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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: sanofi-aventis Procter & Gamble Pharmaceuticals **Drug substance(s):** risedronate	**Study Identifier:** NCT00353080 **Study code:** EFC6064 (HMR4003B/3001)
Title of the study: A two-year, multicenter, double-blind, randomized, placebo-controlled and parallel group study of oral risedronate 5 mg daily in the prevention of osteoporosis in osteopenic postmenopausal women (more than 5 years postmenopausal)	
Study center(s): Multicenter, multinational (14 active centers in Europe)	
Study period: Date first subject enrolled: 04-Dec-2002 Date last subject completed: 20-Apr-2005	
Phase of development: III	

Objectives:

Primary objective: To confirm the superiority of 5 mg daily risedronate as compared to placebo in maintaining or increasing bone mass in osteopenic postmenopausal women as assessed by percent changes from baseline in lumbar spine bone mineral density (BMD) at Month 24.

Secondary objectives:

- To confirm the efficacy of 5 mg daily risedronate in postmenopausal women as assessed by:
  - Percent changes in lumbar spine BMD at Month 12 as compared to placebo
  - Percent changes in proximal femur (total proximal femur, femoral neck, and trochanter) BMD from baseline at Month 12 and Month 24 as compared to placebo
  - Percent of responders to study treatment (subjects with a positive change in lumbar spine BMD from baseline) as compared to placebo at Month 12 and Month 24
  - Percent changes in bone turnover markers after 12 and 24 months of treatment as assessed by measurement of urinary type I collagen crosslinked N-telopeptide (U-NTX) and serum bone-specific alkaline phosphatase (S-BAP) levels
- To confirm general safety of 5 mg daily risedronate as compared to placebo

Methodology: Multinational, 2-year, randomized, double-blind, placebo-controlled, parallel group study in which subjects were randomized to receive either risedronate 5 mg daily or placebo in 2:1 ratio

Number of subjects: Planned: 159 Randomized: 171 Treated: 170

Diagnosis and criteria for inclusion:

The female subjects were to be postmenopausal for more than 5 years, or more than 5 years after surgical menopause and with at least one risk factor for osteoporosis. Menopause was defined as 12 months without menses based on medical history. Subjects who were postmenopausal secondary to surgery had to have serum FSH ≥30 U/L and estradiol ≤150 pmol/L. Major inclusion criteria were established for lumbar spine baseline T-score between –2.5 and –1 SD below the mean value in normal young women [0.772 g/cm^2 <lumbar spine BMD<0.937 g/cm^2 (Hologic) or 0.882 g/cm^2 <lumbar spine BMD<1.062 g/cm^2 (Lunar)].

Investigational product: risedronate

Dose: 5mg

Administration: oral – one tablet once daily

Duration of treatment: 24 months

Duration of observation: until 14 days after the date of the subject's last dose of investigational product

Reference therapy: placebo identical to risedronate 5mg tablet

Dose: not applicable

Administration: oral – one tablet once daily

Criteria for evaluation:

Efficacy:

The primary efficacy variable was the percent change from baseline to endpoint in lumbar spine BMD. The endpoint value was the Month 24 lumbar spine BMD value when available; when the Month 24 value was missing, a value was imputed using the last-observation-carried-forward (LOCF) principle.

Secondary efficacy variables were percent changes from baseline in lumbar spine BMD at Month 12 and Month 24; percent changes from baseline in proximal femur BMD at Month 12, Month 24, and endpoint; percent of responders (subjects with a positive change in lumbar spine BMD from baseline) at Month 12, Month 24, and endpoint; and percent changes in bone turnover markers (BTMs) after 12 and 24 months of treatment and at endpoint as assessed by measurement of U-NTX and S-BAP levels.

Safety:

Safety was evaluated by summaries of reported adverse events and changes in routine clinical laboratory tests and vital signs.

Statistical methods:

The primary efficacy variable was the percent change from baseline to endpoint in lumbar spine BMD with imputation using the LOCF principle. The primary analysis was based on the modified intention-to-treat (MITT) population (all subjects who received at least one dose of study medication and who had, for a given efficacy parameter, both a baseline and a post-baseline measurement). The MITT population was defined for a given efficacy parameter. The number of subjects included in each analysis could vary with the studied parameter depending on available data.

Analysis of the primary efficacy variable was performed using an analysis of variance (ANOVA) model that included factors for treatment and pooled investigative site. The analysis of lumbar spine BMD at endpoint in the per-protocol population (PP) and the analysis of covariance taking into account the baseline lumbar spine BMD as covariate were considered supportive of the primary efficacy analysis. The per-protocol population was defined as all ITT subjects with at least 18 months of treatment, an efficacy evaluation at or after 18 months, and no major protocol violation. Secondary efficacy variables were analyzed using the same ANOVA model as used for the primary efficacy variable.

All safety variables were analyzed using the safety population composed of all randomized subjects who received at least 1 dose of study medication. Subjects in this population were analyzed as treated. Safety was evaluated by summarizing the incidence of adverse events and changes from baseline and/or outside the normal range for clinical laboratory tests, vital signs, and physical examinations.

Summary:

Study population:

A total of 171 subjects were randomized in this study. Subject disposition is presented in the following table:

	Number (%) of subjects		
	Risedronate 5 mg Daily	Placebo	Overall
Screened			232
Randomized	114 (100.0)	57 (100.0)	171 (100.0)
Randomized but not treated	0 (0.0)	1 (1.8)	1 (0.6)
ITT population[a]	114 (100.0)	56 (98.2)	170 (99.4)
MITT population[b]	111 (97.4)	53 (93.0)	164 (95.9)
PP population[c]	92 (80.7)	40 (70.2)	132 (77.2)
Discontinued before study completion	16 (14.0)	12 (21.1)	28 (16.4)
Reason for discontinuation			
Adverse event	10 (8.8)	9 (15.8)	19 (11.1)
Protocol violation	1 (0.9)	0 (0.0)	1 (0.6)
Voluntary withdrawal without AE	4 (3.5)	3 (5.3)	7 (4.1)
Other	1 (0.9)	0 (0.0)	1 (0.6)
Completed study	98 (86.0)	45 (78.9)	143 (83.6)
Safety population[d]	115	55	170

[a] Intention-to-treat (ITT) Population: all subjects who were randomized and had received at least one dose of study medication (treatment group as randomized).

[b] Modified Intention-to-treat (MITT) population: all ITT subjects who had, for at least one efficacy parameter, both a baseline and a post-baseline measurement. The number of subjects represents the maximum number of subjects.

[c] Per-Protocol Population (PP): ITT subjects without major protocol violation, with at least 18 months of treatment, an efficacy evaluation at or after 18 months.

[d] Safety Population: all subjects who have received at least one dose of study medication (treatment group as treated).

Analysis of the demographics showed that in the overall ITT population, 50.6% of subjects were 65 years of age or older, 100% were Caucasian, and the mean number of years since last menses was 18.3 years. There were no statistically significant differences between treatment groups at baseline for lumbar spine BMD. One subject was not treated according to the randomization schedule: she was randomized to, and initially treated with, placebo, but was later mistakenly given risedronate for one month. This subject was considered a placebo subject in efficacy analyses and a risedronate subject in safety analyses.

Efficacy results:

The following table compares the percent change from baseline in lumbar spine BMD in the 5 mg daily risedronate group and in the placebo group in the MITT population.

	Risedronate 5 mg Daily		Placebo		Treatment comparison (risedronate – placebo)	
Visit	N	Mean[a] (SE)	N	Mean[a] (SE)	LS mean[a] difference (95% CI)	*P*-value[a]
Baseline BMD (g/cm^2)	111	0.84 (0.00)	53	0.84 (0.01)		0.5936
Percent change from baseline						
Month 12	98	3.07* (0.33)	43	0.44 (0.50)	2.63 (1.46; 3.80)	<0.0001
Month 24	95	4.58* (0.41)	43	0.29 (0.62)	4.28 (2.83; 5.73)	<0.0001
Endpoint	106	4.49* (0.38)	53	0.05 (0.54)	4.44 (3.14; 5.74)	<0.0001

* Indicates a statistically significant adjusted mean percent change (alpha=0.05) in BMD between baseline and the specified visit.

[a] Adjusted means, least square means, 95% CI, and *P*-values are from a 2-way ANOVA model with fixed effects for treatment and pooled center.
BMD = bone mineral density, MITT = modified intent to treat, LS = least squares, CI = confidence interval, ANOVA = analysis of variance.

There was a statistically significant increase from baseline in lumbar spine BMD at endpoint in the risedronate group as compared to the placebo group in the MITT population (p<0.0001).

The mean treatment difference between risedronate and placebo at endpoint was 4.44% [95% CI, 3.14%; 5.74%].

Efficacy results (cont'd):

There were statistically significant increases in lumbar spine BMD at Month 12 and Month 24 in the risedronate group as compared to the placebo group in the MITT population.

Lumbar spine BMD results in the PP population were consistent with those in the MITT population.

In addition, the lumbar spine BMD analysis was performed using an ANCOVA model to fulfill Swedish regulatory requirement. The results were also consistent with those in the MITT population.

The total proximal femur BMD, femoral neck BMD, and trochanter BMD at Month 12, Month 24, and endpoint were statistically significantly greater in the risedronate group than in the placebo group.

The percent decrease from baseline in BTMs after 12 and 24 months of treatment and at endpoint was significantly greater in the risedronate group than in the placebo group.

The proportion of responders was statistically significantly greater in the risedronate group than in the placebo group at all time points.

Safety results:

The following points summarize the safety findings of 5 mg daily risedronate in this study:

Overall the frequency of Treatment Emergent Adverse Events (TEAEs) was comparable between both treatment groups (risedronate, 85.2%; placebo, 81.8%). The most common TEAEs by preferred term (i.e., reported by >10% of subjects in either treatment group) were arthralgia (risedronate, 6.1%; placebo, 12.7%) and hypertension (risedronate, 11.3%, placebo, 5.5%).

There were no deaths reported in the study.

Fifteen subjects, including 12 in the risedronate group and 3 in the placebo group, experienced a total of 19 serious TEAEs. One serious TEAE (a duodenal ulcer haemorrhage in a placebo subject) was assessed as probably related to study drug by the investigator. All other SAEs were considered as doubtfully related by the investigators.

The percentage of subjects who prematurely withdrew from the study due to a TEAE was higher in the placebo group than in the risedronate group (risedronate, 8.7%; placebo, 16.4%). In both treatment groups, the most common TEAE leading to withdrawal occurred in the Gastrointestinal Disorders system organ class (SOC) (risedronate, 4.3%; placebo, 7.3%).

The percentage of subjects who experienced an upper gastrointestinal (UGI) TEAE or other clinically-relevant gastrointestinal (GI) events was higher in the placebo group than in the risedronate group (risedronate, 18.3%; placebo, 25.5%). The 2 most common UGI or other clinically-relevant GI TEAEs in both treatment groups were nausea (risedronate, 5.2%; placebo, 9.1%) and dyspepsia (risedronate, 3.5%; placebo, 7.3%). Upper GI TEAEs rated as moderate-to-severe occurred in a comparable percentage of subjects in the risedronate group (3.5%) and the placebo group (5.5%).

There were no clinically meaningful differences between treatment groups in mean change from baseline to end of study for any clinical laboratory analyses or vital sign. Few subjects had clinically noteworthy abnormal laboratory values at the end of the study.

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