Summary ID# 8175

Clinical Study Summary: Study B3D-MC-GHCN

The Effect of Teriparatide on Distal Radius Fracture Healing

Date summary approved by Lilly: 12 May 2008

Title of Study: The Effect of Teriparatide on Distal Radius Fracture Healing	
Investigator(s): This multicenter study included 14 principal investigators.	
Study Center(s): This study was conducted at 14 study centers in 7 countries.	
Length of Study: 2 years, 6 months Date first patient enrolled: 03 December 2004 Date last patient completed: 25 June 2007	**Phase of Development:** 2
Objectives: Primary: To compare the effect of 8 weeks of subcutaneous treatment with teriparatide 20 µg/day or 40 µg/day versus placebo on time to radiographic fracture healing (defined by cortical bridging) in postmenopausal women with a unilateral, dorsally angulated, distal radius (Colles') fracture. Secondary: To compare the effect of 8 weeks of treatment with teriparatide 20 µg/day or 40 µg/day versus placebo on (1) radiologic parameters, (2) pain and hand function and grip strength, and (3) vital signs, clinical laboratory test results, and reports of adverse events (AEs).	
Study Design: Phase 2, prospective, randomized, parallel, double-blind, placebo-controlled, multicentered, multinational study to evaluate the effect of teriparatide on fracture healing in postmenopausal women who had sustained a Colles' fracture. The study duration was 17 weeks plus a 36-week safety extension. The study comprised 4 periods: Screening, Treatment, Follow-up, and Safety Extension.	
Number of Patients Planned: 105 Randomized: 36 teriparatide 20 µg, 34 teriparatide 40 µg , 36 placebo Completed: 29 teriparatide 20 µg, 26 teriparatide 40 µg, 27 placebo	

Diagnosis and Main Criteria for Inclusion:

Ambulatory postmenopausal (≥2 years without regular menses) women 45 to 85 years of age having sustained a unilateral, dorsally angulated fracture of the distal radius within the past 10 days. Patients must have received conservative treatment of the fracture, including closed reduction and immobilization, be free of severe or chronically disabling conditions other than the distal radius fracture, and be willing and able to satisfactorily use a pen-type delivery system or be willing to receive daily subcutaneous injections from a care partner trained to use the injector. Patients were required to give informed consent and to be able to cooperate with study procedures.

Test Product, Dose, and Mode of Administration: Teriparatide 20 µg or 40 µg subcutaneously, once daily, injected into the left or right lower abdominal wall or outer thigh.

Reference Therapy, Dose, and Mode of Administration: Placebo injection given subcutaneously once daily into the left or right lower abdominal wall or outer thigh.

Duration of Treatment: 17 weeks with a 36-week safety extension.

Variables:

Efficacy:

Primary: Time to radiographically healed fracture (interval between occurrence of the fracture and time when bridging of 3 of the 4 cortices was determined)

Secondary: (1) time to early endosteal healing, (2) time to partial endosteal healing, (3) time to trabecular union, (4) time to cortical bridging, (5) evaluation of anatomical deformity, (6) assessment of Patient-Rated Wrist Evaluation scores, and (7) assessment of grip strength as determined by a Jamar® dynamometer

Safety:

(1) AEs, including serious adverse events (SAEs), early discontinuations due to AEs, (2) clinical laboratory test results, and (3) physical examination

Evaluation Methods:

Statistical: Time to fracture healing was analyzed by survival analysis using the Wilcoxon test. Hypotheses for teriparatide 20 µg versus placebo and teriparatide 40 µg versus placebo were tested sequentially, each at a 2-sided alpha equal to 0.05, using a gatekeeping strategy: if teriparatide 40 µg versus placebo was not significant, inference for teriparatide 20 µg versus placebo was not performed. The life table method was used to estimate the cumulative probability of healing with respect to time and to obtain the median healing time. The Cox regression model was used to test the treatment effect after adjusting for possible explanatory variables. Secondary endpoints were analyzed in the same manner as time to fracture healing. Anatomical deformity endpoints were analyzed using the Cochran Mantel Haenszel test. Functional efficacy endpoints were analyzed using mixed-model repeated measures (MMRM) methodology. All analyses were done at 2-sided alpha equal to 0.05. Efficacy and safety analyses were performed on a modified intent-to-treat population (patients receiving at least 1 dose of study drug); analyses of the primary efficacy variable were also performed on per protocol population (patients without major protocol violations). Longitudinal efficacy analyses were performed on patients with at least 1 post-randomization observation for the variable of interest.

Summary:

Overall, 80% of the patients who were randomly assigned to treatment completed the study. There were no significant differences between groups in the number of patients who completed or discontinued the study. There were no significant differences between treatment groups with regard to baseline demographics and baseline injury characteristics. The median age of the study population was 61 years and approximately two-thirds of the patients were white. There were no significant differences between groups in the nature of the wrist fracture, or the baseline pain score.

The median time to healing of 3 of 4 cortices was approximately 9 weeks for both placebo and teriparatide 40 µg-treated patients. The finding of no difference across treatment groups was consistent in all of the secondary analysis endpoints as well. There were no statistically significant between-treatment differences in the time to early or partial endosteal healing, trabecular union, or cortical bridging. Although the time to healing was shorter in the teriparatide 20-µg treatment group than in the placebo group, (-2.7 to -0.6 weeks) with $p = 0.006$, the gatekeeping design for the a priori statistical analysis used to control for type 1 error would not declare the teriparatide versus placebo value to be significant. However, the overall test among the three groups is significant ($p = 0.015$). All of the patients demonstrated significant improvement in scores on pain, functional, and grip strength regardless of treatment. The expected 11-week healing time for patients treated with placebo was based on a 1997 study by Kristiansen et al. Although it is unclear why patients treated with placebo in Study B3D-MC-GHCN (GHCN) exceeded the predicted placebo healing model, why teriparatide failed to show an effect, or why no dose response to teriparatide was observed, it should be noted that patients in Study GHCN had less complicated fractures, while those in the Kristiansen study had more complex fractures that today would have made them ineligible for the GHCN study.

None of the teriparatide-treated patients experienced sustained hypercalcemia or an SAE. Overall, 3 patients, all treated with placebo, experienced SAEs, and only 1 patient, also treated with placebo, developed sustained hypercalcemia. The only teriparatide-related AE that led to a patient withdrawing from the study was nausea in a patient in the 40-µg treatment group. One placebo patient discontinued due to an AE of right distal radius fracture. There was 1 death during the study of a patient in the placebo group due to a malignant lung neoplasm 102 days after the first dose of study drug.

There was no significant difference in change from baseline at any timepoint in systolic and diastolic blood pressure. Heart rate was significantly increased in the teriparatide 40 µg/day group when compared to baseline (week 3, 4 beats per minute [BPM] $p=0.014$; week 6, 4.5 BPM $p=0.024$; and endpoint, 4 BPM $p=0.028$), but teriparatide 20 µg/day and placebo measurements were not significantly different from baseline at any timepoint.