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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-108-Memphis: A Multicenter, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Oral 1α -Hydroxyvitamin D_2 in Reducing Elevated Blood Parathyroid Hormone Levels in End Stage Renal Disease Patients on Hemodialysis

INVESTIGATORS AND STUDY CENTER(S):

This was a multi-center study conducted at ten investigative sites within the United States.

STUDIED PERIOD:

First patient enrolled: 20 June 1996
Last patient completed: 14 August 1997

PHASE OF DEVELOPMENT:

Phase 3

OBJECTIVES:

To evaluate the safety and efficacy of oral Hectorol® as a therapy for secondary hyperparathyroidism in patients with Stage 5 Chronic Kidney Disease on hemodialysis.

METHODOLOGY:

This was a Phase 3, randomized, multi-center study. The study consisted of an 8-week washout period, a 16-week open-label treatment period with Hectorol®, and an 8-week double-blind period. During the 8-week double-blind period, subjects were randomly assigned to either Hectorol® or placebo.

NUMBER OF PATIENTS (PLANNED AND ANALYZED):

No. Enrolled: 108
No. Treated: 76
No. Completed: 65 (61 per protocol)

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Subjects were male or female between the age of 20 to 75 years who had been on three times weekly hemodialysis treatment for at least four months, with a history of elevated iPTH values (>400 pg/mL)

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION:

Hectorol® (doxercalciferol capsules): 2.5 mcg soft gelatin capsules. The initial dose was 10 mcg after each hemodialysis session.
Oral dose taken three times a week.

DURATION OF TREATMENT:

The total study duration was 32 weeks, including an 8-week washout period, a 16-week open-label Hectorol® treatment, and an 8-week Hectorol® or placebo treatment.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION:

Placebo contained the same inactive ingredients in identical proportions to Hectorol®. Taken as an oral dose three times a week.

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, serum osteocalcin) were also evaluated.

Criteria for Evaluation - Safety:
Safety was evaluated based on adverse events in addition to serum calcium and phosphorus.

STATISTICAL METHODS:
Comparisons were considered statistically significant if the two-sided p-value was ≤ 0.05.

Statistical Methods - Efficacy:
Baseline values for plasma iPTH were an average of the data collected during the last three visits during the washout period (Weeks -2, -1 and 0).

Treatment groups were compared with respect to each of the evaluable parameters recorded at baseline using a t- test or a Wilcoxon two-sample test, as appropriate. At each post-baseline visit during the double-blind period, the treatment groups were compared with respect to original values and percent of baseline values using either a t-test or a Wilcoxon two-sample test, as appropriate. Additionally, the significance of the change from baseline within each treatment group for each of the evaluable parameters at each of the time points was determined using either a paired t-test or a Wilcoxon one-sample test, as appropriate.

For each of the evaluable parameters, an intent-to-treat analysis was also performed. This analysis included all subjects randomized to receive drug. Included in this analysis was an endpoint analysis which focused on the data collected at the last visit for each subject. The significance of the change from baseline for each of the evaluable parameters was determined using either a paired t-test or a Wilcoxon one-sample test, as appropriate.

Statistical Methods - Safety:
All adverse experiences were recorded. Serum calcium and serum phosphorus were analyzed in a similar manner to iPTH. For other laboratory parameters, the treatment groups were compared in two ways: 1) the proportion of subjects with values within the normal range were compared using Fisher's exact test; and 2) the mean values were compared using a t-test or Wilcoxon two-sample test, as appropriate. Each of these analyses was performed at each sampling time during the double-blind period. In addition, the significance of the change from baseline within each treatment group for each parameter was determined using either a paired t-test or a Wilcoxon one-sample test, as appropriate.

SUMMARY / CONCLUSIONS:

Summary / Conclusions - Demographics:
The 76 subjects enrolled into open-label period had ages between 27 and 75 years (mean = 52.3 years) and had been on hemodialysis treatment for at least 4 months (mean = 55.6 months). Thirty-four subjects were male and 42 were female; 75 were African American and one was Caucasian. Sixty-four (84.2%) subjects had received prior treatment with oral or intravenous $1\alpha,25(OH)_2D_3$.

Summary / Conclusions - Efficacy:
Both intent-to-treat (ITT; N = 76) and per protocol (PP; N = 61) analyses were performed. The results presented below are from the per protocol analyses, unless otherwise noted.

Prescribed Dose: The mean weekly prescribed dose declined progressively during the open-label period from 29.7 mcg at Week 0 to 20.0 mcg at Week 16 ($p < 0.001$). The mean prescribed dose further decreased in subjects who continued treatment with Hectorol® during the double-blind period from 19.8 mcg for Week 16 to 17.3 mcg at Week 23. However, the placebo mean dose increased from 20.3 mcg for Week 16 to 31.4 mcg for Week 23. The primary reasons for suspensions and decreases in doses were over-suppression of plasma iPTH and elevations of serum calcium and/or serum phosphorus.

Intact Parathyroid Hormone (iPTH): At baseline the plasma iPTH was 984.7 pg/mL. With initiation of Hectorol® treatment at 10 mcg per hemodialysis session, mean iPTH decreased rapidly, yielding statistically significant reductions ($p < 0.01$) at Weeks 1 through 16.

Fifty one (83.6%) subjects reached the pre-determined target iPTH range of 150 to 300 pg/mL during treatment with Hectorol®. This target range was reached after 7 to 117 days of Hectorol® therapy (mean = 40.0 days). Fifty eight of the 61 subjects (95.1%) achieved iPTH suppression of ≥ 30% on or before Week 16 of the study. This clinically meaningful response occurred after 6 to 98 days of Hectorol® therapy (mean = 20.1 days). The mean dose of Hectorol® administered to achieve ≥ 30% iPTH suppression was 9.7 mcg per hemodialysis session. By the end of the open-label period (Week 16), the plasma iPTH was reduced to 402.6 3 pg/mL ($p < 0.001$). The reduction in plasma iPTH, relative to baseline, was 56.8% ($p < 0.001$).

The mean plasma iPTH level at Week 16 for subjects randomized to Hectorol® was 351.2 pg/mL. By the end of study, mean plasma iPTH remained unchanged at 373.1 pg/mL ($p = 0.779$). In contrast, the mean plasma iPTH at Week 16 for placebo subjects was 454.1 pg/mL and increased to 871.9 pg/mL at Week 24 ($p < 0.001$).

In Hectorol® subjects, the change in mean plasma iPTH from a baseline value of 961.4 pg/mL to 373.1 pg/mL at Week 24 was significant ($p < 0.001$). For placebo subjects, the change in mean plasma iPTH from the mean baseline level of 1009.4 pg/mL to 871.9 pg/mL at Week 24 was not statistically significant. Significant differences in mean iPTH were noted between treatment groups at the last six weeks during the double-blind period ($p < 0.001$).

During the double-blind period, subjects randomized to Hectorol® had a significant decrease in mean plasma iPTH of up to 67.9% from baseline levels. In placebo subjects, the mean iPTH values rapidly returned to the baseline level; a significant increase in mean relative iPTH of 41.9% was observed during the double-blind period ($p < 0.001$). Mean relative iPTH at end of study was not statistically different from the baseline level ($p = 0.113$) for placebo subjects.

An intent-to-treat endpoint analysis focused on the last iPTH value collected for all treated subjects showed that mean plasma iPTH: (1) decreased from a baseline value of 981.5 pg/mL to 656.7 pg/mL ($p < 0.001$) in the open-label period; (2) decreased from a baseline value of 973.9 pg/mL to 489.0 pg/mL ($p < 0.001$) in Hectorol® subjects during the double-blind period; and, (3) was unchanged from a baseline value of 991.0 pg/mL to 853.0 pg/mL ($p = 0.051$) in placebo subjects in the double-blind period.

Osteocalcin: A significant mean increase in osteocalcin was observed after four weeks of open-label treatment with Hectorol® (Week 4: 85.2 ng/mL; $p = 0.001$) and continued to decrease through the open-label treatment to a mean of 64.0 ng/mL from a mean value at baseline of 77.3 ng/mL ($p < 0.001$). In the Hectorol® randomized subjects, mean osteocalcin decreased further to 49.6 ng/mL by the end of the study. In the placebo group, the mean osteocalcin at the end of the study remained unchanged from the Week 16 mean of 73.2 ng/mL ($p = 0.342$). There was no difference observed between treatment groups in the percent of subjects within the normal range. Similar changes were seen in mean osteocalcin expressed as a percentage of baseline.

Bone-Specific Alkaline Phosphatase: A decrease in mean bone-specific alkaline phosphatase (BSAP) was observed after 4 weeks of open-label Hectorol® treatment and continued through the open-label treatment to 33.5 U/L compared with 64.3 U/L at baseline ($p < 0.001$). In the double-blind period, the Hectorol® subjects had a mean BSAP decrease from 31.8 U/L at the end of the open-label treatment to 28.0 U/L at the study end ($p = 0.010$). However, the placebo subjects had their mean BSAP increase to 45.3 U/L at the study end from 35.4 U/L ($p = 0.017$) at the end of the open-label treatment. There was no detectable difference in mean BSAP values or percentage of subjects in the normal range between the Hectorol® and placebo groups during the double-blind period.

Summary / Conclusions - Safety Results:
Thirty two serious adverse events occurred in 24 patients during treatment with Hectorol® (all subjects during the open-label Treatment period 1 and the subjects randomized to receive active in treatment period 2). All serious adverse events were assessed as not related to study drug by the Investigators. One patient death occurred in a patient after 20 weeks of Hectorol®. The patient, who had a history of severe left ventricular dysfunction with congestive heart failure, died of cardiopulmonary arrest during surgery under general anesthesia. The death was assessed as not related to Hectorol® therapy by the Investigator.

Ten non-serious adverse events with possible or unknown causality to the test medication were reported in 10 subjects that received Hectorol®. Of these, six patients experienced events assessed as possibly related to study drug, including events of: stomach ache (2 patients), gastrointestinal discomfort (1 patient), diarrhea (1 patient), headache (1 patient), constipation (2 patients), and difficulty sleeping (1 patient). Four patients experienced events with an unknown relationship to study drug, including events of: dizziness, weakness and chest pain (1 patient); eye pain (1 patient); arthritis pain – hands, hips and knees (1 patient); and hyperkalemia (1 patient).

Forty two episodes of hypercalcemia (defined as serum calcium above 11.2 mg/dL) occurred in 24 patients during treatment period 1 and 10 episodes of hypercalcemia occurred in 9 patients receiving active study drug in treatment period 2. Fifty two episodes of hyperphosphatemia (defined as serum phosphorus above 8.0 mg/dL) occurred in 33 patients during treatment period 1 and 13 episodes of hyperphosphatemia occurred in 10 subjects randomized to active drug during treatment period 2.

Laboratory Parameters:
Serum calcium: A mean increase of 0.75 mg/dL in serum calcium from baseline was observed during the 16 weeks of open-label treatment with Hectorol®; this increase was statistically significant ($p < 0.001$) but well within the normal range (8.4 - 10.2 mg/dL). Approximately the same increase in mean serum calcium from baseline (0.71 mg/dL) was observed at end of treatment period 2 (Week 24) in subjects randomized to active drug. Although statistically significant ($p < 0.001$), this increase was not clinically significant.

Serum phosphorus: Mean serum phosphorus increased by 0.94 mg/dL during the 16-week open-label treatment with Hectorol®. This mean change from baseline was statistically significant ($p<0.001$) however was within the protocol-specified acceptable range of ≤ 6.9 mg/dL. A statistically significant increase in mean serum phosphorus of up to 0.91 and 0.76 mg/dL from baseline continued to the end of the study (Week 24) in both active and placebo groups ($p < 0.001$ and $p < 0.008$, respectively).

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

Based on report prepared on: 10 February 1998
Synopsis prepared on: 24 June 2006