2 SYNOPSIS

NAME OF COMPANY **Genzyme Corporation** **55 Cambridge Parkway** **Cambridge, MA 02142-1234** NAME OF FINISHED PRODUCT **Renagel®** NAME OF ACTIVE INGREDIENT sevelamer hydrochloride	SUMMARY TABLE Referring to Part …… of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

Title of Study:

An Open Label, Randomised, Parallel Design Study to Investigate the Efficacy and Safety of Sevelamer Hydrochloride (Renagel®) Compared with Calcium Acetate in Peritoneal Dialysis Patients

Investigators / Study Centres:

A total of 15 investigators from 17 investigative sites in Belgium (1), Denmark (3), France (1), Italy (2), Spain (2), The Netherlands (1), and United Kingdom (5 and 2 satellite sites) participated in this study.

Publication (reference):

There are no publications based on this study.

Studied Period (first patient enrolled, last patient completed):

The first patient enrolled on 23 December 2004 and the last patient completed on 06 March 2006.

Phase of Development:

Phase 3

Objectives:

Primary Objective(s)

In peritoneal dialysis patients:

- To compare the effects of sevelamer dosed three times per day (TID) and calcium acetate dosed TID on serum phosphorus.
- To investigate the safety and tolerability of sevelamer.

Secondary Objective(s)

In peritoneal dialysis patients to compare the effects of sevelamer TID and calcium acetate TID on:

- Serum calcium-phosphorus product ($CaxPO_4$).
- Serum lipids (total cholesterol, LDL cholesterol, non-HDL cholesterol, HDL cholesterol and triglycerides).
- A number of plasma biomarkers: random blood glucose, glycosylated haemoglobin (HbA1C), bone specific alkaline phosphatase (BSAP), uric acid, and C-reactive protein (CRP).

Methodology:

This was an open label, randomised, parallel design study. Following a two-week phosphate binder wash-out period, eligible patients were randomised to sevelamer hydrochloride TID or calcium acetate TID in a 2:1 fashion stratified according to centre and whether or not the patient was anuric. The treatment period consisted of 12 weeks of therapy with study medication. There was a one-week wash-out period following the active treatment period before patients were returned to treatment with their

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usual phosphate binder.

Number of Patients (planned and analysed):

A total of 150 patients were planned for randomisation, and 253 patients were screened. A total of 143 patients were randomised in a 2:1 fashion to study treatment and were included in the safety analyses: 97 patients received sevelamer hydrochloride (sevelamer group) and 46 patients received calcium acetate (calcium group). The primary analysis was based on the Per Protocol (PP) Set which included 72 patients (74%) patients in the sevelamer group and 31 patients (67%) in the calcium group.

Diagnosis and Main Criteria for Inclusion/Exclusion:

This study enrolled chronic kidney disease (CKD) patients who had received peritoneal dialysis (CAPD, APD, or CCPD) for 8 weeks or longer and who had a serum phosphorus level >5.50 mg/dL (1.77 mmol/L) after 2 weeks washout from their usual phosphate binder.

Test Product, Dose, and Mode of Administration; Batch Number:

Sevelamer hydrochloride was supplied as 800-mg Renagel® tablets. The 800-mg tablets contain 800 mg of sevelamer hydrochloride on an anhydrous base, 3.2 mg of colloidal silicon dioxide, and 3.2 mg of stearic acid. Study drug was supplied in bottles of 180 tablets.

According to randomisation, patients were initiated on sevelamer 2 x 800 mg tablets TID taken with each meal. The dose of study medication was titrated as needed at each visit to achieve target serum phosphorus concentrations <5.50 mg/dL (1.77 mmol/L). The dose escalations were by 3 tablets per day (1 tablet TID). If the serum phosphorus level fell below 3.0 mg/dL (0.96 mmol/L), the dose of study medication was to be reduced by 3 tablets per day.

Batch numbers: [redacted]

Reference Therapy, Dose and Mode of Administration; Batch Number:

Calcium acetate was provided as tablets containing 538 mg calcium acetate, 33.5 mg of starch, 24.8 mg of lactose, 6.7 mg magnesium stearate and 67 mg of microcrystalline cellulose (Pinewood Laboratories, Ireland). Calcium acetate was supplied in tubs of 100 tablets.

According to randomisation, patients were initiated on calcium acetate 3 x 538 mg tablets TID taken with each meal. The dose of study medication was titrated at each visit to achieve target serum phosphorus concentrations <5.50 mg/dL (1.77 mmol/L). The dose escalations were by 3 tablets per day (1 tablet TID). If the serum phosphorus level fell below 3.0 mg/dL (0.96 mmol/L), the dose of study medication was to be reduced by 3 tablets per day.

Batch numbers: [redacted]

Duration of Treatment:

The study included a 2-week phosphate binder washout period, a 12-week randomised treatment period and a 1-week follow-up period. The total study duration was 15 weeks.

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Criteria for Evaluation:

Safety: Safety analyses were performed on all patients who received study medication.
Safety endpoints included the incidence of adverse events (AEs) and serious adverse events (SAEs), vital signs (blood pressure, and heart rate and respiratory rate), the number of hypercalcaemic episodes, and the changes in clinical laboratory evaluations.

Efficacy: The primary efficacy endpoint was the change in serum phosphorus level from the end of washout (baseline) to Week 12/Final. Secondary efficacy endpoints included the change from baseline to Week 12/Final for the following endpoints: serum $CaxPO_4$ product, total cholesterol, LDL cholesterol, non-HDL cholesterol, HDL cholesterol, triglycerides, CRP, BSAP, random blood glucose, HbA1C, and uric acid. The primary and secondary efficacy comparisons were between sevelamer TID and calcium acetate TID.

Statistical Methods:

All data collected in this study were documented using summary tables and patient data listings. Computations for all results were performed using SAS® computer software package. Categorical variables were summarised by frequencies and percentages. Continuous variables were summarised by the number of non-missing observations of patients, mean, standard deviation, median, minimum and maximum values.
The primary efficacy analysis was an assessment of non-inferiority with respect to change from baseline in serum phosphorus levels at Week 12/Final among the Per-Protocol Set. A Full Analysis Set (FAS) analysis was performed as a confirmatory analysis. Specifically, a one-sided 97.5% upper confidence bound was estimated for the difference in serum phosphorus change between treatment groups (difference = sevelamer - calcium). If this confidence bound was less than 0.94 mg/dL (0.3 mmol/L), then non-inferiority was concluded. If non-inferiority was established and this confidence bound is less than 0 mmol/L, then superiority would be concluded.
The change from baseline at Week 12/Final in the following parameters was analysed: total cholesterol, non-HDL cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, calcium-phosphorus product, and plasma biomarkers (CRP, uric acid, BSAP, HbA1C, random blood glucose). For secondary endpoints, comparisons between treatment groups were assessed using a two-sided Wilcoxon rank sum test and changes within treatment groups was assessed using Wilcoxon sign rank test. All these analyses were tested at the alpha = 0.05 (2-tailed) level of significance unless otherwise specified. P-values <0.05 were considered statistically significant.
All treatment emergent AEs and those related to study treatment were summarised and tabulated by treatment group for each system organ class and preferred term, both overall and by severity. The incidence of treatment emergent AEs were compared between treatment groups using Fisher's exact test.

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Treatment emergent SAEs were also tabulated. Vital signs (temperature, weight, heart rate, respiratory rate, and systolic and diastolic blood pressure) at baseline and Week 12, as well as the change from baseline to Week 12, were summarised by treatment group and compared between treatment groups using the Wilcoxon rank sum test. Within treatment group changes were assessed using Wilcoxon signed rank tests.

Change from baseline to Week 12/final for safety laboratory data was compared between treatment groups using the Wilcoxon rank sum test. Within treatment group changes were assessed using Wilcoxon signed rank tests. The incidence of hypercalcaemic events (serum calcium (albumin-adjusted) ≥11.0 mg/dL) were tabulated over time by treatment group. The proportion of patients with any hypercalcaemic events during study treatment were compared between treatment groups using Fisher's exact test.

Summary – Conclusions

Of the 143 patients in the Safety Set (93 male; 50 female) the mean age was 54.4 years (range 19 to 91 years). Most patients were Caucasian (90%) with Blacks (2%), Asians (5%), and Others (3%) comprising the remaining population. A small portion of the patients (10%) were smokers, 22% of the patients had diabetes, and 84% of the patients reported hypertension at baseline. There were no differences with regard to these baseline characteristics between the two treatment groups.

Renal and medical histories were similar for both treatment groups. The most common primary causes of chronic kidney renal disease were unspecified other causes (32%), glomerulonephritis (20%), diabetes (18%), and polycystic kidneys (13%). The median time that patients had been on peritoneal dialysis before the start of the study was 14.4 months (range 1.9 to 255.3 months).

Overall usage of prior and new/changed concomitant medications was similar for the treatment groups with the exception of vitamin D which was started or changed during the study in a greater percentage of sevelamer patients. All patients were on a phosphate-binder before study entry with calcium carbonate or calcium acetate being used by the majority (62%) of patients.

In the FAS, median percentage compliance during the treatment period was comparable between the treatment groups (91.9% for sevelamer and 88.0% for calcium). The mean daily prescribed dose of study medication at start of study was 4.8 g for the sevelamer group and 4.8 g for the calcium group. The mean prescribed daily dose increased in both groups during the study to reach 6.9 g in the sevelamer group and 5.3 g in the calcium group at the end of treatment. The mean actual daily dose was 5.9 g for sevelamer and 4.3 g for calcium.

Safety:

A total of 317 treatment-emergent AEs occurred in 108 (75.5%) patients during the randomised treatment period. A similar percentage of patients experienced treatment emergent AEs in the two

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treatment groups: 75 (77.3%) of patients in the sevelamer treatment group (n=97) experienced 240 AEs; 33 patients (71.7%) in the calcium treatment group (n=46) experienced 77 treatment emergent AEs. The highest frequency of treatment emergent AEs for both treatment groups occurred in the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) of Gastrointestinal disorders. A statistically significant higher number of patients in the sevelamer group experienced gastrointestinal adverse events (p=0.003). In the sevelamer group, 79 gastrointestinal events occurred in 47 patients (48.5%). The most commonly occurring gastrointestinal events (in >5% patients) in the sevelamer treatment group were (by MedDRA preferred term): dyspepsia [21 events in 17 patients (17.5%)]; peritonitis [11 events in 11 patients (11.3%)]; vomiting [12 events in 11 patients (11.3%)]; diarrhoea [10 events in 7 patients (7.2%)]; nausea [6 events in 6 patients (6.2%)]; and abdominal distension [5 events in 4 patients (4.1%)]. In the calcium group, 17 gastrointestinal events occurred in 10 patients (21.7%). The most commonly occurring gastrointestinal events (in >5% patients) in the calcium treatment group were (by MedDRA preferred term): diarrhoea [5 events in 4 patients (8.7%)] and dyspepsia [4 events in 4 patients (8.7%)]. Events of dyspepsia, vomiting, diarrhoea, nausea and abdominal distension were seen in previous studies with sevelamer and are consistent with the known safety profile of sevelamer.

A majority of treatment emergent adverse events were mild to moderate in intensity. In the sevelamer group, 14 patients (14.4%) experienced a severe AE; in the calcium group, 10 patients (21.7%) experienced a severe AE. Severe adverse events occurring in more than one patient in the sevelamer group include (by MedDRA preferred term): diarrhoea [two patients (2.1%)]; peritonitis [two patients (2.1%)]; chest pain [two patients (2.1%)]; and renal transplant [two patients (2.1%)]. All other severe adverse events in the sevelamer group occurred in a single patient each. Severe adverse events occurring in more than one patient in the calcium group include (by MedDRA preferred term): constipation [two patients (4.3%)]; hypercalcaemia [two patients (4.3%)]; and renal transplant [three patients (6.5%)]. All other severe events in the calcium group occurred in a single patient each.

In the sevelamer group, 80 treatment emergent AEs in 35 (36.1%) patients were considered related (i.e., possible, probable, or definite) to study drug. In the calcium group, 27 treatment emergent AEs in 16 patients (34.8%) were considered related to study drug. A higher percentage of patients on sevelamer experienced treatment related AEs coding to MedDRA SOC GI disorders (p=0.086). The most frequently occurring treatment related adverse events (in >5% patients) in the sevelamer group were (by MedDRA preferred term): dyspepsia [14 events in 12 patients (12.4%)]; diarrhoea [8 events in 5 patients (5.2%)]; and nausea [5 events in 5 patients (5.2%)]. A statistically significant higher number of patients in the calcium group experienced treatment related AEs coding to MedDRA SOC of Investigations (p=0.035). The treatment related AE coding to this MedDRA SOC occurring in more than 5% of patients on calcium was (by MedDRA preferred term) blood calcium increased [4 events in 3

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patients (6.5%)]. Other frequently occurring treatment related adverse events (in >5% patients) in the calcium group were (by MedDRA preferred term): hypercalcaemia [5 events in 5 patients (10.9%)]; dyspepsia [3 events in 3 (6.5%) patients]; and pruritus [3 events in 3 patients (6.5%)]. A majority of treatment related adverse events were mild to moderate in intensity. Two patients (2.1%) on sevelamer experienced 6 severe, treatment related AEs and 3 patients (6.5%) on calcium experienced six severe treatment related AEs. In the sevelamer group, 2 patients (2.1%) experienced severe, treatment related diarrhoea; all other severe, treatment related events occurred in a single patient each. In the calcium group, 2 patients (4.3%) experienced severe treatment related hypercalcaemia; all other severe, treatment related events occurred in a single patient each.

A total of 24 patients (16.8%) experienced 31 serious, treatment emergent AEs: 26 serious adverse events (SAEs) occurred in 19 patients (19.6%) in the sevelamer group, and 5 SAEs occurred in 5 patients (10.9%) in the calcium group. The difference in SAE frequency between the two treatment groups was not statistically significant (p=0.236). No SAEs were assessed as related to study drug by the Investigator. The most frequently occurring treatment-emergent SAE was peritonitis [8 events in 8 patients (8.2%) in the sevelamer group and 2 events in 2 patients (4.3%) on calcium]. Two patients died during the study; both patient deaths were assessed as not related to study drug by the Investigator. One patient in the sevelamer group died of unknown causes 6 weeks after starting study drug. One patient in the calcium group died due to a road traffic accident 11 days after starting study drug.

Thirty patients discontinued the study due to AEs, 17 patients (18%) in the sevelamer group and 13 patients (28%) in the calcium group. The most common AE that led to study discontinuation was renal transplant (4 patients in the sevelamer group; 4 patients in the calcium group; p=0.270).

No clinically significant changes in laboratory parameters occurred during treatment. At Weeks 2, 4, and 12, hypercalcaemia (i.e., albumin-adjusted serum calcium ≥11.0 mg/dL) occurred in a statistically significantly higher number of patients in the calcium group than in the sevelamer group. At Week 12/Final, 8 of the 44 patients (18.2%) in the calcium group had documented hypercalcaemia in comparison with only 2 of the 95 patients (2.1%) in the sevelamer group. Vital sign parameters remained within normal ranges and did not show clinically significant changes over time. Physical exam changes were consistent with patients' kidney disease and peritoneal dialysis status.

Efficacy:

The primary endpoint was analysed in the PP Set. Treatment for 12 weeks with sevelamer hydrochloride (sevelamer) was non-inferior to 12-week treatment with calcium acetate (calcium) in reducing serum phosphorus levels. The mean serum phosphorus content at Baseline was 7.48 mg/dL (2.40 mmol/L) in the sevelamer group and 7.29 mg/dL (2.34 mmol/L) in the calcium group. At Week 12/Final the values were 5.86 mg/dL (1.88 mmol/L) in the sevelamer group and 5.48 mg/dL (1.76 mmol/L) in the calcium

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group, which represented statistically significant changes ($p<0.001$) from Baseline of -1.61 mg/dL (-0.52 mmol/L) and -1.81 mg/dL (-0.58 mmol/L), respectively. The difference in mean change (*difference = sevelamer – calcium*) was 0.197 mg/dL (0.061 mmol/L) with an upper 97.5% confidence bound of 0.741 mg/dL (0.237 mmol/L) thus establishing non-inferiority of sevelamer compared to calcium based on a pre-specified non-inferiority margin of 0.929 mg/dL (0.3 mmol/L). The Full Analysis Set results were comparable.

A sub-group analysis for the primary efficacy endpoint was also performed separately within the anuric and non-anuric strata. These results parallel those seen in the total patient sample.

Both treatments resulted in statistically significant decreases in serum calcium-phosphorus product from baseline to Week 12/Final.

A statistically significant decrease from baseline for total-, LDL-, and non-HDL cholesterol was observed in the sevelamer group, but not the calcium group. No changes occurred for HDL cholesterol in either treatment group. For triglycerides, there was a statistically significant increase in terms of the percentage change from baseline to Week 12/Final in both the sevelamer and calcium groups.

Uric acid showed a statistically significant decrease from baseline to Week 12/Final in the sevelamer group. A statistically significant increase ($p<0.001$) in BSAP was seen during treatment with sevelamer only. There was no within or between treatment group differences in change from baseline to end of study for random blood glucose, CRP, HbA1C.

Albumin-adjusted serum calcium concentration increased in a statistically and clinically significant manner in the calcium group, but not in the sevelamer group. Serum intact parathyroid hormone decreased in a statistically significant manner in the both the sevelamer and calcium groups with no difference in change from baseline between the two groups.

Conclusion:

[redacted]