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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00268632
		Study Code:	HMR4003B_4001
Generic drug name:	Risedronate	**Date:**	15/Oct/2007

Title

A Multicenter Prospective Study to Assess the Impact of Physician's Reinforcement on the Subject's. Compliance and Persistence on Treatment Using Feedback on Bone Markers in Previously Undiagnosed, Postmenopausal Osteoporotic Women Treated with Risedronate.

Investigator(s), study site(s)

Multinational, multicenter study in 172 centers in the following countries: Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Czech Republic, France, Germany, Ireland, Italy, Mexico, Portugal, Slovakia, South Africa, Spain, Switzerland, The Netherlands, United Kingdom, United States.

Study duration and dates	**Start of inclusion**: August 11, 1999 **End of inclusion**: February 17, 2001 (note the recruitment period per center after initiation was 4-6 months) **End of study** February 5, 2002.	**Phase**	IIIB

Objectives

Primary
The primary objective was to assess the impact of physician's reinforcement using bone marker data (at week 10 and 22) on the treatment adherence of postmenopausal osteoporotic women. The primary analysis for both persistence (time until treatment discontinuation) and adherence (persistence + compliance) was performed over time and compared between both randomized groups.

Secondary
Secondary objectives were:

1. • To establish the profile of the unrecognized osteoporotic woman [no prevalent vertebral deformities (PVD-), no risk factors (RF-)] using a risk factor questionnaire for osteoporosis;
2. • To determine the efficacy of risedronate on the decrease of type I collagen breakdown products (urinary NTX and serum CTX) after 10 and 22 weeks of treatment in osteoporotic postmenopausal women;
3. • To assess the change in bone mineral density (BMD) at week 52 compared to baseline of both total hip and lumbar spine;
4. • Osteoporosis-related genotyping.

Study design

A multinational, multicenter, prospective study with stratified cluster randomization (country or pool of countries being the stratifying factor and the center being the cluster). Clusters were randomized into reinforcement (Re+) and non-reinforcement (Re-) study centers. Only Re+ centers reinforced compliance and persistence using feedback on bone marker data.

Number of subjects planned

The study was planned to include 2236 subjects were to be enrolled and treated with study medication at 172 centers. The minimum/maximum number of subjects included in the treatment phase per center was 11/15, the target number of subjects being 13 per center.

Inclusion criteria

Ambulatory women, not previously diagnosed for osteoporosis, between 65 and 80 years of age and not having used oral or parenteral glucocorticoids (≥5 mg prednisone or equivalent per day) within 3 months of starting study drug or for more than one month within six months prior to study entry).

Treatments

Each subject received 5 mg risedronate daily for a period of 52 weeks, supplemented with 500 mg calcium and 400 IU vitamin D daily.

Compliance and persistence data

The primary data were the compliance and persistence (time until treatment discontinuation) data during the risedronate treatment phase measured by the electronic monitoring caps.

Efficacy data

Level of urinary NTX (uNTX) and serum CTX (sCTX) after 10 and 22 weeks of treatment.
BMD of total hip and lumbar spine after 52 weeks of treatment.

Safety data

Occurrence of adverse events (AE)

Statistical procedures

The effect of intervention on persistence (time until treatment discontinuation) was tested using a Cox regression model. The effect of prevalent fractures (yes/no), risk factors at baseline (yes/no) and the interaction between both was tested by means of covariates in the above model. The multiple regression analysis included additional variables measured at either the cluster level, or the individual level (e.g. age, sex, etc.). Time to discontinuation was graphically presented by plotting Kaplan-Meier survival curves. Additionally, the daily percentage of adherers was compared over time between both randomized groups by a binomial regression model. A logistic regression approach was used to predict the risk for one woman to be an osteoporotic woman.

Interim analysis

No interim analysis was conducted.

Results - Study subjects and conduct

In total, 7153 women were screened and eventually 2382 were treated [1228 in reinforcement (Re+) group and 1154 in non-reinforcement (Re-) group]. Overall, 2302 subjects were considered for the primary efficacy analysis (intent-to-treat population, including all subjects with MEMS data) [1189 in Re+ group and 1113 in Re- group].

A total of 2023 treated subjects completed the trial. Among the 359 treated subjects who discontinued (15%), the main reasons for premature discontinuation were the occurrence of a new adverse event (AE) or worsening of an existing AE (59%), as well as the wish of the subject to discontinue the study (26%).

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Results – Efficacy

A significant relationship between the type of message and persistence was observed (p=0.0161). Compared with the Re- group, the message given to patients based on a positive uNTX response (≥30% decrease) delivered to patients in Re+ group corresponded to a significant improvement in persistence, i.e. with a 29% decrease in the risk of discontinuation (HR=0.71, p=0.02); the message given to those based on a negative uNTX response (≥30% increase) led to a lower persistence (HR=2.22, p=0.005); and a message based on a stable BTM response resulted in a similar persistence (HR=1.02, p=0.92).

Our findings showed that the type of reinforcement message affects persistence. However, because compliance to prescribed therapy affects both persistence and uNTX outcomes, this raises the question of whether the observed effect of reinforcement based on uNTX responses is a causal effect resulting from the information delivered to the reinforced patients or simply a consequence of patient compliance.

In the latter situation, patient compliance would be a confounding factor for the relationship between the type of message delivered and patient persistence. In order to assess this hypothesis, we compared the effect of uNTX on persistence between patients in Re- group and patients in Re+ group after adjusting for patient compliance. The results of this analysis showed that in the Re- group there is no additional effect of uNTX results on patient persistence, whereas in Re+ group, the uNTX results significantly affected patient persistence ($p<0.05$). This result confirms the causal effect of delivering the BTM feedback message on patients' persistence to prescribed therapy.

In addition to the effect of the type of feedback in the Re+ group described above, multiple regression analysis showed that a significant improvement in persistence was observed overall in patients who were more compliant with prescribed therapy. For example, a 10% increase of compliance (i.e. the proportion of prescribed drug taken) is associated with a decrease of the hazard of discontinuation of 35%. Similarly, those patients in both Re+ and Re- groups that elected at baseline to take study medication before breakfast had a 24% reduction in the hazard of discontinuation. In contrast, for patients with ongoing morbidity there was a 27% increase in the hazard of discontinuation for each five additional comorbidities. A significant interaction was observed between the size of the centers and the randomization group. In the Re- group, no association was found, whereas, in the Re+ group the hazard of discontinuation decreased as the center size increased, regardless of the type of feedback received. After adjustment for all significant confounding factors (including center size), the type of feedback delivered to the patients in the Re+ group remained a significant factor associated with persistence.

A separate analysis of the impact of reinforcement on persistence in patients without main risk factors (RF-) and patients with at least one main risk factor (RF+) revealed that reinforcement was more effective in patients without risk factors (i.e. low-trauma fracture sustained at .45 years of age, history of maternal hip fracture and low body weight <57 kg) (n=710). In patients without main risk factors, reinforcement significantly increased persistence in patients with a positive uNTX response (HR=0.55, p=0.022). A negative or neutral message did not significantly affect the persistence of the RF- group.

Analysis of daily proportion of adherers after the first reinforcement visit (week 13) showed a significant decrease in adherence over time ($p<0.0001$) in both randomization groups. Adherence was significantly higher in the Re+ group compared to Re- group ($p=0.0103$).

In the screening population, a logistic regression model was implemented to predict the risk for a women to be osteoporotic (n=2556, 36.6%). The presence of low trauma fracture (LTF), weight and height loss were the most predictive factors for being osteoporotic ($p<0.0001$). According to the model, subjects with LTF have a 98% higher risk for osteoporosis. Subjects of whom the mother ever suffered from fractures after age of 50, subjects with larger difference in height between age of 25 and current age, and subjects with late menarche also have a higher risk for osteoporosis (20%, 6% and 5%, respectively). By contrast, the risk for osteoporosis decreases by 25-30% for subjects taking postmenopausal female sex hormones or oral contraceptive pills and for subjects consuming milk at age.50. Other protective factors included in the model were weight (7% lower risk), daily tea intake (6%), and age at start of menopause (2%), and milk product consumption (1%). However, assessment of the diagnostic accuracy of the predictive model, by means of ROC analysis, showed that this predictive model based on the assessed risk factors was not a reliable surrogate for BMD measurement.

Risedronate treatment was associated with statistically significant decreases in bone markers (uNTX and sCTX) in both the reinforcement (Re+) and non-reinforcement (Re-) groups. Most of the decrease in uNTX and sCTX was seen by 10 weeks (decrease of 35% and 49% for NTX and CTX, respectively), with further small reductions observed after 22 weeks (4% and 6% for NTX and CTX, respectively).
The probability of a positive response for uNTX was higher for subjects with a higher baseline uNTX value. No significant effect of baseline sCTX value on the percent decrease in sCTX was observed. Compliance and strata (group of countries) were significant determinants of both uNTX and sCTX changes from baseline. In general, subjects with higher compliance were more likely to have higher percentage decreases in bone markers. In addition, subjects with a positive BTM response at week 10 also had a significantly higher probability to show a positive response at week 22.

After 52 weeks of treatment, BMD increased by 2.2% at the total hip [femoral neck (1.7%), trochanter (2.7%), intertrochanter (2.1%), Ward's triangle (3.9%)] and by 4.0% at the lumbar spine. No statistically significant difference in mean increase in BMD from baseline could be detected between the Re+ and Re- group. However, analysis of BMD percent change from baseline in the three categories of Re+ group based on the type of reinforcement message revealed a statistically significant difference in BMD changes compared to the Re- group. Higher BMD increases were observed among patients receiving reinforcement based on positive uNTX response while lower increases were observed among patients receiving reinforcement based on negative uNTX response. A mixed effects model showed that there was a strong association between changes in bone markers at week 10 and 22, and BMD changes at week 52. Adherence to prescribed therapy was also a strong predictor for changes in BMD.

At baseline, vertebral fractures were seen in 30% of the subjects. At week 52, the percentage of subjects with new vertebral fractures as compared to baseline was 1.9%. The incidence of new vertebral fractures was higher in the Re- group as compared to the Re+ group (2.7% versus 1.2%, respectively, $p=0.0488$ logistic regression). The incidence of new osteoporotic non-vertebral fractures (reported as adverse event) was 2% in both the Re+ and Re- groups ($p=0.6002$, logistic regression).

Findings of the subject satisfaction questionnaire showed that at one year 85% of the subjects reported that they would continue with risedronate treatment. Overall, 92% of the subjects in both the Re+ and Re- groups scored overall experience with treatment as good to excellent, with only 1.7% of the Re+ and 2.6% of the Re- subjects ($p=0.0253$, Chi-square test) reporting a poor overall experience. The usefulness of the information (given by the investigator) on response to risedronate was rated significantly higher for subjects in the Re+ group compared with those in the Re- group (93% versus 63%, respectively, $p<0.0001$, Chi-square test).

Results – Safety

Adverse events were experienced by 63% of the subjects. The AEs reported by 5% or more of the subjects consisted of infection (6%), back pain (5%) and arthralgia (5%). Upper GI events were reported by 14% of the subjects, and included mainly dyspepsia (4%) and abdominal pain (4%). Upper GI events were mostly considered as mild in severity (66%).

Most AEs (85%) were considered to be not related to the trial medication. The most common drug related events were classified as disorders of the digestive system, and consisted of dyspepsia (3%), abdominal pain (2%), gastritis (2%), constipation (2%) and GI disorders (1%) and nausea (1%).

Serious adverse events (SAE) were reported by 8% of the treated subjects. The most commonly reported SAE was bone trauma fracture (1%). Four percent of the SAEs were considered as related to the use of study drug. In 8 subjects, SAE resulted in death. None of the AEs leading to death were considered drug related. Of the treated subjects, 204 subjects (9%) discontinued treatment because of an AE (predominantly disorders of digestive system, 3%), and 5 subjects (0.2%) discontinued the study as a result of a drug-related SAE.

Date of the report: 11-Jan-2005