Protocol No. GTC-36-302: An Open Label, Dose Titration 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 16 sites in the United States.

Studied Period

First patient entered: 6 June 1996
Last patient completed: 4 December 1996

Phase of Development

Phase 3

Objectives
Primary

- Determine the efficacy of Renagel® treatment in lowering serum phosphorus in hemodialysis patients
- Determine the safety of Renagel® in hemodialysis patients

Secondary

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

Methodology

This phase 3, open label dose titration study was conducted to determine the safety and efficacy of Renagel® in lowering serum phosphorus levels in hemodialysis patients. Following the screening visit, patients underwent a two week phosphate binder washout period. Patients who were hyperphosphatemic (serum phosphorus > 6.0 mg/dL) during the washout period were eligible to enter the study treatment period. At the end of each of three two week Renagel® treatment periods, the investigator could titrate the Renagel® dose to achieve a serum phosphorus level between 2.5 and 5.5 mg/dL. Following Renagel® treatment, patients underwent a second washout per

Number of Patients (Planned and Analyzed)

No. Enrolled / Treated: 217/172
No. Completed: 144

Diagnosis and Main Criteria for Inclusion

Patients included in the study were adult males or females on a stable three-times weekly hemodialysis regimen and on stable doses of calcium and/or aluminum based phosphate binders.

Test Product, Dose, and Mode of Administration

Sevelamer hydrochloride (Renagel®): 465 mg (440 mg anhydrous) capsules

Starting dose was two, three or four 440 mg capsules three times per day with meals based on the washout serum phosphorus level.

Administered orally with meals

Duration of Treatment

Renagel® treatment lasted for 8 weeks. The total study duration was 13 weeks

Reference Therapy, Dose and Mode of Administration

Not applicable

CRITERIA FOR EVALUATION
Efficacy

The primary efficacy parameter is the change in serum phosphorus during the Renagel® treatment period. Secondary efficacy parameters include the change in intact parathyroid hormone and the change in serum lipid levels (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) during the Renagel® period.

Safety

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

STATISTICAL METHODS
Efficacy

Serum phosphorus, calcium, iPTH, and lipids (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides) are summarized for all study visits and for changes during the first washout, the treatment period, and the second washout period. The Wilcoxon signed rank test was used to assess the changes between timepoints.

Response to Renagel® treatment was defined as returning to either the pre-washout serum phosphorus level or to 5.5 mg/dL, whichever was attained first. The number and percent of patients attaining response over time and by effective actual dose is presented overall and by vitamin D usage.

Spearman rank correlation analyses were performed to assess the relationship between changes in serum phosphorus and iPTH, phosphorus and calcium, and iPTH and calcium.

Safety

All adverse experiences were summarized by body system and by preferred term for the safety population. Treatment emergent adverse events, defined as newly occurring or worsening events following the start of Renagel® treatment, were presented by Renagel® dose (low: < 8 capsules per day, medium: > 8 and < 12 capsules per day, high: > 12 capsules per day). Chi-square tests were used to analyze possible differences among dose level groups.

The intensity of adverse events experienced was summarized for 1) all treatment emergent adverse events and for 2) treatment emergent events possibly or probably related to Renagel® treatment. The patient's most severe event at any given dose level was used for this analysis.

Laboratory data were summarized for each study visit, for all changes between baseline and final, and for the change between final visit and the end of the second washout period for the safety population. These results are presented overall and by dose level (low, medium, high) defined as the last Renagel® dose used prior to that visit. Wilcoxon signed rank tests were used to assess changes in laboratory values overall and within dose level groups. Kruskal-Wallis tests were used to assess possible differences across dose level groups.

The frequency of physical exam changes was summarized by body system for the safety population. Changes in vital signs assessed between screening and the end of treatment and between the end of treatment and the end of the second washout were also presented using summary statistics. Wilcoxon signed rank tests were used to assess changes in vital signs, including weight, pulse, systolic blood pressure, and diastolic blood pressure.

SUMMARY – CONCLUSIONS
Demographics and Renal History

The mean age of the patients was 53 years. Sixty-four percent of the patients were male and 36% were female. Fifty-two percent of the patients were African-American, 34% were Caucasian, 13% were Hispanic, 1% was Asian and 1% was classified as “other” race. The primary cause of ESRD included hypertension (30%), diabetes (23%), nephritis (13%), polycystic kidney disease (5%) and “other” (28%).

Efficacy

Serum phosphorus: Mean serum phosphorus on previous phosphate binder was 6.8 mg/dL. Following two weeks of phosphate binder washout, mean serum phosphorus was 9.1 mg/dL. At the end of the Renagel® treatment period, mean serum phosphorus was 6.6 mg/dL. The mean change in serum phosphorus from baseline to the end of Renagel® treatment was -2.5 mg/dL ($p < 0.0001$). Following two weeks of a second phosphate binder washout period, mean serum phosphorus was 8.0 mg/dL, establishing that the control of serum phosphorus observed during the treatment period was attributable to Renagel®.

Serum phosphorus response: A total of 136 patients (81.0%) achieved response to Renagel® treatment. The majority of patients achieved response after three weeks of Renagel® use.

Serum calcium: Eighty-four percent of the patients previously used calcium-based phosphate binders. As expected, calcium declined during the initial washout period when calcium-based binders were discontinued. Mean serum calcium on previous phosphate binder was 9.6 mg/dL. Following two weeks of phosphate binder washout, mean serum calcium was 9.1 mg/dL. At the end of the Renagel® treatment period, mean serum calcium was 9.4 mg/dL. The mean change in serum calcium during Renagel® treatment was 0.3 mg/dL ($p < 0.0001$). At the end of the second washout period, mean serum calcium was 9.2 mg/dL.

Serum intact PTH: Median serum iPTH on previous phosphate binder was 208 pg/mL. Following two weeks of phosphate binder washout, median serum iPTH was 316 pg/mL. At the end of the Renagel® treatment period, median serum iPTH was 224 pg/mL ($p < 0.0001$). Following two weeks of a second phosphate binder washout period, median serum iPTH was 307 pg/mL ($p < 0.0001$).

Correlation of serum phosphorus, calcium, and PTH: The changes in serum phosphorus and serum calcium from baseline to the last value on treatment were negatively correlated and statistically significant ($r = -0.2389$, p-value = 0.0018). The changes in serum phosphorus and iPTH from baseline to the last value on treatment were positively correlated but the result was not statistically significant ($r = 0.1306$, p-value = 0.0936). The changes in serum calcium and iPTH from baseline to the last value on treatment were negatively correlated and statistically significant ($r = -0.2252$, p-value = 0.0035).

Serum lipids: Mean LDL cholesterol was 102.0 mg/dL at baseline and 75.6 mg/dL at the end of Renagel® treatment. The mean change in LDL cholesterol from baseline to the end of treatment was 26.4 mg/dL (p-value < 0.0001), while the mean percent change from baseline to the end of treatment was -18.2%. At the end of the second washout, mean LDL cholesterol was 101.1 mg/dL.

Total cholesterol changed significantly from baseline to the end of Renagel® treatment. Mean total cholesterol changed -25.9 mg/dL (from 171.0 mg/dL, p-value < 0.0001). The percent change in total cholesterol from baseline to the end of Renagel® treatment was -13.9%. Cessation of Renagel® treatment was followed by a subsequent increase of 23.8 mg/dL (from 168.3 mg/dL, p-value < 0.0001) by end of the second washout. Total cholesterol reductions during Renagel® treatment likely reflect the reductions observed with LDL cholesterol.

HDL cholesterol and triglycerides did not change significantly from baseline to the end of Renagel® treatment.

Safety Results

Adverse Experiences: Renagel® was well tolerated by the study patients. Overall, a total of 499 adverse events occurred among 130 patients (75.6%) during the Renagel® treatment period. Most treatment emergent adverse events were of mild intensity. Digestive was the body system with the most frequent occurrence of adverse events during Renagel® treatment, with 135 events among 74 patients (43%). The most frequent single event was pain, with 35 events experienced by 25 patients (14.5%).

Overall, there were 159 events among 56 patients in the low dose group, 156 events among 66 patients in the medium dose group, and 184 events among 54 patients in the high dose group. There was a statistically significant difference in patient based incidence rates across dose groups for “any adverse event” (p=0.0005); however the incidence of events appeared to decrease with higher doses of Renagel®. The most frequent treatment emergent adverse events within a body system involved the digestive system. However, the differences across Renagel® dose groups were not statistically significant.

There was a low incidence of treatment-related adverse events; overall, there were 81 treatment-related events among 43 patients (25%). In the low dose group, there were 26 events related to study treatment among 14 patients; in the medium dose group, there were 35 events related to study treatment among 23 patients; in the high dose group, there were 20 events related to study treatment among 14 patients. There was no statistically significant difference in the patient-based incidence rates across dose levels overall, by body system, or for individual adverse events. Treatment-related adverse events involving the digestive system were the most common, with 60 events occurring among 39 patients (22.7%). The most frequent treatment related digestive disorders were: diarrhea, dyspepsia, vomiting, nausea, and constipation.

During the first washout, 2 serious adverse events occurred among 2 patients (1.2%). During the treatment period, 33 serious adverse events occurred among 29 patients (16.0%). During the second washout period, 9 serious adverse events occurred among 8 patients. Three deaths were reported during the study; two occurred after the Renagel® washout period at the end of the study and one occurred during the first washout period. These events were judged by the investigators to be not related to Renagel® treatment.

Laboratory values, physical exams and vital signs: There were no clinically significant changes in safety laboratory parameters. Furthermore, there were no clinically significant changes in vital signs or physical exam abnormalities.

Based on Report Prepared on: 16 September 1997
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