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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-114-Memphis: A Multicenter, Open-label Study of the Efficacy and Safety of Intravenous 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 multicenter study conducted at ten locations in theUnited States.

STUDIED PERIOD:

First patient enrolled: 16 July 1997
Last patient completed: 30 December 1997

PHASE OF DEVELOPMENT:

Phase 3

OBJECTIVES:

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

METHODOLOGY:

This study was a Phase 3, multicenter, open-label, 12-week treatment, crossover extension of 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). The study consisted of an 8-week Washout Period followed by a 12-week Hectorol Treatment Period.

Patients had hemodialysis 3 times per week and laboratory measurements at regular intervals.

If patients experienced hypercalcemia (serum calcium > 11.2 mg/dL) or hyperphosphatemia (serum phosphorus > 8.0 mg/dL), Hectorol was stopped until the serum calcium or phosphorus was lowered and then resumed at a lower dose. In patients with mild hypercalcemia (serum calcium of >10.5 to 11.2 mg/dL) or moderate hyperphosphatemia (serum phosphorus of 7.0 to 8.0 mg/dL) the calcium-based phosphate binder and/or study drug was reduced. If the plasma iPTH was less than 150 pg/mL, the study drug was stopped and resumed at a lower dose the following week.

NUMBER OF PATIENTS (PLANNED AND ANALYZED):

No. Enrolled: 57
No. Treated: 42
No. Completed: 42

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Patients who participated in Protocol BCI-CH-108-Memphis were eligible for enrollment into the Washout Period. Patients were male or female, between the ages of 20 to 75 years, who had been on hemodialysis three times a week for at least four months, with a history of elevated iPTH values (> 400 pg/mL).

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION:

Hectorol: 2 mcg/mL intravenous solution
The initial dose was 4 mcg after each hemodialysis session (12 mcg/week).
Doses were given intravenously three times per week.

DURATION OF TREATMENT:

8-week Washout Period followed by 12-week Treatment Period.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION:

Not applicable

CRITERIA FOR EVALUATION:

Criteria for Evaluation - Efficacy:
Plasma iPTH was evaluated for evidence of the test drug's efficacy; bone-specific serum markers were also monitored at selected intervals.

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

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 for plasma iPTH, calcium, and phosphorus were defined as the average of the data collected during the last three visits of the Washout Period.

At each post-baseline determination, as well as the last visit for each subject, the significance of the change from baseline for each of the evaluable parameters was determined using a paired t-test.

Statistical Methods – Safety:
All adverse events were recorded.

At each post-baseline determination as well as at the last visit for each subject, the significance of the change from baseline for calcium and phosphorus was determined using a paired t-test.

SUMMARY / CONCLUSIONS

Summary / Conclusions - Demographics:
The 42 patients enrolled in the treatment period were aged between 28 and 76 years (mean = 51 years) and had been on hemodialysis for at least 4 months (mean = 61 months). Twenty patients were male and twenty-two were female; all 42 patients were African-American.

Summary / Conclusions – Efficacy:
Both intent-to-treat (ITT; N= 42) and per protocol (PP; N = 40) analyses were performed. The results presented below are from the per protocol analyses, unless otherwise noted.

Parathyroid Hormone (PTH): At baseline, mean plasma iPTH was 774.2 pg/mL. After treatment was initiated, mean iPTH decreased to 428.4 pg/mL by the end of the study ($p < 0.001$). Thirty-seven of the 40 patients (92.5%) achieved iPTH

suppression of ≥ 30% on or before Week 10 of the study. The average dose of Hectorol required to achieve ≥ 30% iPTH suppression was 3.9 mcg per hemodialysis session. By the end of the study, plasma iPTH was reduced to 54.5% of the baseline value ($p < 0.001$). Twenty-nine (72.5%) of the 40 patients reached the pre-determined target iPTH range of 150 to 300 pg/mL during treatment with Hectorol.

Osteocalcin: Baseline mean osteocalcin was 73.9 ng/mL and decreased to 69.8 ng/mL at the end of the study ($p = 0.229$).

Bone-Specific Alkaline Phosphatase (BSAP): A statistically significant decrease in mean BSAP was observed after 4 weeks of treatment which continued through the end of the study to a mean of 35.7 U/L at Week 12 compared to a mean of 54.2 U/L at baseline ($p < 0.001$).

Summary / Conclusions – Safety Results:
Adverse events: There were no non-serious adverse events with possible or unknown causality to the study drug. Four treatment emergent serious adverse events occurred in four patients during the 12- week doxercalciferol Treatment Period. No patients died during the 12-week doxercalciferol Treatment Period. All serious adverse events were assessed as not related to study drug by the investigator.

Five episodes of hypercalcemia (defined as serum calcium above 11.2 mg/dL) occurred in five patients during treatment with doxercalciferol. Nineteen (19) episodes of hyperphosphatemia (serum phosphorus above 8.0 mg/dL) occurred in 15 patients during treatment with doxercalciferol.

Serum Calcium: A mean increase of 0.60 mg/dL in serum calcium from baseline was observed during the 12-week doxercalciferol Treatment Period; this increase was statistically significant ($p = 0.001$) but well within the normal range (8.4 - 10.2 mg/dL).

Serum Phosphorus: A mean increase of 1.0 mg/dL in serum phosphorus was observed during the 12-week doxercalciferol Treatment Period. This increase was statistically significant ($p < 0.001$), but remained within the protocol-specified acceptable range of ≤ 6.9 mg/dL.

Clinical Chemistry, Hematology, Vital Signs: A significant decrease in serum total alkaline phosphatase was observed after 8 weeks of treatment with intravenous doxercalciferol which continued through Week 12. No other clinically meaningful changes in clinical chemistry, hematology, or vital signs were observed.

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