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-119: 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 multi-center study conducted at four locations in the United States.

STUDIED PERIOD:

First patient enrolled: 16 September 1998
Last patient completed: 03 May 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: 32
No. Treated: 25 (12 Hectorol, 13 placebo)
No. Completed: 22 (11 Hectrol, 11 placebo)

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Subjects were between the ages of 18 and 85 years, with elevated plasmas 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 monitored during the study.

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 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 25 patients enrolled into the Treatment Period had ages between 36 and 81 years (mean = 60 years). Seventeen patients were men and 8 were women; 3 were African-American, 21 were Caucasian, and one was self-designated as "Other".

Summary / Conclusions – Efficacy:
The intent-to-treat analysis included all 25 subjects who entered the Treatment Period (12 on Hectorol, 13 on placebo).

Average Prescribed Dose: The mean weekly dosages 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 1.68 mcg/day by the end of the study. The mean dose in the placebo group increased to 5.35 mcg/day by the end of the study.

Plasma iPTH: At baseline, mean plasma iPTH was 217.8 pg/mL in the Hectorol group and 155.3 pg/mL in the placebo group ($p = 0.07$). With initiation of Hectorol treatment, mean iPTH decreased to 143.3 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 166.4 pg/mL ($p = 0.49$).

At the end of the Treatment Period, 7 (58%) of 12 subjects in the Hectorol group had achieved plasma iPTH suppression of ≥ 30% from baseline. Only one (7.7%) of the 13 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 36.1% for Hectorol subjects and increased by 13.0% for placebo subjects ($p = 0.003$).

Osteocalcin: Baseline mean serum osteocalcin was 111.2 ng/mL in the Hectorol group and 88.8 ng/mL in the placebo group ($p = 0.42$). With Hectorol treatment, mean osteocalcin decreased to 89.3 ng/mL by the end of the study ($p = 0.06$). Mean osteocalcin levels trended upward from baseline in the placebo group reaching 94.8 ng/mL ($p = 0.30$) 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 55.9 U/L in the Hectorol group and 32.2 U/L in the placebo group ($p = 0.19$). After initiation of Hectorol treatment, mean BSAP decreased to 42.5 U/L by the end of the study ($p = 0.02$ vs. baseline). Mean BSAP in the placebo group was 29.1 U/L at the end of the study ($p = 0.34$). No differences between the treatment groups reached statistical significance during the Treatment Period.

At the end of the study, mean reduction in BSAP from baseline was 29.9% for Hectorol subjects and 1.7% for placebo subjects ($p = 0.01$).

Summary / Conclusions – Safety Results:
Adverse Events: One hundred ninety (190) treatment emergent adverse events occurred during the study. Seventy-five (75) treatment emergent adverse events occurred in patients on active Hectorol. All 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.

No patient deaths occurred during the study. Six serious adverse events occurred in five patients during the study. Four serious adverse events occurred in four patients randomized to the placebo group. Two serious adverse events occurred in one patient randomized to active Hectorol therapy. The events (chest discomfort radiating into jaw and angina/chest pain) occurred after study Week 12, resolved, and were assessed as not related to study drug by the Investigator.

Two episodes of hypercalcemia (serum calcium > 10.7 mg/dL) occurred in one subject receiving Hectorol treatment at Week 4 and Week 16. Baseline serum calcium for this patient was 10.4 mg/dL, and was as high as 10.7 mg/dL during the Baseline Period. No episodes of hypercalcemia occurred in patients who received placebo. There were 6 episodes of hyperphosphatemia (serum phosphorus > 5.0 mg/dL) in 6 patients during the Washout Period. During the Treatment Period, there were 10 episodes of hyperphosphatemia in 6 patients receiving active treatment and 6 episodes in 5 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 level was 8.88 mg/dL in the Hectorol group and 8.80 mg/dL in the placebo group ($p = 0.80$). At the end of the study, mean serum calcium was 9.18 mg/dL in the Hectorol group and 8.99 mg/dL in the placebo group ($p = 0.54$). 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 4.24 mg/dL in the Hectorol group and 4.07 mg/dL in the placebo group ($p = 0.62$). At the end of the study, mean serum phosphorus was 4.35 mg/dL in the Hectorol group and 4.24 mg/dL in the placebo group ($p = 0.70$). The increases in mean serum phosphorus relative to baseline were not statistically significant in either treatment group ($p > 0.29$). Serum phosphorus did not differ between groups at any time during the Treatment Period ($p > 0.05$).

Urine Calcium: Baseline mean 24-hour urine calcium was 16.8 mg in patients treated with Hectorol and 20.9 mg in patients receiving placebo ($p = 0.48$). At the end of the study, mean urine calcium was 23.6 mg/24 hours in the Hectorol group and 20.0 mg/24 hours in the placebo group ($p = 0.61$). 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