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
Bone Care International, Inc., Middleton, WI 53652 (Bone Care was acquired by Genzyme Corporation July 2005)

TITLE OF STUDY:

Protocol BCI-CH-106: Effect of Oral 1α-Hydroxyvitamin D_2 on 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 three sites in the United States.

STUDIED PERIOD:

First patient enrolled: 07 December 1994
Last patient completed: 09 October 1995

PHASE OF DEVELOPMENT:

Phase 2

OBJECTIVES:

To evaluate the efficacy of oral Hectorol® in reducing elevated plasma intact parathyroid hormone (iPTH) levels in patients with Stage 5 Chronic Kidney Disease on hemodialysis.

METHODOLOGY:

This was a Phase 2, open-label study conducted at three centers. The study consisted of an 8-week washout period followed by a 12-week open-label treatment period with Hectorol®.

NUMBER OF PATIENTS (PLANNED AND ANALYZED):

No. Enrolled: 39
No. Treated: 27
No. Completed: 24

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Subjects included in this study were men and women, aged 20 to 75 years, 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): 1 mcg soft gelatin capsules

Dose: The initial dose was 4 mcg daily before breakfast or 4 mcg three times weekly following dialysis; dose titration to higher or lower doses was allowed dependent on iPTH, calcium, and phosphorus levels. Investigators were given the option of administering Hectorol® three times per week following meals rather than daily.

DURATION OF TREATMENT:

8-week washout period followed by 12-week active treatment period.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION:

Not applicable.

CRITERIA FOR EVALUATION:

Criteria for Evaluation - Efficacy:
Serum iPTH; serum osteocalcin and serum bone specific alkaline phosphatase were also measured.

Criteria for Evaluation - Safety:
Safety was evaluated on reported adverse events, as well as on changes in serum calcium, serum phosphorus, CBC, and blood chemistries.

STATISTICAL METHODS:

Statistical significance was declared if the two-sided p-value < 0.05.

Statistical Methods - Efficacy:
Baseline values for all evaluable parameters were defined as the data collected during the last visit during the washout period. At each post-baseline determination, 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:
The frequency of adverse experiences was determined.

For serum calcium and serum phosphorus, baseline values were defined as the data collected during the last visit during the washout period. At each post-baseline determination, the significance of the change from baseline 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 27 subjects who received Hectorol® treatment were between 27 and 74 years of age. Twenty subjects were male and seven were female. Twenty-four (88.9%) of the subjects had received prior treatment with lα,25$(OH)_2D_3$.

Summary / Conclusions - Efficacy:
The results presented below are from the per protocol analysis of the 24 subjects who completed the study.

At baseline, the mean serum iPTH level was 643 pg/mL. After two weeks of treatment, the iPTH levels had decreased significantly ($p < 0.001$), and there was a steady decline throughout the remainder of the treatment period. Twenty-one (21) of 24 subjects (88%) reached the target iPTH. The lowest iPTH mean was 165 pg/mL, with a mean suppression of 75.4% from the baseline value ($p < 0.001$ compared to baseline). At the end of the treatment period, the mean serum iPTH was 293 pg/mL ($p < 0.01$ compared to baseline). The response time to Hectorol® was variable (2-8 weeks) and was not related to the baseline levels of iPTH. Hectorol® decreased the mean serum osteocalcin baseline of 52.9 ng/mL to 29.1 ng/mL ($p = 0.181$) at Week 4 and 13.9 ng/mL ($p = 0.019$) at Week 12. Hectorol® decreased the mean serum bone specific alkaline phosphatase (BSAP) baseline of 14.8 U/L to 9.9 U/L ($p < 0.001$) at Week 12.

Summary / Conclusion - Safety:
Four serious adverse events occurred in patients during the 12 weeks of administration of Hectorol®. All serious adverse events occurring in the treatment period resolved and were determined to be not related to study drug. Six other adverse events occurred during the study. All non-serious adverse events were mild to moderate in severity. Three of these events (headache, decreased appetite, and right lower quadrant cramp) were acute and determined to have an unknown relationship to study drug.

During the study, two episodes of hypercalcemia (defined as serum calcium above 11.2 mg/dL) occurred in two patients during treatment with Hectorol®. There were six episodes of hyperphosphatemia (defined as serum phosphorus above 8.0 mg/dL) in six patients during treatment with Hectorol®.

The baseline mean serum calcium level was 8.8 mg/dL. At the end of the treatment period, the mean serum calcium was 9.3 mg/dL. The mean increase of 0.5 mg/dL during the treatment was significant ($p = 0.017$) but well within the normal range (≤ 10.2 mg/dL).

Serum phosphorus on treatment differed from baseline only after 10 weeks. The mean serum phosphorus level at baseline was 5.1 mg/dL, compared to 5.3 mg/dL at the end of treatment ($p = 0.665$).

Based on report prepared on: 15 December 1997
Synopsis prepared on: 24 June 2006