# Protocol GTC-10-202: 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 5 sites in the United States.

**Studied Period**

First patient enrolled: 30 October 1995
Last patient completed: 15 April 1996

**Phase of Development**

Phase 2

**Objectives**

The objectives of this study were to determine:

- The efficacy of Renagel® in lowering serum phosphorus in hemodialysis patients
- The safety of Renagel® in hemodialysis patients
- The effect of Renagel® treatment on lipid profiles in hemodialysis patients
- The effect of Renagel® treatment on intact parathyroid hormone levels in hemodialysis patients

**Methodology**

This was a phase 2, open label study conducted to determine the safety and efficacy of Renagel® in lowering serum phosphorus in hemodialysis patients.

The study lasted approximately 12 weeks and consisted of a screening visit, an initial phosphate binder washout period, a treatment period, and a final phosphate binder washout period. Patients were treated with Renagel® for eight weeks. During the initial washout period, phosphate binders were discontinued and serum phosphorus levels were monitored to establish that the patients were hyperphosphatemic (serum phosphorus > 6.0 mg/dL). At two week intervals during the Renagel® treatment period, the dose level was titrated to achieve serum phosphorus control (between 4 and 5.5 mg/dL, inclusive). Following the Renagel® treatment period, patients underwent a second two-week washout period during which Renagel® treatment was discontinued and serum phosphorus allowed to rise, confirming that the observed drop in phosphorus during the Renagel® treatment period was due to Renagel® treatment and not another factor. During the entire study period, patients maintained their regular dialysis schedule and normal eating habits.

**Number of Patients (Planned and Analyzed)**

No. Enrolled / Treated: 48/48
No. Completed: 41

**Diagnosis and Main Criteria for Inclusion**

Patients included in the study were adults 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®): 500 mg capsules (465 mg anhydrous)

The Renagel® starting dose was one, two or three 500 mg capsules three times per day with meals. Dose was titrated up one capsule per meal at the end of each two-week period if necessary to achieve serum phosphorus control.

Renagel® was administered orally with meals.

**Duration of Treatment**

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

**Reference Therapy, Dose and Mode of Administration**

Not applicable

**CRITERIA FOR EVALUATION**
**Efficacy**

Efficacy was evaluated based on change in serum phosphorus during the Renagel® treatment period.

**Safety**

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

**STATISTICAL METHODS**
**Efficacy**

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

Statistical analyses were performed on the change in serum phosphorous, parathyroid hormone, and calcium during Renagel® treatment using paired t-tests and ANOVA with treatment group and study site as factors.

Statistical analyses were also performed on the change in serum cholesterol (total, LDL, HDL and triglycerides) during Renagel® treatment using paired t-tests and ANOVA with treatment group and study site as factors.

**Safety**

Patients were categorized into one of three actual daily dose groups with the low group including all patients with a mean actual daily dose < 6.4 capsules/day, the medium group including patients with a mean actual daily dose $\geq$ 6.4 and < 10 capsules/day, and the high group including patients with a mean actual daily dose of $\geq$ 10 capsules/day. All safety analyses were conducted by actual daily dose groups.

Adverse experiences that began or worsened during the treatment or follow-up periods were regarded as treatment-emergent adverse experiences. The difference in incidence rates of treatment-emergent adverse experiences among the three mean actual daily Renagel® dose groups were compared using Fisher's exact test for rates of any adverse event and

for those occurring in at least 10% of patients. The changes in laboratory values during Renagel® treatment were analyzed using descriptive statistics and paired t-tests.

**SUMMARY – CONCLUSIONS**

**Demographics and Renal History**

The average age of the patients was 52 years. Thirty patients were male (62%) and 18 (37%) were female. Twenty-four of the patients were Caucasian (50%), 20 (42%) were African-American, 3 (6%) were Hispanic, and one was East Indian. The primary cause of ESRD was diabetes for 17 patients (35%), hypertension for 14 (29%) patients, nephritis for 5 (10%) patients, polycystic kidneys for 3 (6%) patients, pyelonephritis for 2 (4%) patients, and other reasons for 7 (15%) patients.

**Efficacy**

The overall mean baseline washout serum phosphorus was 8.1 mg/dL. Serum phosphorus significantly decreased from baseline to the end of Renagel® treatment (mean decrease of 1.4 mg/dL, p=0.0001). Serum phosphorus significantly increased from the end of Renagel® treatment to the end of the second washout (mean increase of 1.5 mg/dL, p=0.0001).

The initial prescribed Renagel® dose resulted in a substantial reduction in serum phosphorus. Titration of the dose after two weeks of Renagel® treatment lead to further reduction, returning the mean serum phosphorus to pre-washout levels following 4 weeks of Renagel® treatment.

Mean serum calcium was 9.5 mg/dL at screening and at the washout start. As anticipated, mean serum calcium level declined slightly when calcium-based phosphate binders were removed during the washout period. Serum calcium levels remained within the normal range (8.5 mg/dL and 10.3 mg/dL) and did not return to pre-washout levels throughout the rest of the study.

Median PTH at screening was 292 pg/mL. PTH levels appeared to increase during the washout period, likely due to the significant rise in serum phosphorus and slight decline in serum calcium. Median PTH levels declined after the start of Renagel® treatment and returned toward pre-washout levels. When Renagel® treatment ceased, PTH rose to washout levels. Changes in PTH correlated with changes in serum phosphorus (r=0.51, p=0.01) and serum calcium (r=-0.34, p=0.01)

There was a statistically significant change in total cholesterol during Renagel® treatment. Overall, the total cholesterol decreased 24.7 mg/dL (from 176.9 mg/dL, p=0.0001). LDL cholesterol decreased 23.4 mg/dL (from 97.7 mg/dL, p=0.0001). HDL cholesterol and triglycerides did not significantly change during Renagel® treatment.

**Safety Results**

Thirty-three out of 48 patients reported at least one treatment emergent experience. The most common treatment emergent events were diarrhea in 6 patients (12.5%), and constipation, vomiting, and peripheral edema in 5 patients each (10.4%). Of these, 4 constipation events (8.3%) and 4 diarrhea events (8.3%) were judged by the investigator as possibly or probably related to study treatment. Most adverse events were judged mild or moderate in intensity. There was no apparent dose-relationship in regard to the incidence of treatment-emergent adverse events.

One patient died during the course of the study, which was considered unrelated to Renagel®. Nine patients reported 11 serious adverse events, all of which were judged by the investigator as unrelated to Renagel®.

Chloride changed significantly during Renagel® treatment, overall. Mean increase in chloride was 2.7 mEq/L from 98.8 mEq/L at baseline. Carbon dioxide content also changed significantly during Renagel® treatment. Mean decrease in carbon dioxide was 1.6 mEq/L from 18.8 mEq/L. The changes in chloride and bicarbonate were most likely due to the modest decrease in base consumption due to discontinuation of calcium acetate or carbonate. Finally, alkaline phosphatase changed significantly during Renagel® treatment, overall. Mean alkaline phosphatase increased 30.7 U/L from 105.4 U/L at baseline. There was no statistically significant difference among the three dose groups for any of these laboratory parameters.

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

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