increased risk of new fracture is a potential clinical concern that needs to be addressed prior to use in pediatric patients with osteogenesis imperfecta.

2. INTRODUCTION

2.1 Overview

The Applicant has submitted one pivotal, Phase 3 study (Study 2003100) to support the changes to the ACTONEL labeling regarding use in pediatric patients in order to determine the exclusivity extension. Table 1 presents a brief summary of this study.

Table 1: Brief Summary of Clinical Study for ACTONEL® (risedronate sodium)

Study Number (No. of Sites / Country) Dates of Study Conduct	Subject Population	Primary Endpoints	Treatments	Number Randomized (ITT)	Design[1]
2003100 (6/ U.S. & 13/ Europe & 2/ Others) Nov. 2004 to Apr. 2008	OI Patients ≥ 4 and < 16 years of age with weight ≥ 10 kg and high risk of fractures.	The percent change from baseline in lumbar spine BMD at month 12	Risedronate Placebo **Total**	97 (94) 50 (49) **147 (143)**	R, DB, PC, MC, PG

[1] R = Randomized, DB = Double-blind, PC = Placebo Control, MC = Multi Center, PG = Parallel Group

This was a 1-year, randomized, double-blind, placebo-controlled, multicenter, parallel group study with 2 additional years of open-label treatment. Pediatric patients 4 years or older with OI were enrolled at 20 study centers in North America, Australia, Europe, South America, and South Africa. Patients weighing 10-30 kg received risedronate 2.5 mg or placebo daily and patients weighing more than 30 kg received risedronate 5 mg or placebo daily. All patients were required to take a daily supplement of calcium and vitamin D. The objective of this study was to assess the safety and efficacy of risedronate sodium in this pediatric patient population.

2.2 Data Sources

The study report and additional information for this study were submitted electronically. The SAS data sets for the study were complete and well documented. These items are located in the Electronic Document Room at \\Cdsesub1\evsprod\NDA020835\0052 under submission date 1/26/2009.

3. STATISTICAL EVALUATION

3.1 Design of Study 2003100

Study 2003100 was a 1-year, randomized, double-blind, placebo-controlled, multicenter, parallel group study with 2 additional years of open-label treatment, to determine the efficacy of risedronate compared to placebo in children ≥ 4 to < 16 years of age with osteogenesis imperfecta (OI). Eligible patients were stratified by age (4 through 9 and 10 through 15) within each country and then randomized (2:1, active vs. placebo) to receive either risedronate tablet (2.5 mg or 5 mg) or matched placebo to be taken once a day for 1 year. Patients weighing 10-30 kg received risedronate 2.5 mg or placebo daily and patients weighing more than 30 kg received risedronate 5 mg or placebo daily. All patients have received risedronate treatment during the 2-year open-label period.

Dual-energy x-ray absorptiometry (DXA) scans of the lumbar spine and total body were acquired at Screening and Months 6 and 12, and an x-ray of the hand/wrist was acquired at Screening or baseline, and Month 12. Clinical laboratory tests were performed at several visits. Bone biopsies were performed at baseline and Month 12 on all patients who gave consent.

The primary efficacy assessment based on the dual x-ray absorption (DXA) measurement of the lumbar spine and a single DXA measurement of the total body at baseline and at Month 12. The lumbar spine DXA scan was evaluated by the central facility, (b) (4) The primary efficacy population was the ITT population, which consisted of all patients who were randomized and took at least one dose of study drug.

The primary endpoint was the percent change from baseline in lumbar spine BMD at month 12 using LOCF on ITT study population. The following null hypothesis was tested:

$$H_0: \mu_{Rised} = \mu_{PL} \qquad \text{Vs.} \quad H_A: \mu_{Rised} \neq \mu_{PL}$$

where μ_{Rised} is the population mean percent change from baseline for the risedronate treatment group and μ_{PL} is the population mean percent change from baseline for the placebo group. The primary statistical analysis was conducted using one-way ANCOVA model for ITT and PP populations.

In addition, the following secondary endpoints were also evaluated:

1. percent change from Baseline in total body BMC at endpoint
2. change from Baseline in Quality of Life (QOL) as determined by PedsQL™ pediatric QOL questionnaire at endpoint
3. improvement from Baseline in musculoskeletal pain relief as determined by FACES pain rating scale at endpoint.
4. incidence and rate of all clinical fractures, both vertebral and non-vertebral, over the first year using recurrent fractures analysis
5. incidence and rate of clinical non-vertebral fractures over the first year using recurrent fractures analysis
6. incidence and rate of new morphometric vertebral fractures over the first year.

All secondary efficacy analyses were based on the ITT population. In order to control the type I error rate of 0.05 on the secondary efficacy endpoints, a closed testing procedure was used in the order above.

The same model as described in the primary efficacy analysis was used for all the continuous secondary efficacy variables. Cochran-Mantel-Haenszel test stratified by age group and pooled country was the planned statistical test for the treatment differences between risedronate and placebo in incidence of morphometric vertebral fractures.

3.2 Results

3.2.1 Subject Disposition and Baseline Characteristics

A total of 231 patients were screened, of which 147 patients were randomized (97 to receive risedronate and 50 to receive placebo). Of these, 143 received at least one dose of study drug. Four (4) patients (1 placebo and 3 risedronate) never received study drug. No patients in the placebo group and 7 (7.4%) patients in the risedronate group discontinued on or prior to Month 12. The most common reason for discontinuation prior to Month 12 was voluntary withdrawal (0 in placebo; 4 (4.3%) in risedronate group). The summary of analysis datasets are summarized in Table 2.

Table 2: Analysis Populations

Analysis Population	Treatment Group		
	Placebo	Risendronate	Total
	N (%)	N (%)	N (%)
Randomized	50	97	147
Treated (ITT)	49 (100%)	94 (100%)	143 (100%)
Completed Month 12	49 (100%)	87 (92.6%)	136 (95.1%)
Discontinued Prior to Month 12	0 (0.0%)	7 (7.4%)	7 (4.9%)
Adverse Event	0 (0.0%)	1 (1.1%)	1 (0.7%)
Protocol Violation	0 (0.0%)	1 (1.1%)	1 (0.7%)
Voluntary Withdrawal	0 (0.0%)	4 (4.3%)	4 (2.8%)
Other: Lost to Follow-up	0 (0.0%)	1 (1.1%)	1 (0.7%)

(Source: Reviewer's Analysis)

For ITT population, demographic and baseline characteristics for both treatment groups were similar with respect to age (median age of 9 years), and gender (50% male and 82% Caucasian). There were 81 patients in the 4 to 9 years old age group and 62 patients in the 10 to 15 years old age group; and the percentage of patients in these age groups were similar for the 2 treatment groups.

The Z-score for lumbar spine BMD at baseline was similar for both groups. However, there was a statistically significant difference between the 2 groups for the total body Z-score (p=0.0444).

Table 3: Bone Mineral Density at Baseline (ITT Population)

Parameter Statistic	Placebo (N=49)	Risedronate (N=94)	p-value
Z-score for Lumbar Spine			
n	48	89	0.9084
Mean (SD)	-2.091 (1.132)	-2.071 (0.913)	
Median	-2.025	-1.975	
Min, Max	-5.22, 0.89	-5.22, -0.44	
Z-score for Total Body			
n	45	88	0.0444
Mean (SD)	-1.824 (1.060)	-1.417 (1.112)	
Median	-1.900	-1.200	
Min, Max	-4.20, 0.50	-5.20, 1.10	

(Source: 2003100-HMR4003I/3001 Study Report for Year 1; Table 7, page 39)

3.2.2 Efficacy Results

The Applicant's result for the primary efficacy endpoint is presented in Table 4. The mean percent change from baseline in lumbar spine BMD was 7.6% for the placebo group and 16.3% for the risedronate group at Endpoint (Month 12 using LOCF). The results from the analysis using the per-protocol population with evaluable data at baseline and Month 12 were consistent with the primary efficacy analysis using ITT population (?). I concur with the Applicant's results.

Table 4: Lumbar Spine BMD – Percent Change from Baseline (Least Squares Means)

	Placebo (N=49)		Risedronate (N=94)		Risedronate-Placebo	
Population Visit	n	LS Mean (95% CI)	n	LS Mean (95% CI)	LS Mean Diff (95% CI)	p-value
Intent-to-treat						
Baseline (g/cm^2)	47	0.538	86	0.553		
Endpoint	**47**	**7.594*** **(5.081, 10.107)**	**86**	**16.289*** **(14.416, 18.162)**	**8.695** **(5.688, 11.703)**	**<0.0001**
Per-protocol						
Baseline (g/cm^2)	41	0.542	68	0.550		
Month 12	41	8.270* (5.718, 10.822)	68	16.509* (14.495, 18.523)	8.239 (5.127, 11.351)	<0.0001

(Source: 2003100-HMR4003I/3001 Study Report for Year 1; Table 13, page 45)

According to the Applicant, because the test result of the second endpoint in the ordered list of secondary endpoints was not statistically significant, the type-I error rate was protected only for the primary efficacy analysis (percent change from baseline in lumbar spine BMD at Endpoint) and the first analysis in the closed testing procedure (percent change from baseline in total body BMC at Endpoint). Despite lack of hierarchical ordering of secondary endpoints by clinical importance, the sponsor reported the results of the incidence of new morphometric vertebral fractures. Using exact test, without pre-specified adjustment for age and country, their result did

not show any statistically significant (p-value = 0.0693) differences in new fractures between risedronate and placebo treated patients.

We conducted logistic regression analysis which included age group, gender, race and pooled country as covariates. Only age group was statistically significant. Therefore, the Cochran-Mantel-Haenszel test stratified by age group was used to test the treatment difference. There were 31.9% and 16.7% new fracture in the risedronate and placebo group, respectively, which was statistically significant (p-value = 0.0448). However, the p-value reported by the Applicant was 0.0693 using Fisher's Exact Test. As showed in Table 5, there are more new fractures in patients with age between 4 and 9. The data by OI type (Type I or Type III and IV) are consistent with what we found for overall results.

Table 5: Patients with New Morphometric Vertebral Fractures at Endpoint (Intent-to-treat)

Age Group	Treatment Group	At Least One New Vertebral Fracture	No New Vertebral Fracture	Total	p-value
All Ages	**Placebo**	8 (16.7%)	40 (83.3%)	48	0.0448
	Risedronate	29 (31.9%)	62 (68.1%)	91	
4-9 years	**Placebo**	7 (25.0%)	21 (75.0%)	28	0.2457
	Risedronate	19 (38.0%)	31 (62.0%)	50	
10-15 years	**Placebo**	1 (5.0%)	19 (95.0%)	20	0.0667
	Risedronate	10 (24.4%)	31 (75.6%)	41	

(Source: Reviewer's Analysis)

3.3 Evaluation of Safety

Details of safety analysis can be found in clinical reviewer's review.

4. FINDINGS IN SUBGROUP POPULATIONS

Subgroup analyses were performed for the primary efficacy endpoint by age category (age < 10, and age ≥ 10), weight category (10-30 kg and > 30 kg), and the OI type at baseline based on the ITT population. The results were consistent across these subgroups.

5. CONCLUSIONS

The results based on single study supports the efficacy of risendronate sodium in improving the bone mineral density after one year of treatment. However, treatment with risedronate also showed a statistically significant increase in new vertebral fractures compared to placebo. Therefore, the benefit seen with regards to bone mineral density appears to be outweighed by the risk of fracture associated with risendronate sodium in pediatric patients with osteogenesis imperfecta.

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