Protocol GTC-36-203: A Randomized, Open Label, Dose Titration Study of Renagel® Phosphate Binder versus Renagel® Phosphate Binder with Calcium Carbonate 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 5 sites in the United States.

Studied Period

First patient entered: 21 October 1996
Last patient completed: 27 March 1997

Phase of Development

Phase 2

Objectives

The objectives of this study were to determine:

- The efficacy of Renagel® and Renagel® with evening calcium carbonate supplements in lowering serum phosphorus in hemodialysis patients
- The effect of Renagel® and Renagel® with evening calcium carbonate supplements on intact parathyroid hormone levels in hemodialysis patients
- The effect of Renagel® and Renagel® with evening calcium carbonate supplements on lipid profiles in hemodialysis patients
- The safety of Renagel® and Renagel® with evening calcium carbonate supplements in hemodialysis patients

Methodology

This was a phase 2, randomized, open label, dose titration, parallel design study. Following the screening visit, patients underwent a two-week washout period. During this time, phosphate binders were discontinued and serum phosphorus levels were monitored to establish that the patients were hyperphosphatemic (serum phosphorus > 6.0 mg/dL). Eligible patients were randomized to receive either Renagel® or Renagel® with an evening calcium supplement for twelve weeks. At three week intervals during the treatment period, dose was titrated to achieve a target serum phosphorus level. Following the treatment period, patients underwent a second phosphate binder washout period.

Number of Patients (Planned and Analyzed)

No. Enrolled / Treated: 94/75 (37 Renagel®/38 Renagel® with calcium carbonate)
No. Completed: 55

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 a stable phosphate binder regimen.

Test Product, Dose, and Mode of Administration

Sevelamer hydrochloride (Renagel®): 465 mg capsules
Administered orally with meals

Duration of Treatment

The total study duration was 16 weeks including an initial two-week phosphate binder washout period, a 12-week randomized treatment period and a final two-week washout period.

Reference Therapy, Dose and Mode of Administration

Sevelamer hydrochloride (Renagel®): 465 mg capsules and Calcium carbonate (Tums Ex®): 750 mg tablets containing 300 mg of elemental calcium.

Sevelamer hydrochloride – administered orally with meals.

Calcium Carbonate - administered orally on empty stomach at bedtime

CRITERIA FOR EVALUATION
Efficacy

The primary efficacy analyses are based on the change in serum phosphorus from the end of the first wash-out to the end of the Renagel® treatment period. Secondary efficacy parameters included the change in intact parathyroid hormone and the change in serum lipid levels (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) during the Renagel® treatment period.

Safety

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

STATISTICAL METHODS
Efficacy

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

Serum phosphorus and intact parathyroid hormone results were summarized for all study visits and for the changes during the first washout, randomized treatment period, and second washout. The Wilcoxon signed rank test was used to assess changes within treatment groups while the Wilcoxon rank sum test was used to compare changes between treatment groups.

Hypercalcemia was defined as serum calcium levels greater than or equal to 10.4 mg/dL. The proportion of patients with hypercalcemic events by week was summarized overall for both the washout and treatment periods. Fisher's exact test was used to compare the incidence of hypercalcemia between treatment groups.

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 the Fisher's exact test.

Laboratory data were summarized for each study visit, for changes between baseline and final, and for change between the final visit and the end of washout. Wilcoxon signed rank tests were used to assess changes in laboratory values within treatment groups while differences between treatment groups were compared using the Wilcoxon rank sum test.

SUMMARY – CONCLUSIONS
Demographics and Renal History

The mean age was 59 years. Sixty-seven percent of patients were male and 33% were female. Fifty-seven percent of the patients were Caucasian, 39% were African-American, 3% were Hispanic and 1% were Asian. The primary cause of ESRD included diabetes (37%), hypertension (29%), nephritis (13%), polycystic kidney disease (5%), pyelonephritis (1%) and "other" (13%).

Efficacy

Serum phosphorus: In the Renagel® treatment group, the mean serum phosphorus level was 8.9 mg/dL at baseline following two weeks of phosphate binder washout and the mean change in serum phosphorus from baseline to the end of treatment was -2.4 mg/dL ($p<0.0001$). In the Renagel® and calcium carbonate treatment group, the mean serum phosphorus level was 8.1 mg/dL at baseline and the mean change in serum phosphorus from baseline to the end of treatment was -2.3 mg/dL ($p<0.0001$). There were no statistically significant differences in serum phosphorus reduction from baseline to the end of treatment between Renagel® and Renagel®® with calcium carbonate treatment ($p=0.4442$).

Serum phosphorus response: Response to treatment was defined as serum phosphorus levels reaching either the patient's pre-washout level or 5.5 mg/dL, which ever came first. A total of 33 patients (94.3%) achieved response with Renagel® treatment, with the majority of patients achieving first response within the first two weeks of treatment. For Renagel® with calcium carbonate treatment, 34 patients (94.4%) achieved response during the study with the majority of patients achieving first response within the first two weeks of treatment. There was no statistically significant difference between Renagel® treatment and Renagel® with calcium carbonate treatment in the percentage of patients achieving serum phosphorus response ($p =1.0000$).

Serum calcium: In Renagel® treatment group, the mean serum calcium level was 9.4 mg/dL at baseline and the mean change in serum calcium from baseline to the end of treatment was 0.0 mg/dL ($p=0.8331$). In the Renagel® with calcium carbonate treatment group, the mean serum calcium level was 9.4 mg/dL at baseline and serum calcium levels increased significantly from baseline to the end of treatment by 0.3 mg/dL ($p=0.0394$). There was no statistically significant difference in serum calcium change from baseline to the end of the treatment between Renagel® and Renagel® with calcium carbonate treatment ($p=0.0872$).

Incidence of hypercalcemic events: Hypercalcemic events were defined as serum calcium levels greater than or equal to 10.4 mg/dL. At pre-washout on their own phosphate binders, eight (23%) patients in the Renagel® group and 13 (36%) patients in the Renagel® with calcium group experienced at least one episode of hypercalcemia. During the washout period, 2.9% of the patients in the Renagel® group and 15.3 % of the patients in the Renagel® with calcium group experienced at least one episode of hypercalcemia. Finally, the average incidence of hypercalcemia during the treatment period was 2% and 21% for the two groups, respectively (not statistically significant from washout). The change in the incidence of hypercalcemia events from baseline to the end of treatment was not significant for either the Renagel® treatment group or the Renagel® with calcium carbonate group, thus confirming that Renagel® does not promote hypercalcemia.

Serum iPTH: In the Renagel® treatment group, the median serum iPTH level was 282 pg/mL at baseline and the median change from baseline to the end of treatment was -22.5 pg/mL ($p=0.41$). In the Renagel® with calcium carbonate treatment group, the median serum iPTH level was 217 pg/mL at baseline and the median change from baseline to the end of treatment was -67 pg/mL ($p=0.008$). There was no statistically significant difference between the two treatment groups for the change in serum iPTH from baseline to the end of treatment ($p=0.07$).

Serum lipids: In the Renagel® treatment group, the mean total cholesterol was 169.7 mg/dL at baseline and 140.4 mg/dL at the end of treatment. The mean change in total cholesterol from baseline to the end of the treatment was -29.8 mg/dL ($p<0.0001$), while the mean percent change from baseline to the end of treatment was -16.5% ($p<0.0001$). In the Renagel® with calcium carbonate treatment group, the mean total cholesterol was 176.1 mg/dL at baseline and 149.3 mg/dL at the end of treatment. The mean change in total cholesterol from baseline to the end of treatment was -26.4 mg/dL ($p<0.0001$), while the mean percent change from baseline to the end of treatment was -15.1% ($p<0.0001$). There was no statistically significant difference in total cholesterol reduction from baseline to the end of treatment between Renagel® and Renagel® with calcium carbonate treatment.

In the Renagel® treatment group, the mean LDL cholesterol was 108.9 mg/dL at baseline and 75.9 mg/dL at the end of treatment. The mean change in LDL cholesterol from baseline to the end of treatment was -34.7 mg/dL ($p<0.0001$), while the mean percent change from baseline to the end of treatment was -30.7% ($p<0.0001$). In the Renagel® with calcium carbonate treatment group, the mean LDL cholesterol was 110.4 mg/dL at baseline and 80.8 mg/dL at the end of treatment. The mean change in LDL cholesterol from baseline to the end of treatment was -27.7 mg/dL ($p<0.0001$), while the mean percent change from baseline to the end of treatment was -24.9% ($p<0.0001$). There was no statistically significant difference in LDL cholesterol reduction from baseline to the end of treatment between Renagel® and Renagel® with calcium carbonate treatment.

In the Renagel® treatment group, the mean HDL cholesterol was 33.0 mg/dL at baseline and 35.5 mg/dL at the end of treatment. The mean change in HDL cholesterol from baseline to the end of treatment was 3.0 mg/dL ($p=0.0090$), while the mean percent change from baseline to the end of treatment was 9.5% ($p=0.0117$). In the Renagel® with calcium carbonate treatment group, the mean HDL cholesterol was 34.2 mg/dL at baseline and 36.5 mg/dL at the end of treatment. The mean change in HDL cholesterol from baseline to the end of treatment was 4.1 mg/dL ($p=0.0101$), while the mean percent change from baseline to the end of treatment was 12.6% ($p=0.0037$). There was no statistically significant difference in the change in HDL cholesterol from baseline to the end of treatment between Renagel® and Renagel® with calcium carbonate treatment.

Serum triglyceride levels did not significantly change during the twelve week treatment period in either treatment group.

Safety Results

Adverse experiences: Overall there were 134 treatment emergent adverse events among 29 patients (78.4%) in the Renagel® treatment group and there were 168 treatment emergent adverse events among 36 patients (94.7%) in the Renagel® with calcium carbonate treatment group ($p=0.0467$). The body system with the most frequent adverse event was the digestive system, with 36 adverse events among 20 patients (54.1%) in the Renagel® treatment group, and 50 adverse events among 25 patients (65.8%) in the Renagel® with calcium carbonate treatment group ($p=0.3506$). The incidence of nausea significantly differed between the treatment groups with 12 adverse events among 10 patients (26.3%) in the Renagel® with calcium carbonate treatment group, compared to 2 adverse events among 2 patients (5.4%) in the Renagel® treatment group ($p=0.0245$). There were 2 hypercalcemic events among one patient (2.6%) in the Renagel® with calcium carbonate group ($p=1.0000$), which were judged to be related to study treatment.

Overall, there were 25 treatment-related adverse events among 16 patients (43.2%) in the Renagel® treatment group and 26 treatment-related adverse events among 15 patients (39.5%) in the Renagel® with calcium carbonate treatment group ($p=0.8165$). Most treatment-related adverse events were of mild intensity for both treatments. The digestive system had the most treatment-related adverse events with 23 events among 14 patients (37.8%) in the Renagel® treatment group and 20 events among 12 patients (31.6%) in the Renagel® with calcium carbonate treatment group ($p=0.6321$). The most common digestive disorders related to both treatments were constipation, flatulence, vomiting, dyspepsia, and nausea.

There were 9 serious adverse events among 5 patients (13.5%) in the Renagel® treatment group and 14 serious adverse events among 9 patients (23.7%) in the Renagel® with calcium carbonate treatment group; none of these were judged to be related to treatment. Two deaths occurred during the study; one during the washout period and one during Renagel® treatment. Both deaths were judged to be unrelated to Renagel® treatment.

Laboratory values, physical exams and vital signs: There were no clinically significant changes in safety laboratory parameters with either Renagel® or Renagel® with calcium carbonate treatment. Furthermore, there were no clinically significant changes in vital signs or physical exam abnormalities.

Based on Report Prepared on: 16 September 1997
Synopsis Prepared on: 13 October 2005