Protocol GTC-45-901: An Extended Use Study of Renagel® in Hemodialysis Patients.

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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 24 sites in the United States.

Studied Period

First patient entered: 30 September 1996
Last patient completed: 20 February 1998

Phase of Development

Phase 3 Extension Study

Objectives
Primary

- Confirm the safety of extended treatment with Renagel® in hemodialysis patients
- Confirm the efficacy of extended treatment with Renagel® in lowering serum phosphorus in hemodialysis patients

Secondary:

- Determine the effect of extended Renagel® treatment on lipid profiles in hemodialysis patients
- Determine the effect of extended Renagel® treatment on intact parathyroid hormone levels in hemodialysis patients

Methodology

This phase 3, open label, dose titration, extended use study was conducted to confirm the safety and efficacy of extended treatment with Renagel® in lowering serum phosphorus levels in hemodialysis patients. Following the screening visit, patients underwent a two-week phosphate binder washout period. During this time phosphate binders were discontinued and serum phosphorus levels were monitored. Following the washout period, patients entered the extended 44 week Renagel® treatment period. Following Renagel® treatment, patients underwent a second two week washout period during which Renagel® treatment was discontinued. Serum phosphorus levels were measured to determine if serum phosphorus reductions were due to Renagel® treatment or other factors.

Number of Patients (Planned and Analyzed)

No. Enrolled / Treated: 195 / 192
No. Completed:123

Diagnosis and Main Criteria for Inclusion

Patients eligible for participation in the study were three-times per week hemodialysis patients on a stable phosphate binder regimen who had completed a dose titration study of Renagel® and who after consultation with their nephrologist wished to continue Renagel®.

Test Product, Dose, and Mode of Administration

Sevelamer hydrochloride (Renagel®): 465 mg (440 mg anhydrous) capsules and 426 mg (403 mg anhydrous) capsules (beginning May 1997)

Renagel® starting dose was determined by the investigator based on the patient's previous Renagel® experience, the patient's dietary phosphate intake, and the investigator's clinical judgment. During the treatment period, the investigator could titrate the Renagel® dose in an attempt to achieve a serum phosphorus level between 2.5 and 5.5 mg/dL, inclusive.

Administered orally three times daily with meals.

Duration of Treatment

The total study duration was 48 weeks including an initial two-week phosphate binder washout, 44 weeks of Renagel® therapy and a final two-week washout.

Reference Therapy, Dose and Mode of Administration

Not applicable

CRITERIA FOR EVALUATION
Efficacy

The change in serum phosphorus, calcium, intact parathyroid hormone, and lipid levels (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) were examined to assess the efficacy of Renagel® treatment over the duration of the study.

Safety

Safety was evaluated on the basis of adverse experiences and changes in laboratory values.

STATISTICAL METHODS

All statistical analyses are based on two-tailed hypothesis tests with a significance level of 0.05.

Efficacy

Laboratory data were summarized for each study visit, for all changes between baseline and final, and for the change between the final visit and the end of the second washout period. These results are presented overall and by dose level (low, medium, high tertiles of mean prescribed daily dose). Wilcoxon signed rank tests were used to assess changes in laboratory values overall and within dose level groups. The dose trends in the change from baseline were assessed using linear regression models in which the dose level was parameterized as a single continuous factor and a t-test was used to assess the significance of the linear trend across dose level groups.

Safety

Treatment emergent adverse events are presented by Renagel® dose. Patients are classified with respect to their average prescribed Renagel® dose level into low (< 5.0 g), medium (5.0-6.75 g), and high (> 6.75 g) dose groups.

Dose level trends in the incidence of treatment emergent adverse events were tested using logistic regression models in which dose was parameterized as a single continuous factor. Wald Chi-squared tests were used to assess possible differences among dose level groups (null hypothesis: regression parameter for the dose level factor equals zero).

The intensity of adverse events experienced is summarized for all treatment emergent adverse events and for treatment emergent events possibly or probably related to Renagel® treatment. The patients' most severe event at any given dose was used for this analysis.

Serious adverse events were summarized for the washout and treatment periods.

Safety laboratory data were summarized for each study visit, for all changes between baseline and final, and for the change between the final visit and the end of the second washout period. These results are presented overall and by dose level (low, medium, high tertiles of mean prescribed daily dose). Wilcoxon signed rank tests were used to assess changes in laboratory values overall and within dose level groups.

SUMMARY – CONCLUSIONS
Demographics and Renal History

The mean age of the patients was 56 years. Sixty-two percent of the patients were male and 37% were female. Fifty-four percent of the patients were African-American, 35% were Caucasian, 7% were Hispanic, 2% were Asian and 1% were "other." The primary cause of ESRD included hypertension (34%), diabetes (30%), nephritis (14%) polycystic kidneys (3%) and "other" (20%).

Efficacy

Serum phosphorus levels changed significantly during Renagel® treatment; mean serum phosphorus decreased 2.2 mg/dL (from 8.7 mg/dL, $p < 0.0001$). The change in serum phosphorus was associated with Renagel® dose ($p = 0.0460$); greater reductions in serum phosphorus were attained with higher doses of Renagel® treatment. Serum calcium levels changed significantly during Renagel® treatment. Mean serum calcium increased 0.3 mg/dL (from 9.1 mg/dL, $p < 0.0001$); however, this change was not dose related. Intact parathyroid hormone did not significantly change from baseline (median = 286.5 pg/mL) to final (median = 254.0 pg/mL); however there was a statistically significant dose trend with reductions observed at low and moderate dose groups and elevations observed at higher dose group ($p = 0.0032$).

Total cholesterol changed significantly during Renagel® treatment; mean total cholesterol decreased 27.9 mg/dL (from 175.3 mg/dL, $p < 0.0001$). This change was not dose related. LDL cholesterol changed significantly during Renagel® treatment. Mean LDL cholesterol decreased 31.5 mg/dL (from 106.5 mg/dL, $p < 0.0001$); however, this change was not dose related. Mean HDL cholesterol increased 5.9 mg/dL (from 36.4 mg/dL, $p<0.0001$). There was a significant trend among the three dose groups ($p = 0.0007$), with greater increases in HDL associated with higher Renagel® doses. Triglycerides did not significantly change during Renagel® treatment.

Safety Results

Overall, a total of 3,255 adverse events occurred among 187 patients (97.4%) during the Renagel® treatment period. There were 1,006 events among 55 patients (96.5%) in the low dose group, 826 events among 48 patients (100.0%) in the medium dose group, and 1,423 events among 84 patients (96.6%) in the high dose group. The overall incidence of patients with any treatment emergent adverse event did not increase with higher doses of Renagel®.

Statistically significant linear dose trends, in which a higher incidence of treatment emergent adverse events were observed at higher doses of Renagel®, were seen with hypochromic anemia ($p = 0.0359$), increased cough ($p = 0.0340$), and cardiovascular disorder ($p = 0.0269$). Given the large number of adverse events tested, these events may have tested significant by chance alone.

Treatment related adverse events were defined as possibly or probably related to Renagel® treatment as judged by the investigator. There were 129 treatment related adverse events among 49 patients (25.5%); including 25 events related to study treatment among 9 patients (15.8%) in the low dose group, 41 events related to treatment among 16 patients (33.3%) in the medium dose group, and 63 events related to treatment among 24 patients (27.6%) in the high dose group. There was no statistically significant linear dose trend for the overall incidence of treatment related adverse events ($p = 0.1555$). Furthermore, there were no statistically significant linear dose trends for any body system category or for individual treatment related adverse events.

The digestive system category had the most treatment related adverse events, with 74 events occurring among 33 patients (17.2%). A marginally significant linear dose trend was observed with dyspepsia ($p=0.0509$), in which a higher incidence of treatment related dyspepsia was observed with higher doses of Renagel®. Other frequent treatment related digestive events included: nausea (20 events among 14 patients), flatulence (10 events among 8 patients), diarrhea (8 events among 8 patients), and vomiting (14 events among 7 patients).

There were 164 serious adverse events among 86 patients (44.8%) during Renagel® treatment. Serious adverse events were most prevalent within the cardiovascular system category. No serious adverse events were judged by the investigators to be related to Renagel®. Sixteen deaths were recorded during the study. These events were judged by the investigators to be unrelated to Renagel® treatment.

Statistically significant changes from baseline to end of Renagel® treatment were observed in serum magnesium (0.1 + 0.3 mEq/L, p=0.0007), uric acid (-0.8 + 1.3 mg/dL, p<0.0001), chloride (1.3 + 4.2 mEq/L, p<0.0001), and bicarbonate (1.3 + 4.8 mEq/L, p=0.0003), and alkaline phosphatase (32.3 + 72.6 U/L, p<0.0001). Statistically significant increases in total iron, iron binding capacity, and ferritin were found. A significant dose trend was observed for iron saturation. This increase in iron parameters was most likely due to changes in intravenous iron use. A second possible explanation is due to patients discontinuing calcium-containing binders which are known to decrease iron absorption. In addition, statistically and clinically significant increases in vitamin D 1,25-dihydroxy were observed. These increases were likely due to increases in vitamin D use supplementation.

There were no clinically significant changes in vital signs or physical exam abnormalities.

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