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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-144: A Phase 4, Single-center, Open-label, Randomized Study to Determine Clinically Appropriate Doses of Doxercalciferol Injection when Converting from Paricalcitol Injection for Secondary Hyperparathyroidism in ESRD Patients on Hemodialysis

INVESTIGATORS AND STUDY CENTER(S):

This was a single-center study conducted in the United States.

STUDIED PERIOD:

First patient enrolled: 08 September 2003
Last patient completed: 17 August 2004

PHASE OF DEVELOPMENT:

Phase 4

OBJECTIVES:

To determine clinically appropriate doses of doxercalciferol injection when converting patients from paricalcitol injection to doxercalciferol injection; and
To evaluate titrated doxercalciferol doses to achieve and/or maintain iPTH values within the target range of 150 to 300 pg/mL.

METHODOLOGY:

This was a Phase 4, open-label, randomized study. The study consisted of a 4-week Baseline Period, a 6-week Fixed Dose Period, and a 12-week Dose Titration Period. At the beginning of the 6-week Fixed Dose Period, patients were randomly assigned to doses of doxercalciferol equal to 35%, 50%, or 65% of the paricalcitol doses that patients were previously receiving.

NUMBER OF PATIENTS (PLANNED AND ANALYZED):

No. Enrolled: 27
No. Treated: 27 (9 at 35% conversion, 8 at 50% conversion, 10 at 65% conversion)
No. Completed: 23
Due to difficulties in subject recruitment this study was discontinued early.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Patients included in this study were 18 years of age or older; on hemodialysis two to three times per week for a minimum of six months; with baseline iPTH between 150 and 800 pg/mL, who had been receiving paricalcitol for a minimum of three months, including a stable dose regimen for at least four weeks.

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION:

Hectorol® (doxercalciferol injection), 4 mcg/2 mL ampules
Doses of doxercalciferol were equal to 35%, 50%, or 65% of the paricalcitol doses that patients were previously receiving.
Initial doses ranged from 0.4 to 7 mcg per administration.
Doses were administered at the dialysis clinic by bolus intravenous injection.

DURATION OF TREATMENT:

22 weeks (4-week Baseline Period followed by up to 6 weeks of treatment at a fixed dose, followed by 12 weeks of treatment at titrated doses).

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION:

Paricalcitol injection
Doses ranged from 1 to 14 mcg per injection.
Doses were administered at the dialysis clinic by bolus injection.

CRITERIA FOR EVALUATION:

Criteria for Evaluation - Efficacy:
The primary endpoint was the change from baseline in iPTH values after six consecutive weeks of doxercalciferol fixed-dosing to determine the appropriate dose conversion factor to convert patients from paricalcitol to doxercalciferol injection dosing.

Criteria for Evaluation - Safety:
Safety was evaluated based on adverse events and analysis of corrected serum calcium, serum phosphorus, and corrected calcium times phosphorus product.

STATISTICAL METHODS:

Statistical Methods - Efficacy:
Baseline iPTH data were summarized by descriptive statistics to compare results among the three dose groups. Baseline iPTH was defined as the average of all results during the paricalcitol period. Descriptive statistics of iPTH results were provided by sample collection time point and dose group. Additionally, percent change from baseline data were summarized descriptively at each time point during doxercalciferol dosing. A regression analysis of change from baseline iPTH values based on the average of all fixed dosing doxercalciferol values versus dose group was performed to predict the appropriate dose conversion factor.

Statistical Methods – Safety:
Treatment emergent adverse events were tabulated. Baseline data were summarized by descriptive statistics to compare corrected serum calcium, serum phosphorus, and corrected calcium times phosphorus product results among the three dose groups. Baseline was defined as the average of all results during the paricalcitol period. Descriptive statistics of corrected serum calcium, serum phosphorus, and corrected calcium times phosphorus product results were provided by sample collection time point and dose group. Additionally, percent change from baseline data were summarized descriptively at each time point during doxercalciferol dosing.
Incidences of hypercalcemia, hyperphosphatemia, and elevated corrected calcium times phosphorus product were calculated and compared during the paricalcitol and doxercalciferol fixed dosing periods using Wilcoxon's signed-rank test.

SUMMARY / CONCLUSIONS

Summary / Conclusions - Demographics:
Of the 27 patients enrolled, 70% (19/27) were men, 41% (11/27) were Caucasian, and 59% (16/27) were African American. The mean age was 55 years. Demographic characteristics were similar across the treatment groups, except the 35% conversion factor was predominantly African American (89%; 8/9); the 50% conversion factor and the 65% conversion factor were 50% and 40% African American, respectively.

Summary / Conclusions – Efficacy:
Linear regression analysis revealed a conversion factor of 57% as the dose of doxercalciferol comparable to paricalcitol, which would result in equal suppression of iPTH.

Summary / Conclusions – Safety Results:

A total of nine treatment emergent adverse events occurred in eight patients during the study. Four non-serious adverse events were reported in four patients. One non-serious event (rash maculopapular) was assessed by the investigator as moderate and definitely related to study drug. All other non-serious adverse events were assessed as mild and not related to study drug.
Five serious adverse events were reported in five patients during the study. All serious adverse events were assessed as not related to study drug by the Investigator. One patient died of cardio-respiratory arrest after 38 days of doxercalciferol treatment. One patient died of cerebral vascular accident after completing the study. Both patient deaths were assessed as not related to study drug by the Investigator.
Corrected serum calcium, serum phosphorus and corrected calcium times phosphorus product were comparable while subjects were receiving either paricalcitol or doxercalciferol. In this small cohort, there was no difference in the incidence of hypercalcemia (defined as corrected serum calcium > 10.2 mg/dL), hyperphosphatemia (defined as serum phosphorus > 5.5 mg/dL) or elevated corrected calcium times phosphorus product (> 55 mg^2/dL^2).

Based on report prepared on: 23 May 2005
Synopsis prepared on: 07 August 2006