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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00790101
		Study Code:	HMR4003B_4033
Generic drug name:	Risedronate	**Date:**	13/Nov/2008

Title of the study:	An 18-Month, Multicenter, Parallel-Group Study to Determine The Relative Efficacy of Risedronate Versus Raloxifene in Subjects Who Have Discontinued Hormone Replacement Therapy (HRT) for Early Intervention in Osteoporosis	
Investigator(s), Study center(s):	Multicenter study with multiple investigators, 65 sites planned (range 55-70); 5 sites had actually enrolled subjects at the early termination of the trial	
Study dates: Date first patient enrolled: 16-June-2004 Date last patient completed: 05-Nov-2004	**Study duration:** Duration per subject (planned): 18 months	**Phase of development:** Ph. IV clinical study
Objectives:	**The primary objective of the study was** to compare the effects of risedronate and raloxifene on lumbar spine (LS) bone mineral density (BMD) in women with osteopenia who were treated with HRT, and discontinued HRT at least 3 months, but no greater than 18 months, prior to the study. **The secondary objectives of this study were:** • To compare the effects of risedronate, raloxifene, and placebo on BMD of the hip. • To compare the effects of risedronate, raloxifene, and placebo on bone turnover markers (urinary N-telopeptide cross links [NTX] and serum C-telopeptides [CTX], N-terminal propeptides human collagen type 1 [P1NP], bone specific alkaline phosphatase [BSAP], and osteocalcin [OC]). • To compare quality of life using the Menopause Specific Quality of Life (MENQOL) questionnaire in subjects on risedronate, raloxifene, and placebo. • To compare safety and tolerability of risedronate, raloxifene, and placebo. • To analyze epidemiological and other risk factors associated with early bone loss and response to therapy. • To determine the magnitude of LS BMD loss in women previously treated with HRT but who discontinued and were then given placebo. • To compare the effects of risedronate, raloxifene, and placebo on C-reactive protein (CRP), interleukin-6 (IL-6), osteoprotegerin (OPG), and receptor activator of NF kappa B ligand (RANKL) proteins. • To compare quantitative computerized axial tomography (QCT) measurements of bone quality and strength, and their relationship to BMD measurements, as insights into the comparative effects of risedronate, raloxifene, and placebo on bone.	

Study Design:	This was a multi-center, randomized, double-blind, double-dummy study designed to compare the effects of risedronate, raloxifene, and placebo on BMD, bone turnover markers, and other markers of anabolic activity in postmenopausal women who previously received HRT. A total of 630 eligible subjects were to be randomized to receive risedronate 35 mg once a week, raloxifene 60 mg daily, or placebo in a 3:3:1 ratio, such that 270 subjects were to be in each of the raloxifene and risedronate arms and 90 subjects were to be in the placebo arm. This study was terminated because of study timing relative to results of the Women's Health Initiative (WHI) trial. The results of the WHI led to a sharp decrease in the use of HRT, such as conjugated estrogens, because the risks of HRT were found to outweigh the benefits. WHI results were published in July, 2002, and the current study, designed to evaluate early bone loss and treatment effects of risedronate and raloxifene in subjects recently discontinuing estrogen therapy, had enrolled its first subject in June, 2004.
Number of subjects planned:	A total of 630 subjects were to be randomized to provide 473 evaluable subjects. At the time of stopping the trial, only 6 subjects had been randomized.
Inclusion criteria:	• Postmenopausal, ambulatory females, from 50 to 65 years of age, if natural menopause, and from 55 to 65 years of age, if surgical menopause ("postmenopausal" defined as the absence of menses for at least 12 continuous months). • Willing to provide written informed consent. • In general good health as determined by medical history, physical examination, and laboratory tests. • LS BMD T-score between –1.0 and –2.4, inclusive. • At least one analyzable BMD site at both the hip (left or right) and LS spine (at least 3 measurable lumbar spine vertebrae, without fracture or sufficient degenerative disease). • Currently receiving no medications for the treatment or prevention of osteoporosis. • Had been on continuous HRT for at least 1 year prior to enrollment. The HRT must have ended at least 3 months, but no greater than 18 months, prior to the baseline visit.
Treatments:	There were to be 3 treatment groups receiving treatment for 18 months: • Risedronate: risedronate 35 mg once a week with 6 days of placebo and raloxifene placebo (due to a packaging error, the subject randomized to this arm actually only received 35 mg risedronate once every other week). • Raloxifene: raloxifene 60 mg daily and risedronate placebo daily. • Placebo: raloxifene placebo daily and risedronate placebo daily.
Criteria for evaluation:	
Safety Data:	Adverse events (AEs) were to be recorded at clinic visits (visit 2 [baseline] and visits 3-8 [on-treatment]) or at early termination, and monitored according to standard operating procedures (Aventis). Serum chemistry and hematology were to be performed at visit 1 (screening), at visit 6 (month 12) or at the time of early termination. Vital signs and weight were to be performed at visit 1 (screening), visit 2 (baseline), visits 3-8 (on-treatment), or at the time of early termination.

Statistical procedures:	Due to the short duration of this trial (terminated when only 6 subjects were randomized), the originally planned statistical analyses were not executed. The emphasis of this report was on safety. The Aventis Guidelines for the Analysis and Reporting of Safety Data from Clinical Trials was used for the definition of safety variables. The safety population was defined as those subjects who received at least 1 dose of study medication.
Interim analysis	No interim analysis was performed.
Results – Study subjects and conduct:	The number of subjects screened for this study was 32. All subjects were female. Of these, 26 subjects were not randomized. The other 6 subjects comprised the safety population and were randomly assigned to one of the following treatment groups: • Risedronate: risedronate 35 mg once a week with 6 days of placebo and raloxifene placebo (n=1). (Due to a packaging error, the subject randomized to this arm actually only received 35 mg risedronate once every other week). • Raloxifene: raloxifene 60 mg daily and risedronate placebo (n=3). • Placebo: raloxifene placebo daily and risedronate placebo daily (n=2). Waivers were granted for 2 raloxifene-treated subjects' protocol deviations (age of 54 years with surgical menopause for a 1st subject; randomized past the 6-week window allowed for screening for a 2nd subject). For the 6 randomized and treated subjects, the age ranged from 54 to 61 years. Five risedronate or raloxifene subjects were white and 1 placebo subject was black among the 6 treated subjects. Body weight ranged from 60.3 to 81.8 kg and body mass index (BMI) ranged from 24.2 to 30.8 kg/m^2.
Results – Efficacy:	Due to the early termination of this trial, no statistical analyses were performed concerning efficacy parameters.
Results – Safety:	The trial was terminated early and therefore, only 3 TEAEs were reported during treatment with study medication. For each AE, causality was assessed as not being related to study medication, no action was taken, and all subjects continued in the trial until the study was terminated. Raloxifene-treated subject experienced pain of moderate intensity in the lower right extremity for 3 days followed by 9 days at a mild intensity. The subject recovered without sequelae. One AE from a subject taking placebo included increased blood alkaline phosphatase of mild intensity which was considered ongoing. No deaths, serious adverse events, discontinuations from the study due to AEs, or overdoses were reported during the trial. Laboratory results and vital sign measurements at baseline and at early termination of the trial were not considered of clinical interest.
Date of report:	06-January-2005