SYNOPSIS

NAME OF COMPANY Genzyme Corporation 500 Kendall Street Cambridge, MA 02142, USA	SUMMARY TABLE Referring to Part …… of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:
NAME OF FINISHED PRODUCT **Renvela®** NAME OF ACTIVE INGREDIENT **sevelamer carbonate**		

TITLE OF STUDY:

A Randomised, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Sevelamer Carbonate Tablets Dosed Three Times a Day in Hyperphosphataemic Chronic Kidney Disease Patients Not on Dialysis

INVESTIGATORS AND STUDY CENTERS:

Investigators at 53 sites in Austria, France, Germany, Greece, Hungary, Italy, Portugal, Spain and Sweden were included in the study. Patients were randomised at only 5 sites.

PUBLICATION (REFERENCE):

Not applicable

STUDIED PERIOD:

First Patient Enrolled: 8 January 2009

Last Patient Completed: 8 September 2009

PHASE OF DEVELOPMENT: Phase 3

OBJECTIVES:

The objectives of this study in hyperphosphataemic Chronic Kidney Disease (CKD) patients not on dialysis were as follows:

Primary objective

to compare the efficacy and safety of sevelamer carbonate and placebo dosed 3 times a day (TID) on serum phosphorous levels.

Secondary objectives

to compare the effects of sevelamer carbonate dosed TID and placebo dosed TID on the following:

- Serum total cholesterol and low density lipoprotein (LDL) cholesterol
- Serum corrected calcium-phosphorous product (CaxP)

Tertiary objectives

to compare the effects of sevelamer carbonate dosed TID and placebo dosed TID on the following: plasma biomarkers including random blood glucose, glycosylated haemoglobin (HbA1C), bone specific alkaline phosphatase (BSAP), uric acid, high sensitivity C-reactive protein (hs CRP), fetuin A, fibroblast growth factor

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METHODOLOGY:

This was a Phase 3, multi-site, randomised, double-blind, placebo-controlled study comparing the efficacy and safety of sevelamer carbonate and placebo tablets dosed TID in hyperphosphataemic CKD patients not on dialysis. The study consisted of 4 periods: Screening Period (up to 2 weeks), Washout Period (14 to 21 days), Titration Period (12 weeks), and Maintenance Period (12 weeks). The 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 12-week Titration Period.

Informed consent was obtained and patients were screened for eligibility. Patients with a serum phosphorus level of ≥4.6 mg/dL (≥1.49 mmol/L) and ≤ 5.5 mg/dL (≤1.76 mmol/L) either at Screening or after Washout, as applicable, and who met all other entry criteria were randomised to receive a starting dose of sevelamer carbonate 4.8 g daily (2 x 800 mg tablets TID) or matching placebo based on a 2:1 block randomisation scheme, stratified by Baseline serum phosphorous ≤5.0 mg/dL versus >5.0 mg/dL (1.61 mmol/L).

During the 12-week Titration Period, patients returned to the study site every 3 weeks. Samples for laboratory measurements were collected at each visit. Investigational Product was titrated in increments of ± 2.4 g daily (± 1 x 800 mg tablet TID) at each study visit to attain a serum phosphorous level of ≥2.5 and ≤4.5 mg/dL (≥0.80 and ≤1.45 mmol/L).

At the end of the 12-week Titration Period patients continued into the 12-week Maintenance Period. During the Maintenance Period, patients returned to the study site every 3 weeks. Samples for laboratory measurements were collected at each visit. Investigational Product was maintained at the last daily dose established at end of the Titration Period (Study Visit 4 [Week 9]). Adjustments to the dosage of Investigational Product during the 12-week Maintenance Period were allowed and were made, as required, in increments of ± 0.8 to 2.4 g daily (± 1 to 3 x 800 mg tablet daily) at each visit to attain a serum phosphorous level of ≥2.5 and ≤4.5 mg/dL (≥0.80 and ≤1.45 mmol/L). The maximum daily dose allowed was 14.4 g (6 x 800 mg TID).

Patients who began haemodialysis or peritoneal dialysis or underwent renal transplantation were to be withdrawn from the study. At the Investigator's discretion, patients who met the following criteria may have been withdrawn for safety reasons:

- Serum phosphorous level >5.5 mg/dL (>1.76 mmol/L) at 2 consecutive visits, after Week 3.
- Serum LDL >150 mg/dL (>3.88 mmol/L) at 2 consecutive visits after Week 3.
- Requiring greater than the protocol-specified maximum daily dose of 14.4 g (6 x 800 mg TID) of Investigational Product at any point.

At Study Visit 9 (Week 24) /Early Termination (ET), Investigational Product was discontinued and the patients returned to their pre-treatment phosphate binder(s) where applicable.

Adverse events (AEs) and concomitant medications were assessed from the time that informed consent was obtained through to the end of the study (Week 24 or ET). Any serious adverse event (SAE) occurring within 30 days of the end of the study (Week 24 or ET) was also collected.

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NUMBER OF PATIENTS (PLANNED AND ANALYZED):

A total of 144 evaluable patients (96 sevelamer carbonate and 48 placebo) were originally planned for this study. Due to difficulty enrolling eligible patients, the study was terminated prematurely by the Sponsor. Therefore, the study was limited to the 27 patients enrolled at the time of study termination. Of these, 19 patients were screen failures and 3 patients were ineligible due to phosphorus levels < 4.6 mg/dL (<1.49 mmol/L) after washout. A total of 5 patients were randomised (2 sevelamer carbonate; 3 placebo). of these, 1 patient completed the study, 1 discontinued due to AEs (diarrhoea and vomiting), 1 discontinued due to other (hyperphosphatemia) and 2 discontinued due to the early termination of the study.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

Inclusion Criteria:

Patients must have met the following criteria to be enrolled in the study:

1. Willing and able to provide written informed consent.
2. Men or women 18 years of age or older.
3. if on phosphate binder(s), willing to stop the phosphate binder and enter a 14-21 day Washout Period.
4. Had been, in the opinion of the Investigator, stable on a phosphate-controlled diet at Screening and willing to avoid any intentional changes, such as fasting or dieting for the duration of the study.
5. Had the following central laboratory measurements:
   - if not taking a phosphate binder at Screening, a serum phosphorous measurement ≥4.6 mg/dL (≥1.49 mmol/L) and ≤5.5 mg/dL (≤1.76 mmol/L) at Screening.
   - if taking a phosphate binder at Screening, a serum phosphorous measurement ≥4.6 mg/dL (≥1.49 mmol/L) and ≤5.5 mg/dL (≤1.76 mmol/L) after the 14-21 day Washout Period; at the Post-Washout Visit.
6. Willing and able to take the Investigational Product as a phosphate binder for the duration of the study.
7. Willing and able to maintain screening doses of lipid-lowering medication for the duration of the study, except for safety reasons.
8. Willing and able to maintain doses of medication for control of hyperparathyroidism from Screening through Week 12, except for safety reasons.
9. 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.
10. Willing, if female and of childbearing potential (pre-menopausal and not surgically sterile), to use an effective contraceptive method throughout study, which includes barrier methods, hormones, or intrauterine device(s).
11. Expecting not to initiate dialysis or have a kidney transplant for the duration of this study.
12. Considered compliant with phosphate binders (if applicable).
13. Had not participated in any other investigational drug studies within 30 days prior to enrolment.
14. Had a level of understanding and willingness to cooperate with all visits and procedures as described by

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the study personnel.

15. Able to be contacted by phone or other remote means in order to be informed of Investigational Product dose changes.

Exclusion Criteria:

Patients were to be excluded from this study if they did not meet the specific inclusion criteria, or if they were/had:

1. Active dysphagia or swallowing disorder or a predisposition to or current bowel obstruction, ileus, or severe gastrointestinal motility disorders including severe constipation.
2. Previous major gastrointestinal tract surgery.
3. in the opinion of the Investigator, active ethanol or drug abuser, excluding tobacco use.
4. Used anti-arrhythmics for arrhythmias or anti-seizure medications for seizures.
5. At Screening, the following central laboratory measurements:
   - Serum 25-hydroxyvitamin D <10 ng/mL (<25 nmol/L),
   - Serum intact parathyroid hormone ≥600 pg/mL (≥66 pmol/L), and
   - Serum LDL >140 mg/dL (>3.59 mmol/L).
6. in the opinion of the Investigator, any clinically significant unstable medical condition, for example: poorly controlled diabetes mellitus, poorly controlled hypertension, active vasculitis, HIV infection.
7. Pregnant or breast-feeding.
8. Evidence of active malignancy except for basal cell carcinoma of the skin.
9. Unable to comply with the requirements of the study.
10. A known hypersensitivity to the Investigational Product or any of its constituents.
11. Any other condition, which in the opinion of the Investigator, would mean participation in the study would not be in the patient's best interest.

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

Sevelamer carbonate: 800 mg tablets to be taken orally with meals TID; Batch Numbers: [redacted]

DURATION OF TREATMENT:

The duration of the study was up to 29 weeks and was divided into 4 periods: Screening Period (up to 2 weeks), Washout Period (14 to 21 days [only for patients on a phosphate binder at Screening]), Titration Period (12 weeks) and Maintenance Period (12 weeks). Serious adverse events were collected for an additional 30 days following the end of the study.

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

Placebo: tablets matching sevelamer carbonate tablets in size, shape, and colour to be taken orally with meals TID; Batch Numbers: [redacted]

CRITERIA FOR EVALUATION:

EFFICACY:

Primary Efficacy Endpoint

The primary efficacy endpoint was serum phosphorous change from Baseline to Week 12/Titration Period Early Termination (TPET).

Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- Phosphorus response during the Titration Period defined as serum phosphorus ≤4.5 mg/dL (≤1.45 mmol/L) at any time point up to and including Week 12/TPET.
- Phosphorous response during the Maintenance Period defined as the time-weighted average of serum phosphorous from Week 12 to Week 24/ET being ≤4.5 mg/dL (≤1.45 mmol/L).
- Serum phosphorus time-weighted average during the Maintenance Period.
- Change from Baseline to Week 12/TPET and time-weighted average during the Maintenance Period for the following analytes:
    - Serum total cholesterol
    - Serum LDL cholesterol
    - Serum corrected calcium-phosphorus product

Tertiary Efficacy Endpoints

Additional Tertiary efficacy parameters:

- Change from Baseline to Week 12/TPET and/or from Baseline to Week 24/ET for plasma biomarkers including:
    - random blood glucose
    - HbA1C
    - BSAP
    - uric acid
    - hs CRP
    - Fetuin A
    - FGF 23
    - Cystatin C

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SAFETY:

Safety endpoints included:

- Frequency of AEs including clinically significant changes in physical examination.
- Change from Baseline in Vital signs (blood pressure, heart rate, respiratory rate and temperature).
- Changes from Baseline in serum chemistry, haematology, lipid profile, 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D, clotting profile, liver function tests, and intact parathyroid hormone levels.

STATISTICAL METHODS:

As a consequence of the small number of patients enrolled at the time of study termination, no statistical analysis or comparison between treatment groups could be performed for any endpoint. No summary tables were created and no statistics were calculated due to the small number of patients. Instead, the raw data for all randomised patients was assessed on an individual patient basis.

SUMMARY – CONCLUSIONS

A total of 5 patients were randomised in the study. Of these, 3 patients were randomized to placebo and 2 patients to sevelamer carbonate. All 5 randomised patients were white and 4 of the 5 were male.
The ages of the patients ranged from 41 to 73 years of age.

EFFICACY:

Not applicable.

SAFETY:

There were no SAEs during the study. Four (80%) of the 5 randomised patients experienced 7 AEs. There were 2 events in 1 patient who received sevelamer carbonate and 5 events in 3 patients who received placebo. All events were mild or moderate in intensity. One patient who was randomised to placebo, experienced diarrhoea and vomiting assessed as definitely related to the Investigational Product by the Investigator. These events resulted in the discontinuation of this patient from the study. One patient who was randomised to sevelamer carbonate, experienced nausea and vomiting assessed as probably related to the Investigational Product by the Investigator. in addition, 2 patients, who were not eligible for randomisation and did not receive Investigational Product, experienced 2 AEs. Both events were assessed as mild in intensity and not related or remote/unlikely related by the Investigator. Overall, AEs occurring during the study were consistent with the patients' underlying renal disease, and the current sevelamer carbonate labelling.

Given that this study investigated patients with chronic renal disease, the numerous laboratory values outside the normal ranges were consistent with the patients' underlying renal disease. One patient had serum phosphorous levels >5.5 mg/dL (>1.76 mmol/L) at 2 consecutive visits after Week 3 resulting in his discontinuation from the study.

CONCLUSIONS:

[redacted]