## 2. SYNOPSIS

| NAME OF COMPANY<br>**Genzyme Europe Research**<br>**310 Cambridge Science Park**<br>**Milton Road, Cambridge, UK,**<br>**CB4 0WG**<br>NAME OF FINISHED PRODUCT<br>**Renvela™**<br>NAME OF ACTIVE INGREDIENT<br>**Sevelamer Carbonate** | SUMMARY TABLE<br>Referring to Part ……<br>of the Dossier:<br><br>Volume:<br><br>Page:<br><br>Reference: | FOR NATIONAL AUTHORITY USE ONLY: |
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**TITLE OF STUDY:**
An Open Label, Dose Titration Study Of Sevelamer Carbonate Tablets Dosed Three Times A Day In Hyperphosphatemic Chronic Kidney Disease Patients Not On Dialysis

**INVESTIGATORS / STUDY CENTRES:**

A total of 25 centres participated in this study; 20 investigative sites in Europe and 5 in Australia. Nineteen of the 25 sites (15 in Europe and 4 in Australia) enrolled patients.

**PUBLICATION (REFERENCE):**

Not Applicable

**STUDIED PERIOD:**

First Patient Enrolled: 14 February, 2006

Last Patient Last Visit: 23 January, 2007

**PHASE OF DEVELOPMENT:** Phase 3

**OBJECTIVES:**

Primary Objectives:

In hyperphosphatemic chronic kidney disease (CKD) patients not on dialysis:

- Evaluate the efficacy of sevelamer carbonate tablets dosed three times a day (TID) with meals in controlling serum phosphorus levels
- Evaluate the safety and tolerability of sevelamer carbonate tablets dosed TID with meals

Secondary Objectives:

In hyperphosphatemic CKD patients not on dialysis, evaluate sevelamer carbonate tablets dosed TID with meals on the following:

- Serum calcium-phosphorus product
- Serum lipid profile (total cholesterol, high density lipoprotein [HDL] cholesterol and low density lipoprotein [LDL] cholesterol)
- Percent responders (serum phosphorus between 2.7 mg/dL and 4.6 mg/dL [0.86 mmol/L and 1.47 mmol/L], inclusive) at Day 56/early termination (ET)

**METHODOLOGY:** This was a Phase 3, multi-centre, open-label, single arm, dose titration study in hyperphosphatemic CKD patients not on dialysis.

The study consisted of four periods: a 2-week screening period, a 2-week washout period, an 8-week treatment period followed by a second 2-week washout period. The initial 2-week washout period was only applicable for those eligible patients taking phosphate binder(s) at screening. Eligible patients who were not taking phosphate binder(s) at screening proceeded directly to the start of the 8-week treatment period.

Informed consent was obtained. At screening, blood samples were obtained from all patients including pregnancy testing for women of childbearing potential. Inclusion/exclusion criteria, medical history and medication history were reviewed, height and weight were measured and a physical examination was

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performed. Patients with a serum phosphorus level > 5.5 mg/dL (1.76 mmol/L) either at screening or after washout, as applicable, and who met all other entry criteria were eligible for study treatment. For purposes of analyses, the screening visit was used as the baseline visit for patients who were not taking phosphate binder(s) at study entry, while Day 0 was used as the baseline for patients taking phosphate binders at study entry.

Patients started treatment with sevelamer carbonate at a dose of 4.8 g daily (2 x 800 mg tablets TID). Blood draws were obtained every 2 weeks for the 8-week treatment period beginning at baseline (i.e. Days 0, 14, 28, 42, and 56). The sevelamer carbonate dose was titrated to a maximum dose of 12 g/day (15 x 800 mg tablets) during the treatment period in increments of 2.4 g daily (1 x 800 mg tablet TID) at visits on Days 14, 28, and 42 to attain a target serum phosphorus level ≥ 2.7 mg/dL and ≤ 4.6 mg/dL (≥ 0.86 and ≤ 1.47 mmol/L). At Day 56/ET blood samples were taken, sevelamer carbonate was stopped and patients entered a second washout phase. During the treatment period, patients were supplemented with a daily dose of 400 IU of the native form of vitamin D to minimize the effects of any dietary absorption of vitamin D that may occur during treatment with sevelamer carbonate, this was to be taken at bedtime away from the dose of sevelamer carbonate. This supplement was to be given in addition to any active vitamin D therapy routinely prescribed at the start of the study.

At Day 70, after the second washout period, a final blood sample was obtained and patients were returned to their pre-treatment phosphate binders(s), if applicable.

Adverse events (AEs) and concomitant medications were assessed from the time that informed consent was obtained through to the end of the study (Day 70). Any serious adverse event (SAE) occurring within 30 days of study completion or termination was also reported.

**NUMBER OF PATIENTS (PLANNED AND ANALYSED):** It was planned that a total of 28 patients would be treated. Recruitment continued until 30 September, 2006 allowing enrolment of additional patients for the purpose of increasing the understanding of the safety profile in the CKD population. Approximately 50 to 60 patients were expected to be enrolled by this date. A total of 129 individual patients were screened for this study. Of these, 12 patients were re-screened. Of the screened patients, 49 were dispensed sevelamer carbonate and treated. The Safety Set (49 patients) included all patients who received at least one dose of sevelamer carbonate. The Full Analysis Set (FAS) consisted of 46 patients and the Per-Protocol Set (PPS) consisted of 35 patients.

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**DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:**

**INCLUSION:**

Patients who met all of the following inclusion criteria were eligible to participate in this study:

1. Men or women 18 years of age or older
2. If taking phosphate binder(s), the patient was willing to stop and enter a 2-week washout period
3. Willing to avoid any intentional changes in diet such as fasting or dieting
4. Had the following central laboratory measurements:
   a) If not on a phosphate binder, a serum phosphorus measurement ≥ 5.5 mg/dL (1.76 mmol/L) at screening (Visit 1)
   b) If taking a phosphate binder(s) at screening, a serum phosphorus measurement ≥ 5.5 mg/dL (1.76 mmol/L) after the 2-week washout period at Visit 1a (Day 0)
5. At screening (Visit 1), had the following central laboratory measurements:
   a) 25-hydroxyvitamin D ≥ 10 ng/mL
   b) iPTH ≤ 800 pg/mL
6. Willing and able to take sevelamer carbonate alone as a phosphate binder for the duration of the study
7. Willing and able to maintain screening doses of lipid medication, 1, 25 dihydroxyvitamin D, and/or cinacalcet for the duration of the study, except for safety reasons
8. Willing and able to avoid antacids and phosphate binders containing aluminium, magnesium, calcium or lanthanum for the duration of the study unless prescribed as an evening calcium supplement
9. If the patient was female, and of childbearing potential (pre-menopausal and not surgically sterile), was willing to use an effective contraceptive method throughout the study, which included barrier methods, hormones, or intra-uterine devices
10. Not expecting to initiate dialysis for the duration of this study
11. Considered compliant in using phosphate binders (if applicable)
12. Willing and able to provide informed consent
13. Had not participated in any other investigational drug studies within 30 days prior to enrolment
14. Was of the level of understanding and willingness to cooperate with all visits and procedures, as described by the study personnel

**EXCLUSION:**

Patients who met any of the following exclusion criteria were not eligible for participation in this study:

1. Had active bowel obstruction, dysphagia, swallowing disorder or severe gastrointestinal (GI) motility disorders
2. Active ethanol or drug abuse, excluding tobacco use
3. Using anti-arrhythmic or anti-seizure medications for arrhythmia or seizure disorders
4. In the opinion of the investigator, the patient had poorly controlled diabetes mellitus or hypertension; active vasculitis; HIV infection; or any clinically significant unstable medical condition
5. Was pregnant or breast-feeding
6. Had evidence of active malignancy, except for skin basal cell carcinoma
7. Was unable to comply with the requirements of the study
8. Had known hypersensitivity to sevelamer or any constituents of the study drug
9. Had any other condition, which in the opinion of the investigator would prohibit the patient's inclusion in the study

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**TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION; BATCH NUMBER:**

Sevelamer carbonate tablets: one to five 800 mg tablets taken orally TID with the meals as directed by the physician, titrated to reach a target of serum phosphorus ≥ 2.7 mg/dL and ≤ 4.6 mg/dL (≥ 0.86 mmol/L and ≤ 1.47 mmol/L). Patients started treatment with sevelamer carbonate at a dose of 4.8 g daily (2 x 800 mg tablets TID). Batch numbers: [redacted]

**DURATION OF TREATMENT:**

Patients were treated with sevelamer carbonate for up to 8 weeks.

**REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION; BATCH NUMBER:**

No Reference Therapy.

**CRITERIA FOR EVALUATION:**

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

**Efficacy:** The primary efficacy parameter was the change from baseline in serum phosphorus levels. Change from baseline in levels of serum total, LDL, and HDL cholesterol and levels of serum calcium-phosphorus product were evaluated as secondary efficacy parameters. The percentage of responders at the end of study, defined as the percentage of patients reaching the serum phosphorous target range between 2.7 mg/dL and 4.6 mg/dL (0.86 mmol/L and 1.47 mmol/L), inclusive, was also evaluated as a secondary efficacy parameter.

**STATISTICAL METHODS:**

**Safety:** AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 9.1. All treatment emergent AEs and those related to sevelamer carbonate were summarised and tabulated for each MedDRA System Organ Class (SOC) and Preferred Term, both overall and by severity. For tabulations by severity, only a subject's most severe event within the category (e.g. overall, SOC, or Preferred Term) was counted. Treatment emergent SAEs were also tabulated.

Physical examination findings (including weight) at screening were tabulated.

Vital signs (heart rate, respiratory rate, and systolic and diastolic blood pressure) at baseline and Day 56/ET, as well as the change from baseline to Day 56/ET, were summarised and assessed using Wilcoxon signed rank tests.

Data were summarised for laboratory evaluations performed at each study visit, along with the changes between screening and baseline, baseline and Day 56/ET, and Day 56 and Day 70. Changes were analysed using Wilcoxon signed rank tests.

**Efficacy:** Descriptive statistics (N, mean, median, standard deviation, minimum, maximum, and 95% confidence interval) are presented for serum phosphorus measurements at all study visits and for the changes between screening and baseline, baseline and Day 56/ET, and Day 56 to end of the second washout. A Wilcoxon signed rank test was used to assess the changes.

The proportion of patients attaining serum phosphorus response (serum phosphorus between 2.7 mg/dL and 4.6 mg/dL [0.86 mmol/L and 1.47 mmol/L], inclusive) at each post baseline visit and for Day 56/ET were tabulated including number, percent, and 95% confidence intervals.

Descriptive statistics are presented for serum total cholesterol, LDL cholesterol, HDL cholesterol, and serum calcium-phosphorus product at all study visits and for the changes between screening and baseline, baseline and Day 56/ET, and Day 56 to end of the second washout. A Wilcoxon signed rank test

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was used to assess the changes.

**SUMMARY RESULTS:**

**Demographics and Renal History:** Sixty-five percent of patients were male and 35% of patients were female, with a mean age of 62.0 years. Most patients were Caucasian (45 [92%]), with 1 Black patient (2%), 2 Asian patients (4%) and 1 patient (2%) listed as Other (Indian) comprising the rest of the population. The most common primary causes of chronic kidney disease were "other" (22%), diabetes (18%), glomerulonephritis (16%) and polycystic kidney disease (16%). Sixty-one percent of patients were taking a phosphate binder prior to entry. A total of 35% of the patients were classified as CKD stage 4 (GFR 15-29 mL/minute/1.73m$^2$), with the remaining 65% of the patients being classified CKD stage 5 (GFR <15 mL/minute/1.73m$^2$) according to Kidney Disease Outcomes Quality Initiative definitions.

**Safety Results:** The mean ± SD days on sevelamer carbonate was 51.6 ± 16.8 days. The mean actual daily dose was 5.38 ± 1.69 g. The mean percent compliance was 87.7%.

During the study, 49 patients received sevelamer carbonate and were included in the Safety Set. In total, 137 treatment emergent AEs occurred in 44 patients (89.8%) during the study. The most frequently occurring AEs were coded to the MedDRA SOC Gastrointestinal Disorders (46.9%). Gastrointestinal Disorders occurring in >5% of patients included (by MedDRA Preferred Term): nausea (12 events in 11 [22.4%] patients), constipation (7 events in 6 [12.2%] patients), diarrhoea (8 events in 5 [10.2%] patients), vomiting (6 events in 5 [10.2%] patients) and flatulence (3 events in 3 [6.1%] patients). The majority of AEs were mild to moderate in intensity. Six (12.2%) patients experienced severe events, the majority of which occurred as single events in a single patient, except for lower respiratory tract infection (2 patients) and fluid overload (2 patients).

Eleven (22.4%) patients experienced 19 SAEs. The most frequent SAE by MedDRA Preferred Term was arteriovenous fistula operation (4 events in 4 (8.2%) patients). All 4 arteriovenous fistula operations involved the creation of, or surgery on a dialysis access. No SAEs were judged by the investigator to be related to sevelamer carbonate.

One patient died during the course of this study. The patient, who discontinued the study due to an SAE of pleural effusion, died due to bronchopneumonia approximately 1 month after stopping sevelamer carbonate. Bronchopneumonia with an outcome of death was assessed by the investigator as not related to sevelamer carbonate.

Statistically and clinically significant changes were seen in mean serum bicarbonate levels which increased by 1.3 mEq/L (p=0.005). Statistically significant changes were also seen in the following laboratory parameters from baseline to Day 56/ET: iPTH, creatinine, PT, and eosinophil levels. Of the laboratory changes, only the increase in serum bicarbonate was considered to be of clinical relevance.

Mean values for all vital sign parameters were within the normal range. There were no clinically significant changes in vital signs overall or trends in vital signs changes over time.

**Efficacy Results**: The primary efficacy analysis was the change from baseline in serum phosphorus levels. Mean baseline serum phosphorus levels were 6.2 mg/dL (2.0 mmol/L) for the FAS. The corresponding mean levels at Day 56/ET were 4.8 mg/dL (1.6 mmol/L). The decrease in serum phosphorus values from baseline to Day 56/ET was statistically significant (mean -1.4 mg/dL [-0.5 mmol/L], p value < 0.001).

By the end of study treatment (Day 56/ET), 50% of patients in the FAS reached the titration target level of serum phosphorus ≥ 2.7 and ≤ 4.6 mg/dL (≥ 0.86 mmol/L and ≤ 1.47 mmol/L) following treatment with sevelamer carbonate.

The mean serum calcium (albumin-adjusted)-phosphorus product at baseline was 53.07 mg$^2$/dL$^2$

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(4.3 $mmol^2/L^2$) for the FAS. There was a statistically significant decrease in levels from baseline to Day 56/ET (mean -10.39 $mg^2/dL^2$ [-0.8 $mmol^2/L^2$]), p value < 0.001).

There was a statistically significant decrease in serum levels of total cholesterol and LDL cholesterol levels from baseline to Day 56/ET (both p values < 0.001). There was no clinically meaningful change in serum HDL cholesterol or triglycerides.

**SUMMARY CONCLUSIONS:**

[redacted]