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Sponsor/company: sanofi-aventis	ClinialTrials.gov Identifier: NCT00351091
Generic drug name: Risedronate	Study Code: HMR4003B_2501
	Date: 29/Aug/2007

Title

A six month, multicenter, randomized, double-blind, active controlled, parallel group study to estimate the pharmacodynamic response of two Risedronate regimens compared with 5mg daily: 150 mg monthly dose for six months and 15 mg daily for thirty days followed by 150 mg monthly dose for 5 months in postmenopausal women with low bone density.

Investigator(s), study site(s)

Multicenter (7 sites)
Project Medical Officer: Dr. Monika Madalinska, Aventis Pharmaceuticals Poland

Study duration and dates	First dose: November 12, 2002	Phase	II
	Last visit: June 6, 2003		

Objectives

Primary

The primary objective of this pilot study was to estimate the percent change from baseline at Month 6 Week 4 in urine NTX bone turnover marker for a monthly 150 mg dose of Risedronate administered for 6 months and a loading dose regimen of 15 mg daily risedronate over a 1-month treatment period followed by 150 mg monthly risedronate dosing for 5 months, both compared to a 5 mg risedronate daily dose administration for 6 months.

Secondary

Secondary objectives were:

- To estimate the percent change from baseline at specified visits other than Month 6 Week 4 in urine NTX for the monthly 150 mg dose of risedronate administered for 6 months and the loading dose regimen of risedronate over a 6-month treatment period, both compared to the 5 mg daily dose of risedronate.
- To estimate the percent change from baseline at all specified visits in serum CTX and bone specific alkaline phosphatase for the monthly 150 mg dose of risedronate administered for 6 months and the loading dose regimen of risedronate over a 6month treatment period, both compared to the 5 mg daily of risedronate.

- To estimate the percent change from baseline at Month 6 Week 4 in lumbar spine BMD for the monthly 150 mg dose of risedronate administered for 6 months and the loading dose regimen of risedronate over a 6-month treatment period, both compared to the 5 mg daily dose of risedronate.
- To evaluate the general safety of the risedronate administered as 150 mg monthly for a total treatment period of 6 months, or 15 mg daily for 30 days followed by 150 mg on a monthly basis for a total treatment period of 6 months.

Study design

This pilot study was a 6-month, multicenter, randomized, double-blind, active-controlled, parallel-group study, performed in a postmenopausal women with low bone density at 7 sites in Poland.

Number of subjects planned

The study was planned to include 150 (50 in each of 3 dose groups) postmenopausal women.

Inclusion criteria

The female subjects were 65-80 years of age, ambulatory, and menopausal for 5 or more years. They were in general good health as determined by medical history, physical examination, and laboratory tests. Major inclusion criteria required a lumbar spine baseline BMD within the following criterion (7-9):

a. **Hologic**: = 0.827 g/cm² (Young normal reference BMD for L1-L4 in females.

Mean = 1.047 g/cm² SD = 0.11 g/cm²), or

b. **Lunar**: = 0.942 g/cm² (Young normal reference BMD for L1-L4 in females.

Mean = 1.182 g/cm² SD = 0.12 g/cm²), or

c. **Norland**: = 0.768 g/cm² (Young normal reference BMD for L1-L4 in females.

Mean = 1.086 g/cm² SD = 0.159 g/cm²)

Treatments

The subjects were randomized in a 1:1:1 ratio to receive 1 of the following treatments:

- Oral risedronate 5 mg daily for 6 months
- Oral risedronate 50 mg daily for first 3 consecutive days of every month for 6 months, followed by oral placebo daily for the remaining days in each month
- Oral risedronate 15 mg daily for 30 consecutive days, followed by 50 mg daily for 3 consecutive days (150 mg total) of every month for 5 months, followed by oral placebo daily for the remaining days in each month

All subjects received a daily supplement of 500 mg elemental calcium and 200 IU vitamin D.

Efficacy data

Primary Efficacy Variable

The primary efficacy variable was the percent change from baseline in urine NTX at Month 6 Week 4 (Visit 14).

Secondary Efficacy Variables

Secondary efficacy variables were:

- Percent change from baseline in lumbar spine BMD at Month 6 Week 4 (Visit 14) and/or Endpoint.
 - Percent changes from baseline in serum CTX and bone specific alkaline phosphatase at all specified visits and Endpoint.
 - Percent changes from baseline in urine NTX at all specified visits and Endpoint (other than Month 6 Week 4).
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Safety data

The safety variables were:

- Change from baseline in vital signs or physical examination.
 - Adverse events reported by the subject or noted by the Investigator.
 - Standard hematology, blood chemistry, and urinalysis.
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Statistical procedures

The primary objective of the study was to estimate the percent change from baseline at Month 6 Week 4 (Visit 14) in urine NTX for the 2 new dosing regimens compared to the risedronate 5 mg Daily dose. It was estimated that the within-group standard deviation of the NTX percent change at Month 6 Week 4 would be below 35% , and, 80% of the subjects randomized would have evaluable values at baseline and Month 6 Week 4. Under these assumptions, the 95% 2-sided confidence interval (CI) for the difference between each treatment group of the 150 mg Monthly and the Loading +150 mg Monthly regimen versus the 5 mg Daily would extend the observed mean difference by no more than 13.2%. In addition, we expected 40 subjects with evaluable values at baseline and Month 6 Week 4. Based on these assumptions, the 95% 2-sided CI for the within-group mean percent change would extend the observed value by no more than 9.3% for each treatment group.

A 2-way analysis of variance (ANOVA) model with treatment group and center as fixed effects and percent change in NTX at Month 6 Week 4 as the response was used to construct the confidence intervals. The primary efficacy analysis was performed using the primary efficacy or per-protocol population, which for the primary efficacy variable was identical to the intent-to-treat population.

The secondary efficacy variables of percent change from baseline in lumbar spine BMD and other bone turnover markers were analyzed using the same model as used for the primary efficacy analysis, using the intent-to-treat population.

Interim analysis

No interim analysis was conducted.

Results - Study subjects and conduct

A total of 362 subjects were screened for the study and 150 were randomized and treated with Risedronate: 48 with 5 mg daily; 50 with 150 mg monthly; and 52 with Loading +150 mg Monthly. Of the randomized and treated subjects, 4 withdrew before completing the study: 1 from the 5 mg Daily group, 1 from the 150 mg Monthly group, and 2 from the Loading +150 mg Monthly group. The intent-to-treat (ITT) and the per-protocol populations were identical for the primary efficacy endpoint.

Results – Baseline

Treatment groups were similar at baseline in age, years since last menses, race, and body mass index among treatment groups for each of the 3 analysis populations. In addition, treatment groups were similar at baseline in BMD, bone turnover markers, and clinical laboratory analytes.

Results – Efficacy

The following points summarize the comparison of the 2 monthly risedronate treatments to the 5 mg Daily risedronate treatment with regards to the efficacy measurements in this study:

The primary efficacy analysis was the differences in percent change from baseline in urine NTX at Month 6 Week 4 between each monthly dose and the risedronate 5 mg Daily dose. For the 150 mg Monthly vs. the daily group the mean difference in urine NTX was -3.54% (CI -15.71%; 8.64%). For the Loading + 150 mg Monthly group vs. the 5 mg Daily group, the mean difference in urine NTX was -2.02% (CI -14.13%; 10.10%).

The analysis above was repeated with Endpoint values other than Month 6 Week 4. Endpoint values were the last available data for subjects who took at least 1 dose of study medication and had at least 1 post-baseline value.

For the 150 mg Monthly group vs. the 5 mg Daily group, the mean difference in urine NTX was -3.47% (CI -15.38%; 8.43%). For the Loading +150 mg Monthly group vs. the 5 mg Daily group, the mean difference in urine NTX was -1.62% (CI -13.40%; 10.16%). Within-treatment percent changes from baseline for NTX at Month 6 Week 4 and Endpoint are given below for the ITT population.

Urine NTX: Within-treatment LS Mean Percent Change from Baseline at Month 6 Week 4 and Endpoint

	N	5 mg Daily	N	150 mg Monthly	N	Loading+150 mg Monthly
M6W4	47	-39.88 (-48.57; -31.19)	49	-36.34 (-44.86; -27.82)	50	-37.86 (-46.30; -29.43)
Endpoint	48	-40.03 (-48.53; -31.54)	50	-36.56 (-44.89; -28.23)	52	-38.42 (-46.58; -30.25)

Differences in CTX percent change from baseline at Month 6 Week 4 between the 150 mg Monthly group and the Loading + 150 mg Monthly group vs. the 5 mg Daily group were compared. For the 150 mg Monthly dose vs. the 5 mg Daily comparison, the mean difference was -6.42% (CI -20.88%; 8.04%). For the Loading + 150 mg Monthly dose vs. the 5 mg Daily dose comparison the mean difference was -2.83% (CI -17.22%; 11.56%). Within-treatment percent changes from baseline for CTX at Month 6 Week 4 and Endpoint are given below.

CTX: Within-treatment LS Mean Percent Change from Baseline at Month 6 Week 4 and Endpoint

	N	5 mg Daily	N	150 mg Monthly	N	Loading +150 mg Monthly
M6W4	47	-55.98 (-66.30; -45.66)	49	-49.56 (-59.68; -39.44)	50	-53.15 (-63.17; -43.13)
Endpoint	48	-56.02 (-66.64; -45.40)	50	-46.70 (-57.12; -36.28)	52	-54.11 (-64.32; -43.89)

Differences in bone specific alkaline phosphatase percent change from baseline at Month 6 Week 4 between the 150 mg Monthly group and the Loading+ 150 mg Monthly group vs. the 5 mg Daily group were compared. For the 150 mg Monthly dose vs. the 5 mg Daily dose comparison, the mean difference was 0.43% (CI -6.70%; 7.56%). For the Loading + 150 mg Monthly dose vs. the 5 mg Daily dose comparison the mean difference was 2.05% (CI -5.05%; 9.15%). Within treatment percent changes from baseline for alkaline phosphatase at Month 6 Week 4 and Endpoint are given below:

Bone-specific Alkaline Phosphatase: Within-treatment LS Mean Percent Change from Baseline at Month 6 Week 4 and Endpoint

	N	5 mg Daily	N	150 mg Monthly	N	Loading +150 mg Monthly
M6W4	47	-34.41 (-39.50; -29.32)	49	-34.83 (-39.82; -29.84)	50	-36.46 (-41.40; -31.52)
Endpoint	48	-33.66 (-38.77; -28.55)	50	-34.19 (-39.20; -29.18)	52	-36.22 (-41.13; -31.31)

Differences in lumbar spine BMD percent change from baseline at Month 6 Week 4 between the 150 mg Monthly group and the Loading + 150 mg Monthly group vs. the 5 mg Daily group were compared. For the 150 mg Monthly dose vs. the 5 mg Daily dose comparison the mean difference was 0.20% (CI -1.15%; 1.55%). For the Loading + 150 mg Monthly dose vs. the 5 mg Daily dose comparison the mean difference was -0.58% (CI -1.93%; 0.76%). Within-treatment percent changes from baseline for LS BMD at Month 6 Week 4 are given below:

Lumbar Spine BMD: Within-treatment LS Mean Percent Change from Baseline at Month 6 Week 4

	N	5 mg Daily	N	150 mg Monthly	N	Loading+150 mg Monthly
M6W4	47	3.22 (2.26; 4.18)	49	3.02 (2.08; 3.97)	50	3.80 (2.87; 4.74)

For all efficacy parameters, the 2 monthly doses showed similar efficacy results to the daily dose in percent change from baseline at Month 6 Week 4.

Results – Safety

The following points summarize the safety measurements for the 5 mg daily, 150 mg monthly, and the Loading + 150 mg Monthly risedronate treatments in this study.

Overall, the percentage of subjects reporting adverse events (AEs) was similar across treatment groups. All but 3 adverse events were mild or moderate in severity. Of 120 adverse events reported, 91 were considered doubtfully related to study medication by the Investigators. The number and percentage of subjects who experienced an upper gastrointestinal (GI) event was similar across treatment groups.

Five subjects experienced serious AEs during this study. The number and percent of subjects reporting serious AEs was similar across treatment groups, as was the number/percent of subjects who withdrew due to AEs. None of the events leading to withdrawal were considered related to study drug by the Investigators.

No deaths or significant overdose was reported during this study. Upper GI events reported by 11 subjects included dyspepsia (1 event), abdominal pain (10 events) and gastroesophageal reflux disease (1 event). Three subjects experienced moderate-to-severe upper GI AEs; all were cases of abdominal pain that occurred in the loading and monthly dose groups. Although endoscopy could not be made mandatory, it was strongly recommended an endoscopy be performed at the earliest possible time, if the subject consented, in all subjects who developed a moderate to severe upper GI AE. No subject underwent endoscopy for evaluation of an upper GI AE.

For clinical laboratory data, mean percent changes from baseline, numbers of subjects with shifts outside the normal range for each laboratory analyte, and the number of subjects with abnormal laboratory values of potential clinical significance were similar among the treatment groups.

There were no meaningful differences in changes in vital signs across treatment groups.

Date of the report: 29-Jan-2004