These results are supplied for informational purposes only. Prescribing decisions should be made based on the approved package insert in the country of prescription.

NAME OF SPONSOR/COMPANY:

Genzyme Corporation, 500 Kendall Street, Cambridge, MA 02142
Bone Care International, Inc., Middleton, WI 53652 (Bone Care was acquired by Genzyme Corporation July 2005)

TITLE OF STUDY:

Protocol BCI-CH-115: Effect of Oral 1α-Hydroxyvitamin D_2 on Elevated Blood Parathyroid Hormone Levels in Patients with Mild to Moderate Chronic Renal Failure

INVESTIGATORS AND STUDY CENTER(S):

This was a multicenter study conducted at three locations in the United States.

STUDIED PERIOD:

First patient enrolled: 03 November 1997
Last patient completed: 09 January 2000

PHASE OF DEVELOPMENT:

Phase 3

OBJECTIVES:

To establish the safety and efficacy of oral Hectorol® as a therapy for secondary hyperparathyroidism in pre-dialysis patients with mild to moderate chronic renal insufficiency (Stage 3 and Stage 4 Chronic Kidney Disease (CKD)).

METHODOLOGY:

This was a Phase 3, randomized, multi-center study. The study consisted of an 8-week Washout Period followed by a 24-week double-blind Treatment Period. During the 24-week double-blind period, patients were randomly assigned to either Hectorol or placebo.

NUMBER OF PATIENTS (PLANNED AND ANALYZED):

No. Enrolled: 40
No. Treated: 30 (15 Hectorol, 15 placebo)
No. Completed: 24 (13 Hectrol, 11 placebo)

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Subjects were between the ages of 18 and 85 years, with elevated plasma iPTH (> 85 pg/mL), and serum creatinine between 1.8 to 5.0 mg/dL (for men) or 1.6 to 4.0 mg/dL (for women).

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION:

Hectorol: 0.5 mcg soft gelatin capsules
The initial dose was 1 mcg per day.
Doses were taken orally every day before breakfast.

DURATION OF TREATMENT:

8-week Washout Period followed by 24-week Treatment Period.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION:

Placebo contained the same inactive ingredients in identical proportions and appearance to Hectorol.
Doses were taken orally every day before breakfast.

CRITERIA FOR EVALUATION:

Criteria for Evaluation - Efficacy:
Plasma iPTH was evaluated for evidence of the test drug's efficacy. Bone-specific serum markers (e.g., bone-specific alkaline phosphatase (BSAP), serum osteocalcin) were also evaluated.

Criteria for Evaluation - Safety:
Serum and urine calcium were evaluated for safety. Additionally, adverse events were evaluated for safety.

STATISTICAL METHODS:
Comparisons were considered to be statistically significant if the two-sided p-value was ≤ 0.05. Missing values were imputed using last observation carried forward.

Statistical Methods - Efficacy:
Baseline values were defined as the mean of the data collected during Weeks -4 and 0 of the Washout Period. At each time point, descriptive statistics were calculated. Also, the significance of the mean difference from baseline at each time point was assessed by paired t-test.

At baseline and at each time point during the Treatment Period, the treatment groups were compared, and the significance of differences in means was assessed via a two-sample t-test. For certain parameters (plasma iPTH, BSAP, and serum osteocalcin), the data were also recalculated as a percent of baseline and the analyses were performed on these percentages. All of the above analyses were performed on an intent-to-treat basis.

Statistical Methods – Safety:
Baseline values were defined as the mean of the data collected during Weeks -4 and 0 of the Washout Period. At each time point, descriptive statistics were calculated. Also, the significance of the mean difference from baseline at each time point was assessed by paired t-test.

At baseline, and throughout the Treatment Period, the treatment groups were compared, and the significance of differences in means was assessed via a two-sample t-test. For serum calcium and serum phosphorus, the data were also recalculated as a percent of baseline and the analyses were performed on these percentages. All of the above analyses were performed on an intent-to-treat basis.

Adverse experiences were recorded, and their frequency determined for each treatment group. For each type of serious, unexpected adverse event or drug-related adverse experience, the treatment groups were compared with respect to the percent of patients experiencing the adverse effect by Fisher's exact test.

SUMMARY / CONCLUSIONS

Summary / Conclusions - Demographics:
The 30 patients enrolled into the Treatment Period had ages between 52 and 84 years (mean = 68.4 years). Twenty-eight patients were men and two were women; 19 were African-American, 7 were Caucasian, and 4 were Hispanic.

Summary / Conclusions – Efficacy:
The intent-to-treat analysis included all 30 subjects who entered the Treatment Period (15 on Hectorol, 15 on placebo).

Average Prescribed Dose: The mean weekly dosage of study drug remained at the initial level of 1 mcg (2 capsules) for subjects receiving Hectorol until Week 4. Thereafter, the mean dose in the Hectorol group increased to 1.57 mcg/day by the end of the study. The dose in the placebo group increased to 4.93 mcg/day by the end of the study.

Plasma iPTH: At baseline, mean plasma iPTH was 220.2 pg/mL in the Hectorol group, and 185.3 pg/mL in the placebo group ($p = 0.40$). With initiation of Hectorol treatment, mean iPTH decreased to 97.3 pg/mL ($p < 0.001$ vs. baseline) at the end of the study. In contrast, mean iPTH remained unchanged from baseline levels in the placebo group throughout the entire Treatment Period, ending at 167.5 pg/mL ($p = 0.16$).

At the end of the Treatment Period, 13 (87%) of 15 subjects in the Hectorol group had achieved plasma iPTH suppression of ≥ 30% from baseline. Only one (7%) of the 15 subjects receiving placebo achieved iPTH suppression of ≥ 30% by the end of the study.

At the end of the study, mean reduction of iPTH from baseline was 53.9% for Hectorol subjects and 10.2% for placebo subjects ($p < 0.001$).

Osteocalcin: Baseline mean serum osteocalcin was 67.6 ng/mL in the Hectorol group and 67.0 ng/mL in the placebo group ($p = 0.96$). With Hectorol treatment, mean osteocalcin decreased to 46.9 ng/mL by the end of the study ($p < 0.001$). Mean osteocalcin levels trended slightly downward but remained statistically unchanged from baseline in the placebo group, reaching 60.8 ng/mL ($p = 0.20$) by the end of the study. No differences between the groups reached statistical significance during the Treatment Period.

Bone-Specific Alkaline Phosphatase (BSAP): Baseline mean serum BSAP was 25.3 U/L in the Hectorol group and 27.5 U/L in the placebo group ($p = 0.40$). After initiation of Hectorol treatment, mean BSAP decreased to 18.3 U/L by the end of the study ($p < 0.001$ vs. baseline). Mean BSAP in the placebo group was 25.5 U/L at the end of study ($p = 0.27$). The mean difference between the treatment groups was statistically significant at the end of the study ($p = 0.004$).

At the end of the study, mean reduction in BSAP from baseline was 26.3% for Hectorol subjects and 5.2% for placebo subjects ($p = 0.01$).

Summary / Conclusions – Safety Results:
Adverse Events: One-hundred thirty (130) treatment emergent adverse events occurred during the study with 47 events occurring in patients randomized to active treatment. One non-serious adverse event (nausea), reported in a subject who received Hectorol, was assessed as related to study drug (0.8%). All other treatment emergent adverse events were assessed as not related or probably not related to study drug. An analysis of the incidence rates for serious and non-serious adverse events by treatment group showed no significant differences.

One death occurred during the study in a patient randomized to placebo. The patient died at Week 15 of the study due to cardiorespiratory arrest. The Investigator determined the event as not related to study drug. Fifteen serious treatment emergent adverse events occurred in nine patients during the study. Seven serious adverse events (39%) occurred in four patients receiving Hectorol. All serious adverse events were considered not related to study drug.

No episodes of hypercalcemia (serum calcium > 10.7 mg/dL) occurred in the Hectorol group and one episode of hypercalcemia occurred in one subject in the placebo group. During the Treatment Period, there were 5 episodes of hyperphosphatemia (serum phosphorus > 5.0 mg/dL) in four patients receiving active treatment and 3 episodes in three patients receiving placebo treatment. No episodes of hypercalciuria (defined as 24-hour urine calcium excretion greater than 200 mg or fasting urine calcium/creatinine ratio above 0.25) occurred during the Treatment Period in either the active or placebo groups.

Serum Calcium: Baseline mean serum calcium was 8.62 mg/dL in the Hectorol group and 8.83 mg/dL in the placebo group ($p = 0.28$). At the end of the study, mean serum calcium was 9.11 mg/dL in the Hectorol group and 8.9 mg/dL in the placebo group ($p = 0.32$). The increase in mean serum calcium from baseline was significant only in patients treated with Hectorol ($p = 0.01$); however, mean serum calcium did not differ between the treatment groups at any time during the study ($p > 0.14$).

Serum Phosphorus: At baseline, mean serum phosphorus was 3.85 mg/dL in the Hectorol group and 3.73 mg/dL in the placebo group ($p = 0.61$). At the end of the study, mean serum phosphorus was 4.21 mg/dL in the Hectorol group and 3.64 mg/dL in the placebo group ($p = 0.005$). The increase in serum phosphorus relative to baseline was significant for the Hectorol group ($p = 0.011$). Serum phosphorus differed between Hectorol and placebo groups at Weeks 20 and 24 ($p \leq 0.02$).

Urine Calcium: Baseline mean 24-hour urine calcium was 33.7 mg in patients treated with Hectorol and 37.8 mg in patients receiving placebo ($p = 0.74$). At the end of the study, mean urine calcium was 48.1 mg/24 hours in the Hectorol group and 34.8 mg/24 hours in the placebo group ($p = 0.43$). No statistically significant changes in 24-hour urine calcium relative to baseline levels were observed in either the Hectorol or placebo group throughout the Treatment Period. No differences between treatment groups reached statistical significance during the Treatment Period.

Clinical Chemistry, Hematology, Vital Signs: There were no clinically significant changes in other clinical chemistry or hematology laboratory parameters or vital signs.

Based on report prepared on: 16 January 2002
Synopsis prepared on: 10 November 2006