Protocol GTC-49-301: A Randomized, Open Label, Parallel Design Study of Sevelamer Hydrochloride (Renagel®) and Calcium-Based Phosphate Binders in Hemodialysis Patients – Treat to Goal.

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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 taking place at 15 sites in the United States (7) and Europe (8).

Studied Period

First patient entered: 5 May 1999
Last patient completed: 25 January 2001

Phase of Development

Phase 3

Objectives
Primary

The primary objectives of the acute phase (first 12 weeks of treatment) and for the chronic phase (12-52 weeks of treatment including the acute phase) of the study were to compare the effects of Renagel® and calcium acetate/carbonate (calcium) on serum phosphorus and on the serum calcium-phosphorus product.

The effects of Renagel® and calcium on serum intact parathyroid hormone (iPTH) were also compared in the chronic phase.

Secondary

The secondary objectives of the acute and chronic phases of the study were to compare the effects of Renagel® and calcium on:

- Serum calcium (adjusted for albumin) and the incidence of hypercalcemic episodes
- The percentage of patients with an optimal outcome
- The frequency of phosphate binder dose adjustment
- Serum lipid profiles

The secondary objectives for the chronic phase of the study were also to compare the effects of Renagel® and calcium on:

- Cardiovascular calcification (coronary arteries, aortic valve, mitral valve, aorta, myocardium, and lung)
- The percentage of patients whose serum iPTH was greater than 300 pg/mL that were able to start or increase vitamin D therapy
- Changes in bone specific alkaline phosphatase (BSAP), osteocalcin, and c-telopeptides
- Serum iron profiles

Methodology

This was a phase 3, 52 week, randomized, open label, multi-center parallel study to compare the effects of Renagel® to calcium acetate/carbonate in hemodialysis patients. Following a screening visit, patients underwent a two-week phosphate binder washout period. Patients who developed hyperphosphatemia, (serum phosphorus $\geq$ 5.5 mg/dL) during the washout period were eligible for study drug treatment. Patients were randomized to either Renagel® or calcium acetate (US)/carbonate (EU). The investigator monitored levels of serum phosphorus and calcium in order to titrate the phosphate binder dose at regular intervals during the study to achieve a serum phosphorus level between 3.0 mg/dL (0.97 mmol/L) and 5.0 mg/dL (1.61 mmol/L), while maintaining serum calcium levels (adjusted for albumin) less than 10.5 mg/dL (2.63 mmol/L).

Following the first 12 weeks of treatment, an extended 40-week chronic phase treatment period commenced and patients continued their assigned Renagel® or calcium treatment. If the week 12 serum iPTH was > 300 pg/mL and safety laboratories were within required parameters as specified by the vitamin D dosing instructions, the investigator was to start vitamin D or if the patient was currently on vitamin D, increase the dosage. Serum phosphorus, calcium, and iPTH levels were monitored and these measurements were used to adjust the phosphate binder and vitamin D doses as necessary to maintain optimal therapy [serum phosphorus between 3.0 mg/dL (0.97 mmol/L) and 5.0 mg/dL (1.61 mmol/L); serum calcium (adjusted for albumin) $\geq$ lower limit of normal and < 10.5 mg/dL (2.63 mmol/L); and serum iPTH between 150 and 300 pg/mL].

In addition, EBT scans were performed at baseline, 26 weeks, and 52 weeks of treatment. Imaging was performed with a 100-msec scanning time and a single slice thickness of three mm. Thirty-six to 40 tomographic slices were obtained for each patient. Tomographic imaging was electrocardiographically triggered at 60 or 80 percent of the R-R interval and proceeded from the level of the carina to the diaphragm. All areas of calcification with a minimal density of 130 Hounsfield Units (HU) within the borders of the coronary arteries, aorta, mitral and aortic valves were computed. The total volume of calcification was first calculated using a highly reproducible method described by Callister, et al (Callister T, Janowitz W, Raggi P. “Sensitivity of two electron beam tomography protocols for the detection and quantification of coronary artery calcium”, AJR Am J Roentgenol. 2000 Dec;175(6):1743-6.). The total calcium volume score was derived from the following areas: coronary arteries, aorta, mitral valve and aortic valve. The calcium score originally described by Agatston et al (Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. , “Quantification of coronary artery calcium using ultrafast computed tomography”, J Am Coll Cardiol. 1990 Mar 15;15(4):827-32.) was also calculated. In addition to considering the volume of calcification, the “Agatson score” incorporates its density, multiplying the volume of calcification by a weighted density coefficient and then combing individual area scores to derive a final volume x density score. To ensure the continuity and consistency of the calcium score interpretation, a single expert investigator unaware of the patients’ clinical status reviewed all EBT scans.

Number of Patients (Planned and Analyzed)

No. Enrolled and Treated: 246/202 (100 Renagel®, 102 calcium)
No. Completed: 135 (61 Renagel®, 74 calcium)

Diagnosis and Main Criteria for Inclusion

Male and female adult patients on stable three-times weekly hemodialysis and a stable phosphate binder regimen.

Test Product, Dose, and Mode of Administration

Sevelamer hydrochloride (Renagel®): 800 mg tablets

Administered orally with meals.

Duration of Treatment

Two week washout period followed by a 52 week treatment period

Reference Therapy, Dose and Mode of Administration

Calcium carbonate (Calciumcarbonat Sertuerner): 500 mg tablets (EU)
Calcium acetate (PhosLo®): 667 mg (tablets) (US)
Administered orally with meals.

CRITERIA FOR EVALUATION
Efficacy

Primary Measures: Efficacy was evaluated on the basis of changes in serum phosphorus and serum calcium-phosphorus product from Day 0 to Week 12 (acute phase) and from Day 0 to Week 52 (chronic phase). Changes in serum iPTH from Day 0 to Week 52 were also evaluated.

Secondary Measures: Efficacy was evaluated during the acute and chronic phases by comparing the effects of Renagel® and calcium on:

- Serum calcium (adjusted for albumin) and the incidence of hypercalcemic episodes
- The percentage of patients with an optimal outcome
- The frequency of phosphate binder dose adjustment
- Changes in serum lipid profiles from Day 0 to Week 12 and from Day 0 to Week 52

During the chronic phase, efficacy was also evaluated by comparing the effects of Renagel® and calcium on:

- Cardiovascular calcification (coronary arteries, aortic valve, mitral valve, aorta, myocardium and lung)
- The percentage of patients whose serum iPTH was greater than 300 pg/mL that started or increased vitamin D therapy
- Changes in markers of bone turnover (BSAP, osteocalcin, and c-telopeptides) from Day 0 to Day 52
- The changes in serum iron profiles from Day 0 to Week 52

Safety

- Safety was evaluated on the basis of adverse events and changes in laboratory measures and physical exams

STATISTICAL METHODS
Efficacy

Two-tailed hypothesis tests were used and determined to be statistically significant if $p < 0.05$.

Descriptive statistics for serum phosphorus, calcium-phosphorus product, iPTH, and serum calcium were presented for each visit as well as for changes between Day 0 and the Week 12, 24 and 52 measurements. Wilcoxon rank sum tests were used to compare the treatment groups. In addition, changes within each treatment group were assessed using Wilcoxon signed rank tests.

The frequency of patients who attained serum phosphorus levels less than or equal to 5.0, 5.5, and 6.5 mg/dL were presented for each treatment group by visit and overall. Differences between the groups were assessed using Fischer's exact test.

The proportion of patients with hypercalcemic events was summarized by week and treatment group for both the washout and treatment periods. Fischer's exact test was used to compare the incidence of hypercalcemia between the treatment groups.

Frequency of Ca x P $\leq$ 52, 55, 60 and 72 mg2/dL2 was presented for each treatment group by visit and overall. Differences between groups were assessed using Fischer's exact test.

The number and percent of serum intact parathyroid hormone responders (defined as iPTH between 150 and 300 pg/mL inclusive) was presented by treatment for any response during the acute phase and for each visit during the chronic phase. Fischer's exact test was used to compare the treatment groups.

The frequency of patients that achieved optimal outcome was calculated at each post-baseline visit and for any incidence during the acute and chronic phases separately. Differences between the groups were assessed using Fischer's exact test.

The frequency of binder dose adjustment in the acute and chronic phases was compared across treatment groups using Fischer's exact test. The overall number of dose adjustments was compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) test to control for diabetes status.

The frequency of patients starting or increasing vitamin D with iPTH > 300 pg/mL during the chronic phase was summarized by treatment group and was analyzed using Fischer's exact test. Starting or increasing vitamin D was defined as starting or increasing usage between the current visit date and the day before the following visit date, inclusive.

Descriptive statistics were presented for each lipid parameter and iron level by treatment and visit. In addition, the change from baseline to the end of the acute and chronic phases is also presented. Wilcoxon signed rank tests were used to assess the changes within treatment groups, and the Wilcoxon rank sum test was used to compare changes between treatment groups.

Descriptive statistics were presented by treatment group for bone specific alkaline phosphatase (BSAP), osteocalcin, and c-telopeptides at Day 0, and Week 52 and for the change during the study. BSAP was also summarized at Week 24. The changes within treatment groups were assessed using the Wilcoxon signed rank test and compared between treatment groups using the Wilcoxon rank sum test.

Descriptive statistics were presented by location (coronary arteries, aortic valve, mitral valve, aorta, myocardium and lung) for each of the following metrics at Weeks 0, 26 and 52: volume score, density, number of lesions and Agatson score. Descriptive statistics of calcification volume and Agatson scores were also presented by baseline calcification groups for coronary arteries [baseline groups were none, mild to moderate (1-400), severe (401-1000), and very severe (>1000)], aortic valve [baseline groups were none and any], mitral valve [baseline groups were none and any] and aorta [baseline groups were none, 1st tertile among patients with baseline calcification, 2nd tertile among patients with baseline calcification., and 3rd tertile among patients with baseline calcification]. Wilcoxon signed rank tests were used to assess changes from baseline within treatment groups and Wilcoxon rank sum test was used to compare changes from baseline between the treatment groups.

Safety

The number and percent of patients who experienced treatment emergent adverse events and the number and percent of patients who experienced treatment emergent adverse events that were determined to be possibly or probably related to study treatment were calculated overall, by primary system organ class and by intensity. The difference in the incidence of treatment emergent adverse events between treatment groups was tested using Fisher's exact test. The incidence of treatment emergent serious adverse events was also summarized.

Laboratory measures at each visit as well as changes between Screening and Baseline, Acute Final, Week 24, and Chronic Final and changes between Baseline and Acute Final, Week 25, and Chronic Final were summarized. Wilcoxon signed rank tests were used to assess the changes within treatment groups, and the Wilcoxon rank sum test was used to compare changes between the treatment groups.

Changes in vital signs were calculated from Baseline to Week 52 or early termination. Wilcoxon signed rank tests were used to assess the changes within treatment groups and the Wilcoxon rank sum test was used to compare changes between the treatment groups. The frequency of physical exam changes from screening was summarized by treatment group and was analyzed using Fisher's exact test.

SUMMARY – CONCLUSIONS
Demographics and Renal History

The average age of the patients was 57 years. Sixty-five percent of the patients were male and 35% were female. Sixty-eight percent of the patients were Caucasian, 20% were African-American, 2% were Hispanic, 6% were Asian, and 4% were "other. The primary cause of ESRD included diabetes (26%), glomerulonephritis (21%), hypertension (16%), polycystic kidneys (10%) and "other" (28%).

Efficacy

There were statistically significant ($p < 0.0001$) reductions in serum phosphorus in the Renagel® and calcium groups from Day 0 to the end of both the acute (Renagel®, 1.9 mg/dL; calcium, 2.1 mg/dL) and chronic (Renagel®, 2.2 mg/dL; calcium 2.0 mg/dL) phases, however there was no statistically significant difference between the treatment groups in these reductions (acute phase, $p = 0.6992$; chronic phase; $p = 0.4831$). Patients in the Renagel® group attained mean serum phosphorus levels of 5.6 mg/dL at the end of the acute phase and 5.2 mg/dL at the end of the chronic phase. Patients in the calcium

group attained mean serum phosphorus levels of 5.2 mg/dL at the end of both the acute and chronic phases. A total of 74% of Renagel® patients and 80% of calcium patients reached the therapeutic target or serum phosphorus levels less than or equal to 5.0 mg/dL during the acute phase and 83% of Renagel® patients and 86% of calcium patients reached this therapeutic target level during the chronic phase.

There were statistically significantly greater increases in mean serum calcium in the calcium group compared to the Renagel® group at the end of both the acute and chronic phases ($p < 0.0001$). The mean increase of 0.479 mg/dL in serum calcium at the end of the acute phase in the calcium group was statistically significant ($p < 0.0001$); however, the mean increase of 0.061 mg/dL in the Renagel® group was not statistically significant ($p = 0.1811$). Similar results were observed at the end of the chronic phase, where the mean increase of 0.466 mg/dL in the calcium group was statistically significant ($p < 0.0001$), but the mean decrease of 0.016 mg/dL in the Renagel® group was not statistically significant ($p = 0.5668$). Patients in the Renagel® group attained mean serum calcium levels of 9.44 mg/dL at the end of the acute phase, while patients in the calcium group attained mean serum calcium levels of 9.80 mg/dL. At the end of the chronic phase, patients in the Renagel® group attained mean serum calcium levels of 9.38 mg/dL, while patients in the calcium group attained mean serum calcium levels of 9.74 mg/dL.

A statistically significantly greater percentage of patients in the calcium group experienced hypercalcemic events, as defined as serum calcium > 10.5 mg/dL, during both the acute (Renagel® 13%; calcium 41%; $p < 0.0001$) and chronic phase (Renagel® 17%; calcium 43%; $p = 0.0005$) of the study.

Statistically significant ($p < 0.0001$) reductions in the serum calcium-phosphorus product were observed for both treatment groups at the end of both the acute (Renagel®, 17.28 [mg/dL]2; calcium, 16.94 [mg/dL]2) and chronic phases (Renagel®, 20.69 [mg/dL]2; calcium, 15.64 [mg/dL]2). These differences were not statistically significant between the treatment groups (acute phase, $p = 0.7335$; chronic phase, $p = 0.1046$). Patients on Renagel® achieved a mean serum calcium-phosphorus product level of 53.25 (mg/dL)2 during the acute phase and 48.53 (mg/dL)2 during the chronic phase. Patients on calcium achieved a mean serum calcium-phosphorus product level of 50.99 (mg/dL)2 during the acute phase and 50.70 (mg/dL)2 during the chronic phase.

Renagel® demonstrated less over-suppression of iPTH than calcium, where, as displayed by the median serum iPTH levels at the end of acute (Renagel®, 198.00 pg/mL; calcium, 112.00 pg/mL) and chronic phases (Renagel®, 215.00 pg/mL; calcium, 128.00 pg/mL), greater than 50% of calcium patients demonstrated over-suppression of iPTH. There was a statistically significantly greater proportion of iPTH response (defined as iPTH between 150 pg/mL and 300 pg/mL inclusive) in the Renagel® group during the acute phase (Renagel®, 36%; calcium, 20%; $p = 0.0442$). Although there was a greater proportion of iPTH response in the Renagel® group (37%) than in the calcium group (25%) at the end of the chronic phase, this difference was not statistically significant ($p = 0.1178$).

The frequency of patients who achieved optimal outcome, defined as serum phosphorus $\leq$ 5.0 mg/dL (1.61 mmol/L), serum calcium levels (adjusted for albumin) < 10.5 mg/dL (2.63 mmol/L) during the acute phase and serum phosphorus $\leq$ 5.0 mg/dL (1.61 mmol/L), serum calcium levels (adjusted for albumin) < 10.5 mg/dL (2.63 mmol/L), and serum iPTH between 150 and 300 pg/mL, inclusive during the chronic phase, was comparable between Renagel® and calcium groups during the acute (Renagel®, 74%; calcium 76%; $p = 0.8688$) and chronic (Renagel®, 46%; calcium, 41%; $p = 0.5231$) phases.

The number of patients who had their binder dose adjusted overall was similar between the Renagel® and calcium groups in both the acute ($p = 0.9178$) and chronic phases ($p = 0.2896$). A statistically significantly greater proportion of patients in the calcium group required binder dose adjustments due to hypercalcemia during the chronic phase (Renagel®, 0%; calcium, 23.4%; $p < 0.0001$).

There were no statistically significant differences between Renagel® and calcium in the number of patients with iPTH greater than 300 pg/mL who started or increased vitamin D during the chronic phase.

Renagel® patients attained mean total cholesterol (TC) levels of 146.81 mg/dL during the acute phase and 140.64 mg/dL during the chronic phase. These levels corresponded to statistically significant ($p < 0.0001$) percent decreases from Day 0 of 18.97 mg/dL and 19.10 mg/dL, respectively. These decreases were also statistically significantly ($p < 0.0001$) greater than decreases in the calcium group at the end of the acute and chronic phases. Renagel® patients achieved mean low-density lipoprotein cholesterol (LDL-C) levels of 69.71 mg/dL during the acute phase and 63.97 mg/dL during the chronic phase. These levels corresponded to statistically significant ($p < 0.0001$) percent decreases from Day 0 of 31.83 mg/dL and 36.56 mg/dL, respectively. These decreases were also statistically significantly ($p < 0.0001$) greater than decreases in the calcium group at the end of the acute and chronic phases. There were no statistically significant differences observed between treatment groups in the percent change of HDL cholesterol (HDL-C) or triglycerides (TG) at the end of the acute or chronic phases.

Patients in the Renagel® group had a statistically significantly greater mean increase in iron binding capacity (IBC) than patients in the calcium group at the end of the acute phase (Renagel®, 21.14 mcg/dL; calcium, 10.41 mcg/dL; p = 0.0037). At the end of the chronic phase, there was a 1.8 mcg/dL mean increase in IBC for patients in the Renagel® group and a 21.0 mcg/dL mean decrease in IBC for patients in the calcium group. This treatment group difference was statistically significant (p = 0.0030).

In the Renagel® group, there were statistically significantly greater mean increases in the osteoblast markers osteocalcin (Renagel®, 58.86 ng/mL; calcium, 15.80 ng/mL; p = 0.0003) and BSAP (Renagel®, 20.39 U/L; calcium, 6.81 U/L; p < 0.0001) at the end of the chronic phase.

Overall, patients in the Renagel® group had a median change of 0.00 in coronary artery calcification by Agatston score from Week 0 to 52, while patients in the calcium group had a median increase of 36.55. This difference was statistically significant in favor of the Renagel® group (p = 0.0398). Similar results were observed from Week 0 to 26 where patients in the Renagel® group had a median change of 0.00 in coronary artery calcification by Agatston score, while patients in the calcium group had a median increase of 55.70 (p = 0.0022). Overall, patients in the Renagel® group had a median change of 0.00 in aortic calcification by Agatston score from Week 0 to 52, while patients in the calcium group had a median increase of 75.05. This difference was statistically significant in favor of the Renagel® group (p = 0.0104). Similar results were observed from Week 0 to 26 where patients in the Renagel® group had a median change of 0.00 in aortic calcification by Agatston score, while patients in the calcium group had a median increase of 10.80 (p = 0.0298). In the coronary arteries among patients with a calcification score of at least 30 at baseline, patients in the Renagel® group had a median increase of 5.77% by Agatston score from Week 0 to 52, while patients in the calcium group had a median increase of 25.38%. This difference was statistically significant in favor of the Renagel® group (p = 0.0173). Similar results were observed from Week 0 to 26 where patients in the Renagel® group had a median increase of 0.09% by Agatston score, while patients in the calcium group had a median increase of 14.33% (p = 0.0120). Similar results were observed for the volume score. In the aorta among patients with a calcification score of at least 30 at baseline, patients in the Renagel® group had a median increase of 4.60% by Agatston score from Week 0 to 52, while patients in the calcium group had a median increase of 28.36%. This difference was statistically significant in favor of the Renagel® group (p = 0.0161). Similar results were observed from Week 0 to 26 where patients in the Renagel® group had a median increase of 0.62% by Agatston score, while patients in the calcium group had a median increase of 23.73% (p = 0.0101). Overall, Renagel® patients had a median weekly change in coronary artery calcification of 0.0 by Agatston score while calcium patients progressed 0.94 weekly (p = 0.0092). A comparable difference was observed in the volume score though it was not statistically significant (p = 0.1119). Overall, Renagel® patients had a median weekly change of 0.00 in aortic calcification by the Agatston score while calcium patients progressed at 1.49 weekly (p = 0.0079). A comparable difference was observed in the volume score though it was not statistically significant (p = 0.1272).

Safety Results

Overall, both Renagel® and calcium were well tolerated. A significantly greater number of calcium patients experienced adverse events of general disorders and administration site conditions (calcium, 55.4%; Renagel®, 37.4%; p = 0.0112), musculoskeletal, connective tissue and bone disorders (calcium, 47.5%; Renagel®, 29.3%; p = 0.0091), and respiratory, thoracic and mediastinal disorders (calcium, 38.6%; Renagel®, 22.2%; p = 0.0141). A statistically significantly greater number of gastrointestinal disorders possibly or probably related to study treatment were observed in the Renagel® group (Renagel®, 37.4%; calcium, 16.8%; p = 0.0014). In the Renagel® group, twice as many EU patients experienced gastrointestinal events that were possibly or probably related to study treatment than US patients (US, 24.1%; EU, 53.5%). Of note, patients in the EU had more gastrointestinal abnormalities at screening than US patients (US, 14%; EU, 38%).

A total of 99 patients experienced one or more serious adverse events (SAEs) during the study (Renagel®, 41; calcium, 58). These events were principally due to general and site administration disorders (Renagel®, 11.1%; calcium 14.9%; p=0.5295), vascular disorders (Renagel®, 8.1%; calcium 13.9%; p=0.2588), cardiovascular disorders (Renagel® 8.1%; calcium, 10.9%; p=0.6310) and infections (Renagel®, 6.1%; calcium, 11.9%; p=0.2163). Six patients in the Renagel® group and five patients in the calcium group died after randomization and treatment. One Renagel® treated patient suffered sudden death, which was deemed possibly related to study treatment at the time of a hospitalization for an intestinal obstruction and intestinal perforation, due to a therapeutic enema. All other deaths and SAEs were considered unrelated to study treatment by the investigator.

Routine biochemical parameters were similar between the treatment groups, with the exception of serum bicarbonate, that was higher in the calcium treated patients (22.1 + 4.4 vs. 19.2 + 4.3) as the calcium salts provide base and Renagel® does not. A statistically greater percentage of patients in the calcium group experienced more cardiac changes, as seen on physical examination, than patients in the Renagel® group (Renagel®, 6.1%; calcium, 15.8%; p = 0.0420). Vital signs were comparable between the treatment groups.

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