# Protocol GTC-45-204: An Open Label, Dose Titration Study of Sevelamer Hydrochloride (Renagel®) in Chronic Renal Failure Patients Not Requiring Dialysis.

*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 12 sites. There were 8 sites in the United States and 4 sites in Europe [France (2 sites), Denmark (1 site) and the United Kingdom (1 site)].

**Studied Period**

First patient entered: 9 June 1998
Last patient completed: 18 August 1999

**Phase of Development**

Phase 2

**Objectives**
**Primary:**

- Determine the efficacy of Renagel® in lowering serum phosphorus in chronic renal failure patients not requiring dialysis
- Determine the safety of Renagel® in chronic renal failure patients not requiring dialysis

**Secondary:**

- Determine the effect of Renagel® on urinary phosphorus excretion in chronic renal failure patients not requiring dialysis
- Determine the effect of Renagel® on intact parathyroid hormone levels in chronic renal failure patients not requiring dialysis
- Determine the effect of Renagel® on lipid profiles in chronic renal failure patients not requiring dialysis

**Methodology**

This phase 2, open-label, multi-center, dose titration study was conducted to determine the safety and efficacy of Renagel® in chronic renal failure patients not on dialysis. After discontinuing any phosphate binders, patients entered a four-week phosphate binder washout period. Patients who developed hyperphosphatemia (serum phosphorus $\geq$ 5.0 mg/dL) received Renagel® treatment for 12 weeks at a starting dose of 6, 9, or 12 capsules per day, depending on the patient's degree of hyperphosphatemia. Based on the patient's serum phosphorus levels obtained at Weeks 3, 6, and 9, the Renagel® dose was titrated to achieve a serum phosphorus between 2.5 and 4.5 mg/dL. After 12 weeks of Renagel® treatment, patients entered a second four-week phosphate binder washout period.

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

No. Enrolled / Treated:140/79
No. Completed:44

**Diagnosis and Main Criteria for Inclusion**

Males and females 18 years of age or older with chronic renal failure not on dialysis with confirmed hyperphosphemia (serum phosphorus $\geq$ 5.0 mg/dL) were eligible for participation in the study. The mean estimated GFR at baseline was 9.5 mL/min/1.73m$^2$. The U.S. National Kidney Foundation recommends initiating renal replacement therapy at a GFR of 10.5 mL/min/1.73m$^2$ in diabetes and at approximately 15 mL/min/1.73m$^2$ in non-diabetics. Thus, the majority of patients in this study had GFR measurements suggesting the need for dialysis or transplantation.

**Test Product, Dose, and Mode of Administration**

Sevelamer hydrochloride (Renagel®): 403 mg capsules
Starting dose was two, three or four 403 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 12 weeks. The total study duration was 20 weeks.

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

Not applicable

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

Efficacy was evaluated on the basis of changes in serum phosphorus during the Renagel® treatment period (e.g. from the last week of the first washout period to the last week of the Renagel® treatment period). Secondary efficacy parameters included response rate at the last week of the Renagel® treatment period, and changes in urinary phosphorus excretion levels, serum intact parathyroid hormone (iPTH), serum lipid profiles, serum calcium levels, and the calcium-phosphorus product levels during the Renagel® treatment period.

**Safety**

Safety was evaluated on the basis of adverse events as well as on the basis of laboratory values, vital signs, and physical examinations.

**STATISTICAL METHODS**
**Efficacy**

Serum phosphorus, urinary phosphorus, serum iPTH, serum lipids, serum calcium, and the calcium-phosphorus product 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.

The proportion of responders, defined as patients whose serum phosphorus either returned to the pre-washout level or below, or were in the normal range (2.5-4.5 mg/dL) overall and at Weeks 3, 6, 9 and 12 were calculated. The proportion of patients with a calcium x phosphorus product < 50, 50-59, 60-71, and $\geq$ 72 mg2/dL2 overall and at Week 3, 6, 9, and 12 were also calculated.

**Safety**

All adverse experiences were recorded in the first washout period (Weeks -4 to 0), the treatment period (Weeks 1 to 12), and the second washout period (Weeks 13 to 16). Frequencies and percents of treatment-emergent adverse events were tabulated for each treatment period and each washout period by dose levels (low, medium, high) of Renagel®. Tables were presented for treatment-emergent adverse events, by intensity or severity, and by relationship to the study drug. No

inferential statistical tests were performed. Discontinuations due to adverse events and serious advents were listed by patient. Descriptive statistics (N, mean, standard deviation) were presented for each laboratory parameter at each timepoint, and for changes and percent changes between screening and Week 0, between Weeks 0 and 12, and between Weeks 12 and 16. Physical examination and vital sign data were summarized, and changes from screening to Week 12 were presented.

Descriptive statistics (N, mean, standard deviation) were presented for each laboratory measurement at each time point, and for changes and for percent changes between screening and Week 0, between Weeks 0 and 12, and between Weeks 12 and 16.

**SUMMARY – CONCLUSIONS**
**Demographics and Renal History**

The average age of the patients was 55 years. Sixty percent of the patients were male and 40% were female. Most patients were Caucasian (76%), with blacks comprising 19% of the population. The most common primary cause of chronic kidney failure was diabetes (25%) and “other” (24%).

The mean estimated GFR at baseline was 9.5 mL/min/1.73m2. The U.S. National Kidney Foundation recommends initiating renal replacement therapy at a GFR of 10.5 mL/min/1.73m2 in diabetes and at approximately 15 mL/min/1.73m2 in non-diabetics. Thus, the majority of patients in this study had GFR measurements suggesting the need for dialysis or transplantation.

**Efficacy**

A statistically significant mean decrease in serum phosphorus level was noted during the treatment period (change of -0.79 mg/dL; $p < 0.001$). Four weeks after the cessation of Renagel® treatment, mean serum phosphorus levels had increased significantly from end of treatment (change of 0.87 mg/dL; $p < 0.001$) and returned to pre-treatment levels indicating that the reduction was drug-related. Consistent with serum phosphorus results, there were statistically significant reductions in urinary phosphorus excretion (change of 0.17 g/day; $p< 0.001$) and calcium-phosphorus product (change of 6.73 mg2/dL2; $p < 0.001$), but not serum intact PTH, after 12 weeks of Renagel® treatment. These trends completely reversed upon cessation of Renagel® treatment, with significant increases to or approaching pre-treatment levels noted during washout indicating that the changes were drug-related. Renagel® treatment was also associated with statistically significant reductions in total cholesterol and LDL cholesterol.

Overall, 76.9% of patients achieved a response at any evaluated time during the treatment period, with a response rate of approximately 50% at Weeks 3, 6, 9, and 12. Response was primarily due to a return of serum phosphorus levels to pre-washout levels (71.8% of patients), rather than a lowering of serum phosphorus to < 4.5 mg/dL (29.5% of patients). Overall, 78.2% of patients achieved an adjusted calcium-phosphorus product of < 50 mg2/dL2 at any time during Renagel® treatment. Few patients (6.4%) had an adjusted calcium-phosphorus product > 72 mg2/dL2, a level generally considered to be associated with increased mortality in dialysis patients.

No changes in mean serum calcium, HDL cholesterol, or triglycerides levels were observed over the course of the 12 weeks of Renagel® treatment (Weeks 0 to 12).

**Safety Results**

No patients died during the study. During the Renagel® treatment period, 69 (88%) patients reported a total of 226 adverse events (AEs). The most frequently reported AEs (> 10%) were uremia (27%), nausea (24%), constipation (15%), vomiting (12%), and dyspepsia (12%). As this was an uncontrolled study, the underlying percentage of renal failure patients suffering from these adverse events is not known. Overall, 35 (44%) patients reported a total of 46 treatment-emergent AEs classified as of possible or probable relationship to study drug. The nine (9) AEs of probable relationship were all in the digestive system (constipation, dyspepsia, dysphagia, eructation, flatulence, nausea, and vomiting) and were reported in one or two patients each. Treatment-emergent AEs that appeared to have some relationship to Renagel® dose were dyspepsia, diarrhea, anemia, hypertonia, asthenia, hypertension, and infection.

Nineteen (24%) patients experienced a total of 31 SAEs during the Renagel® treatment period. The most frequently reported SAE during the treatment period was uremia (13 patients, or 17%), primarily due to worsening of pre-existing chronic renal failure. All other SAEs occurred in only one or two patients each. All SAEs were considered not related to Renagel®, with two SAEs (rectal bleeding, epigastric pain with nausea) regarded as remotely related to Renagel®.

A total of 21 (27%) patients were discontinued due to adverse events during the Renagel® treatment period. The most frequently reported AEs leading to withdrawal were uremia (15 patients, or 19%), vomiting (4 patients, or 5%), and nausea (3 patients, or 4%). All other individual AEs leading to withdrawal occurred in only one patient each during any study period. Most AEs resulting in discontinuation were regarded as not related to Renagel®. Nausea and vomiting in two patients and abdominal pain in one patient were considered possibly related to Renagel®. A higher proportion of U.S. patients (35%) than European patients (13%) in the safety population discontinued due to AEs.

As is typical for the population of patients with chronic renal failure, all patients had numerous laboratory values outside the normal ranges. Out-of-range values (high/low) were often present at both the baseline/Week 0 and final/Week 12 visits. Clinically meaningful changes were noted serum chloride, CO2 content, and vitamin D 25-OH.

Mean chloride level, which was within the normal range at baseline, increased slightly during Renagel® treatment (+1.69 mEq/L from 106.57 mEq/L). Mean chloride level returned to within the normal range after a two week washout. Mean changes from baseline to the end of Renagel® treatment appeared to be dose-related; however, no adverse events of hyperchloremia were reported.

Mean CO2 content level, which was below the lower limit of normal at baseline due to the severity of renal failure in these patients, decreased during Renagel® treatment (-2.61 mEq/L from 17.90 mEq/L). Following a two-week washout, mean CO2 content had returned to baseline. Mean changes from baseline to the end of Renagel® treatment appeared to be dose-related. Adverse events of metabolic acidosis were reported in four patients during the study. Acidosis is a common accompaniment of renal disease due to the failure of the kidney to excrete acid and generate bicarbonate. This results in a primary metabolic acidosis that is observed in nearly all renal failure patients. Once renal failure patients start dialysis, the base provided with the dialysate solution reverses this acidosis.

Although vitamin D 25-OH levels were within the normal range at both baseline and the end of Renagel® treatment, a reduction in mean serum levels of vitamin D 25-OH (-6.24 ng/mL, -5.99%) change was recorded at the end of Renagel® treatment. Following a two-week washout, the mean serum vitamin D 25-OH level had returned to the pretreatment value. The changes in vitamin D 25-OH levels from baseline to the end of Renagel® treatment appeared to be dose-related. Predialysis patients often have low levels of vitamin D 25-OH due to uremia related anorexia.

No clinically significant trends or mean changes in vital signs or physical examinations were noted from screening to end of treatment.

Based on Report Prepared on: 11 September 2000
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