Protocol GTC-45-206: An Open Label, Dose Titration Study of Sevelamer Hydrochloride (Renagel®) in Pediatric Dialysis 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 single center study conducted in the United States.

Studied Period

First patient entered: 12 January 2000
Last patient completed: 17 January 2001

Phase of Development

Phase 2

Objectives
Primary:

- Determine the efficacy of sevelamer hydrochloride in lowering serum phosphorus and serum calcium-phosphorus product in pediatric dialysis patients
- Determine the safety of sevelamer hydrochloride in pediatric dialysis patients

Secondary:

- Determine the effect of sevelamer hydrochloride on lipid profiles in pediatric dialysis patients
- Determine the effect of sevelamer hydrochloride on intact parathyroid hormone levels in pediatric dialysis patients

Methodology

This was a phase 2, single-center, open-label dose titration pilot study to examine the safety and efficacy of sevelamer hydrochloride in pediatric dialysis patients. Following screening, patients underwent a four week phosphate binder run in period. During this time, the patient maintained stable doses of calcium and/or aluminum phosphate binders and vitamin D therapy. At the end of the phosphate binder run in period the patient entered the two week washout period during which all phosphate binder medication was stopped. Following the washout period, patients received Renagel® treatment

for 24 weeks. During this period the dose of Renagel® was titrated to achieve a target serum phosphorus level. At the end of the Renagel® treatment period, patients returned to their original phosphate binders.

Number of Patients (Planned and Analyzed)

No. Enrolled / Treated:17/17
No. Completed:12

Diagnosis and Main Criteria for Inclusion

Pediatric dialysis patients aged 2 to 17 years of age, on stable doses of calcium or aluminum based phosphate binders were eligible for the study.

Test Product, Dose, and Mode of Administration

Sevelamer hydrochloride (Renagel®): 403 mg capsules
Sevelamer hydrochloride (Renagel®): 800 mg tablets
Administered orally with meals

Duration of Treatment

Renagel® treatment was for 24 weeks. The total study duration was 32 weeks.

Reference Therapy, Dose and Mode of Administration

Not applicable

CRITERIA FOR EVALUATION
Efficacy

The primary efficacy analysis was based on the change in serum phosphorus and the change in serum calcium-phosphorus product from the end of the washout period to the end of the Renagel® treatment period. Secondary efficacy parameters included the change in serum lipid levels (LDL cholesterol, total cholesterol, HDL cholesterol, and triglycerides) and the change in intact parathyroid hormone levels during the Renagel® treatment period.

Safety

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

STATISTICAL METHODS
Efficacy

Serum phosphorus, serum calcium, serum calcium x phosphorus product, serum iPTH, and serum lipids were presented at all study visits and for the changes during the Renagel® treatment period. Wilcoxon signed rank tests were used to assess the changes.

Serum iPTH response was defined as achieving a serum iPTH level between 200 and 400 pg/mL. The number and percent of patients in response over time were presented.

Safety

Adverse Experiences: Adverse events starting during the run-in, washouts, and treatment periods were listed overall, by body system, and by MedDRA preferred term.

Laboratory: Laboratory measures at each time point and changes between baseline and endpoint were summarized.

SUMMARY – CONCLUSIONS
Demographics and Renal History

The mean age of all patients was 11.8 years. Most patients were Hispanic (65%), with Caucasians comprising 17% and Blacks comprising 12% of the population. The primary cause of renal failure was glomerulonephritis in four (24%) patients, congenital in four (24%) and polycystic kidney in one patient (6%). The remaining eight (47%) patients cited “other” as the primary cause of renal failure

Efficacy

Serum Phosphorus: For the entire population, mean serum phosphorus while the patients were on their previous phosphate binders was 5.2 ± 1.27 mg/dL. Following two weeks of washout, the serum phosphorus rose to 7.5 ± 2.24 mg/dL. After four weeks of treatment at the initial prescribed dose, mean serum phosphorus fell to 6.8 ± 1.44 mg/dL. Titration of the dose during subsequent weeks lowered the serum phosphorus levels further so that by the end of the Renagel® treatment period the mean was 6.3 ± 1.51 mg/dL. The mean change in serum phosphorus during the Renagel® treatment period was –0.35 ± 2.41 mg/dL (p = 0.5711).

In a subset of patients who completed the trial per protocol, the mean serum phosphorus while the patients were on their previous phosphate binders was 5.3 ± 1.44 mg/dL. Following two weeks of washout the serum phosphorus rose to 7.5 ± 2.02 mg/dL. After four weeks of treatment at the initial prescribed dose, mean serum phosphorus fell to 6.7 ± 1.49 mg/dL. Titration of the dose during subsequent weeks lowered the serum phosphorus levels further so that by the end of the Renagel® treatment period the mean was 6.3 ± 1.51 mg/dL. The mean change in serum phosphorus during the Renagel® treatment period was –1.2 ± 2.11 mg/dL (p = 0.0771).

Serum Calcium: Mean serum calcium while the patients were on their previous phosphate binders was 9.5 ± 0.86 mg/dL. Following 2 weeks of washout, the serum calcium decreased to 9.0 ± 1.47 mg/dL. After four weeks of treatment at the initial prescribed dose, mean serum calcium rose to a level similar to that seen on the patients’ previous phosphate binders, 9.4 ± 1.11 mg/dL. The mean calcium level by the end of the Renagel® treatment period was 9.1 ± 0.66 mg/dL. The mean change in serum calcium during the Renagel® treatment period was 0.2 ± 1.17 mg/dL (p = 0.9629).

Serum iPTH: Median serum iPTH while the patients were on their previous phosphate binder was 254.0 pg/mL. Following 2 weeks of washout the serum iPTH rose to 588.0 pg/mL. After four weeks of treatment at the initial prescribed dose, median serum iPTH rose to 786.5 pg/mL. Titration of the dose during subsequent weeks lowered the serum iPTH levels so that by the end of the Renagel® treatment period the median was 606.5 pg/mL. The median change in serum iPTH during the Renagel® treatment period was 5.0 pg/mL (p = 0.5245).

Nine patients (56%) achieved a serum iPTH response during the study with the majority of those patients (31%) achieving a response within the first four weeks of Renagel® treatment.

Calcium x Phosphorus Product: Mean serum calcium x phosphorus product while the patients were on their previous phosphate binders was 49.5 ± 13.4 mg2/dL2. Following 2 weeks of washout the serum calcium x phosphorus product rose to 66.3 ± 21.1 mg2/dL2. After four weeks of treatment at the initial prescribed dose, mean serum calcium x phosphorus product fell to 64.0 ± 16.4 mg2/dL2. Titration of the dose during subsequent weeks lowered the serum calcium x phosphorus product levels further so that by the end of the Renagel® treatment period the mean was 57.4 ± 14.0 mg2/dL2. The mean change in serum calcium x phosphorus product during the Renagel® treatment period was –4.5 ± 17.3 mg2/dL2 (p = 0.4954).

Serum Lipids: Mean serum LDL cholesterol while the patients were on their previous phosphate binders was 90.3 ± 34.2 mg/dL. At the end of the Renagel® treatment period the mean was 61.4 ± 34.1 mg/dL. The mean change in serum LDL cholesterol during the Renagel® treatment period was –17.8 ± 29.4 mg/dL (p = 0.1953). The mean percent change was –24% (p = 0.1484).

Mean serum total cholesterol while the patients were on their previous phosphate binders was 186.6 ± 80.2 mg/dL. By the end of the Renagel® treatment period the mean was 153.0 ± 50.5 mg/dL. The mean change in serum total cholesterol during the Renagel® treatment period was –23.9 ± 56.9 mg/dL (p = 0.3003) and the mean percent change was –7.3 % (p = 0.4238). Mean serum HDL cholesterol while the patients were on their previous phosphate binders was 41.8 ± 8.4 mg/dL. HDL cholesterol remained essentially unchanged during the study. The mean at the end of the Renagel® treatment period was 39.5 ± 8.7 mg/dL. The mean change in serum HDL cholesterol during the Renagel® treatment period was –0.3 ± 10.8 mg/dL (p = 0.9150) and the mean percent change was 2.1% (p = 0.8984).

Median serum triglycerides while the patients were on their previous phosphate binders was 207.0 mg/dL. The median at the end of the Renagel® treatment period was 237.0 mg/dL. The median change in serum triglycerides during the Renagel® treatment period was 5.0 mg/dL (p = 0.8552) and the median percent change was 16.8 % (p = 0.1726).

Safety Results

Overall, a total of 188 adverse events occurred during the study. All seventeen patients had an adverse event. There were 21 adverse events among 9 patients during the run-in period and 19 adverse events among 6 patients during the washout period. Most of these adverse events were mild in intensity. All seventeen patients had a treatment emergent adverse event (adverse event that began or worsened during the treatment period). There were 148 adverse events during the Renagel® treatment period. Most of these adverse events were mild in intensity. Five treatment emergent adverse events (occurring in four patients) were considered related to Renagel® treatment. They were conjunctivitis, hyperphosphatemia (2 patients) and nausea (2 patients). All treatment related adverse events were mild in intensity.

Overall, 23 serious adverse events occurred in nine patients. There were no deaths during this study. Two serious adverse events occurred in two patients during the run-in period and four serious adverse events occurred in one patient during the washout. Seventeen treatment emergent serious adverse events occurred in eight patients. Most of these serious adverse events were mild or moderate in intensity and none were considered to be related to the study treatment. There were two adverse events that resulted in discontinuation of the study. Both were due to kidney transplants and neither was considered related to the study treatment.

Renagel® caused no unusual alterations in safety laboratory in children during this study. There were no clinically significant changes in laboratory

parameters. Furthermore, there were no clinically significant changes in vital signs or physical examinations.

Based on Report Prepared on: 3 January 2002
Synopsis Prepared on: 13 October 2005