GD3-199-301: A Randomized, Parallel, Open-Label Study to Compare Once Per Day Sevelamer Carbonate Powder Dosing with Three Times Per Day Sevelamer Hydrochloride Tablet Dosing in Chronic Kidney Disease Patients on Hemodialysis

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NAME OF SPONSOR/COMPANY

Genzyme Corporation, 500 Kendall Street, Cambridge, Massachusetts, 02142

INVESTIGATORS AND STUDY CENTER(S)

This was a multicenter study conducted at 29 sites in the United States. One additional site screened, but did not randomise any patients.

STUDIED PERIOD

First patient enrolled: 27 January 2006

Last patient completed: 19 March 2007

PHASE OF DEVELOPMENT

Phase 3

OBJECTIVES

Objectives:

Primary objectives:

In chronic kidney disease (CKD) patients on haemodialysis to:

1. Evaluate the efficacy of sevelamer carbonate powder dosed once per day (QD) with the largest meal compared to sevelamer hydrochloride tablets dosed three times per day (TID) with meals on the control of serum phosphorus.

2. Evaluate the safety and tolerability of sevelamer carbonate powder dosed QD with the largest meal compared with sevelamer hydrochloride tablets dosed TID with meals.

Secondary objectives:

In CKD patients on haemodialysis, to evaluate the effects of sevelamer carbonate powder dosed QD with the largest meal to sevelamer

hydrochloride dosed TID with meals on the following:

1. Serum calcium (adjusted for albumin)-phosphorus product.

2. Serum lipids (total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol).

METHODOLOGY

This was a randomised, parallel, open-label study in CKD patients on haemodialysis. The study consisted of three periods: a two-week screening period, a two-week phosphate binder washout period, and a 24-week randomised treatment period.

Eligible patients entered a two-week phosphate binder washout period starting at Week -2.

At Week 0, eligibility was assessed again. Patients whose serum intact parathyroid hormone (iPTH) was ≤ 800 pg/mL (800 ng/L) at screening and whose serum phosphorus was > 5.5 mg/dL (> 1.78 mmol/L) following washout (Week 0) were randomised (stratified by screening iPTH ≤ 400 or > 400 pg/mL [≤ 400 or > 400 ng/L] and presence or absence of cinacalcet treatment at Week 0) to one of two treatment groups in a 2:1 fashion:

1. sevelamer carbonate powder dosed QD with the largest meal or

2. sevelamer hydrochloride tablets dosed TID with meals.

During the 24-week randomised treatment period, patients were required to return for a study visit every two weeks for the first eight weeks on treatment (Weeks 2, 4, 6, and 8) and every four weeks thereafter (Weeks 12, 16, 20 and 24).

The starting dose of the study treatment was 4.8 g daily for both treatment groups. The study treatment dose was to be titrated up or down in increments of 2.4 g daily (i.e. one 2.4 g powder sachet QD or one 800 mg tablet TID) at each visit to reach a target serum phosphorus ≥ 3.5 and ≤ 5.5 mg/dL (≥1.13 and ≤ 1.78 mmol/L). Therapy for hyperparathyroidism was to be started, stopped, or titrated every four weeks to reach a target serum iPTH of ≥150 and ≤ 300 pg/mL (≥ 150 and ≤ 300 ng/L). Cinacalcet was to be initiated or the dose increased if the PTH and calcium-phosphorus product remained above target levels after maximum titration of vitamin D and phosphate binding therapy. At Week 24 or early termination (ET) study treatment was stopped, and patients returned to their usual phosphate binder(s).

Adverse events (AEs) and concomitant medications were collected from the time of obtaining informed consent and through the end of the study. Serious adverse events (SAEs) were collected during this time and for 30 days following study treatment or study termination.

Number of Patients (planned and TREATED):

Number randomized (planned): 207

Number randomized/treated: 217/213

Number completed: 155

NUMBER OF PATIENTS (ANALYZED):

Number in Full Analysis Set (FAS): 213

Number in Per Protocol Set (PPS): 148

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Men or women 18 years of age or older, on a stable haemodialysis regimen three times per week for three months or longer, taking a phosphate binder(s) and had a serum phosphorus measurement > 5.5 mg/dL (> 1.78 mmol/L) at randomisation (Week 0) and a most recent serum iPTH measurement ≤ 800 pg/mL (≤ 800 ng/L).

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION

sevelamer carbonate powder for oral suspension, 2.4 g sachets

The starting dose for patients randomised to sevelamer carbonate powder was 4.8 g daily (two 2.4 g sachets with the largest meal). The dose was to be titrated up or down in increments of 2.4 g daily as needed to reach a target serum phosphorus level of ≥ 3.5 and ≤ 5.5 mg/dL (≥ 1.13 and ≤ 1.78 mmol/L).

DURATION OF TREATMENT

24 weeks

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION

sevelamer hydrochloride tablets, 800 mg tablets for oral administration

The starting dose for patients randomised to sevelamer hydrochloride tablets was 4.8 g daily (two 800 mg tablets with each meal). The dose was to be titrated up or down in increments of 2.4 g daily as needed to reach a target serum phosphorus level of ≥ 3.5 and ≤ 5.5 mg/dL (≥ 1.13 and ≤ 1.78 mmol/L).

CRITERIA FOR EVALUATION
Efficacy:

The treatment groups were compared on the basis of the change in serum phosphorus from baseline (Week 0) to Week 24/Early Termination (ET). The treatment groups were also compared with respect to the time weighted average of serum phosphorus, the percentage of serum phosphorus responders at Week 24/ET, and the change in calcium (adjusted for albumin)-phosphorus product and serum lipids from baseline to Week 24/ET.

Safety:

Safety was evaluated on the basis of AEs (reported and/or observed), changes in clinical laboratory evaluations and vital signs. Clinically significant changes in physical examination were recorded and evaluated as AEs.

STATISTICAL METHODS

SAFETY:
Adverse events were classified using the standardized Medical Dictionary for Regulatory Activities (MedDRA) version 9.1. The number of events as well as the number and percentage of patients in each treatment group experiencing

pre-treatment AEs and SAEs was summarised for any event, by System Organ Class (SOC) and by preferred term. The number of events as well as the number and percentage of patients in each treatment group experiencing treatment-emergent AEs, treatment-related events and SAEs was also summarised for any event, by SOC and by preferred term. Adverse events were also summarised by severity, in which a patient's most severe event within a category (e.g. SOC, preferred term) was counted. No statistical testing of the AE data was conducted.

Changes in laboratory values and vital signs were assessed using the Wilcoxon signed rank tests to compare the within treatment group changes and Wilcoxon rank sum tests to compare the between treatment group differences.

EFFICACY:
The primary efficacy analysis was an assessment of non-inferiority with respect to change from baseline in serum phosphorus levels at Week 24/ET among the PPS. Specifically, a two-sided 95% confidence interval was estimated for the difference in mean serum phosphorus change between treatment groups (diff = sevelamer carbonate powder QD – sevelamer hydrochloride tablets TID). If the upper confidence bound (one sided 97.5% upper confidence bound) was less than 1 mg/dL (0.32 mmol/L), then non-inferiority was to be concluded. A FAS analysis was performed as a confirmatory analysis.

The secondary efficacy analyses included the time-weighted average in serum phosphorus (excluding first month of treatment), the percentage of serum phosphorus responders at Week 24/ET, and the change from baseline to Week 24/ET in serum calcium-phosphorus product and serum lipids. Time-weighted average of serum phosphorus was summarised for the PPS and the FAS. Wilcoxon rank sum tests were used to compare the time weighted average in serum phosphorus of the two treatment groups. Percent responders [serum phosphorus between 3.5 and 5.5 mg/dL (1.13 and ≤ 1.78 mmol/L), inclusive] were summarised for the PPS and the FAS at each assessment timepoint. Fisher's exact test was used to compare the two treatment groups. The change from baseline to Week 24/ET in serum calcium (albumin-adjusted)-phosphorus product and serum lipids was analyzed for the PPS and FAS. The Wilcoxon signed rank test was used to assess the within treatment group changes, while the Wilcoxon rank sum test was used to assess the between treatment group differences.

SUMMARY / CONCLUSIONS

Demographics and Renal History

The average age was 58 years, ranging from 20 to 85 years. Sixty-one percent of the patients were male and 39% were female. Fifty-four percent of the patients were African American, 43% were white, and 3% were "Other". The most common primary causes of CKD were diabetes (38%), hypertension (31%), and other (20%).

Efficacy

In the PPS, the mean serum phosphorus at baseline after two weeks of washout was 7.3 ± 1.3 mg/dL (2.36 ± 0.43 mmol/L) for the sevelamer carbonate powder QD group and 7.6 ± 1.3 mg/dL (2.45 ± 0.41 mmol/L) for the sevelamer hydrochloride tablet TID group. At Week 24/ET, the mean serum phosphorus was 5.3 ± 1.4 mg/dL (1.71 ± 0.45 mmol/L) for the sevelamer carbonate powder QD group and 4.6 ± 1.0 mg/dL (1.50 ± 0.32 mmol/L) for the sevelamer hydrochloride tablet TID group, which represented statistically significant changes ($p < 0.001$) from baseline of -2.0 ± 1.8 mg/dL (-0.66 ± 0.57 mmol/L) and -2.9 ± 1.3 mg/dL (-0.96 ± 0.42 mmol/L) for the sevelamer

carbonate powder QD and sevelamer hydrochloride tablet TID groups, respectively. The upper confidence bound was 1.50 mg/dL (0.48 mmol/L); therefore non-inferiority of sevelamer carbonate powder QD compared to sevelamer hydrochloride tablets TID based on a pre-specified non-inferiority margin of 1 mg/dL (0.32 mmol/L) was not demonstrated. The FAS results were similar, thus confirming these findings.

In the PPS, the mean time weighted serum phosphorus was 5.3 ± 0.9 mg/dL (1.70 ± 0.30 mmol/L) for the sevelamer carbonate powder QD group and 4.9 ± 0.7 mg/dL (1.59 ± 0.24 mmol/L) for the sevelamer hydrochloride tablet TID group. The time weighted average was significantly different between treatment groups (p=0.021).

At Week 24/ET, the difference in percentage of serum phosphorus responders (73%) in the sevelamer hydrochloride tablets TID group compared with the sevelamer carbonate powder QD group (56%) approached statistical significance (p=0.052).

There were statistically significant reductions from baseline in serum calcium-phosphorus product in both the sevelamer carbonate powder QD group [-15.7 mg^2/dL^2 (-1.27 ± 1.25 $mmol^2/L^2$), p<0.001] and the sevelamer hydrochloride tablet TID group [-21.0 mg^2/dL^2 (-1.70 ± 1.30 $mmol^2/L^2$), p<0.001]. The decrease in serum calcium-phosphorus product was significantly greater with sevelamer hydrochloride tablet TID treatment (p=0.008).

There were statistically significant reductions from baseline in serum total, LDL and non-HDL-cholesterol in both the sevelamer carbonate powder QD group [-15.9 mg/dL (-0.41 mmol/L) or -8.7%, -17.2 mg/dL (-0.45 mmol/L) or -19.1% and -16.9 mg/dL (-0.43 mmol/L) or -12.7% for total, LDL and non-HDL cholesterol, respectively; all p-values <0.001] and the sevelamer hydrochloride tablet TID group -33.3 mg/dL (-0.88 mmol/L) or -20.7%, -33.2 mg/dL (-0.86 mmol/L) or -39.1%, and -34.0 mg/dL (-0.90 mmol/L) or -29.4% for total, LDL, and non-LDL cholesterol, respectively; all p-values <0.001]. The decrease in serum total, LDL and non-HDL cholesterol was significantly greater with sevelamer hydrochloride tablet TID treatment (p<0.001 for total, LDL and non-HDL-cholesterol).

Safety Results:

In the Safety Set, the mean actual daily dose was 6.2 ± 2.6 g/day of sevelamer carbonate powder QD and 6.7 ± 3.0 g/day of sevelamer hydrochloride tablets TID. In the PPS, the mean actual daily dose was 6.9 ± 2.7 g/day of sevelamer carbonate powder QD and 7.3 ± 3.0 g/day of sevelamer hydrochloride tablets TID.

Adverse experiences

The overall percent of patients with treatment emergent AEs was similar between treatment groups with 723 AEs in 124 (87.9%) sevelamer carbonate powder QD patients and 430 AEs in 66 (91.7%) sevelamer hydrochloride tablet TID patients. In both treatment groups, the highest frequency of treatment emergent AEs occurred in the MedDRA SOC of Gastrointestinal Disorders with 147 AEs in 66 (46.8%) sevelamer carbonate powder QD patients and 75 AEs in 35 (48.6%) sevelamer hydrochloride tablet TID patients.

The most frequently occurring treatment emergent AEs (>15% patients) were (by MedDRA preferred term): nausea (37 events in 30 [21.3%] sevelamer carbonate powder QD patients and 11 events in 8 [11.1%] sevelamer hydrochloride tablet TID patients), diarrhoea (38 events in 25 [17.7%] sevelamer carbonate powder QD patients and 21 events in 13 [18.1%] sevelamer hydrochloride tablet TID patients), vomiting (29 events in 24

[17.0%] sevelamer carbonate powder QD patients and 7 events in 6 [8.3%] sevelamer hydrochloride tablet TID patients), and arteriovenous fistula thrombosis (12 events in 8 [5.7%] sevelamer carbonate patients and 19 events in 13 [18.1%] sevelamer hydrochloride patients).
The majority of treatment-emergent AEs were mild or moderate in intensity. Based on the most severe occurrence of a particular treatment emergent AE, 22 (15.6%) sevelamer carbonate powder QD patients and 19 (26.4%) sevelamer hydrochloride tablet TID patients experienced at least one severe AE. The majority of severe treatment emergent events occurred in a single patient each during the randomised treatment period. The majority of severe events in the sevelamer carbonate powder QD group coded to the SOC Infections and Infestations. The majority of severe events in the sevelamer hydrochloride tablet TID group coded to the SOC Vascular Disorders.

Overall, there were a total of 72 treatment-related events in 43 (30.5%) sevelamer carbonate powder QD patients and 26 treatment-related events in 13 (18.1%) sevelamer hydrochloride tablet TID patients. All but two patients experienced treatment-related AEs that were mild or moderate in intensity. Treatment-related AEs were most frequently seen in the SOC of Gastrointestinal Disorders. The most frequently occurring (> 4% patients) treatment-related AEs coding to the SOC of Gastrointestinal Disorders were (by MedDRA preferred term): diarrhoea (17 events in 12 [8.5%] sevelamer carbonate powder QD patients and 5 events in 4 [5.6%] sevelamer hydrochloride tablet TID patients), nausea (18 events in 14 [9.9%] sevelamer carbonate powder QD patients and 4 events in 2 [2.8%] sevelamer hydrochloride tablet TID patients), vomiting (8 events in 8 [5.7%] sevelamer carbonate powder QD patients and 1 event in 1 [1.4%] sevelamer hydrochloride tablet TID patient), and constipation (1 event in 1 [0.7%] sevelamer carbonate powder QD patient and 4 event in 4 [5.6%] sevelamer hydrochloride tablet TID patients). The most frequently occurring (>4% patients) treatment-related AE coding to the SOC General Disorders and Administrative Site Conditions was (by MedDRA preferred term): oral administration complication (6 events in 6 [4.3%] sevelamer carbonate powder QD patients and no events in the sevelamer hydrochloride tablet TID patients).

A total of 5 patients died prior to receiving study treatment. Each of these deaths was reported as not related to the study by the Investigator. A total of 3 (2.1%) sevelamer carbonate powder QD patients and 4 (5.6%) sevelamer hydrochloride tablet TID patients died during the randomised treatment period. All treatment emergent deaths were consistent with the patients' underlying renal disease and comorbidities and were assessed as not related to the study treatment by the Investigators.

There were a total of 85 SAEs in 33 (23.4%) sevelamer carbonate powder QD patients and 72 SAEs in 28 (38.9%) sevelamer hydrochloride tablet TID patients. In general, SAEs coded to similar SOCs during sevelamer carbonate powder QD and sevelamer hydrochloride tablet TID treatment and were consistent with the patients' underlying renal disease and comorbidities. In both treatment groups, the highest frequency of treatment emergent SAEs occurred in the MedDRA SOCs of Infections and Infestations [19 SAEs in 15 (10.6%) sevelamer carbonate powder QD patients and 12 SAEs in 11 (15.3%) sevelamer hydrochloride tablet TID patients] and Cardiac Disorders [17 SAEs in 9 (6.4%) sevelamer carbonate powder QD patients and 16 SAEs in 9 (12.5%) sevelamer hydrochloride tablet TID patients]. The most frequently reported (>4% patients) SAE (by preferred term) were congestive cardiac failure [7 events in 5 (3.5%) sevelamer carbonate powder QD patients and 7 events in 4 (5.6%) sevelamer hydrochloride tablet TID patients], coronary artery disease [1 event in 1 (0.7%) sevelamer carbonate powder QD patient and 3 events in 3 (4.2%) sevelamer hydrochloride tablet TID patients], arteriovenous fistula thrombosis [3 events in 2 (1.4%) sevelamer carbonate powder QD patients and 5 events in 4 (5.6%) sevelamer hydrochloride tablet TID patients] and pneumonia [6 events in 6 (4.3%) sevelamer carbonate powder QD patients and 3 events in 3 (4.2%) sevelamer hydrochloride tablet

TID patients].

One patient experienced an SAE of probable faecal impaction considered possibly related to sevelamer hydrochloride. There were no treatment emergent SAEs assessed by the Investigator as related to sevelamer (carbonate).

A total of 17 (12.0%) sevelamer carbonate powder QD patients and 4 (5.6%) sevelamer hydrochloride tablet TID patients discontinued due to adverse events. In the sevelamer carbonate powder QD group, five patients discontinued due to oral administration complications (bad taste of study drug, gagging when taking study drug), eight patients discontinued due to gastrointestinal disorders (nausea, vomiting, bloatedness, diarrhoea, rectal bleeding), and four patients discontinued for other events (worsening hyperphosphataemia, renal transplant, cerebrovascular accident, and central line infection). All of the oral administration complications and 7 of the 8 gastrointestinal disorders that led to discontinuation during sevelamer carbonate powder QD treatment were classified as related to study treatment by the Investigators. All four patients in the sevelamer hydrochloride group who discontinued did so due to a serious adverse event (cardiac arrest, myocardial infarction, septic shock, intracranial bleed), none of which was classified as related to study treatment by the Investigators.

Laboratory values and vital signs

There was a statistically significant increase (2.4 mEq/L; $p<0.001$) from 97.8 to 100.1 mEq/L in serum chloride in the sevelamer hydrochloride tablet TID group, but no change in the sevelamer carbonate powder QD group (0.5 mEq/L; $p=0.084$). The change in serum chloride was statistically significant between treatment groups ($p=0.001$).

There was a statistically significant decrease in serum carbon dioxide (-1.0 mEq/L; $p<0.008$) from 21.9 to 20.9 mEq/L in the sevelamer hydrochloride tablet TID group but no change in the sevelamer carbonate powder QD group (0.1 mEq/L; $p=0.532$). The change in serum carbon dioxide was statistically significant between treatments groups ($p<0.006$).

There were no clinically significant changes observed for safety laboratory parameters. Additionally, no clinically significant changes in vital signs were observed during the randomised treatment periods.

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