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

TITLE OF STUDY:

BCI-CH-147: A Phase IV, Multi-Center, Open-Label Study to Evaluate the Appropriate Initial Dose of Hectorol® Injection (doxercalciferol) When Converting ESRD Patients on Hemodialysis from Zemplar® Injection (paricalcitol) Administered for Treatment of Secondary Hyperparathyroidism

INVESTIGATORS AND STUDY CENTER(S):

This was a multi-center study conducted at five study sites in the US.

STUDIED PERIOD:

First patient enrolled: 19 July 2004
Last patient completed: 23 May 2005

PHASE OF DEVELOPMENT:

Phase 4

OBJECTIVES:

The primary objective of this study was to define an equivalent dose of doxercalciferol and paricalcitol by evaluating the clinical outcomes [primarily that of intact parathyroid hormone (iPTH)] and safety with a stable dose of doxercalciferol when converting patients from a stable dose of paricalcitol.
The secondary objective was to evaluate the clinical outcomes of titrating doses of doxercalciferol at 4-week intervals in patients converted from paricalcitol therapy

METHODOLOGY:

This was a 20-week, Phase 4, multi-center, open-label study. The study began with a 4-week fixed dose paricalcitol period, after which patients were switched from paricalcitol to doxercalciferol. Patients received a fixed initial dose of doxercalciferol for 4 weeks based on the conversion factor group, either 50% or 65%, available at the time of study entry. After 4 weeks on this fixed dose of doxercalciferol, patients entered a 12-week dose-titration period to achieve or maintain iPTH in a target range of 150-300 pg/mL

NUMBER OF PATIENTS (PLANNED AND ANALYZED):

No. Planned: 50
No. Treated: 42 (50% group, N=31; 65% group, N=11)
No. Completed: 32 (50% group, N=22; 65% group, N=10)
Study enrollment was completed at 42 subjects due to difficulty in recruitment

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Adult Stage 5 CKD patients on hemodialysis three times weekly, receiving paricalcitol as their only vitamin D treatment for at least 6 months and two measurements of the following during the 4-week baseline period: serum iPTH measurements between 150-1000 pg/mL, corrected serum calcium (cCa) < 10.0 mg/dL, serum phosphorus (P) ≤ 6.5 mg/dL, and calcium phosphorus product (cCa x P) of < 70 mg^2/dL^2.

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION:

Hectorol (doxercalciferol injection)
The first treatment group converted from their current paricalcitol dose to doxercalciferol dose using a conversion factor of 50%. The second treatment group converted from their current paricalcitol dose to doxercalciferol dose using a conversion factor of 65%.

DURATION OF TREATMENT:

The total study duration was 20 weeks, including a 4-week fixed paricalcitol period, a 4-week fixed doxercalciferol period, and a 12-week doxercalciferol dose titration period.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION:

Zemplar Injection (paricalcitol)
The patient's pre-study paricalcitol dose was used throughout the 4 week fixed paricalcitol period.

CRITERIA FOR EVALUATION:

Efficacy:
The primary endpoint was the mean change in average iPTH values between 4 consecutive weeks of paricalcitol fixed-dosing and 4 consecutive weeks of doxercalciferol fixed-dosing to determine the appropriate dose conversion factor. Additional efficacy parameters included mean change between the average laboratory value [cCa, P, and corrected calcium x phosphorus product (cCa x P)] during fixed doxercalciferol dosing and the average laboratory value during paricalcitol baseline period.
Safety:
Safety was assessed by adverse events (AEs) and changes in laboratory parameters.

STATISTICAL METHODS:

Efficacy:
The mean change between doxercalciferol and paricalcitol stable dose period and 95% confidence interval for this mean change were calculated for iPTH. In addition, a paired t-test was performed comparing the baseline (stable paricalcitol dose) and stable doxercalciferol dose means. The proportion of patients with iPTH values within the target range (150-300 pg/mL) was summarized by conversion group.
Safety:
All treatment-emergent adverse events (TEAEs), whether or not related to study drug, that occurred during the study were recorded. The number and percentage of patients with at least one TEAE, as classified by system organ class and preferred term, were summarized by relationship for each conversion factor group. In addition, drug-related AEs were classified by severity.

Laboratory values were summarized by sample collection time point and conversion group using descriptive statistics. Changes from baseline for these parameters were summarized as well.

SUMMARY / CONCLUSIONS

Demographics:
The mean age was 58 years in the 50% dose conversion group and 63 years in the 65% group. Males comprised 74% and 54% of the patients in the 50% and 65% dose conversion groups, respectively. Fifty-five percent of patients in both dose conversion groups were Black or African American.
Efficacy:
For the intent to treat population, mean iPTH increased during the doxercalciferol fixed dose period in both groups (24 ± 49 pg/mL and 25 ± 68 pg/mL for the 50% and 65% dose groups, respectively), but the increase was only statistically significant in the 50% dose conversion group (95% CI 4.6-44.2; p=0.0170). Similar results were seen in the per-protocol population. During the dose titration period, 100% of patients were able to attain at least one iPTH value in the target range (150 to 300 pg/mL).

Safety Results:
Overall, paricalcitol and doxercalciferol injection were well-tolerated in this study. The nature of the adverse events reported was consistent with the administration of vitamin D analogues in CKD patients.

During the 4-week paricalcitol fixed-dosing period 14 adverse events were reported in 7 patients; none of these adverse events were treatment-related. During the 16-week doxercalciferol dosing period (fixed dose and dose titration) 58 adverse events were reported in 21 patients. The most frequently reported adverse events during doxercalciferol dosing were hypocalcemia reported by 4 (9.5%) patients and blood phosphorus increased reported by 3 (7.1%) patients. All cases of hypocalcemia and blood phosphorus increased were mild and none required a change in the dose of study drug. Of the 58 adverse events that occurred during doxercalciferol dosing, a total of 9 treatment-related adverse events occurred in 7 patients. Most treatment-related adverse events were mild to moderate in intensity.
Six serious adverse events occurred in 4 patients during paricalcitol dosing. None of these events were assessed as related to the study medication by the Investigator. Thirty (30) serious adverse events occurred in 11 patients during doxercalciferol dosing. The majority of serious adverse events were determined to be not related to the study drug by the Investigator. Two events, arthralgia and pain in limb, occurring in the same patient, were considered possibly related to the study medication by the Investigator. There was one death reported (cardiac arrest) approximately 3 months after discontinuing doxercalciferol treatment and withdrawing from the study; the death was assessed as not related to study drug by the Investigator.
Serum calcium, phosphorous and calcium-phosphorus product were well-controlled throughout the switch between therapies.

Based on report prepared on: 02 February 2007
Synopsis prepared on: 18 November 2008