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Sponsor / Company : sanofi-aventis **Drug Substance :** RISEDRONATE SODIUM		**Study Identifier** : NCT00345644 **Study Code** : HMR4003B_3507	
Title of the study:	A non-invasive evaluation of bone microarchitecture modification in osteopenic postmenopausal women by 3D-peripheral quantitative computed tomography: a 24-month, monocenter, double-blind, randomized, parallel group study comparing weekly oral risedronate 35 mg and placebo		
Study center(s):	One single center		
Study period: Date first subject enrolled: 13 March 2006 Date last subject completed: 22 June 2009		**Phase of development:** IIIb	
Objectives:	**Primary:** To compare weekly oral dose of risedronate 35 mg and placebo with respect to percent change at 12-month for distal radius trabecular Bone Volume / Tissue Volume (BV/TV) in osteopenic postmenopausal women as measured by three-Dimensional peripheral Quantitative Computed Tomography (3D-pQCT). **Secondary:** To compare the percent change from Screening/Baseline between the 2 treatment groups for the following measurements: • Bone mineral density (BMD) of the lumbar spine, femoral neck, femoral trochanter, and total proximal femur using dual-energy X-ray absorptiometry (DXA) scan at 12, and 24 months; • 3D-pQCT analysis of distal radius and distal tibia bone microarchitecture data at 6, 12, and 24 months; • Bone turnover markers (BTMs): fasting serum carboxyterminal cross-linked telopeptide of type 1 bone collagen (CTX-1), serum aminoterminal propeptide of type 1 procollagen (PINP) and urine cross-linked N-telopeptides of type I collagen (urine NTX) at 3, 6, 12 and 24 months.		
Methodology:	24-month, double-blind, randomized (2:1), placebo-controlled, parallel-group, monocenter study. The study consisted of a screening period of up to 6 weeks (Visit 1), an inclusion visit (baseline , M0, Visit 2) and 5 follow-up visits planned at M3 (Visit 3), M6 (Visit 4), M12 (Visit 5), M18 (Visit 6) and M24 or in case of early termination (Visit 7). Patients were randomized at baseline.		
Number of subjects:	Planned: 156	Randomized: 163	Treated: 163
Evaluated:	mITT (modified Intent To Treat): 154 PP (Per Protocol): 115 PP2: 102	Safety: 163	
Diagnosis and criteria for inclusion:	Postmenoposal women, between 55 and 75 years of age, with osteopenia confirmed by DXA, with at least 1 radius and tibia without history of fracture, in good health, who had given a written informed consent. History of tremor, of recent hyperparathyroidism or thyroid disorder, of generalized bone disorders, evidence of osteoporosis, treatments likely to interfere with the efficacy criteria were the main exclusion criteria.		

Investigational product:	Risedronate	
Dose:	35 mg tablets, 1 per week	
Administration:	Oral route	
Duration of treatment: 24 months		**Duration of observation:** 24 months
Reference therapy:	Placebo	
Dose:	1 tablet per week	
Administration:	Oral route	
Criteria for evaluation:		
Efficacy:	**Primary:** Percent change from baseline in Bone Volume / Tissue Volume at distal radius at month 12 **Secondary:** Change and percent change from baseline in 3D-pQCT data (BV/TV (Bone Volume/Tissue Volume), TbTh (Apparent Trabecular Thickness), TbN (Apparent Trabecular Number), TbSp (Apparent Trabecular Separation), CTh (Cortical Thickness) at distal radius and tibia at months 6, 12 and 24). Change and percent change from baseline in DXA BMD data at months 12 and 24 (lumbar spine, femoral neck, femoral trochanter, total proximal femur) Change and percent change from baseline in BTM markers (CTX-1, PINP, and urine NTX) at months 3, 6, 12 and 24.	
Safety:	Physical examination, vital signs, collection of Adverse Events with special interest for Upper GastroIntestinal (UGI) and fractures, clinical laboratory tests.	
Statistical methods:	Primary analysis: ANCOVA with treatment as fixed effect and baseline value as a covariate, and Last Observation Carried Forward **(**LOCF) for missing values in mITT population. Secondary analyses: mITT population (plus PP and PP2 for BV/TV) Interim analysis: efficacy evaluation at Month 12. Safety analyses: Summary by descriptive statistics.	

Summary: Baseline characteristics	One-hundred and ninety subjects were screened over a 15 month period of time. Of these 163 were randomized and treated, 54 in the placebo group and 109 in the risedronate group. In the mITT population, subjects were mostly Caucasian (98.1% in the placebo group and 96% in the risedronate group) with a mean (SD) age of 61 (4.3) years in the placebo group and 62 (5.7) years in the risedronate group. Their mean (SD) Body Mass Index was 23.2 (2.53) kg/m² in the placebo group and 23.5 (3.10) kg/m² in the risedronate group. The risk factor questionnaire showed that the proportion of subjects with family history of mother fracture since the age of 50 was higher in the risedronate group (28.7%) than in the placebo group (18.9%). This was also the case for personal history of fracture after the age of 45 (19.8% vs. 9.4%). The mean (SD) total spine T-score was similar in the two treatment groups; -1.77 (0.464) for subjects from the placebo group and -1.78 (0.573) for subjects from risedronate group. The mean (SD) total femur T-score was slightly lower but without clinical relevance for subjects from the placebo group [-1.31 (0.472)] than for subjects from the risedronate group [-1.23 (0.491)] The results for serum bone markers at baseline were very similar in the two treatment groups. The mean (SD) value for serum type I collagen C-telopeptide was 0.528 (0.1759) ng/mL in the placebo group and 0.521 (0.1795) ng/mL in the risedronate group, and the serum intact N-terminal propeptide of type I collagen was 61.00 (22.029) ng/mL in the placebo group and 61.20 (20.452) ng/mL in the risedronate group. The results at baseline for urine N-telopeptide cross-links were also close in the two treatment groups. The mean (SD) raw values were 298 (372.6) nmol BCE/L and 332 (269.7) nmol BCE/L in the placebo and risedronate groups, respectively; the urine creatinine adjusted results were 41.1 (15.65) nmol BCE/mmol Creat and 43.2 (15.16) nmol BCE/mmol Creat, respectively. The mean (SD) results for distal radius at baseline were similar in the two treatment groups: BV/TV [placebo: 0.110 (0.0283), risedronate: 0.110 (0.0252)], TbN [placebo: 1.523 (0.2431)/mm, risedronate: 1.570 (0.2417)/mm], TbTh [placebo: 0.072 (0.0118) mm, risedronate: 0.070 (0.0121) mm], TbSp [placebo: 0.604(0.1275) mm , risedronate: 0.585(0.1216) mm] and CTh [placebo: 0.713 (0.1381) mm, risedronate: 0.734 (0.1695) mm]. This was also the case for the mean (SD) results of distal tibia BV/TV [placebo: 0.114 (0.0265), risedronate: 0.118 (0.0260)], TbN [placebo: 1.467 (0.2604)/mm, risedronate: 1.485 (0.2753)/mm], TbTh [placebo: 0.078 (0.0141) mm, risedronate: 0.080 (0.0145) mm], TbSp [placebo: 0.628 (0.1463) mm, risedronate: 0.627 (0.2071) mm] and CTh [placebo: 0.914 (0.1985) mm, risedronate: 0.928 (0.1981) mm].
Efficacy results:	There was no statistically significant difference between the two treatment groups for the primary analysis of the primary efficacy endpoint (percent change of distal radius BV/TV at month 12 (LOCF) in the mITT population) (p = 0.81). This result was confirmed by the secondary analysis of this criterion in the PP population (p = 0.47) and by all other analyses (ANOVA with LOCF or repeated measures analysis, at Months 6, 12 and 24, in the mITT, PP and PP2 populations). Statistically significant differences in favor of risedronate were found for the following analyses on 3D-pQCT indices in the mITT population (secondary endpoints):

	Site	**Index**	**Time**	**Variable**	**LOCF**	**LS mean difference, p value**
	Distal tibia	**BV/TV**	Month 24	Percent change	Without	0.90%, p =0.033
				Change	Without	0.001, p = 0.037
		TbN	Month 6	Percent change	With	2.38%, p = 0.044
		TbSp	Month 6	Change (mm)	With	-0.014, p = 0.038
					Without	-0.014, p = 0.048
			Month 24	Change (mm)	With	-0.020, p = 0.028
					Without	-0.022, p = 0.039
		CTh	Month 12	Percent change	With	1.07%, p = 0.046
				Change (mm)	With	0.010, p = 0.023
					Without	0.010, p = 0.029
			Month 24	Percent change	With	1.60%, p = 0.020
					Without	1.68%, p = 0.024
				Change (mm)	With	0.013, p = 0.018
					Without	0.014, p = 0.022
	Distal radius	**CTh**	Month 24	Percent change	With	2.50%, p = 0.003
					Without	2.60%, p = 0.004
				Change (mm)	With	0.012, p = 0.018
					Without	0.013, p = 0.025
	No significant differences between the two treatment groups were found for any analysis for distal radius TbTh, TbN, TbSp and for distal tibia TbTh.					
	Statistically significant differences in favor of risedronate were found for both change and percent change for all types of analyses (ANCOVA using LOCF for missing values and ANCOVA for repeated measures) in the mITT population at both Months 12 and 24 for lumbar spine BMD, femoral neck BMD, femoral trochanter BMD, total femur BMD and corrected total femur BMD ($p < 0.01$ for all analyses).					
	Statistically significant differences in favor of risedronate were found for both change and percent change for all types of analyses (ANCOVA with LOCF for missing values or ANCOVA for repeated measures) in the m ITT population at each time point for serum CTX-1, PINP and urine NTX/creatinine ($p < 0.001$ for all analyses).					

Safety results		**Placebo (N = 54)**	**Risedronate (N= 109)**
	Number of subjects with at least one TEAE	47 (87.0%)	96 (88.1%)
	Number of subjects with at least one possibly related TEAE	4 (7.4%)	8 (7.3%)
	Number of subjects with at least one serious TEAE	5 (9.3%)	9 (8.3%)
	Number of subjects with TEAEs leading to treatment discontinuation	1 (1.9%)	8 (7.3%)
	Number of subjects with AEs with fatal outcome	0	0
	Number of subjects with at least one upper gastrointestinal TEAE	7 (13.0%)	14 (12.8%)

Issue date:	23 APR 2012