GD3-163-201: A Double-Blind, Cross-Over Design Study of Sevelamer Hydrochloride (Renagel®) and Sevelamer Carbonate in Chronic Kidney Disease Patients on Hemodialysis

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NAME OF SPONSOR/COMPANY

Genzyme Corporation 500 Kendall Street, Cambridge, Massachusetts, 02142

INVESTIGATORS AND STUDY CENTER(S)

This was a multicenter study conducted at 13 sites in the United States.

STUDIED PERIOD

First patient entered: 30 March 2005
Last patient completed: 15 March 2006

PHASE OF DEVELOPMENT

Phase 2/3

OBJECTIVES

ObjectiveS:

Primary Objective

The primary objectives of this trial were to:

- Compare the effects of sevelamer carbonate and sevelamer hydrochloride on the control of serum phosphorus in CKD patients on hemodialysis.

- Compare the safety and tolerability of sevelamer carbonate and sevelamer hydrochloride in CKD patients on hemodialysis.

Secondary Objective

The secondary objective of this trial was to:

- Compare the effects of sevelamer carbonate and sevelamer hydrochloride on serum lipid profiles in CKD patients on hemodialysis.

METHODOLOGY

This was a double-blind, randomized, cross-over study in CKD patients on hemodialysis. The study consisted of five periods: an up to two-week Screening Period, a five-week Run-In Period, two eight-week Treatment Periods and a two-week Washout Period. Eligible patients entered the Run-In Period during which sevelamer hydrochloride was prescribed to all patients. The Investigator had one opportunity during this period to titrate the sevelamer hydrochloride dose, Sensipar dose, vitamin D therapy and hemodialysis prescription (dialysate calcium level, dialysate bicarbonate level, treatment time), if necessary. Once these procedures were completed, the patient was randomized in a 1:1 fashion to one of the two treatment sequences: sevelamer carbonate for eight weeks followed by sevelamer hydrochloride for eight weeks or sevelamer

hydrochloride for eight weeks followed by sevelamer carbonate for eight weeks. The starting dose for the Treatment Period was individualized for each patient based on the most recently prescribed daily dose during the Run-In Period. Following the Treatment Period, the patients entered a two-week Washout Period.

NUMBER OF PATIENTS (PLANNED AND ANALYZED)

Number Enrolled / Treated: 101 / 79
Number Completed Treatment / Washout: 69 / 40

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Patients included in this study were men and women, 18 years or older, on a stable 3-times weekly hemodialysis regimen and on sevelamer hydrochloride alone or in combination therapy.

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION

sevelamer carbonate (Renvela®): 800 mg tablets administered orally

DURATION OF TREATMENT

The study consisted of five periods: an up to two-week Screening Period, a five-week sevelamer hydrochloride (Renagel®) Run-In Period, two eight-week Treatment Periods and a two-week Washout Period.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION

sevelamer hydrochloride (Renagel®): 800 mg tablets administered orally

CRITERIA FOR EVALUATION
Safety:

Safety was evaluated on the basis of adverse experiences (reported and/or observed) and changes in laboratory values and vital signs.

Efficacy:

The treatment regimens were compared on the basis of serum phosphorus at the end of each treatment period using the time-weighted mean of the phosphorus values from the last three visits in each treatment period. The treatment regimens were also compared with respect to total, LDL and HDL cholesterol, and triglycerides, using the mean of values for each parameter from the two post-baseline assessments in each treatment period.

STATISTICAL METHODS

Safety:

The frequency and percent of patients and the frequency of events were presented for each study period, for those events judged by the investigator to be possibly or probably related to each study treatment, and for serious adverse events. The difference in the incidence of treatment emergent adverse events between the randomized treatment groups was evaluated using McNemar's test.

Changes in laboratory values and vital signs were assessed using the Wilcoxon rank sum test to compare treatment regimens and Wilcoxon signed rank test to assess within treatment regimen changes.

Efficacy:

The primary efficacy measure was based on a comparison of serum phosphorus control observed during each treatment regimen. The effects of sevelamer carbonate and sevelamer hydrochloride on the control of serum phosphorus were determined by using equivalence testing. Equivalence was assessed using natural-log transformed time-weighted mean

serum phosphorus data. Least squares means for each treatment and the mean squared error from a mixed effect regression model with a random subject effect and fixed sequence, period, and treatment effects was used to derive the 90% confidence interval for the difference between sevelamer carbonate (test) and sevelamer hydrochloride (reference) data on the log scale which was then exponentiated to yield an estimate of the efficacy ratio and corresponding confidence interval. This test required that the 90% confidence interval for the ratio be within the interval (0.80, 1.25) to conclude equivalence. The same mixed effect regression models were also used for the lipid parameters to detect if there were statistically significant differences between the treatment regimens.

Serum phosphorus levels at the end of treatment, at the end of washout, and the change from the end of treatment to the end of washout were summarized overall and by treatment sequence. The changes were assessed using Wilcoxon signed rank tests.

SUMMARY / CONCLUSIONS

Demographics and Renal History
The average age was 58 years, ranging from 29 to 88 years. Fifty-one percent of the patients were male and 49% were female. Sixty-seven percent of the patients were black or African American, 27% were white, and 6% were “Other”. The most common primary causes of chronic kidney disease were diabetes (42%), hypertension (23%), other unspecified causes, (21%), and glomerulonephritis (9%).

Efficacy
The mean serum phosphorus was 4.6 ± 0.9 mg/dL during sevelamer carbonate treatment and 4.7 ± 0.9 mg/dL during sevelamer hydrochloride treatment. The geometric least square mean ratio (sevelamer carbonate/sevelamer hydrochloride) was 0.99 with a corresponding 90% confidence interval of 0.95-1.03. The confidence interval is within the interval of 0.80-1.25, indicating that sevelamer carbonate and sevelamer hydrochloride are equivalent in controlling serum phosphorus.

The proportion of patients with a time-weighted average serum phosphorus within the acceptable range (3.5-5.5 mg/dL) was calculated as a secondary analysis. A total of 71% of patients during sevelamer carbonate treatment and 70% of patients during sevelamer hydrochloride treatment were within this range.

An analysis was also conducted by dose group (≤ 4.8, > 4.8 to 9.6 and ≥ 9.6 g/day) to assess the homogeneity of the equivalence ratio over the range of underlying hyperphosphatemia. The confidence interval within each dose group was within the interval of 0.80-1.25 indicating that sevelamer carbonate and sevelamer hydrochloride were equivalent regardless of dose group.

A two-week Washout Period was included following the active treatment period to confirm that the patients enrolled in this trial were hyperphosphatemic. At the end of the randomized treatment periods the serum phosphorus was 5.0 ± 1.3 mg/dL in all patients participating in the washout. Following the two-week Washout Period, the serum phosphorus level increased significantly (1.5 ± 1.9 mg/dL; $p<0.001$). This increase in serum phosphorus during the Washout Period was seen regardless of the salt form of sevelamer prescribed immediately preceding the washout.

The mean total cholesterol was 144.0 ± 33.9 mg/dL during sevelamer carbonate treatment and 139.0 ± 33.6 mg/dL during sevelamer hydrochloride treatment. The mean LDL cholesterol was 59.5 ± 24.9 mg/dL during sevelamer carbonate treatment and 56.0 ± 23.3 mg/dL during sevelamer hydrochloride treatment. These values were statistically different ($p=0.009$ and $p=0.035$ for total and LDL cholesterol, respectively), but the difference is not clinically meaningful. HDL cholesterol and triglycerides levels did not statistically differ between treatment regimens.

Safety
The mean prescribed daily dose of both sevelamer carbonate and sevelamer hydrochloride was 7.2 ± 3.1 g/day. The mean actual daily dose for both sevelamer carbonate and sevelamer hydrochloride was 6.0 ± 2.8 g/day. No patients changed their sevelamer daily dose during randomized treatment. Compliance was similar with both sevelamer carbonate (85%) and sevelamer hydrochloride (86%).

During the randomized treatment periods, there were 195 adverse events in 60 (82.2%) patients during sevelamer carbonate treatment and 226 adverse events in 65 (83.3%) patients during sevelamer hydrochloride treatment. The body system with the highest frequency of treatment emergent AEs was the digestive system, with 25 events in 15 (20.5%) patients during sevelamer carbonate treatment, and 45 events in 28 (35.9%) patients during sevelamer hydrochloride treatment. The number of patients experiencing at least one gastrointestinal adverse event while on sevelamer carbonate was significantly lower than while on sevelamer hydrochloride ($p=0.007$). However, no statistically significant differences were observed between the treatment regimens for any specific adverse event within the gastrointestinal disorders.

The most frequently occurring adverse events were nausea (9 events in 7 [9.6%] patients during sevelamer carbonate treatment and 13 events in 10 [12.8%] patients during sevelamer hydrochloride treatment), vomiting (7 events in 6 [8.2%] patients during sevelamer carbonate treatment and 8 events in 8 [10.3%] patients during sevelamer hydrochloride treatment), and arteriovenous fistula thrombosis (3 events in 3 [4.1%] patients during sevelamer carbonate treatment and 9 events in 9 [11.5%] patients during sevelamer hydrochloride treatment). The majority of adverse events were mild or moderate in intensity. Severe AEs occurred in 5 (6.8%) patients during sevelamer carbonate treatment and 6 (7.7%) patients during sevelamer hydrochloride treatment.

Overall, there were 20 treatment-related adverse events in 12 (16.4%) patients during sevelamer carbonate treatment and 33 treatment-related adverse events in 15 (19.2%) during sevelamer hydrochloride treatment. The most frequently occurring treatment-related AEs were: nausea (2 events in 2 [2.7%] patients during sevelamer carbonate treatment and 5 events in 2 [2.6%] patients during sevelamer hydrochloride treatment); gastroesophageal reflux disease (1 event in 1 [1.4%] patient during sevelamer carbonate treatment and 4 events in 3 [3.8%] patients during sevelamer hydrochloride treatment); and vomiting (2 events in 2 [2.7%] patients during sevelamer carbonate treatment and 1 event in 1 [1.3%] patient during sevelamer hydrochloride treatment). All treatment-related adverse events were mild or moderate in severity.

During the Run-In Period, when all patients received treatment with sevelamer hydrochloride, the patterns of adverse event frequency were similar to those observed among patients who received sevelamer hydrochloride during the randomized treatment period. There was one serious adverse event during this period, faecoloma, that was mild in intensity and judged to be possibly related to sevelamer hydrochloride.

Two patients died during the study, one patient in each treatment regimen. Both deaths were not related to study treatment. During the randomized treatment periods, 17 serious adverse events occurred in 8 (11.0%) patients during sevelamer carbonate treatment and 17 serious adverse events occurred in 11 (14.1%) patients during sevelamer hydrochloride treatment. None of the serious adverse events were judged by the Investigator to be related to study treatment.

A total of 6 patients discontinued the study during sevelamer hydrochloride treatment due to adverse events. The most common AE that led to discontinuation was Renal transplant (2 patients). No patients discontinued during sevelamer carbonate treatment due to an adverse event.

A total of 47 patients entered the washout period of the study. Overall, 16 patients (34%) experienced 43 adverse events. The majority of events occurring during the washout period were mild or moderate. No patient deaths occurred. Five serious adverse events occurred in four patients (8.5%) all of which were judged to be unrelated to study treatment.

In this study, baseline laboratory measurements were taken following a sevelamer hydrochloride run-period.

There was a statistically significant increase from baseline in serum carbon dioxide (+1.3 mEq/L; $p<0.001$) during sevelamer carbonate treatment but not during sevelamer hydrochloride treatment (-0.3 mEq/L; $p=0.833$). The change in serum carbon dioxide was statistically significantly different between treatment regimens ($p<0.001$).

There was a statistically significant decrease (-2.6 mEq/L; $p<0.001$) from baseline in serum chloride during sevelamer carbonate treatment, but no change during sevelamer hydrochloride treatment (0.0 mEq/L; $p=0.733$). The change in serum chloride was statistically significantly different between treatments ($p<0.001$).

No significant changes in vital signs were observed during the randomized treatment periods.

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