Protocol GTC-68-208: A Randomized, Open Label, Parallel Design Study of Sevelamer Hydrochloride (Renagel®) in Chronic Kidney Disease 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 12 sites in the United States.

Studied Period

First patient entered: 15 October 2002
Last patient completed: 9 September 2003

Phase of Development

Phase 2

Objectives

The primary objectives of this study were to determine the effect of sevelamer hydrochloride on serum intact parathyroid hormone (iPTH) and low-density lipoprotein cholesterol (LDL-C) in chronic kidney disease (CKD) patients, and to determine the safety and tolerability of sevelamer hydrochloride in patients with Stage III or Stage IV CKD not requiring dialysis.

The secondary objectives were to determine the effects of sevelamer hydrochloride on markers of bone turnover (serum bone-specific alkaline phosphatase [BSAP], serum N-telopeptide, urine N-telopeptide, and urine deoxypyridinoline), excretion of calcium and phosphorus, urinary proteinuria, serum highly sensitive C-reactive protein (hsCRP), serum 25-hydroxyvaitamin D (vitamin D 25-OH), serum 1,25-dihydroxyvitamin D (vitamin D 1,25-OH), serum glucose, and serum phosphorus in patients with Stage III or Stage IV CKD not requiring dialysis.

Methodology

This was a phase 2, multicenter, randomized, open-label, parallel-design study consisting of three periods: a six-week diet period, a six-week treatment period, and a two-week washout period. **Patients with Stage III or Stage IV CKD not requiring dialysis** entered a six-week low-phosphorus diet period. Following the diet period, eligible patients were randomized to one of three doses [0.4 g three times per day (t.i.d.), 1.6 g t.i.d., or 3.2 g t.i.d.] of Renagel® for a 6-week treatment period after which the patients entered a two-week washout period.

Number of Patients (Planned and Analyzed)

No. Enrolled, Randomized, and Treated: 207/77
No. Completed:66

Diagnosis and Main Criteria for Inclusion

Patients enrolled in the study included men or women 18 years of age or older with Stage III and Stage IV CKD not requiring dialysis. Only patients with hyperparathyroidism following 4 weeks on a low-phosphorus diet were eligible for randomization to Renagel® treatment.

Test Product, Dose, and Mode of Administration

Sevelamer hydrochloride (Renagel®): 400 mg tablets
Sevelamer hydrochloride (Renagel®): 800 mg tablets
Dose groups were randomly assigned (0.4 g t.i.d., 1.6 g t.i.d., or 3.2 g t.i.d)
Administered orally with meals

Duration of Treatment

The Renagel® treatment period was 6 weeks. The total study duration was 14 weeks.

Reference Therapy, Dose and Mode of Administration

Not applicable

CRITERIA FOR EVALUATION
Efficacy

The primary efficacy variables were change and percent change in serum iPTH and LDL-C from baseline to endpoint.

Secondary efficacy variables included change and percent change in serum phosphorus, serum vitamin D 25-OH, serum vitamin D 1,25 OH, serum hsCRP, serum glucose, serum BSAP, serum N-telopeptide, urine N-telopeptide, urine deoxypyridinoline, urinary phosphate, urinary calcium, and urinary protein from baseline to endpoint.

Other efficacy variables included change and percent change in serum calcium (adjusted for albumin), the product of serum calcium (adjusted for albumin) and phosphorus, serum total cholesterol (total-C), serum high-density lipoprotein cholesterol (HDL-C), serum non-high density lipoprotein cholesterol (non-HDL-C), serum triglycerides (TG), and the ratio of urinary protein to urinary creatinine from baseline to endpoint.

Safety

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

STATISTICAL METHODS
Efficacy

The primary null hypothesis was that there was no difference between the treatment groups in percent change in serum iPTH from baseline to endpoint. For efficacy parameters, summary statistics were calculated for each visit, baseline, endpoint, and change and percent change from baseline to endpoint by treatment group. Changes and percent changes from baseline to endpoint were tested within each treatment group using the Wilcoxon signed-rank test and between treatment groups using the Kruskal-Wallis test.

Safety

Safety was assessed by evaluating the incidence of adverse events and changes in laboratory measurements and vital signs. Adverse events were summarized for each treatment group by system organ class and preferred term using the Medical Dictionary for Regulatory Authorities (MedDRA). The number and percentage of patients with treatment emergent adverse events (adverse events that occurred for the first time on or after the date of first dose of study medication, or first occurred prior to the first dose and worsened in severity during the active treatment period) were tabulated by MedDRA system organ class and preferred term for each treatment group. Treatment group differences in the proportion of patients with treatment emergent adverse events were tested using the Cochran-Armitage trend test for each system organ class and preferred term category. Treatment emergent adverse events by intensity, treatment emergent adverse events possibly or probably related to study medications, and treatment emergent adverse events possibly or probably related to study medication by intensity were analyzed in the same manner.

Safety Laboratory measures were analyzed in the same manner as the efficacy variables. The within-group effect on vital signs was tested using the Wilcoxon signed-rank test, while the between treatment group effect was tested using the Kruskal-Wallis test. Physical examination changes that were considered clinically significant were collected and analyzed as adverse events.

SUMMARY – CONCLUSIONS
Demographics and Renal History

Patients were primarily Caucasian (83%), male (79%), with a mean age of 65 years. The most common primary causes of CKD were diabetes (34%) and hypertension (29%). Twenty-four (31%) patients were categorized as having Stage III CKD (30 mL/min ≤ GFR ≤ 59 mL/min), and 53 (69%) patients were categorized as having Stage IV CKD (15 ≤ GFR < 30 mL/min).

Efficacy

Primary efficacy evaluation: Median serum iPTH levels did not change significantly during the diet period for any individual treatment group. Renagel® treatment resulted in dose-dependent reductions in serum iPTH. For the 0.4 g t.i.d. group, the median decrease in iPTH level was 1.0 pg/mL (0.3%) from a baseline level of 177.0 pg/mL. For the 1.6 g t.i.d. group, the median decrease in iPTH level was 15.0 pg/mL (9.9%) from a baseline level of 174.0 pg/mL. For the 3.2 g t.i.d. group, the median decrease in iPTH level was 87.0 pg/mL (38.1%) from a baseline level of 207.5 pg/mL. Overall treatment differences in median percent change in iPTH from baseline to endpoint were statistically significant ($p<0.0001$). Median serum iPTH levels increased statistically significantly during the washout period for the 1.6 g t.i.d. and 3.2 g t.i.d. groups only.

Renagel® treatment resulted in dose-dependent reductions in LDL-C. For the 0.4 g t.i.d. group, the median decrease in LDL-C level was 10.0 mg/dL (11.2%) from a baseline level of 98.5 mg/dL. For the 1.6 g t.i.d. group, the median decrease in LDL-C level was 28.0 mg/dL (24.3%) from a baseline level of 101.0 mg/dL. For the 3.2 g t.i.d. group, the median decrease in LDL-C level was 40.0 mg/dL (42.2%) from a baseline level of 92.0 mg/dL. Overall treatment differences in median percent change in LDL-C from baseline to endpoint were statistically significant ($p=0.0004$). Median LDL-C levels increased during the washout period for the three treatment groups.

Secondary efficacy evaluation: Median serum phosphorus levels did not change significantly during the diet period for any treatment group. Renagel® treatment resulted in a statistically significant change in serum phosphorus level for the 3.2 g t.i.d. group only. For the 0.4 g t.i.d. group, median serum phosphorus level did not change during the randomized treatment period from a baseline level of 3.7 mg/dL. For the 1.6 g t.i.d. group, the median decrease in serum phosphorus level was 0.1 mg/dL (2.0%) from a baseline level of 3.6 mg/dL. For the 3.2 g t.i.d. group, the median decrease in serum phosphorus level was 0.4 mg/dL (12.5%) from a baseline level of 3.9 mg/dL. Overall treatment differences in median percent change in serum phosphorus from baseline to endpoint were statistically significant ($p=0.0113$). Median serum phosphorus levels increased during the washout period for the three treatment groups.

Median vitamin D 25-OH levels decreased during the diet period for the three treatment groups; the median reductions ranged from 0.5 ng/mL to 3.0 ng/mL. During the treatment period, median vitamin D 25-OH levels decreased further. For the 0.4 g t.i.d. group, the median decrease in vitamin D 25-OH level was 2.0 ng/mL (8.3%) from a baseline level of 16.5 ng/mL. For the 1.6 g t.i.d. group, the median decrease in vitamin D 25-OH level was 2.0 ng/mL (8.5%) from a baseline level of 21.5 ng/mL For the 3.2 g t.i.d. group, the median decrease in vitamin D 25-OH level was 3.0 ng/mL (11.9%) from a baseline level of 17.5 ng/mL. The median change in vitamin D 25-OH from baseline to endpoint was statistically significant for the 0.4 g t.i.d. group and of borderline significance for the 3.2 g t.i.d. group. After the washout period, median vitamin D 25-OH levels did not return to baseline levels for any treatment group. The fall in D 25-OH levels independent of treatment group suggests a seasonal effect as the likely explanation.

Median vitamin D 1,25-OH levels did not change significantly during the diet period for any treatment group. During the treatment period, median vitamin D 1,25-OH levels decreased, but the changes did not appear to be related to dose. For the 0.4 g t.i.d. group, the median decrease in vitamin D 1,25-OH level was 1.0 pg/mL (3.2%) from a baseline level of 24.0 pg/mL. For the 1.6 g t.i.d. group, the median decrease in vitamin D 1,25-OH level was 3.0 pg/mL (11.9%) from a baseline level of 25.0 pg/mL. For the 3.2 g t.i.d. group, the median decrease in vitamin D 1,25-OH level was 3.0 pg/mL (9.1%) from a baseline level of 26.0 pg/mL. The median change in vitamin D 1,25-OH from baseline to endpoint was statistically significant for the 3.2 g t.i.d. group and of borderline significance for the 1.6 g t.i.d. group After the washout period, median vitamin D 1,25-OH levels returned close to baseline levels for the three treatment groups. The change in vitamin D 1,25-OH levels were opposite of the changes in iPTH. PTH is known to stimulate 1α-hydroxylase, the rate limiting step in the production of vitamin D 1,25-OH, likely explaining the observed changes.

Median serum hsCRP levels did not change significantly during the randomized treatment period or washout period for any treatment group.

Median serum glucose levels did not change significantly during the diet period, randomized treatment period, or washout period for any treatment group.

Renagel® treatment resulted in statistically significant changes in median serum BSAP levels for the 1.6 g t.i.d. group and the 3.2 g t.i.d. group. For the 0.4 g t.i.d. group, median serum BSAP level did not change during the randomized treatment period from a baseline level of 30.9 U/L. For the 1.6 g t.i.d. group, the median increase in serum BSAP level was 1.4 U/L (7.1%) from a baseline level of 26.3 U/L. For the 3.2 g t.i.d. group, the median increase in serum BSAP level was 1.4 U/L (6.2%) from a baseline level of 25.2 U/L. Overall treatment differences in median percent change in serum BSAP from baseline to endpoint were not statistically significant (p=0.8844). Median serum BSAP levels decreased during the washout period for the three treatment groups, but the changes were statistically significant for the 1.6 g t.i.d. group and the 3.2 g t.i.d. group only.

Median levels of serum N-telopeptide, urine N-telopeptide, and urine deoxypyridinoline did not change significantly during the randomized treatment period for any treatment group.

Renagel® treatment resulted in reductions in median urinary phosphate levels for the three treatment groups, but the change was statistically significant for the 3.2 g t.i.d. group only. For the 0.4 g t.i.d. group, the median decrease in urinary phosphate level was 4.0 mg/dL (9.0%) from a baseline level of 44.0 mg/dL. For the 1.6 g t.i.d. group, the median decrease in urinary phosphate level was 4.0 mg/dL (14.0%) from a baseline level of 42.0 mg/dL. For the 3.2 g t.i.d. group, the median decrease in urinary phosphate level was 12.0 mg/dL (37.4%) from a baseline level of 41.0 mg/dL. Overall treatment differences in median percent change in urinary phosphate from baseline to endpoint were not statistically significant (p=0.1053). Median urinary phosphate levels increased during the washout period for the three treatment groups; the changes were statistically significant for the 3.2 g t.i.d. group and of borderline significance for the 1.6 g t.i.d. group.

Renagel® treatment did not result in statistically significant changes in median urinary calcium levels for any treatment group. Median urinary calcium levels decreased during the washout period for the three treatment groups, but the change was statistically significant for the 3.2 g t.i.d. group only.

Median urinary protein levels did not change significantly during the diet period, randomized treatment period, or washout period for any treatment group.

Other efficacy evaluation: Median levels of serum calcium did not change significantly during the diet period for any treatment group. Renagel® treatment resulted in a statistically significant reduction in median serum calcium level for the 0.4 g t.i.d. group. For the 0.4 g t.i.d. group, the median decrease in serum calcium level was 0.2 mg/dL (1.6%) from a baseline level of 9.5 mg/dL. Median serum calcium levels did not change significantly during the washout period for any treatment group.

Median levels of the product of serum calcium and phosphorus did not change significantly during the diet period for any treatment group. Renagel® treatment resulted in reductions in median levels of serum calcium × phosphorus, but the change was statistically significant for the 3.2 g t.i.d. group only. Median levels of the product of serum calcium and phosphorus increased during the washout period for the three treatment groups.

Renagel® treatment resulted in dose-dependent reductions in total cholesterol. For the 0.4 g t.i.d. group, the median decrease in total cholesterol level was 15.5 mg/dL (9.1%) from a baseline level of 170.0 mg/dL. For the 1.6 g t.i.d. group, the median decrease in total cholesterol level was 27.0 mg/dL (13.3%) from a baseline level of 172.0 mg/dL. For the 3.2 g t.i.d. group, the median decrease in total cholesterol level was 36.0 mg/dL (22.8%) from a baseline level of 180.0 mg/dL. Overall treatment differences in median percent change in total cholesterol from baseline to endpoint were statistically significant (p=0.0055). Median total cholesterol levels increased during the washout period for the three treatment groups.

Renagel® treatment did not result in statistically significant changes in median HDL-C levels for any treatment group. Median HDL-C levels decreased during the washout period for the three treatment groups.

Renagel® treatment resulted in dose-dependent reductions in non-HDL-C. For the 0.4 g t.i.d. group, the median decrease in non-HDL-C was 15.0 mg/dL (11.9%) from a baseline level of 125.0 mg/dL. For the 1.6 g t.i.d. group, the median decrease in non-HDL-C level was 25.0 mg/dL (15.8%) from a baseline level of 133.0 mg/dL. For the 3.2 g t.i.d. group, the median decrease in non-HDL-C level was 38.0 mg/dL (31.3%) from a baseline level of 130.0 mg/dL. Overall treatment differences in median percent change in non-HDL-C from baseline to endpoint were statistically significant (p=0.0089). Median non-HDL-C levels increased during the washout period for the three treatment groups.

Median triglyceride levels did not change significantly during the randomized treatment period or washout period for any treatment group.

Median ratios of urinary protein to urinary creatinine did not change significantly during the diet period, randomized treatment period, or washout period for any treatment group.

Safety Results

Safety evaluation: During the randomized treatment period, 48 of 77 (62.3%) patients experienced a treatment emergent adverse event (TEAE): 17 (65.4%) for the 0.4 g t.i.d. group, 12 (48.0%) for the 1.6 g t.i.d. group, and 19 (73.1%) for the 3.2 g t.i.d. group. Most of the TEAEs experienced by patients in the 0.4 g t.i.d. group and the 1.6 g t.i.d. group were mild in intensity. Most of the TEAEs experienced by patients in the 3.2 g t.i.d. group were moderate in intensity. The most common treatment emergent adverse events were gastrointestinal disorders. There appeared to be a dose relationship with respect to treatment emergent constipation: 3 (11.5%) patients in the 0.4 g t.i.d. group, 3 (12.0%) patients in the 1.6 g t.i.d. group and 8 (30.8%) patients in the 3.2 g t.i.d. group. However, there appeared to be no dose relationship in the incidence of drug-related constipation, as determined by the investigator: 3 (11.5%) patients in the 0.4 g t.i.d. group, 3 (12.0%) patients in the 1.6 g t.i.d. group, and 3 (11.5%) patients in the 3.2 g t.i.d. group.

During the randomized treatment period, 24 of 77 (31.2%) patients experienced a treatment emergent adverse event considered by the investigator to be related to treatment: 6 (23.1%) patients in the 0.4 t.i.d. group, 8 (32.0%) in the 1.6 g t.i.d. group, and 10 (38.5%) in the 3.2 g t.i.d. group. Drug-related TEAEs included gastrointestinal disorders (19.2% in the 0.4 g t.i.d. group, 32.0% in the 1.6 g t.i.d. group, and 23.1% in the 3.2 g t.i.d. group), metabolism and nutrition disorders (7.7% in the 0.4 g t.i.d. group, 4.0% in the 1.6 g t.i.d. group, and 19.2% in the 3.2 g t.i.d. group), and skin and subcutaneous tissue disorders (4.0% in the 1.6 g t.i.d. group). The most common drug-related TEAE was constipation (11.5% in the 0.4 g t.i.d. group, 12.0% in the 1.6 g t.i.d. group, and 11.5% in the 3.2 g t.i.d. group). The other most frequently experienced drug-related TEAEs were dyspepsia (3.8% in the 0.4 g t.i.d. group, 12.0% in the 1.6 g t.i.d. group, and 3.8% in the 3.2 g t.i.d. group), hypophosphatemia (11.5% in the 3.2 g t.i.d. group), and metabolic acidosis (7.7% in the 0.4 g t.i.d. group and 7.7% in the 3.2 g t.i.d. group). The only drug-related treatment emergent adverse event with a relationship to dose was hypophosphatemia, which occurred in 3 (11.5%) patients in the 3.2 g t.i.d. group.

There were no patient deaths during the study. Eight (8) patients had an SAE during the study: two (7.7%) patients in the 0.4 g t.i.d. group, 2 (8.0%) patients in the 1.6 g t.i.d. group, and 4 (15.4%) patients in the 3.2 g t.i.d. group. None of the SAEs were considered by the investigator to be related to treatment. Most of the SAEs were cardiac or respiratory disorders, consistent with this population of patients with CKD. Two of the SAEs led to patient withdrawal from the study: angina pectoris for a patient in the 1.6 g t.i.d. group and aggravated congestive cardiac failure for a patient in the 3.2 g t.i.d. group. Neither one of which were considered related to treatment.

Ten (13.0%) patients withdrew from the study due to an adverse event: 3 (12.0%) in the 1.6 g t.i.d. group and 7 (26.9%) in the 3.2 g t.i.d. group. Most of the adverse events that led to withdrawal were considered by the investigator to be related to treatment. Most of the adverse events were gastrointestinal disorders. Three patients in the 3.2 g t.i.d. group withdrew from the study due to hypophosphatemia; the condition resolved upon discontinuation of study drug.

Median changes in safety laboratory parameters, vital signs, and physical findings were not clinically significant for any treatment group.

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