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-102: Effect of Extended Oral Administration of 1α-Hydroxyvitamin D_2 on Intestinal Calcium Absorption and Bone Mineral Density in Postmenopausal Osteoporotic Women

INVESTIGATORS AND STUDY CENTER(S):

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

STUDIED PERIOD:

First patient enrolled: 14 November 1989
Last patient completed: 22 April 1992

PHASE OF DEVELOPMENT:

Phase 2

OBJECTIVES:

• To evaluate the potential efficacy of oral doxercalciferol in treating postmenopausal osteoporosis, as determined by stabilization of, or increases in, spinal, femoral and total body bone mineral density;

• To examine the safety of chronic oral doxercalciferol administration to postmenopausal osteoporotic patients, with regard to serum calcium, urine calcium, blood urea nitrogen, creatinine clearance, and urine hydroxyproline;

• To evaluate the efficacy of oral doxercalciferol in stimulating intestinal calcium absorption in postmenopausal osteoporotic patients; and,

• To monitor changes in serum levels of osteocalcin, parathyroid hormone, 25-hydroxyvitamin D, and 1α,25-dihydroxyvitamin D in postmenopausal osteoporotic patients treated chronically with doxercalciferol.

METHODOLOGY:

This was a Phase 2, double-blind, placebo-controlled study. The study consisted of a 2-week Baseline Period and up to 104-week Treatment Period. During the double-blind Treatment Period, patients were randomly assigned to either Hectorol® or placebo.

NUMBER OF PATIENTS (PLANNED AND ANALYZED):

No. Enrolled: 60
No. Treated: 60 (31 active, 29 placebo)
No. Completed: 55 (28 active, 27 placebo) completed the first 52 weeks; 41 (20 active, 21 placebo) completed the second 52 weeks

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Patients included in the study were postmenopausal women, between the ages of 60 to 78 years, with anteroposterior (AP) vertebral bone mineral density of 0.70 to 1.05 g/cm^2.

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION:

Doxercalciferol: 0.5 and 1 mcg soft gelatin capsules
The initial dose was 1 mcg/day and doses were increased to 2, 3, 4, or 5 mcg/day during each of the following weeks until the rate of urinary calcium excretion was elevated to approximately 275 – 300 mg/24 hours.
Doses were administered orally before breakfast.

DURATION OF TREATMENT:

2-week Baseline Period followed by treatment for up to 104 weeks

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION:

Placebo contained the same inactive ingredients in identical proportions to Hectorol® and was administered as an oral daily dose before breakfast.

CRITERIA FOR EVALUATION:

Criteria for Evaluation - Efficacy:
The following parameters were evaluated for evidence of efficacy: spinal (AP) and femoral neck bone mineral density; intestinal calcium absorption; and serum osteocalcin.

Criteria for Evaluation - Safety:
The following parameters were evaluated for primary evidence of safety: serum calcium; 24-hour urinary calcium; blood urea nitrogen (BUN); creatinine clearance, and fasting urinary hydroxyproline.
Adverse Events were recorded.

STATISTICAL METHODS:
Comparisons were considered to be statistically significant if the two-sided p-value was $\leq$ 0.05.

Statistical Methods - Efficacy:
Baseline values were defined as the last observation taken during the Baseline Period, except for bone mineral density data. All bone mineral density values taken within 120 days prior to starting on Hectorol® were averaged for the baseline value. 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, the treatment groups were compared with respect to the change from baseline or percent of baseline (for bone mineral density data) using either a t-test or a Wilcoxon two-sample test, as appropriate. Additionally, the significance of the changes from baseline 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 also was performed. This analysis included all patients randomized to receive drug. Included in this analysis was an endpoint analysis which used the data collected at the last visit for each subject. The treatment groups were compared with respect to the changes from baseline using either a t-test or a Wilcoxon two-sample test, as appropriate. Additionally, the significance of the changes 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 and their frequency determined for each treatment group. For both the CBC and clinical chemistry profile parameters, the treatment groups were compared in two ways: (1)the proportion of patients for whom the parameter was normal at baseline and then abnormal, post-baseline, using fisher's exact test, and (2)the mean change from baseline, using a t-test or Wilcoxon two-sample test, as appropriate.
Each of these analyses was performed at each sampling time as well as the end point.

SUMMARY / CONCLUSIONS

Summary / Conclusions - Demographics:
In the group that received doxercalciferol, mean age was 65.6 years, and the women were post-menopausal for a mean of 18.8 years. In the placebo group, the mean age was 65.5 years, and the women were post-menopausal for a mean of 17.6 years.

Summary / Conclusions – Efficacy:
Both intent-to-treat (ITT; n = 56) and per protocol (PP; n = 52) analyses were performed. The results presented below are

from the per protocol analyses, unless otherwise noted.
Due to a DEXA hardware problem, only values for the AP spine and femoral neck bone mineral density could be measured. For femoral neck bone mineral density, there was a statistically significant difference in the treatment groups at both 78 weeks ($p = 0.006$) and 104 weeks ($p = 0.017$). The placebo group demonstrated a significant decrease at both 78 weeks ($p = 0.001$) and 104 weeks ($p = 0.013$). Sixty-eight percent of the patients treated with doxercalciferol showed increases in femoral neck bone mineral density after one year; 53% showed increases after two years. In contrast, only 41% and 30% of patients treated with placebo showed increases after one and two years, respectively.
The AP spinal bone mineral density showed a statistically significant difference in the treatment groups only at 104 weeks ($p = 0.041$). A significant within treatment group change was observed in the placebo group at 104 weeks ($p = 0.042$); no other significant within treatment group changes were seen. Seventy-one percent of the patients treated with doxercalciferol showed increases in AP spinal bone mineral density after one year; 50% showed increases after two years. In contrast, 38% and 37% of patients treated with placebo showed increases after one and two years, respectively.
The doxercalciferol treatment group demonstrated a significantly increased intestinal absorption of radiocalcium at both 52 weeks ($p < 0.001$) and 104 weeks ($p = 0.020$) relative to the baseline level. The placebo treatment group showed no significant changes at 52 weeks or 104 weeks. There was a significant difference between the treatment groups at both 52 weeks ($p = 0.001$) and 104 weeks ($p = 0.023$).
No significant change in serum osteocalcin was detectable over two years of treatment with doxercalciferol versus placebo. Serum osteocalcin increased ($p < 0.05$) from baseline values with both treatments at 13 weeks, and with placebo treatment at 26 weeks.

Summary / Conclusions – Safety Results:

No serious adverse events occurred during the study. The majority of adverse events occurring in both treatment groups were assessed by the Investigator as being mild in intensity and not related to study drug. Two events in two patients were assessed by the Investigator as severe in intensity (positional vertigo, sinusitis), but not related to treatment with doxercalciferol.
For two patients, treatment was briefly suspended due to adverse events. One patient temporarily suspended study drug due to elevated serum creatinine and reduced creatinine clearance levels, which were assessed as not related to study drug. The second patient experienced hypercalcemia which was assessed as related to study drug by the Investigator. One additional patient withdrew from the study due to blurred vision, which was assessed as not related to study drug by the Investigator. Four patients (two on active study drug and two on placebo) were withdrawn due to elevated fasting blood sugar levels.
Observed increases in serum ionized and total calcium from baseline were not clinically significant. Increased doxercalciferol dose was associated with increases in 24-hour urinary calcium excretion that were statistically significant compared to baseline values.
Serum phosphorus was generally unchanged in the two treatment groups over two years. Some statistically significant ($p < 0.05$) changes were occasionally observed within and between groups, but these changes were not clinically significant.
No clinically significant changes in mean renal function measures (BUN, creatinine clearance and serum creatinine levels) were observed during the study.
The fasting urinary hydroxyproline:creatinine ratio showed no clear trends in either treatment group, and inter-group comparisons showed no significant differences.

Based on report prepared on: 23 December 1994
Synopsis prepared on: 11 August 2006