Protocol REN-002-01: Comparison of a Calcium-Free Phosphate Binder (Sevelamer) with a Calcium-Containing Phosphate Binder (Calcium Acetate) in the Treatment of Hyperphosphatemia in Children with Chronic Renal Failure

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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 11 sites in Germany.

Studied Period

First patient entered: 10 October 2001
Last patient completed: 22 May 2003

Phase of Development

Phase 4

Objectives
Primary Objectives

In pediatric patients with chronic kidney disease (CKD) (whether or not receiving dialysis therapy), to compare the effects of sevelamer and calcium acetate treatment on:

- Serum phosphorus levels (hyperphosphatemia)
- Serum calcium-phosphorus product levels
- Plasma intact parathyroid hormone (iPTH) levels, cyclase inhibiting PTH (CIP) levels, cyclase activating PTH levels and CAP/CIP ratio (hyperparathyroidism)
- Incidence of hypercalcemic episodes [(serum calcium > 11 mg/dL (2.75 mmol/L)]

Secondary Objectives

In pediatric patients with CKD (whether or not receiving dialysis therapy), to compare the effects of sevelamer and calcium acetate treatment on:

- Uremic dyslipidemia as measured by serum total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides and lipoprotein (a) [Lp(a)]

- Incidence and severity of adverse events

Methodology

This was a phase 4, multicenter, open-label, randomized study in pediatric subjects with chronic kidney disease on or off dialysis (hemodialysis or peritoneal dialysis). Following a two-week initial washout period, pediatric patients with CKD were exposed to two eight-week treatment periods with sevelamer or calcium acetate in a crossover fashion with a two-week washout between treatment periods.

Number of Patients (Planned and Analyzed)

No. Enrolled, Randomized, and Treated: 44/40/34
No. Completed: 23

Diagnosis and Main Criteria for Inclusion

Patients included in the study were male and female pediatric patients (aged 0 to 18 years) with chronic kidney disease [glomerular filtration rate $\geq$ 20 and < 60 mL/min x 1.73 m2 OR on dialysis (hemodialysis or peritoneal dialysis)] and on constant dosages of phosphate-binder and calcitriol therapy on study entry. Patients, or parents, were required to give written informed consent prior to participation in the study.

Test Product, Dose, and Mode of Administration

Sevelamer hydrochloride (Renagel®): 400 mg tablets
Sevelamer hydrochloride (Renagel®): 403 mg capsules
Administered orally with meals

Duration of Treatment

The total study duration was 20 weeks including 8 weeks of sevelamer treatment, 8 weeks of calcium acetate treatment, and 2 weeks of washout before each treatment period.

Reference Therapy, Dose and Mode of Administration

Calcium acetate (Nephracetat®): 500 mg (tablets)
Administered orally with meals

CRITERIA FOR EVALUATION
Efficacy

Efficacy was assessed by evaluating:

- Effects on serum phosphorus levels
- Number of hypercalemic episodes [(serum calcium > 11 mg/dL (2.75 mmol/L)]
- Effects on the serum calcium-phosphorus product
- Effects on plasma intact parathyroid hormone (iPTH) levels, cyclase inhibiting PTH (CIP) levels, cyclase activating PTH levels and CAP/CIP ratio (hyperparathyroidism)
- Doses of phosphate binders
- Influence on the uremic dyslipidemia as measured by: changes in

serum level of cholesterol, HDL cholesterol, LDL cholesterol, triglycerides and Lp(a)

Safety

Safety was assessed by evaluating:

- The incidence of adverse events
- Changes in laboratory measurements
- Changes in physical examinations and vital signs

STATISTICAL METHODS

For phosphorus, hyperparathyroidism [iPTH, CIP, CAP and CAP/CIP ratio], uremic dyslipidemia [TC, LDL, HDL, TG and Lp(a)], calcium, and calcium-phosphorus product, the values at each study visit and the change from baseline to the end of study treatment were summarized by treatment both within and across treatment sequence groups. The change from baseline was analyzed by mixed effect regression models with a subject random effect and treatment, period, and treatment-by-period fixed effects. For serum phosphorus, the 90% and 95% confidence intervals for the difference in phosphorus reduction between treatment groups was calculated based on the least squares means and mean squared error derived from this model.

The number of hypercalcemic episodes was summarized by treatment group both within and across treatment sequence groups. McNemar's paired comparison test was used to compare the incidence of hypercalcemia for the two treatments.

The difference in incidence of treatment emergent adverse events (proportion of patients with one or more events) between the treatment groups and between the treatment sequences was tested using Fisher's Exact test. Treatment emergent adverse events were defined as adverse events that started or worsened after the first study treatment was given.

The change in safety laboratories from start to end of a treatment period were tested using Wilcoxon's signed rank test.

SUMMARY – CONCLUSIONS
Demographics and Renal History

The patients had a mean age of 12 years and consisted of 65% males and 35% females. The majority of patients were Caucasian (92%) and the three most frequent causes of ESRD were malformations (45%), hereditary disease (20%) and glomerulopathies (27%).

Efficacy

A statistically significant reduction in serum phosphorus was observed during the eight weeks of treatment in both the sevelamer and the Ca acetate groups and in both sequence groups. Equivalence was established relative to the pre-specified equivalence bounds on the mean treatment difference of –0.34 to 0.34 based on the 90% confidence limits.

Mean PTH levels were similar at the beginning of each treatment period (sevelamer 48.61 pmol/L; Ca acetate 40.47 pmol/L) and did not change significantly during the treatment (sevelamer -2.73 pmol/L; Ca acetate 4.26 pmol/L). The difference between sevelamer and Ca acetate was not

significant. Similar results were obtained for CAP, CIP and the CAP/CIP ratio.

Mean calcium-phosphorus product decreased significantly with sevelamer [79.7 to 62.6 mg2/dL2 (6.43 to 5.05 mmol2 /L2); p=0.0007] as well as with Ca acetate [75.8 to 61.9 mg2/dL2 (6.11 to 4.99 mmol2/L2); p=0.0015]. The difference between the two treatment groups was not significant.

Mean total cholesterol decreased significantly with sevelamer [231.8 to 173.4 mg/dL (5.99 to 4.48 mmol/L); p=0.0171], but not with Ca acetate treatment [231.4 to 208.2mg/dL (5.98 to 5.38 mmol/L); p=0.3213]. The difference between the two treatment groups was significant. A similar pattern was shown for LDL cholesterol. For HDL cholesterol, triglycerides, and lipoprotein (a), no significant changes were observed for either treatment.

The number of hypercalcemic episodes [defined as serum calcium >11mg/dL (2.75 mmol/L)] was statistically significantly higher with Ca acetate treatment than with sevelamer treatment (5 versus 0 episodes, respectively; p=0.0005).

Safety Results

Sevelamer was well tolerated in this group of children with chronic kidney disease. Overall, 30 patients (93.8%) in the sevelamer group experienced 119 adverse events (AEs) and 27 patients (90.0%) in the calcium acetate group experienced 113 AEs. The adverse events most frequently reported were gastro-intestinal (21 events in 13 patients for sevelamer; 26 events in 13 patients for calcium acetate). The most frequently occurring adverse events in the sevelamer group were acidosis (11 events in 11 patients), abdominal pain (10 events in 9 patients), hyperparathyroidism (8 events in 7 patients), and headache (6 events in 6 patients). In the calcium acetate group, the most frequent adverse events were nausea (11 events in 7 patients), and rhinitis (7 events in 6 patients). One case of acidosis was also reported for the calcium acetate group.

The Investigators assessed the relationship of all AEs in relation to the use of sevelamer or calcium acetate. In the sevelamer group, 22 adverse events in 14 patients (43.8%) were considered related to the use of study medication, and 17 adverse events in 10 patients (33.3%) in the calcium acetate group were considered related to the use of study medication. The most frequently reported adverse events with a relationship to study drug were: acidosis, aggravation of secondary hyperthyroidism, and nausea in the sevelamer group; and hypercalcemia in the calcium acetate group.

A total of 19 patients experienced 27 serious treatment emergent adverse events during the study. Eight patients (25.0%) experienced 10 serious adverse events during sevelamer treatment and 11 patients (36.6%) experienced 17 serious adverse events during calcium acetate treatment. The serious adverse events were mostly mild to moderate in intensity. All serious adverse events, except two, were considered not or remotely related to study treatment. The serious adverse event ‘acidosis’ was considered definitely related to sevelamer treatment and the serious adverse event ‘hypertension’ was considered possibly related to calcium acetate treatment. All patients recovered from the serious adverse events without sequelae.

In the sevelamer group, there was a statistically significant decrease from baseline in serum copper. This decrease was within the normal range and thus not considered clinically significant. Other laboratory assessments showed statistically significant changes in the treatment groups between the start and end of the treatment period. However, none of these assessments showed shifts from normal to clinically significant abnormal.

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.