2. GHCY Synopsis

Clinical Study Report Synopsis: Study B3D-MC-GHCY

Title of Study: The Effect of Teriparatide Compared with Risedronate on Back Pain in Postmenopausal Women with Osteoporotic Vertebral Fractures

Number of Investigator(s): This multicenter study included 81 principal investigator(s).

Study Center(s): This study was conducted at 78 study center(s) in 12 countries. There were 3 sites where investigators retired or left the study. These investigators were replaced.

Publication(s) Based on the Study: None at this time.

Length of Study:
Date of first subject enrolled: 22 June 2006
Date of last subject completed for 18-month endpoint: 23 June 2010

Phase of Development: 3

Objectives:

Primary: To compare the efficacy of teriparatide 20 μg/day versus risedronate 35 mg/week on the reduction of back pain in postmenopausal women with prevalent osteoporotic vertebral fractures associated with chronic back pain. The efficacy analysis was based on the proportion of subjects reporting at least a 30% reduction in the severity of back pain, from baseline to 6 months of double-blind therapy.

Secondary: (Note: only secondary objectives applicable to the 18-month end points are listed)

- As measured by pain score collected via daily diary during the 7 days prior to each scheduled visit, the proportion of patients who demonstrated at least a 30% reduction in severity of *worst* back pain from baseline to the 18-month endpoint, and at least a 30% reduction in severity of *average* back pain from baseline to 18-month endpoint.
- As measured by pain score collected via daily diary during the 7 days prior to each scheduled visit, the time-to-first occurrence of a ≥30% reduction compared to the baseline pain score in *worst* back pain during 18 months, and *average* back pain during 18 months.
- Mean change in disability and quality of life as assessed by the Roland Disability Questionnaire from baseline to 18 months, and as measured by the European Foundation for Osteoporosis Quality of Life Instrument (QUALEFFO) from baseline to 18 months.
- Safety.

Study Design: This was a prospective, randomized, parallel, double-blind, double-dummy, active-controlled, multicenter, multinational trial conducted in postmenopausal women with chronic back pain associated with osteoporotic vertebral fractures. Subjects were assigned to receive teriparatide 20 μg/day by subcutaneous (SQ) injection and a placebo tablet once weekly, or risedronate 35 mg/week as an oral tablet and a placebo SQ injection once daily. All subjects received supplemental calcium and vitamin D.

Number of Subjects:
Planned: 708 total; 354 teriparatide, 354 risedronate
Randomized, Treated (at least 1 dose): 710 total; 360 teriparatide, 350 risedronate
Completed 18-Month Endpoint: 528 total; 269 risedronate, 259 teriparatide

Diagnosis and Main Criteria for Inclusion: Eligible subjects were postmenopausal women ≥45 years of age with a history of back pain of at least 2 months duration that was, in the opinion of the investigator, likely caused by a minimum of one confirmed moderate osteoporotic vertebral fracture(s). Subjects had to have a baseline pain score of at least 4.0 on the 11-point numeric rating scale and an absolute bone mineral density (BMD) value at the lumbar spine and/or femoral neck and/or total hip bone mineral density (BMD) T-score ≤-2.0.

Study Drug, Dose, and Mode of Administration:
Teriparatide 20 μg, given daily as SQ injection.

Reference Therapy/Comparator, Dose, and Mode of Administration: Comparator: Risedronate tablets: 35 mg, given once weekly. Placebo tablets: given once weekly. Placebo SQ injection: given once daily.

Duration of Treatment:
18 months with primary endpoint at 6 months
Teriparatide Frequency: once daily for 18 months
Risedronate Frequency: once weekly for 18 months

Variables:
Efficacy: Severity of *worst* back pain experienced in the preceding 24 hours, using an 11-point numeric rating scale, recorded daily in a diary by subjects during the week prior to each study visit, was measured. Subjects with ≥30% reduction in worst back pain were considered responders. Other efficacy variables were: severity of *average* back pain, time-to-first occurrence of ≥30% reduction in worst and average back pain, and mean change in disability and quality of life using the Roland Disability Questionnaire and the QUALEFFO.
Safety: Safety variables included deaths, discontinuations due to adverse events (AEs), serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), clinical laboratory tests, and vital sign measurements.

Statistical or Evaluation Methods:
Efficacy: Worst or average back pain scores recorded daily during the week prior to the next visit were averaged for each visit. Secondary objective analyses were performed to compare the teriparatide versus risedronate on the proportion of subjects with ≥30% reduction in severity of *worst* back pain from baseline to 18 months, and for *average* back pain from baseline to 18 months. Percent change of pain was calculated as the pain score at Visit 12 minus the pain score at Visit 2, divided by the pain score at Visit 2, and was performed using Pearson Chi-square test. Time-to-first occurrences of ≥30% worst and average back pain reduction between baseline and 18 months was analyzed by survival analysis, and comparison of the Kaplan-Meier survival curves between treatment groups was conducted using the log-rank test and the Wilcoxon test at a significance level of 0.05. Treatment group comparisons in mean change of total score from the Roland Disability Questionnaire and the QUALEFFO were analyzed using an analysis of covariance model. Type III sum of squares was used for the statistical comparison.
Safety: Adverse events were summarized as TEAEs, with the frequency and percent of subjects who reported TEAEs presented for each treatment group; between-group comparisons were performed using Fisher's Exact test. Serious adverse events, discontinuations due to AEs, laboratory results, and vital sign measurements were tabulated and summarized. Laboratory values were analyzed for changes from baseline and for distribution across the normal reference ranges.

Results Summary: (Note: Only results applicable to the 18-month endpoint are reported here. Refer to the 12-month report for 6- and 12-month results.)

- Disposition and Baseline Characteristics: A total of 528 subjects (risedronate: 269; teriparatide: 259) completed the study to the 18-month endpoint. Subject decision was the only statistically significant reason for discontinuation between treatment groups, with the teriparatide group having a greater number of subjects discontinuing for this reason. The teriparatide group had statistically significantly higher mean baseline measurements for femoral neck BMD compared to risedronate (0.650 versus 0.634, p=0.028) and T-scores (-2.315 versus -2.435, p=0.028).
- Efficacy: There were no statistically significant differences between treatment groups at 18 months of treatment in the proportion of subjects with at least a 30% reduction in *worst* (risedronate: 67%, teriparatide: 68.9%) or *average* (risedronate: 69.3%, teriparatide: 72.2%) back pain severity response rates. No significant treatment group differences were seen for time-to-first occurrence of a ≥30% reduction in worst and average back pain, incidence of new nonvertebral fractures, disability score, quality of life, analgesic use (both in categorizing A through D and MQS scale), Timed Loaded Standing Test, days of disability due to back pain and days of bed rest due to back pain.
- Worsening of *worst* back pain level between 6 and 18 months occurred in 21.0% of teriparatide and 26.8% of risedronate subjects (p=0.076). Worsening of *average* back pain level between 6 and 18 months occurred in 23.6% of teriparatide and 30.6% of risedronate patients (p=0.038).

- There were statistically significantly fewer subjects in the teriparatide group compared to the risedronate group with ≥1 new or worsening vertebral fractures (6.7% versus 11.1%, p=0.047) and ≥1 new vertebral fractures (4.4% versus 9.4%, p=0.011) at 18 months.
- The subjects in the teriparatide group had overall statistically significantly less severe new vertebral fractures compared to the risedronate group (mild 8/16 versus 6/33, moderate 7/16 versus 17/33, severe 1/16 versus 10/33, overall p=0.039).
- The subjects in the teriparatide group had statistically significantly less height loss compared to the risedronate group (0.44 cm versus 0.70 cm, p=0.046) at 18 months.
- At the 18-month endpoint, lumbar spine and femoral neck least square mean (LSmean) percent changes in BMD from baseline were statistically significantly greater for the teriparatide group compared to the risedronate group (lumbar spine LSmean [teriparatide] = 7.829, [risedronate] = 2.633, p<0.001); femoral neck LSmean [teriparatide] = 2.106, [risedronate] = 0.765, p=0.021).
- Safety: There were 9 deaths in the study, including 3 additional deaths since the 12-month time point. The number of deaths was similar between treatment groups, and none of the deaths were considered to be related to study drug, the device, or the protocol procedures.
- Overall, 120 (16.9%) subjects reported SAEs (risedronate 18.6%, teriparatide 15.3%), with no significant difference between treatment groups. The only SAEs with an incidence statistically significant between treatment groups were cardiac disorders (risedronate 2.6%, teriparatide 0.6%, p=0.035) and respiratory, thoracic and mediastinal disorders (risedronate 2.6%, teriparatide 0.6%, p=0.035).
- Overall, a total of 63 subjects (8.9%) discontinued due to an AE, with no significant differences between treatment groups, overall or by category. The highest incidence of discontinuation due to AE was for the system organ class (SOC) gastrointestinal disorders (teriparatide 2.8%, risedronate 1.1%).
- Overall, the total proportion of TEAEs reported for risedronate (81.4%) and teriparatide (79.2%) were not significantly different. Subjects in the teriparatide group had statistically significantly greater numbers of TEAEs versus risedronate for skin injuries not elsewhere classified (NEC) (high level term [HLT], 5.3% versus 2.0%, p=0.027), metabolism and nutrition disorders (SOC, 10.6% versus 6.0%, p = 0.030), potassium imbalance (HLT, 2.2% versus 0.3%, p=0.038), hypokalemia (preferred term [PT], 2.2% versus 0.3%, p=0.038), muscle related signs and symptoms NEC (HLT, 9.2% versus 4.6%, p = 0.018), and muscle spasms (PT, 8.9% versus 4.3%, p=0.015). Increases in muscle spasms are expected with teriparatide and are reported in the teriparatide label. All events of hypokalemia were not serious, and no subjects discontinued because of these events. Scheduled lab results for potassium were comparable between the 2 treatment arms. Subjects in the risedronate group had statistically significantly greater numbers of TEAEs compared to teriparatide for dental and periodontal infections and inflammations (HLT, 2.0% versus 0.3%, p=0.036), vomiting (PT, 6.0% versus 2.5%, p=0.025), spinal fractures and dislocations (HLT, 4.9% versus 1.4%, p=0.009), respiratory, thoracic, and mediastinal disorders (SOC, 16.0% versus 7.5%, p=<0.001), bronchospasm and obstruction (HLT, 4.6% versus 1.1%, p=0.006), asthma (PT, 2.9% versus 0.6%, p=0.020), muscle weakness conditions (HLT, 1.4% versus 0%, p=0.029) and muscular weakness (PT, 1.4% versus 0%, p=0.029).
- The number of subjects with hypercalcemia (defined as any postbaseline serum calcium >11.0 mg/dl [2.76 mmol/L]) was statistically significantly greater in the teriparatide group (3.6% versus 0.6%, p=0.007). Hypercalcemia is an expected event with teriparatide and is reported in the teriparatide label.
- There was a small decrease in mean serum magnesium levels from baseline to endpoint in the teriparatide group compared to the risedronate group. There was no significant increase in TEAEs of hypomagnesemia (teriparatide 2, risedronate 0).

Conclusions:

- The proportion of subjects experiencing at least a 30% reduction of back pain was not significantly different between the teriparatide and risedronate groups at any time point.
- The amount of analgesics used, quality of life, overall disability, days of bed rest, or days of disability were not significantly different between the teriparatide and risedronate groups at any time point.
- New vertebral fractures occurred in significantly fewer subjects in the teriparatide versus the risedronate group; overall, these vertebral fractures were less severe in the teriparatide group compared to the risedronate group; and the subjects in the teriparatide group had significantly less height loss compared to those in the risedronate group.
- Bone mineral density increases were greater in those receiving teriparatide compared with risedronate.
- Overall safety seen in this study appears to be consistent with the known teriparatide safety profile.