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Sponsor/Company:	sanofi-aventis Procter & Gamble Pharmaceuticals	**Study identifier:**	NCT00402441
Drug substance(s):	risedronate	**Study Code:**	HMR4003F/4001
		Date:	20 April 2007

Title of the study:	A one-year, multicenter, randomized, double-blind, placebo-controlled, parallel group study to determine the efficacy and safety of 35-mg risedronate administered once a week in the prevention of osteoporosis in postmenopausal women
Study center(s):	Multicenter (18 centers in the United States)
Publications:	Not applicable
Study period: Date first patient/subject enrolled: 09-Sept-2002 Date last patient/subject completed: 08-June-2004	**Phase of development:** IV
Objectives:	The primary objective of this study was to demonstrate that risedronate 35-mg once weekly was more efficacious than placebo in increasing or maintaining bone mineral density (BMD) of the lumbar spine after 1 year of treatment in women who were non-osteoporotic and 0.5-5 years postmenopausal. Secondary objectives were to demonstrate that risedronate 35-mg once weekly was more efficacious than placebo in increasing or maintaining total proximal femur, femoral neck, and trochanter BMD after 1 year of treatment in women who were 0.5-5 years postmenopausal, and also, to assess the general safety of 35-mg risedronate administered once weekly.
Methodology:	This was a 1-year, randomized, double-blind, placebo-controlled, multicenter, parallel group study
Number of subjects:	Planned: 260 subjects, 130 subjects in each treatment group
Diagnosis and criteria for inclusion:	The female subjects were to be postmenopausal for 0.5-5 years, 45 years of age or older, and had 3 contiguous lumbar spine vertebral bodies (L1-L4) without fracture or degenerative disease. Menopause was defined as 12 months without menses, based on medical history. Subjects who were postmenopausal secondary to bilateral oophorectomy must have serum FSH ≥40 mIU/mL and estradiol ≤20 pg/mL. Inclusion criteria were established for lumbar spine BMD mean value, i.e., >0.772 g/cm^2 (Hologic) or >0.880 g/cm^2 (Lunar). Subjects who had adequate lumbar spine BMD but were osteoporotic by total proximal femur BMD (<0.637 g/cm^2 [Hologic]) or <0.694 g/cm^2 [Lunar]) as determined by dual-energy x-ray absorptiometry (DXA) were excluded.

Investigational product:			
Dose:	Risedronate 35-mg tablet		
Administration:	once weekly		
Duration of treatment:	one year	**Duration of observation:**	one year
Reference therapy:			
Dose:	Placebo tablet		
Administration:	once weekly		
Criteria for evaluation:			
Efficacy:	The primary efficacy variable was the percent change from baseline to endpoint (Month 12 lumbar spine BMD with imputation for missing values using the Last Observation Carried Forward (LOCF) principle). Secondary efficacy variables included the percent change from baseline to Months 6 and 12 in lumbar spine BMD; and the percent change from baseline to Months 6, 12, and endpoint (Month 12 with imputation for missing values using the LOCF principle) in total proximal femur, femoral neck, and trochanter BMD.		
Safety:	Safety was evaluated by means of reported adverse events and changes in routine clinical laboratory tests, vital signs, and physical examinations.		
Statistical methods:	The primary efficacy variable was the percent change from baseline to endpoint in Month 12 lumbar spine BMD with imputation for missing values using the LOCF principle. The primary analysis was based on the modified intent-to-treat (MITT) population (all randomized subjects who received at least 1 dose of study medication and had at least 1 evaluable postbaseline measurement of lumbar spine BMD). 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 Month 12 in the per-protocol population was considered supportive of the primary efficacy analysis. Secondary efficacy variables were analyzed using the same ANOVA model as used for the primary efficacy variable. All safety variables were analyzed using the following population referred as the safety population: the intent-to-treat (ITT) population (all randomized subjects who received at least 1 dose of study medication) with subjects analyzed as treated i.e. any subject exposed to the active treatment at any time during the study was assigned to the active treatment group. 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 280 subjects were randomized in this study. Subject disposition is presented in the following table:

	Number (%) of subjects		
	Placebo	35mg weekly Risedronate	Overall
Screened, not randomized			111
Randomized	142 (100.0)	138 (100.0)	280 (100.0)
Randomized but not treated	0 (0.0)	2 (1.4)	2 (0.7)
ITT population	142 (100.0)	136 (98.6)	278 (99.3)
Discontinued from the study	25 (17.6)	23 (16.7)	48 (17.1)
Reason for discontinuation			
Adverse event	11 (7.7)	7 (5.1)	18 (6.4)
Protocol violation	0 (0.0)	1 (0.7)	1 (0.4)
Voluntary withdrawal	6 (4.2)	8 (5.8)	14 (5.0)
Lost to follow-up	7 (4.9)	6 (4.3)	13 (4.6)
Treatment failure	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (0.7)	1 (0.7)	2 (0.7)
Completed study	117 (82.4)	115 (83.3)	232 (82.9)

In the ITT population overall, 43.5% of subjects were 55 years of age or older, 81.3% were Caucasian, and the mean duration from last menses was 3.3 years. There were no statistically significant differences between treatment groups at baseline in lumbar spine or total proximal femur BMD.

Efficacy results: The following table summarizes the comparison of the 35-mg weekly risedronate treatment group with the placebo treatment group on lumbar spine BMD for the MITT population.

	Placebo		35mg weekly Risedronate		Treatment comparison (risedronate-placebo)	
Visit	N	Mean	N	Mean	LS mean difference (95% CI)	P-value[a]
Baseline BMD (g/cm^2)	133	0.99	131	0.99		
Percent change from baseline						
Month 6	128	-0.51*	126	1.66*	2.16 (1.56, 2.77)	<0.0001
Month 12	117	-1.08*	116	1.92*	3.00 (2.20, 3.80)	<0.0001
Endpoint	133	-1.05*	131	1.83*	2.88 (2.16, 3.61)	<0.0001

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

[a] adjusted means, 95% CI, and p-values are from a 2-way ANOVA model with fixed effects for treatment and pooled center.

LS = least squares, CI = confidence interval, BMD = bone mineral density.

- In comparison with the placebo treatment group, there was a statistically significant increase in lumbar spine BMD at endpoint for the risedronate treatment group in the MITT population.
- There were also statistically significant increases in lumbar spine BMD at Month 6 and Month 12 in the risedronate treatment group compared with the placebo treatment group for the MITT population.
- Lumbar spine BMD in the MITT population was statistically significantly decreased from baseline to Month 6, Month 12, and endpoint in the placebo treatment group and statistically significantly increased from baseline to Month 6, Month 12, and endpoint in the risedronate treatment group.

Efficacy results (cont'd):	- Lumbar spine BMD results in the per-protocol population and in the MITT subgroup of subjects who were within 5 years since last menses were similar to those in the MITT population as a whole. - The total proximal femur BMD, femoral neck BMD, and trochanter BMD at Month 6, Month 12, and endpoint were statistically significantly greater in the risedronate treatment group compared with the placebo group.
Safety results:	The following points summarize the safety findings of 35-mg weekly risedronate in this study: - Overall the frequency of treatment-emergent adverse events was comparable for both treatment groups (placebo, 73.8%; risedronate, 74.5%). The most common treatment-emergent adverse event (i.e., reported by >10% of subjects in either treatment group) was arthralgia (placebo, 7.8%; risedronate, 13.9%). This was the only treatment-emergent adverse event to be reported by more than 10% of subjects in either treatment group. - A total of 17.7% of subjects in the placebo group and 21.2% of subjects in the risedronate treatment group experienced treatment-emergent adverse events that were considered possibly or probably related to the study medication. The most common treatment-emergent adverse event in both treatment groups that was considered possibly or probably related to the study medication was dyspepsia (placebo, 5.0%; risedronate, 3.6%). - Very few subjects had treatment-emergent adverse events rated as severe (placebo, 7.1%; risedronate, 8.0%), and the small differences between treatment groups was not considered clinically important - There were no deaths reported in the study. - Nine subjects, 5 in the risedronate treatment group and 4 in the placebo treatment group, experienced a total of 11 serious treatment-emergent adverse events. No serious treatment-emergent adverse event was reported by more than 1 subject. None of the serious treatment-emergent adverse events was considered related to the study medication. - The percentage of subjects who prematurely withdrew from the study due to a treatment-emergent adverse event was comparable between the treatment groups (placebo, 7.1%; risedronate, 5.1%). In both treatment groups, the most common treatment-emergent adverse events that led to withdrawal occurred in the Gastrointestinal Disorders body system (placebo, 4.3%; risedronate, 3.6%). - The percentage of subjects who experienced an upper gastrointestinal (GI) adverse event was comparable between the treatment groups (placebo, 12.1%; risedronate, 10.9%). The most common upper GI treatment-emergent adverse events were dyspepsia (placebo, 5.7%; risedronate, 5.8%) and gastroesophageal reflux disease (placebo, 2.1%; risedronate, 2.9%). Upper GI treatment-emergent adverse events that were rated as moderate-to-severe occurred in a comparable percentage of subjects in the placebo group (3.5%) and the risedronate group (5.1%). - There were no clinically meaningful differences between treatment groups in mean change from baseline to end of study for any clinical laboratory analyte or vital sign. Few subjects had clinically noteworthy abnormal laboratory values at end of study.
Date of full report:	31 December 2004