

Protocol GTC-10-201: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Design Evaluation of Renagel® in Lowering Serum Phosphorus in Hemodialysis Patients.

*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
Geltex Pharmaceuticals, Inc., Waltham, MA 02451, (Geltex Pharmaceuticals, Inc. was acquired by Genzyme Corporation December 2000)

Investigators and Study Center(s)

This was a multicenter study conducted at 3 sites in the United States.

Studied Period

First patient entered: 17 April 1995
Last patient completed: 15 July 1995

Phase of Development

Phase 2

Objectives

The study objectives were:

- To compare the efficacy of Renagel® with calcium based phosphate binders in lowering serum phosphorus in hemodialysis patients
- To compare Renagel® and placebo for adverse events and laboratory parameters
- To compare Renagel® with placebo for lowering serum cholesterol in hemodialysis patients

Methodology

This was a phase 2, double-blind randomized, parallel-group, placebo-controlled study. The study was eight weeks in duration. The study started with a two-week calcium-based phosphate binder treatment period. The patients then discontinued calcium-based phosphate binders for a two-week washout period. During this period, baseline phosphorus levels were established. In the subsequent phase, the patients were treated for two weeks with either Renagel® or placebo. The study ended with a two-week follow-up period. During the entire study, patients maintained their regular dialysis schedule and normal eating habits.

Number of Patients (Planned and Analyzed)

No. Enrolled:38
No. Treated:36
No. Completed:36

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 a stable calcium-based phosphate binder regimen.

Test Product, Dose, and Mode of Administration

Sevelamer hydrochloride (Renagel®): 500 mg capsules

The Renagel® dose was determined for each patient individually by replacing the calcium acetate or calcium carbonate dose used by the patient in the calcium treatment period with Renagel® on a gram per gram basis.

Renagel® was administered orally with meals.

Duration of Treatment

The total study duration was 8 weeks including two weeks of calcium treatment, followed by a 2-week washout period, followed by a 2-week randomized treatment period (Renagel® vs. placebo), and a 2-week follow-up period.

Reference Therapy, Dose and Mode of Administration

Placebo: 350 mg microcrystalline cellulose (identical in appearance to Renagel®)

The placebo dose was determined by the same method as the Renagel® dose, which was determined for each patient individually by replacing the calcium acetate or calcium carbonate dose used by the patient in the calcium treatment period with Renagel® on a gram per gram basis. The total number of Renagel® capsules calculated by this method was then replaced with an equivalent number of matching placebo capsules.

Placebo administered orally with meals.

CRITERIA FOR EVALUATION

Efficacy

Efficacy was evaluated on the basis of changes in serum phosphorus. Changes in serum cholesterol were also evaluated.

Safety

Safety was evaluated on the basis of adverse events as well as changes in laboratory values and physical examinations.

STATISTICAL METHODS

All statistical tests were performed using a two-tailed approach with a level of significance of 0.05.

Efficacy

Mean serum phosphorus concentrations in the last week of the calcium-based phosphate binder treatment, washout, and Renagel®/placebo treatment periods were calculated by taking the mean of the final 2 measurements of that week. Descriptive statistics were presented for the changes in serum phosphorus between the washout and the calcium-based phosphate binder period as well as between the washout period and the Renagel®/placebo period. Paired t-tests were used to compare the treatment periods.

A test of equivalence of serum phosphorus binding was conducted. The 90% 2-sided confidence interval of the difference between mean change from baseline on the log scale were calculated and equivalence was to be declared if the limits were between log (0.80) and log (1.25).

Renagel® was compared with placebo for its ability to lower serum cholesterol, LDL and HDL based on the changes observed between the washout and Renagel®/placebo treatment periods. Analysis of differences between Renagel® and placebo in change in cholesterol measures were conducted with analysis of variance.

Safety

Adverse events occurring in the Renagel[®]/placebo treatment period that did not occur in, and were not ongoing from, the calcium binder or washout periods were regarded as treatment-emergent adverse events. The difference in incidence of treatment-emergent adverse events between placebo and Renagel[®] were compared using Fisher's exact test. The safety of Renagel[®] was also studied on the basis of changes in laboratory values and changes in physical examinations using descriptive statistics.

The difference in the incidence of adverse events between low dosage (< 6 capsules/day), medium dosage (6 - 9 capsules/day), and high dosage (> 9 capsules/day) were performed using Fisher's exact test. The safety of Renagel[®] at the low, medium and high dosages was also studied on the basis of laboratory values by descriptive statistics. Dosages were based on the average number of capsules taken per day by each patient.

SUMMARY – CONCLUSIONS

Demographics

Mean age was 54 years in the placebo group and 59 years in the Renagel[®] groups. Of the 12 patients in the placebo group 17% were male and 83% were female, 25% were Caucasian and 75% were Black. Of the 24 patients in the Renagel[®] group, 46% were male and 54% were female, 21% were Caucasian, 67% were Black, 8% were Hispanic and 4% were Asian.

Efficacy

Serum Phosphorus: Renagel[®] lowered serum phosphorus statistically significantly more than placebo: -0.68 mg/dL vs. -0.32 mg/dL ($p=0.0367$). In 32 hyperphosphatemic (serum phosphorus > 4.5 mg/dL) patients, Renagel[®] lowered serum phosphorus (from the value at the end of the washout period) statistically significantly more than placebo: -1.36 mg/dL vs. +0.26 mg/dL ($p=0.0101$). Renagel[®] and calcium-based phosphate binders were found to be bioequivalent in all patients studied, as well as in the 32 hyperphosphatemic patients.

Cholesterol: Renagel[®] significantly reduced total cholesterol and LDL cholesterol, but had no effect on HDL cholesterol. During the randomized treatment period, mean total cholesterol decreased by 20.48 mg/dL with Renagel[®] vs. an increase of 0.45 mg/dL with placebo ($p=0.0127$), while mean LDL cholesterol decreased by 17.6 mg/dL with Renagel[®] vs. an increase of 7.3 mg/dL with placebo ($p=0.0026$).

Safety Results

Adverse Events: Throughout the entire study, 8 patients (66.7%) in the placebo group had at least one adverse event versus 16 (66.7%) in the Renagel[®] group. Therefore, the placebo and Renagel[®] groups had identical incidences of adverse events. During the randomized treatment and follow-up phase, 18 patients (6 in the placebo and 12 in the Renagel[®] group) had a total of 28 adverse events (14 events among the 6 patients receiving placebo and 21 events among the 12 patients receiving Renagel[®]). The most common event was thrombosis at the dialysis access site, which occurred in 2 patients (16.7%) in the placebo group and 4 patients (16.7%) in the Renagel[®] group. There were no statistically significant differences in adverse events judged possibly or probably related to treatment between placebo and Renagel[®] ($p=1.000$).

There were no statistically significant differences in the incidence of adverse events based on the daily dose of Renagel[®]. Furthermore, there were no statistically significant differences between placebo and the low, medium, and high doses of Renagel[®] for any adverse event ($p=0.515$) and there were no statistically significant differences in adverse events judged possibly or probably related to treatment between placebo and the low, medium and high doses of Renagel[®] ($p=1.000$).

There were no deaths during the study. During the randomized treatment and follow-up period, 5 of the patients receiving Renagel[®] and 2 of those receiving placebo had serious adverse events, all connected with dialysis access, except for one patient who was hospitalized for hypotension and fainting during dialysis. All serious adverse events were judged unrelated to the study drug.

Laboratory Values, Physical Examinations, and Vital signs: Isolated statistically significant mean changes from baseline and statistically significant intergroup differences in changes from baseline were recorded. There was no discernible pattern in laboratory values and out-of-range laboratory values were mostly not clinically significant and consistent with the patient's underlying disease. Furthermore, there were no clinically significant changes in vital sign or physical exam abnormalities.

Based on Report Prepared on: 15 November 1995

Synopsis Prepared on: 13 October 2005

