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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-LA: 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 eleven investigative sites in the United States.

STUDIED PERIOD:

First patient enrolled: 29 May 1996
Last patient completed: 30 July 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: 104
No. Treated : 62
No. Completed: 45 (38 per protocol)

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Subjects included in this study were men and women aged 20 to 75 years, had been on hemodialysis treatment three times weekly for at least four months with a history of elevated serum 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 dialysis 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 monitored during the study.

Criteria for Evaluation - Safety:
Safety was evaluated based on adverse events, as well as on serum calcium and phosphorus.

STATISTICAL METHODS:

Comparisons were considered to be 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, 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 62 subjects enrolled into open-label treatment period 1 had ages between 22 and 75 years (mean = 52.0 years) and had been on hemodialysis treatment for at least 4 months (mean = 52.9 months). Thirty-four subjects were male and 28 were female; 36 were African-American, 19 were Caucasian, and 7 were Hispanic. Fifty-one (82.3%) of the subjects had received prior treatment with oral or intravenous lα,25$(OH)_2D_3$.

Summary / Conclusions - Efficacy:
Both intent-to-treat (ITT; N = 62) and per protocol (PP; N = 38) analyses were performed. The results presented below are from the per protocol analyses, unless otherwise noted.

Prescribed Dose: The mean weekly prescribed dose progressively declined during treatment period 1 from 29.7 mcg for Week 0 to 16.1 mcg for Week 16 ($p < 0.001$). The mean prescribed dose further decreased in subjects who continued treatment with active drug during the double-blind period from 19.0 mcg for Week 16 to 15.3 mcg for Week 23. However, the mean prescribed dose for subjects switched to placebo treatment rose from 13.8 mcg for Week 16 to 28.5 mcg for Week 23. The primary reasons for suspensions and subsequent decreases in prescribed doses were over-suppression of plasma PTH (most common) and elevations of serum calcium and/or serum phosphorus.

Intact Parathyroid Hormone (iPTH): At baseline, mean plasma iPTH was 757.4 pg/mL. With initiation of Hectorol® treatment at 10 mcg per hemodialysis session, mean iPTH decreased rapidly, yielding statistically significant reductions ($p < 0.001$) at Weeks 1 through 16.

Thirty-four (89.5%) 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 93 days of Hectorol® therapy (mean = 27.5 days). All 38 subjects achieved iPTH suppression of ≥ 30% on or before Week 8 of the study. This clinically meaningful response occurred after 7 to 56 days of Hectorol® therapy (mean = 15.5 days). The mean dose of Hectorol® administered to achieve ≥ 30% iPTH suppression was 9.9 mcg per hemodialysis session. By the end of open-label period (Week 16), the mean plasma iPTH was reduced to 348.6 pg/mL from a baseline of 757.4 pg/mL ($p < 0.001$). The mean reduction in plasma iPTH, relative to baseline, was 52.9% ($p < 0.001$).

The mean plasma iPTH level at Week 16 for subjects randomized to Hectorol® was 386 pg/mL. By the end of the study, mean plasma iPTH remained unchanged at 394.3 pg/mL ($p = 0.911$). In contrast, the mean plasma iPTH at Week 16 for subjects randomized to placebo drug was 317.8 pg/mL, and increased to 662.3 pg/mL at Week 24 ($p < 0.001$).

In subjects randomized to Hectorol®, the change in mean plasma iPTH from a baseline value of 832.5 pg/mL to 394.3 pg/mL at Week 24 was significant ($p < 0.001$). For subjects randomized to placebo, the change in mean plasma iPTH from the mean baseline level of 696.6 pg/mL to 662.3 pg/mL at Week 24 was not statistically significant. Significant differences in mean iPTH were noted between treatment groups at the last four weeks during the double-blind period ($p < 0.050$).

During the double-blind period, subjects randomized to Hectorol® had a significant decrease in mean plasma iPTH of up to 60.5% from baseline levels. In placebo subjects, the mean iPTH values demonstrated a rapid return to the baseline level; a significant increase in mean relative iPTH of 51.5% 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 ($p = 0.914$) for placebo subjects.

An intent-to-treat endpoint analysis which focused on the last iPTH value collected for all treated subjects showed that mean plasma iPTH: (1) decreased from a baseline value of 822.9 pg/mL to 605.5 pg/mL ($p < 0.001$) in the open-label period; (2) decreased from a baseline value of 797.2 pg/mL to 381.3 pg/mL ($p < 0.001$) in Hectorol® subjects during the double-blind period; and (3) was unchanged from a baseline value of 847.1 pg/mL 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: 77.8 ng/mL; $p < 0.001$) and continued to decrease through the open-label treatment to a mean osteocalcin of 55.0 ng/mL from a mean value at baseline of 70.0 ng/mL ($p < 0.001$). In the Hectorol® randomized subjects, osteocalcin remained unchanged (mean = 52.6 ng/mL) by the end of the study ($p = 0.184$) compared to Week 16. In the placebo group, the mean osteocalcin at the end of the study remained unchanged from the Week 16 mean of 54.1 ng/mL ($p = 0.796$). 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 treatment with Hectorol® with a value of 35.0 U/L compared with 58.9 U/L at baseline ($p < 0.001$). In the double-blind period, the Hectorol® subjects' mean BSAP remained unchanged from 47.5 U/L at the end of the open-label treatment, being 41.7 U/L at Week 24 ($p = 0.261$). However, the placebo subjects had their mean BSAP increase to 36.4 U/L at the study end from 24.9 U/L ($p = 0.001$) 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:
No patient deaths occurred during the study. Twenty four serious adverse events occurred in 17 patients while receiving Hectorol® (all subjects during treatment period 1 and patients randomized to receive active study drug in Treatment period 2). All serious adverse events were assessed as not related to study drug. Eighteen non-serious adverse events with

possible or unknown relationship to study drug occurred in seven patients receiving Hectorol®. These events included gastrointestinal discomfort with stomachache and diarrhea, bone ache, joint pains, leg cramps, bloody nose, headache, difficulty sleeping, itchy eyes, urethral bleeding and discharge, bruising and knots under skin, stomach, itching, itching bumps over body and nausea.

Thirty episodes of hypercalcemia (defined as a serum calcium above 11.2 mg/dL) occurred in 24 patients during treatment period 1 and six episodes of hypercalcemia occurred in 5 patients on active study drug during treatment period 2. There were 41 episodes of hyperphosphatemia (defined as serum phosphorus above 8.0 mg/dL) in 26 patients during treatment period 1 and 11 episodes of hyperphosphatemia in 7 patients on active study drug during treatment period 2.

Laboratory Parameters:
Serum Calcium: The observed mean increase of 0.74 mg/dL in serum calcium from baseline during the 16 weeks of open-label treatment with Hectorol® 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 (0.75 mg/dL) was observed at the 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 Phosphorous: The mean increase of 0.66 mg/dL in serum phosphorus from baseline during the 16 weeks of open-label treatment with Hectorol® was within the protocol-specified acceptable range of ≤ 6.9 mg/dL. Mean serum phosphorus was significantly different from baseline at Week 17 to end of the study (Week 24) in both active and placebo group.

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

Based on report prepared on: 03 February 1998
Synopsis prepared on: 24 June 2006