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Abbreviated Clinical Study Report Synposis	

Study Code: RISED_C_00935 **Document Status: Final** **Date: 15 July 2010**

SYNOPSIS

Title of the study:	Bone histomorphometry, microarchitecture and matrix structure and properties in patients receiving long-term risedronate treatment		
Coordinating Investigator:	[redacted]		
Study centers:	The study was planned in 15-20 centers in 10 countries; 5 centers in Austria, Belgium, Germany and the Netherlands actually enrolled subjects for bone biopsies.		
Publications (reference):	None to date		
Study period: Date first subject enrolled: 03 October 2007 Date last subject completed: 26 March 2009		**Phase of development:** Phase IV	
Objectives:	The objective of this study was to collect data on bone histomorphometry, architecture, turnover and material properties from iliac crest biopsies taken from postmenopausal women after ≥ 5 years risedronate treatment. These data were to be used as additional data for the primary and secondary objectives from Studies 2003073 and 2003096 for which the recruitment of 28 subjects who had ≥ 5 years risedronate treatment had not been achieved at the time this study was initiated. The objectives of studies 2003073 and 2003096 were: ~~Primary objective~~: To determine the differences in iliac crest bone histomorphometry and bone quality (including bone microarchitecture and bone matrix structure) in postmenopausal women who had received long-term (>3 and < 5 years or ≥ 5 years) therapy with alendronate and risedronate. ~~Secondary objective~~: To determine if iliac crest bone histomorphometry and/or bone quality changes after 5 or more years of therapy with alendronate or risedronate compared to 3 years of alendronate therapy or 3 years of risedronate therapy in postmenopausal women.		
Methodology:	This was a multicenter, multinational, prospective product registry, which was non-interventional on the therapeutic strategy. The interventional procedures were collection of fasting urine samples and of iliac crest bone biopsies.		
Number of subjects:	Planned: 20 subjects	Enrolled: 6 subjects	Biopsy taken: 5 subjects
Evaluated:		Safety: 6 subjects	Biopsy results: 5 subjects
Diagnosis and criteria for inclusion:	Women who had completed the IMPACT study and continued risedronate treatment (any combination of 5 mg daily or 35 mg once weekly) for ≥ 5 years.		

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Investigational product:	None for the biopsy study itself, although subjects received two tetracycline courses for bone labeling. To be eligible, subjects had to have received risedronate treatment; see IMPACT study.
Dose:	Tetracycline: according to Summary of Product Characteristics (SPC). Risedronate: see IMPACT study.
Administration:	Oral
Batch numbers:	Tetracycline bone labeling: commercial product was used. Risedronate: see IMPACT study.

Duration of treatment:	**Duration of observation:**
Tetracycline bone labeling: two 3-days courses separated by 14 days. Risedronate: subjects should have received risedronate treatment for ≥ 5 years to be eligible; see IMPACT study.	The total duration between Visit 1 (baseline) and Visit 4 (post-biopsy follow-up phone contact) was approximately 55-64 days.

Reference therapy:	Not applicable
Criteria for evaluation:	The current report is an abbreviated report, and as such, only the safety results are being presented in full. The following safety parameters were evaluated, and analyzed using descriptive statistics: • at baseline: physical examination, weight, vital signs • post-baseline, for the duration of the study: adverse events (AEs), concomitant medication • post-biopsy: examination of surgical site The following bone biopsy parameters were evaluated: • Standard static and dynamic histomorphometric parameters • Collagen cross-linking (from FTIR) • Mineral crystallinity (from FTIR) • Mineralization (from qBEI, synchrotron, micro-CT) • Trabecular and cortical architecture (from micro-CT and synchrotron)
Statistical methods:	The safety analysis was done for all subjects enrolled to undergo iliac crest bone biopsy. Quantitative data were described by number of subjects, mean, standard deviation (SD), median and range; categorical variables are presented with frequency and percentage. All data are listed by subject. Urine NTX and creatinine data, as well as bone biopsy parameters are listed by subject.

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Summary:	Mean age was 79 years; median (range) was 78 (77 – 82) years. Mean height was 160 cm; median (range) was 159 (154 – 165) cm. Mean weight was 64 kg; median (range) was 67 (48 – 76) kg. Mean baseline T-score of the non-dominant hip was -1.97; median (range) was -1.5 (-4.4 - -0.6). Mean T-score of the LS was -2.93; median (range) was -3.0 (-3.7 - -1.6). All 6 subjects received the first 3-day tetracycline course and 5 subjects received the second 3-day course after 14 days (n=2) or 15 days (n=3) of rest. One subject, [redacted], received concomitant medication for constipation, hypertension and hypercholesterolemia. One subject experienced treatment-related nausea during the 1st tetracycline labeling course, and was discontinued for this reason and did not undergo bone biopsy. Another subject had a femur hematoma post-biopsy which was considered not treatment-related. Both events were of mild intensity and both subjects recovered completely There were no SAEs and no deaths on-study. NTX was determined in urine to assess compliance to risedronate treatment. Subjects were considered compliant if urine NTX levels were < 50 nmol/mmol creatinine. One was borderline, just above 50 nmol BCE/mmol creatinine; the 5 other subjects were shown to be compliant as measured by urine NTX levels. Mean baseline SBP was 145 mmHg; median (range) was 144 (132 – 164) mmHg. Mean DBP was 80 mmHg; median (range) was 80 (74 – 88) mmHg. Mean heart rate was 79 bpm; median (range) was 78 (66 – 94) bpm. There were no abnormal findings at the baseline physical examination. Biopsy follow-up data showed that the surgical site had not healed properly in one subject 2 months post-biopsy. However, no details on eventual healing problems were provided. There were no infections at the surgical site and no issues related to the bone biopsy in any of the subjects. Of 5 subjects bone biopsies were taken; four of these were evaluable, with parameters of bone structure and architecture in the normal range. The lamellar structure was normal. The bone marrow showed no abnormality, no fibrosis. Single and double tetracycline labels were observed with no evidence for osteomalacia Osteoid parameters were in the lower part of the normal range. The dynamic parameters of the bone formation were low but most of them were in the normal range except the biopsy from one subject. There was no mineralization defect in any of the biopsies.
Conclusions:	[redacted]
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