

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-318

MEDICAL REVIEW(S)

RHPM NDA Overview
August 12, 2009

NDA 22-318 Sevelamer Carbonate powder for suspension, 0.8 gram and 2.4 grams

Sponsor: Genzyme Corporation

Classification: 3/S

Indication: Control of serum phosphorous in patients with chronic kidney disease on dialysis.

Date of Application: March 31, 2008

Date of Approval Letter: August 12, 2009

Goal Date: August 12, 2009

Background

Genzyme Corporation submitted a New Drug Application for a new formulation of Renvela (sevelamer carbonate) powder to control serum phosphorous in patients with chronic kidney disease on dialysis on March 31, 2008. The powder formulation, a 2.4 gram powder for suspension, is for oral suspension. The tablet formulation of Renvela was approved on October 19, 2007 under NDA 22-127. The safety and efficacy of sevelamer carbonate tablets was demonstrated to be similar to the safety and efficacy of sevelamer hydrochloride tablet that was approved on November 03, 1998 under NDA 20-926.

When Renvela tablet was approved, a deferral for pediatric studies was submitted due to the size of the tablet and their goal of developing a powder formulation. The sponsor submitted _____

b(4)

On January 28, 2009, a Complete Response letter was issued to the sponsor noting the single dose strength (2.4 grams) packet would not allow sufficient flexibility in dosing. This would make it impossible to accurately measure a dose less than 2.4 grams, whereas the tablet formulation dose gradations of 800 mg are available.

On February 18, 2009, the sponsor submitted their Complete Response in response to our CR letter. An acknowledgement letter was issued on March 12, 2009 classifying it as a Class I resubmission.

On April 8, 2009, a brief teleconference was held with the sponsor recommending the inclusion of a measuring device with the drug product to provide some assurance appropriate doses can be measured and updating the carton and container labeling noting the inclusion of the measuring device. We further notified the sponsor that the information would need to be reviewed by the Division of Medication Error and Prevention Analysis (DMEPA).

On April 10, 2009, Genzyme submitted _____
_____. Due to the timing of the submission, we were unable to perform a complete review of the information provided and a second CR letter was issued on April 17, 2009.

b(4)

On June 12, 2009, Genzyme submitted their Complete Response in response to the Division's second CR letter dated April 17, 2009. This submission included additional information to include a 0.8 gram powder packet. An acknowledgement letter accepting their resubmission was sent on June 17, 2009 with a goal date of August 12, 2009.

Filing Meeting: May 12, 2008

Reviews (January 27, 2009):

Pharmacology N/A

Medical
Reviewer: Gail Moreschi, M.D.

Conclusion: Approval.

Labeling: The 2.4 gram sachet is not indicated for initial therapy.

Summary: Three times a day dosing of the new powder formula appears to be efficacious. _____

b(4)

Statistical
Reviewer: Ququan (Cherry) Liu, Ph.D.

Conclusion: Approval.

Summary: The conclusion of efficacy is still a concern given a small study with high drop-outs.

Clinical Pharmacology
Primary Reviewer: Islam Younis, Ph.D.

Secondary Reviewer: Robert Kumi, Ph.D.

Conclusion: Approval.

Labeling: Unclear how lower doses will be measured for patients using 800 mg sevelamer carbonate TID when 2.4 gram powder packets are used.

Summary: Additional information for drug interactions studies are needed between sevelamer carbonate and warfarin and further in-vitro bioequivalence studies will be necessary between the tablet and powder formulation.

Chemistry

Reviewer: Donghao (Robert) Lu, Ph.D.

Conclusion: Approval.

Summary: An Environmental Assessment (EA) was submitted and evaluated with NDA 22-127 (sevelamer carbonate) tablets.

Labeling: The product should be named as "Renvela (sevelamer carbonate) for oral suspension" (deleting ' _____' in both label and labeling text). **b(4)**

The sentence " _____" should be deleted.

For the sachet label, the words ' _____' should be moved up. **b(4)**

CDTL

Reviewer: Abraham Karkowsky, M.D., Ph.D.

Conclusion: No approval.

Summary: Single dose strength available (2.4 grams) would not allow sufficient flexibility in dosing, therefore, instructions for dose alterations would not be possible. Furthermore, equivalency could not be defined between the powder and the hydrochloride formulation due to lack of information from the comparative study.

Division Director:

Reviewer: Norman Stockbridge, M.D., Ph.D.

Conclusion: No approval.

Summary: No provisions are made to accurately measure 800 mg from 2400 mg packet for adults. Post-marketing pediatric studies should be conducted using the powder formulation and the details of the study should be part of the sponsor's response to our CR letter.

Method Validation: None requested.

Environmental Assessment: Included in package.

Safety Update: Included in package.

Patent Information: Included in package.

DSI Audits: Not required.

Debarment Certification: Included in package.

Pediatrics: _____ **b(4)**

Review (April 16, 2009)

Chemistry
Reviewer: Donghao (Robert) Lu, Ph.D.

Conclusion: Approval.

Summary: _____ is acceptable. **b(4)**

Labeling: recommend moving the text "2.4 g" up as shown in the review.

Review (August 12, 2009)

Chemistry
Reviewer: Donghao (Robert) Lu, Ph.D.

Conclusion: Approval.

Summary: Stability and _____ data of the 0.8 gram packet are adequate. **b(4)**

Comments/Recommendations:

An approval letter will be drafted and signed by Dr. Stockbridge.

Anna Park
Regulatory Health Project Manager

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22318	ORIG 1		RENVELA

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/s/

ANNA J PARK
08/19/2009

RHPM NDA Overview Resubmission
April 16, 2009

NDA 22-318 Sevelamer Carbonate powder for suspension, 2.4 grams

Sponsor: Genzyme Corporation

Classification: 3/S

Indication: Control of serum phosphorous in patients with chronic kidney disease on dialysis.

Date of Application: February 18, 2009

Date of Approval Letter:

2-month Goal Date: April 18, 2009

Background

Genzyme Corporation submitted a New Drug Application for a new formulation of Renvela (sevelamer carbonate) powder to control serum phosphorous in patients with chronic kidney disease on dialysis on March 31, 2008. The powder formulation, a 2.4 gram powder for suspension, is for oral suspension. The tablet formulation of Renvela was approved on October 19, 2007 under NDA 22-127. The safety and efficacy of sevelamer carbonate tablets was demonstrated to be similar to the safety and efficacy of sevelamer hydrochloride tablet that was approved on November 03, 1998 under NDA 20-926.

When Renvela tablet was approved, a deferral for pediatric studies was submitted due to the size of the tablet and their goal of developing a powder formulation. The sponsor submitted

b(4)

On January 28, 2009, a CR letter was issued to the sponsor noting the single dose strength (2.4 grams) packet would not allow sufficient flexibility in dosing. This would make it impossible to accurately measure a dose less than 2.4 grams, whereas the tablet formulation dose gradations of 800 mg are available.

On February 18, 2009, the sponsor submitted their resubmission. An acknowledgement letter was issued on March 12, 2009 as a Class I resubmission.

On April 8, 2009, a brief teleconference was held with the sponsor recommending the inclusion of a measuring device with the drug product to provide some assurance appropriate doses can be measured and updating the carton and container labeling noting the inclusion of the measuring device. We further notified the sponsor that the information would need to be reviewed by the Division of Medication Error and Prevention Analysis (DMEPA).

On April 10, 2009, the sponsor submitted _____
_____ Due to the timing of the submission, we were unable to perform a complete review of the information provided.

b(4)

Filing Meeting: February 24, 2009

Review:

Chemistry

Reviewer: Donghao (Robert) Lu, Ph.D.

Conclusion: Approval.

Summary: _____
_____ is acceptable.

b(4)

Labeling: recommend moving the text "2.4 g" up as shown in the review.

Comments/Recommendations:

A Complete Response letter will be drafted and signed by Dr. Stockbridge.

Anna Park
Regulatory Health Project Manager

RHPM NDA Overview
January 27, 2009

NDA 22-318 Sevelamer Carbonate powder for suspension, 2.4 grams

Sponsor: Genzyme Corporation

Classification: 3/S

Indication: Control of serum phosphorous in patients with chronic kidney disease on dialysis.

Date of Application: March 31, 2008

Date of Approval Letter:

10-month Goal Date: January 31, 2009

Background

Genzyme Corporation submitted a New Drug Application for a new formulation of Renvela (sevelamer carbonate) powder to control serum phosphorous in patients with chronic kidney disease on dialysis on March 31, 2008. The powder formulation, a 2.4 gram powder for suspension, is for oral suspension. The tablet formulation of Renvela was approved on October 19, 2007 under NDA 22-127. The safety and efficacy of sevelamer carbonate tablets was demonstrated to be similar to the safety and efficacy of sevelamer hydrochloride tablet that was approved on November 03, 1998 under NDA 20-926.

When Renvela tablet was approved, a deferral for pediatric studies was submitted due to the size of the tablet and their goal of developing a powder formulation. The sponsor submitter

b(4)

Filing Meeting: May 12, 2008

Reviews:

Pharmacology N/A

Medical

Reviewer: Gail Moreschi, M.D.

Conclusion: Approval.

Labeling: The 2.4 gram sachet is not indicated for initial therapy.

Summary: Three times a day dosing of the new powder formula appears to be efficacious _____

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Statistical

Reviewer: Ququan (Cherry) Liu, Ph.D.

Conclusion: Approval

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Clinical Pharmacology

Primary Reviewer: Islam Younis, Ph.D.

Secondary Reviewer: Robert Kumi, Ph.D.

Conclusion: Approval.

Labeling: Unclear how lower doses will be measured for patients using 800 mg sevelamer carbonate TID when 2.4 gram powder packets are used.

Summary: Additional information for drug interactions studies are needed between sevelamer carbonate and warfarin and further in-vitro bioequivalence studies will be necessary between the tablet and powder formulation.

Chemistry

Reviewer: Donghao (Robert) Lu, Ph.D.

Conclusion: Approval.

Summary: An Environmental Assessment (EA) was submitted and evaluated with NDA 22-127 (sevelamer carbonate) tablets.

Labeling: The product should be named as "Renvela (sevelamer carbonate) for oral suspension" (deleting _____, in both label and labeling text).

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Conclusion: No approval.

Summary: Single dose strength available (2.4 grams) would not allow sufficient flexibility in dosing, therefore, instructions for dose alterations would not be possible. Furthermore, equivalency could not be defined between the powder and the hydrochloride formulation due to lack of information from the comparative study.

Division Director:

Reviewer: Norman Stockbridge, M.D., Ph.D.

Conclusion: No approval.

Summary: No provisions are made to accurately measure 800 mg from 2400 mg packet for adults. Post-marketing pediatric studies should be conducted using the powder formulation and the details of the study should be part of the sponsor's response to our CR letter.

Method Validation: None requested.

cGMP Inspections:

Environmental Assessment: Included in package.

Safety Update:

Patent Information: Included in package.

DSI Audits: Not required.

DDMAC: N/A

Debarment Certification: Included in package.

Pediatrics:

b(4)

DMEPA Review: Included in package.

Comments/Recommendations:

A Complete Response letter will be drafted and signed by Dr. Stockbridge.

Anna Park
Regulatory Health Project Manager

CLINICAL and STATISTICAL REVIEW

Application Type NDA 22-318
Submission Number
Submission Code

Letter Date March 31, 2008
Stamp Date April 1, 2008
PDUFA Goal Date February 1, 2009

Reviewers Names Gail Moreschi, M.D., M.P.H.
Ququan Liu, M.D., M.S.
Review Completion Date December 1, 2008

Established Name Sevelamer carbonate
(Proposed) Trade Name Renvela
Therapeutic Class Phosphate binder
Applicant Genzyme

Priority Designation S

Formulation Powder for Oral Suspension
Dosing Regimen tid, ~~tid~~ **b(4)**
Indication Hyperphosphatemia
Intended Population Patients on dialysis

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1 EXECUTIVE SUMMARY

In 1998 Renagel (sevelamer hydrochloride) was approved in the United States for the control of hyperphosphatemia in adult patients on hemodialysis. In 2007 a new formula of sevelamer where the counterion was changed from chloride to carbonate was approved (NDA 22-127). In this NDA the Sponsor has submitted a change in the tablet form of sevelamer carbonate to a powder form for patients unable to swallow _____ The Sponsor has submitted two clinical studies comparing the powder formula to sevelamer hydrochloride tablets. The study comparing the powder formula three times a day is small but somewhat efficacious. Utilizing the powder once a day in a larger study did not prove to be efficacious. In the label the Sponsor has recommended only the three times a day dosing. The safety profile of the powder formula appears to be similar the previous sevelamer studies, causing primarily gastrointestinal side effects. Certainly there is a need for a powder formula for some patients _____, therefore these reviewers recommend that the new powder be approved for three times a day dosing.

b(4)

b(4)

1.1 Recommendation on Regulatory Action

Approval

1.2 Recommendation on Postmarketing Actions

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The Sponsor has submitted two clinical studies to demonstrate the safety and efficacy of sevelamer carbonate powder.

1.3.2 Efficacy

Although a small study, the three times a day dosing of the new powder formula appears to be efficacious. The once a day dosing study with the largest meal did not show efficacy.

1.3.3 Safety

This new sevelamer carbonate powder formula appears to have the same safety profile as has been shown with sevelamer over the years since its first approval. Gastrointestinal side effects remain a problem.

1.3.4 Dosing Regimen and Administration

The powder will be given three times a day. Each individual powder sachet will be mixed with _____ of water. The patient is instructed to drink the mixture within 30 minutes of preparation.

b(4)

1.3.5 Drug-Drug Interactions

Six drugs were evaluated with sevelamer hydrochloride: digoxin, warfarin, enalapril, metoprolol, ciprofloxacin, and iron. In these studies, sevelamer hydrochloride was found to have no effect on the bioavailability of digoxin, warfarin, metoprolol, enalapril or iron. However, the bioavailability of ciprofloxacin was decreased by approximately 50% when co-administered with sevelamer hydrochloride.

1.3.6 Special Populations

This new formula is intended for patients unable to swallow _____

b(4)

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Sevelamer hydrochloride (Renagel®) has been on the market since 1998 to treat hyperphosphatemia in patients with chronic renal disease (CKD) on hemodialysis. In 2007 the Sponsor changed the ion from hydrochloride to carbonate in order to decrease the frequency of monitoring serum chloride and bicarbonate. In this NDA the formula has been changed from a tablet to a powder formula.

2.2 Currently Available Treatment for Indications

There are three FDA approved phosphate binders: Renagel® (sevelamer hydrochloride), PhosLo (calcium acetate), and Fosrenol (lanthanum carbonate). This will be the first powder formula.

2.3 Availability of Proposed Active Ingredient in the United States

NA

2.4 Important Issues With Pharmacologically Related Products

NA

2.5 Presubmission Regulatory Activity

NA

2.6 Other Relevant Background Information

NA

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

This review is not currently available and will be submitted separately.

3.2 Animal Pharmacology/Toxicology

This review is not currently available and will be submitted separately.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The Sponsor has submitted two clinical studies for this NDA.

4.2 Tables of Clinical Studies

Table 1: Clinical Studies

Study ID	Number of Study Centres Location(s)	Study Start Enrolment Status, Date Total Enrolment/Enrolment Goal	Design Control Type	Study & Control Drugs Dose and Regimen	Primary Study Objective	Subjects/ Arm Treated/ Completed	Duration	Gender M/F Mean Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint
SVCARB00205	7 sites in the United Kingdom	Started: 31 Jan 2006 Completed: 21 Mar 2007 Screened: 75 enrolled/ 75 planned Randomised: 31 enrolled/ 24 planned	Randomised, open-label, cross-over	Sevelamer carbonate powder for oral suspension 800 mg sachets Sevelamer hydrochloride 800 mg tablets The binder dose at the end of the sevelamer hydrochloride run-in was replaced gram per gram by study drug. The dose was to be maintained throughout the treatment periods. Both to be taken orally TID with meals. Mean actual dose (Safety Set) Sevelamer carbonate: 5.9 ± 2.7 g/day Sevelamer hydrochloride: 6.5 ± 3.3 g/day	Compare the safety and efficacy of sevelamer carbonate powder with sevelamer hydrochloride tablets, each dosed TID	Treated: 31 (31 patients received sevelamer carbonate powder and 28 patients received sevelamer hydrochloride tablets) Completed both treatments: 24	15 weeks: 2-week washout period; 4-week sevelamer hydrochloride run-in period; two 4-week randomised treatment periods; 1-week follow-up period.	68%/ 32% 53 years (27-80 years)	Haemodialysis patients	Time weighted average of serum phosphorus
GD3-199-301	29 sites in the United States	Started: 27 Jan 06 Completed: 16 Mar 07 Screened: 396 enrolled/280 planned Randomised: 217 (144 sevelamer carbonate powder QD; 73 sevelamer hydrochloride tablets TID) enrolled/ 207 (138 sevelamer carbonate powder QD; 69 sevelamer hydrochloride tablets TID) planned	Randomised, open-label, parallel	Sevelamer carbonate powder for oral suspension 2.4 g sachets Sevelamer hydrochloride 800 mg tablets The starting dose was 4.8 g/day of either sevelamer carbonate powder or sevelamer hydrochloride tablets. The dose was to be titrated to reach a serum phosphorus level of ≥ 3.5 and ≤ 5.5 mg/dL (≥ 1.13 and ≤ 1.76 mmol/L). Sevelamer carbonate powder was to be taken QD with the largest meal. Sevelamer hydrochloride tablets were to be taken TID with the meals. Mean actual dose (Safety Set) Sevelamer carbonate powder dosed QD: 6.2 ± 2.6 g/day Sevelamer hydrochloride tablets dosed TID: 6.7 ± 3.0 g/day	Compare the safety and efficacy of sevelamer carbonate powder dosed QD with the largest meal to sevelamer hydrochloride tablets dosed TID with meals	Sevelamer carbonate powder QD: 141 treated/ 93 completed Sevelamer hydrochloride tablets TID: 72 treated/ 62 completed	26 weeks: 2-week washout period, 24-week randomised treatment period	61%/ 39% 58 years (20-85 years)	Haemodialysis patients	Change in serum phosphorus

4.3 Review Strategy

The Sponsor has submitted two clinical studies which were reviewed. This was a joint review between the medical and the statistical reviewers.

4.4 Data Quality and Integrity

It was determined by the review team that a DSI inspection was not required.

4.5 Compliance with Good Clinical Practices

The submitted clinical trials were conducted in accordance with good ethical standards.

4.6 Financial Disclosures

There are no questions raised as to the integrity of the data.

5 CLINICAL PHARMACOLOGY

This review is not currently available and will be submitted separately.

5.1 Pharmacokinetics

5.2 Pharmacodynamics

5.3 Exposure-Response Relationships

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Renagel (sevelamer hydrochloride) was approved in the United States in 1998 for the control of hyperphosphatemia in adult patients on hemodialysis (HD). Renvela (sevelamer carbonate, NDA 22-127) was recently approved in the tablet form. Sevelamer carbonate was developed as an alternate salt form to the original sevelamer hydrochloride; carbonate is an alternative counterion to chloride. Since both salts have the same polymeric structure, a similar efficacy and safety profile should be seen. In this NDA sevelamer carbonate has a new formulation, a powder form, for those who are unable to swallow _____

b(4)

6.1.1 Methods

The Sponsor has submitted 2 clinical studies utilizing the powder formulation which will be reviewed individually as they have different study designs. The first study SVCARB00205 is with the usual three times a day dosing. The second study GD3-199-301 was done with a once a day dosing with the largest meal. In both studies the comparator was sevelamer hydrochloride.

6.1.2 General Discussion of Endpoints

The reduction of serum phosphate has been the accepted endpoint for the treatment of hyperphosphatemia in the adult patient with chronic renal failure (CKD) on hemodialysis (HD).

6.1.3 Study Design

The two studies will be presented separately here because of the differences in their individual study designs.

6.1.3.1 SVCARB00205

Study title: A randomized, cross-over study to demonstrate equivalence of sevelamer carbonate powder and sevelamer hydrochloride tablets dosed three times per day in hemodialysis patients

Study Centers: Patients were enrolled at 7 centers in the United Kingdom (UK).

Study Dates: January 31, 2006 to March 21, 2007

Objectives:

Primary Objectives in hyperphosphatemic chronic kidney disease (CKD) patients on hemodialysis (HD):

1. To demonstrate equivalence of sevelamer carbonate powder to sevelamer hydrochloride tablets dosed three times a day (TID) with meals, on control of serum phosphorus levels.
2. To evaluate the safety and tolerability of sevelamer carbonate powder compared to sevelamer hydrochloride tablets dosed TID with meals.

Secondary Objectives in hyperphosphatemic CKD patients on HD, to compare the effects of sevelamer carbonate powder to sevelamer hydrochloride tablets when dosed TID with meals on:

1. Serum calcium-phosphorus product.
2. Serum lipid profile (total cholesterol, high density lipoprotein [HDL] cholesterol, low density lipoprotein [LDL] cholesterol, and triglycerides).

These secondary objectives will not be reviewed in this NDA.

Study Design:

This was a Phase 3, multi-center, open-label, randomized, cross-over study of sevelamer carbonate powder dosed TID with meals versus sevelamer hydrochloride tablets dosed TID with meals in hyperphosphatemic CKD patients on HD. The study consisted of 6 periods: a 2-week

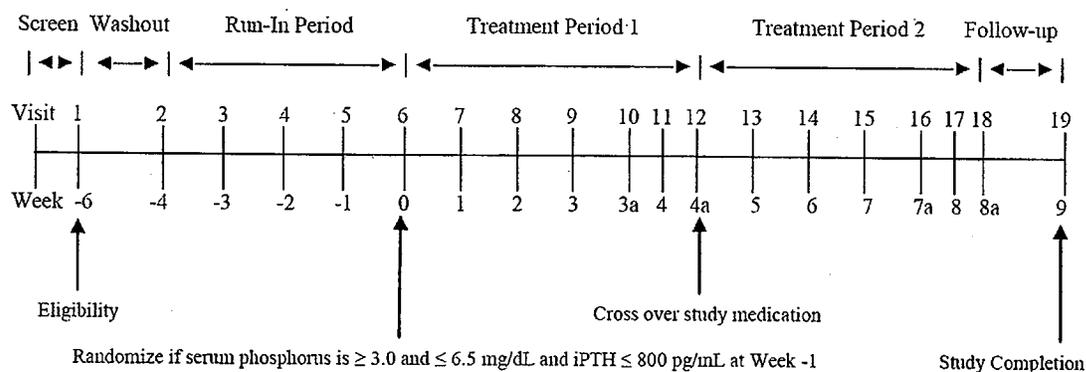
Screening and Washout Period, a 4-week sevelamer hydrochloride tablet Run-In Period, a 4-week Treatment Period (Treatment Period 1), a second 4-week Treatment Period (Treatment Period 2 when the alternative study medication was taken), and a Follow-up visit 1 week after the last study treatment visit.

At Screening, patients had to be taking sevelamer hydrochloride alone or as combination therapy (e.g., using sevelamer hydrochloride and calcium, or metal phosphate binders concomitantly). Patients who fulfilled the entry criteria were asked to discontinue their current phosphate binder(s) and enter a 2-week Washout Period. At the end of the Washout Period, patients who were hyperphosphatemic (serum phosphorus ≥ 5.5 mg/dL or ≥ 1.76 mmol/L) continued into the 4-week Run-In Period. Each patient's binder dose taken prior to the Washout Period was replaced with an equivalent number of 800 mg tablets of sevelamer hydrochloride (not to exceed a total daily dose of 14.4 g or 18 x 800 mg tablets). Patients had weekly visits during the Run-In Period. The dose of sevelamer hydrochloride tablets could be adjusted if necessary at Visits 3 and 4 (Weeks -3 and -2) to keep serum phosphorus levels within a target level of 3.5 and 5.5 mg/dL (1.12 and 1.76 mmol/L), inclusive, by increasing or decreasing by 1 x 800 mg tablet TID (2.4 g/day).

Patients who were eligible to continue into the treatment period were to maintain the dose of the study drug that was last prescribed during the Run-In Period for the remainder of the study. At Baseline (Visit 6, Week 0), eligible patients were randomly assigned to one of two treatment sequences:

- sevelamer carbonate powder dosed TID with meals for four weeks followed by sevelamer hydrochloride tablets dosed TID with meals for four weeks
- sevelamer hydrochloride tablets dosed TID with meals for four weeks followed by sevelamer carbonate powder dosed TID with meals for four weeks.

Figure 1: Study Design



The prescribed dose during the two randomized treatment periods was individualized based on the final sevelamer hydrochloride tablet dose prescribed at the end of the Run-In Period prior to randomization. Patients had weekly study visits for the first 2 weeks and 2 study visits during

each of the last 2 weeks of Treatment Period 1. During Treatment Period 2, patients previously assigned to sevelamer hydrochloride tablets were crossed-over to sevelamer carbonate powder and those previously assigned to sevelamer carbonate powder were crossed-over to sevelamer hydrochloride tablets for an additional 4 weeks of treatment. Patients had weekly study visits for the first 2 weeks and 2 study visits during each of the last 2 weeks of Treatment Period 2. At the end of Treatment Period 2, study medication was discontinued and patients were instructed to return to their pre-study phosphate binder medication. Patients returned for a Follow-up visit 7 days later.

The study was open-label due to the practical considerations involved in blinding patients to study medication assignment (powder vs. tablet).

The Inclusion Criteria included:

Taking sevelamer hydrochloride alone (e.g. not using other types of phosphate binders concomitantly) or on combination therapy (e.g. using sevelamer hydrochloride and calcium containing, or metal phosphate binders concomitantly) not exceeding a total daily binder dose of 14.4 g. for at least 60 days prior to screening.

Had the following documented local laboratory measurements:

- a) Two most recent consecutive serum phosphorus measurements that were ≥ 3.0 and ≤ 7.0 g/dL (≥ 0.96 and ≤ 2.26 mmol/L) within 60 days of screening.
- b) A most recent intact PTH (iPTH) measurement ≤ 900 pg/mL (≤ 99 pmol/L) within 90 days of screening.
- c) A most recent serum calcium (adjusted for albumin) measurement within normal range defined by the local laboratory within 60 days of screening.

If patient was on vitamin D replacement or receiving calcimimetic therapy, the patient must be at a stable dose for at least one month prior to screening and was willing to maintain the same dose throughout the duration of the study, except for safety reasons.

The Exclusion Criteria included patients that had active dysphagia, swallowing disorders, bowel obstruction, or severe gastrointestinal motility disorders.

Treatments:

During the Run-In Period, patients received sevelamer hydrochloride at a dose based on their most recently prescribed phosphate binder dose prior to the Washout Period. The dose of study drug that was last taken during the Run-In Period was to be used throughout the randomized cross-over treatment periods.

During the randomized treatment periods, patients received either sevelamer carbonate powder or sevelamer hydrochloride tablets according to the randomization assignment. Patients were randomized on a 1:1 basis to one of the following two treatment sequences:

- Sevelamer carbonate 800 mg powder TID for four weeks followed by sevelamer hydrochloride 800 mg tablets TID for four weeks.

- Sevelamer hydrochloride 800 mg tablets TID for four weeks followed by sevelamer carbonate 800 mg powder TID for four weeks.

All study medication was taken orally. Patients were instructed to thoroughly mix each individual sevelamer carbonate powder 800 mg sachet with 20 mL of water. A measuring cup was provided to patients to ensure the appropriate volume of water was used. Patients were instructed to drink the mixture within 30 minutes of preparation. Multiple sachets may have been mixed at once, as long as the appropriate amount of water was used (i.e., 1 sachet = 20 mL of water, 2 sachets = 40 mL of water, etc.). No additional preparation was required for sevelamer hydrochloride tablets.

Patients were randomized within each site on a 1:1 basis in blocks of 4 to one of the two treatment sequences. Dose titration, by increasing or decreasing by 1 x 800 mg tablet TID (2.4 g/day), was permitted during the Run-In Period at Visits 3 and 4 (Weeks -3 and -2) to keep serum phosphorus levels within a target range of 3.5 and 5.5 mg/dL (1.12 and 1.76 mmol/L) inclusive. The patient's final dose of sevelamer hydrochloride at the end of the Run-In Period was then to be used during both randomized treatment periods.

Table 2: Schedule of Study Events

	Screening / Start of washout	RUN-IN TREATMENT PERIOD					TREATMENT PERIOD 1			TREATMENT PERIOD 2		
	Visit 1 (Week -6)	Visit 2 (Week -4)	Visit 3 (Week -3)	Visit 4 (Week -2)	Visit 5 (Week -1)	Visit 6 (Week 0) BASELINE	Visits 7, 8, 9, 10, 11 (Weeks 1, 2, 3, 3a, 4)	Visit 12 (Week 4a)	Visits 13, 14, 15, 16, 17 (Weeks 5, 6, 7, 7a, 8)	Visit 18/18E1 (Week 8a)	Visit 19 Follow-up (Week 9)	
Describe Study and Obtain Informed Consent	✓											
Review Inclusion & Exclusion	✓	✓				✓						
Assign Patient Number	✓											
Review Medical and Renal History and prior medications	✓											
Review two consecutive local lab serum phosphorus values within 60 days of screening	✓											
Review most recent iPTH within 90 days of screening	✓											
Review most recent CA (adjusted for albumin) value within 60 days of screening	✓											
Record Height						✓						
Physical Exam (including Vital Signs and weight)		✓				✓		✓		✓		
Serum human chorionic gonadotrophin	✓											
Serum phosphorus, Calcium (albumin-adjusted), albumin, calcium (albumin-adjusted) phosphorus product	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Serum glucose, creatinine, chloride and bicarbonate						✓		✓		✓		
Serum sodium, potassium, BUN	✓	✓				✓		✓		✓		
Serum iPTH					✓	✓		✓		✓		
Serum 25-Vit D and 1,25-Vit D						✓		✓		✓		
Serum Lipid Profile						✓		✓		✓		

	Screening / Start of washout	RUN-IN TREATMENT PERIOD					TREATMENT PERIOD 1			TREATMENT PERIOD 2		
	Visit 1 (Week -6)	Visit 2 (Week -4)	Visit 3 (Week -3)	Visit 4 (Week -2)	Visit 5 (Week -1)	Visit 6 (Week 0) BASELINE	Visits 7, 8, 9, 10, 11 (Weeks 1, 2, 3, 3a, 4)	Visit 12 (Week 4a)	Visits 13, 14, 15, 16, 17 (Weeks 5, 6, 7, 7a, 8)	Visit 18/18E1 (Week 8a)	Visit 19 Follow-up (Week 9)	
Serum Hematology Profile	✓	✓				✓		✓		✓		
Liver function tests	✓	✓				✓		✓		✓		
Serum Storage Sample						✓		✓		✓		
Discontinue phosphorus binder treatment	✓					✓		✓		✓		
Randomize Patient						✓		✓		✓		
Dispense Sevelamer hydrochloride for Run-in		✓										
Dispense study drug per randomization assignment for Treatment Period 1						✓						
Dispense study drug per randomization assignment for Treatment Period 2								✓		✓		
Perform Study Drug Accountability				✓		✓	✓	✓	✓	✓		
Discontinue Study Drug						✓		✓		✓		
Concomitant Medications and AE Assessments						✓	✓	✓	✓	✓	✓	

¹Drug accountability at Visits 9 and 15 only

Efficacy Measurements:

For the primary efficacy parameter, blood samples were measured for serum phosphorus at Weeks 3, 3a, 4, 4a (Treatment Period 1) and Weeks 7, 7a, 8, and 8a (Treatment Period 2). For the secondary efficacy parameters, blood samples were measured for serum calcium-phosphorus product at Weeks 3, 3a, 4, 4a (Treatment Period 1) and Weeks 7, 7a, 8, and 8a (Treatment Period 2) See the above Table 2.

For lipid parameters (total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides), blood samples were measured at Week 4a for Treatment Period 1 and Week 8a for Treatment Period 2. Blood samples taken for analysis on the same day as HD were taken just prior to the start of dialysis. However, these secondary endpoints will not be reviewed here.

6.1.3.2 Study GD3-199-301

Study Title: 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

Study Centers: 29 sites in the United States participated in the trial. One site screened patients but did not enroll any patients.

Study Dates: January 27, 2006 to March 19, 2007

Objectives:

Primary objectives in chronic kidney disease (CKD) patients on hemodialysis 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 hemodialysis, 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).

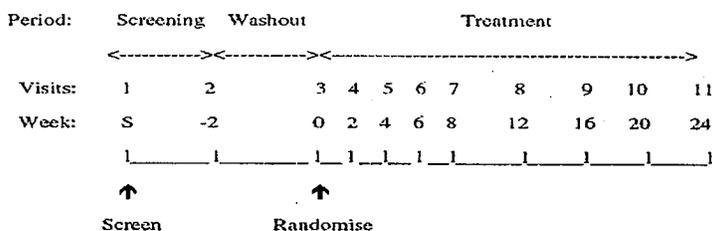
These secondary objectives will not be reviewed here.

Study Design:

This was a randomized, parallel, open-label study in CKD patients on HD to evaluate the safety and efficacy of sevelamer carbonate powder, dosed QD with the largest meal, compared to sevelamer hydrochloride tablets dosed TID with meals. The study consisted of three periods: a

two week screening period, a two-week phosphate binder washout period, and a 24-week randomized treatment period.

Figure 2: Study Schematic



During the Screening Period, patients were screened for eligibility. 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 randomized (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 randomized 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 ≤ 1.76 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).

Inclusion Criteria included:

Had the following documented local laboratory measurements:

- a. Two most recent consecutive serum phosphorus measurements that were ≥ 3.0 and ≤ 6.5 mg/dL (≥ 0.97 and ≤ 2.10 mmol/L) within 60 days of screening
- b. A most recent iPTH measurement ≤ 800 pg/mL (≤ 800 ng/L) within 90 days of screening

Had the following central laboratory measurements:

- a. A serum phosphorus measurement > 5.5 mg/dL (1.78 mmol/L) at randomization (Week 0)
- b. A serum iPTH measurement ≤ 800 pg/mL (≤ 800 ng/L) at screening

Exclusion Criteria included:

Active bowel obstruction, dysphagia, swallowing disorder, or severe gastrointestinal (GI) motility disorders

Treatment:

During the randomized treatment periods, patients received either sevelamer carbonate powder or sevelamer hydrochloride tablets according to the randomization assignment. The patients were randomized in a 2:1 fashion (in favor of carbonate powder) to one of two treatments: sevelamer carbonate powder dosed QD with the largest meal or sevelamer hydrochloride tablets dosed TID with meals. The starting dose was 4.8 g of either sevelamer hydrochloride tablets or sevelamer carbonate powder. Sevelamer carbonate powder (Genzyme Corporation) was supplied as 2.4 g sachets provided in 30 count boxes. TUMS® Regular 500 mg tablets, containing 200 mg elemental calcium were provided in the event that an evening calcium supplement was needed.

Patients were instructed to thoroughly mix each individual sevelamer carbonate powder 2.4 g packet with 2 ounces (oz) of cold water. Patients were instructed to drink the mixture immediately, and not longer than 30 minutes after preparation. If the mixture was not taken immediately after preparation, the patients were instructed to stir the mixture again prior to drinking. Patients were permitted to mix multiple packets at once, as long as the appropriate amount of water was used (i.e. 1 packet = 2 oz. of water, 2 packets = 4 oz. of water, 3 packets = 6 oz. of water, etc.).

Once the Week 0 labs were available, eligible patients were randomized [stratified by screening iPTH ≤ 400 or > 400 pg/mL (≤ 400 or > 400 ng/L) and cinacalcet treatment at Week 0] to one of two treatment groups in a 2:1 fashion in favor of sevelamer carbonate powder:

1. sevelamer carbonate powder dosed QD with the largest meal or
2. sevelamer hydrochloride tablets dosed TID with meals.

Patients with higher PTH levels are likely to have higher levels of phosphorus and can be more difficult to treat. Cinacalcet treatment may result in more effective treatment of hyperparathyroidism and be associated with lower serum phosphorus levels. Therefore, the stratification by PTH and cinacalcet was an attempt to balance the number of patients with severe hyperparathyroidism and cinacalcet use in each group.

The starting dose of 4.8 grams/day for both sevelamer carbonate powder and sevelamer hydrochloride tablets was selected based on the approved dosing instructions for sevelamer hydrochloride tablets. Those instructions recommend a starting dose of 800 to 1600 mg, administered as one to two 800 mg tablets with each meal for a total daily dose 2.4 to 4.8 grams/day. The sevelamer hydrochloride dosing instructions also state that the dose should be titrated until an acceptable phosphorus level is reached. Therefore, dose titration was also suggested for sevelamer carbonate powder and sevelamer hydrochloride tablets in this study.

Patients were instructed to take sevelamer carbonate powder once a day with the largest meal. This was recommended so that sevelamer carbonate would be present in the gastrointestinal tract at the same time as the meal with the greatest phosphate intake.

The starting dose was 4.8 g daily of either sevelamer hydrochloride tablets or sevelamer carbonate powder. The study treatment dose was to be titrated up or down in increments of 2.4 g daily at Visits 4, 5, 6, 7, 8, 9 and 10 (Weeks 2, 4, 6, 8, 12, 16, 20) to reach a target serum phosphorus level of ≥ 3.5 and ≤ 5.5 mg/dL (≥ 1.13 and ≤ 1.78 mmol/L).

Sevelamer hydrochloride tablets were to be taken TID with meals. Sevelamer carbonate powder was to be taken QD with the largest meal. The study was open-label as it was not possible to blind the patients to study treatment assignment due to the different formulations and dosing regimens.

Therapy for hyperparathyroidism may have been started, stopped or titrated every four weeks (Weeks 4, 8, 12, 16, and 20) to reach a target serum iPTH of ≥ 150 and ≤ 300 pg/mL (≥ 150 and ≤ 300 ng/L). Cinacalcet may have been 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. The Investigator retrieved unused study drug at each visit and performed drug accountability.

Table 3: Assessment and Procedures to be Performed at Each Study Visit

	Visit 1 (Screening)	Visit 2 (Week -2)	Visit 3 (Week 0)	Visit 4 (Week 2)	Visit 5 (Week 4)	Visit 6 (Week 6)	Visit 7 (Week 8)	Visit 8 (Week 12)	Visit 9 (Week 16)	Visit 10 (Week 20)	Visit 11/ET (Week 24/ET)
Describe Study and Obtain Informed Consent	√										
Review Inclusion/Exclusion Criteria	√		√								
Assign Patient Number	√										
Review Medical and Renal History	√										
Review two most recent local lab phosphorus values within 60 days of screening and iPTH within 90 days of screening	√										
Physical Exam (Including vital signs)	√										√
Serum Chemistry Profile		√ ¹	√ ²	√ ¹	√ ¹	√ ¹	√ ²				
Serum bCG (Women of Child bearing Potential)	√										
Serum iPTH	√	√	√		√		√	√	√	√	√
C-reactive protein			√								√
Serum 25-OH D and 1,25-OH D			√								√
Serum Lipid Profile (TC, LDL, TG, HDL)			√								√
Serum Haematology Profile ³			√								√
Serum Storage Sample			√								√
Randomise Patient			√								
Dispense Study Drug			√ ⁶	√	√	√	√	√	√	√	√
Perform Study Drug Accountability			√	√	√	√	√	√	√	√	√
USC 24-hour dietary recall	√ ⁴		√ ⁵					√ ⁵			√ ⁵
Questionnaire		√ ⁷						√ ⁷			
AE Assessment											Continuous Monitoring
Concomitant Medications/Therapies											Continuous Monitoring

¹ Chemistry profile at Visit 2, 4, 5, 6, 7, 8, 9 and 10: Serum phosphorus, calcium (adjusted for albumin), albumin, chloride, bicarbonate and calcium-phosphorus product.

² Chemistry profile at Visit 3 and 11/ET: Serum phosphorus, calcium (adjusted for albumin), albumin, calcium-phosphorus product, bicarbonate, chloride, uric acid, sodium, potassium, glucose, BUN, liver function tests (ALT and AST) and creatinine.

³ Haematology profile includes: CBC with differential, platelet count, clotting factors (PT, PTT).

⁴ Review the patient dietary summary and fax patient information to USC.

⁵ On three randomly selected days during the 2-week washout period, mid-way through treatment, and the last 2 weeks of treatment, dietary recalls will be performed by USC.

⁶ Once the laboratory results are available from Visit 3(Week 0), a two-week supply of study drug will be provided to eligible patients at their next clinic visit.

⁷ Patient Satisfaction Questionnaire is to be completed at Week -2 (+/- 2 weeks) and Week 12 (+/- 2 weeks)

The Statistical Plan was submitted January 26, 2007, after the commencement of this study.

Sample Size Consideration:

The sample size was evaluated with respect to the primary efficacy parameter of the study, the change from baseline to Week 24/ET in serum phosphorus. A total of 165 evaluable subjects (2:1 randomization: 110 sevelamer carbonate powder QD, 55 sevelamer hydrochloride tablet TID) were required to achieve 90% power based on a two group student's t-test with a one-sided 2.5% type I error rate for a noninferiority margin of 1 mg/dL (non-inferiority would be concluded if powder QD provides serum phosphorus reduction that is statistically significantly greater than that associated with tablets TID minus 1 mg/dL). Approximately 207 subjects were randomized to one of the two treatment groups to account for anticipated exclusions from the per-protocol populations.

Analysis Populations:

Safety Set (SS): This population consists of all randomized subjects who received at least one dose of study medication.

Full Analysis Set (FAS): This population consists of the subset of the Safety Set with any post-dosing phosphorus assessments.

Per Protocol Set (PPS): This population consists of the subset of the FAS with no major protocol violations as determined by a review prior to database lock.

Study Treatment: Percent compliance, starting prescribed daily dose, ending prescribed daily dose, average prescribed daily dose, average actual dose and duration of study drug were presented by treatment group. Wilcoxon rank sum tests were used to test the difference between the treatment groups for SS, FAS, and PPS populations.

Treatment duration was calculated using the following formula:

$$\text{Duration (weeks)} = (\text{Last Date of Dosing} - \text{First Date of Dosing} + 1) / 7.$$

Treatment compliance was calculated overall as follows:

$$\text{Compliance} = \frac{(\text{Number of Packets Dispensed} - \text{Number of Packets Returned}) \times 100}{(\text{powder}) \text{ Number of Prescribed Packets}}$$

$$\text{Compliance} = \frac{(\text{Number of Tablets Dispensed} - \text{Number of Tablets Returned}) \times 100}{(\text{tablets}) \text{ Number of Prescribed Tablets}}$$

Efficacy Analysis:

The analysis of efficacy endpoints included tabulations of findings at each timepoint and the change from baseline to each post-baseline time point. The final row displayed the change from baseline to Week 24/ET. Data was not carried forward for these analyses with the exception of the Week 24/ET timepoint. Efficacy analysis was done for FAS and PPS populations.

Primary Efficacy Parameter: The primary efficacy analysis was an assessment of non-inferiority with respect to a change from baseline in serum phosphorus levels at Week 24/final among the

Per-Protocol Set. A Full Analysis Set analysis was performed as a confirmatory analysis. Specifically, a two-sided 95% confidence interval was estimated for the difference in serum phosphorus change between treatment groups (diff = sevelamer carbonate powder QD - sevelamer hydrochloride tablets TID). If the upper confidence bound is less than 1 mg/dL, then non-inferiority will be concluded. Serum phosphorus results at each assessment timepoint were tabulated by treatment group.

Demographics:

Patient demographics including age, race, ethnicity, gender, history of diabetes, post-dialysis weight, body mass index (BMI), height and stratification criteria [iPTH \leq 400 pg/mL (\leq 400 ng/L) versus $>$ 400 pg/mL ($>$ 400 ng/L) at Screening and use of cinacalcet at baseline (Week 0)] was summarized by treatment group and overall. Comparability of treatment groups was assessed using Fisher's exact tests for categorical variables and the Wilcoxon rank sum test for continuous variables.

Renal History:

Renal history including primary cause of end stage renal disease (ESRD), time on dialysis, vitamin D use at screening, and history of parathyroidectomy was summarized by treatment group and overall. Comparability of treatment groups was assessed using Fisher's exact tests for categorical variables and the Wilcoxon rank sum test for continuous variables.

Medical History:

The number and percentage of patients reporting a medical history for each body system was summarized by treatment group and overall. Fisher's exact test was used to test for differences between the two treatment groups.

Efficacy Analysis:

The analysis of efficacy endpoints includes tabulations of findings at each time point and the change from baseline to each post-baseline time point. Data was not carried forward for these analyses with the exception of the Week 24/ET time point. Efficacy analyses were done for the FAS and PPS populations.

Primary Efficacy Analysis:

The primary efficacy analysis was an assessment of non-inferiority with respect to change from baseline in serum phosphorus levels at Week 24/final among the PPS. A FAS analysis was performed as a confirmatory analysis. Specifically, a two-sided 95% confidence interval was estimated for the difference in 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 concluded. Serum phosphorus results at each assessment time point were tabulated by treatment group.

Sub-group analyses for the primary efficacy endpoint were also performed separately within the following randomization strata 1) serum iPTH \leq 400 and $>$ 400 pg/mL [\leq 400 and $>$ 400 ng/L]

and 2) cinacalcet use at Week 0. No non-inferiority assessment was made among these subgroups.

Disposition of Patients:

Patients were enrolled at 29 study centers. One site (515) screened, but did not enroll any patients. The first patient signed informed consent on January 27, 2006, and the last patient completed the last visit on March 19, 2007.

A total of 396 patients were screened for this study and of these, 179 patients were screen failures. The most frequent cause of screen failure was exclusionary laboratory measurement: 130 (72.6%) patients. Two hundred and seventeen patients were randomized: 144 were assigned to sevelamer carbonate powder QD and 73 were assigned to sevelamer hydrochloride tablets TID, reflecting the 2:1 randomization design. Four [3 (2.1%) sevelamer carbonate powder QD patients; 1 (1.4%) sevelamer hydrochloride tablet TID patient] of the randomized patients never received study treatment. A total of 62 [51 (35.4%) sevelamer carbonate powder QD patients; 11 (15.1%) sevelamer hydrochloride tablet TID patients] discontinued from the study prematurely. The most frequent causes of discontinuation were adverse event [18 (12.5%) sevelamer carbonate powder QD patients; 4 (5.5%) sevelamer hydrochloride tablet TID patients] and withdrawn consent [18 (12.5%) sevelamer carbonate powder QD patients; 2 (2.7%) sevelamer hydrochloride tablet TID patients]. A higher proportion of sevelamer carbonate powder patients discontinued due to an adverse event or consent withdrawn than sevelamer hydrochloride patients. One hundred and fifty five patients completed the study: 93 (64.6%) sevelamer carbonate powder QD patients and 62 (84.9%) sevelamer hydrochloride tablet TID patients.

Table 4: Patient Disposition by Treatment Group

	Overall	Sevelamer Carbonate Powder QD	Sevelamer Hydrochloride Tablet TID
Screened	396		
Screen Failures			
Withdrawal of Consent Prior to Visit 2 or Visit 3	12 (6.7)		
Exclusionary Medical or Medication History	17 (9.5)		
Exclusionary Laboratory Measurement	130 (72.6)		
Adverse Experience	5 (2.8)		
Other	15 (8.4)		
Randomised Patients	217	144	73
Never Received Study treatment	4 (1.8)	3 (2.1)	1 (1.4)
Discontinued Prematurely			
Adverse Experience	22 (10.1)	18 (12.5)	4 (5.5)
Failure to Comply with Protocol Requirements	4 (1.8)	4 (2.8)	0 (0)
Withdrew Consent	20 (9.2)	18 (12.5)	2 (2.7)
Lost to Follow-up	2 (0.9)	1 (0.7)	1 (1.4)
Death	3 (1.4)	1 (0.7)	2 (2.7)
Other	11 (5.1)	9 (6.3)	2 (2.7)
Completed Study	155 (71.4)	93 (64.6)	62 (84.9)

Two additional sevelamer carbonate powder QD and two additional sevelamer hydrochloride tablet TID patients died during the course of the study. These deaths were not specified as the primary cause of early termination and thus are not included in this table.

Reviewer's comment:

It is interesting to note that the powder formulation given once a day had more drop-outs as this formulation is being developed for the patients' convenience.

Protocol Deviations

There were 5 major protocol deviations among 4 patients (Patients 503111, 505104, 506101 and 522108). Patient 503111 experienced a prolonged hospitalization

During this hospitalization, the patient did not take sevelamer hydrochloride. The prolonged hospitalization also resulted in the final study visit being more than 5 weeks delayed. Patient 505104 had their dose of sevelamer hydrochloride increased to 16.8 g/day (greater than allowed per protocol) on August 10, 2006. The dose was reduced to within protocol specifications (14.4 g/day) on October 4, 2006. Patient 506101 returned 519 sevelamer hydrochloride tablets at the end of study visit. The study site believed the patient's nursing home gave her their supply of sevelamer hydrochloride instead of the patient's study treatment. Patient 522108 received hemodialysis 4 times per week rather than three times per week as specified by the protocol due to interdialytic weight gain.

b(6)

6.1.4 Efficacy Findings

6.1.4.1 Study SVCARB00205

Primary Efficacy Variable:

The primary efficacy measure was a time-weighted average of the serum phosphorus assessments during the last two weeks of each treatment regimen (mean of non-missing assessments from Weeks 3, 3a, 4, and 4a for Treatment Period 1 and mean of non-missing assessments from Weeks 7, 7a, 8, and 8a for Treatment Period 2). Blood samples taken for analysis on the same day as HD were taken just prior to the start of dialysis.

Statistical Methods

Categorical variables were described using frequencies and percents. Continuous variables were described by the number of patients with non-missing assessments, mean, standard deviation, median, minimum, and maximum. All tests were two-sided and were performed at the 5% significance level unless otherwise specified.

The original randomization envelope for Site 02 was misplaced and the randomization envelope originally intended for Site 05 was used instead (as Site 05 was not used to recruit any patients). Therefore, patients enrolled at Site 02 were assigned patient identification numbers designated for Site 05 (0501, etc) and appear as such in the patient data listings.

Analysis Populations:

All patients were administered their treatment assignments in accordance with their randomized sequence assignments. Therefore, for each analysis population, patients were analyzed according to their randomized sequence.

Safety Set:

The Safety Set included all randomized patients who were treated with at least one dose of randomized study medication.

Full Analysis Set:

The Full Analysis Set (FAS) included the subset of Safety Set-evaluable patients with at least one post-baseline assessment of serum phosphorus. A confirmatory assessment of phosphorus control equivalence was conducted using the FAS.

Per Protocol Set:

The Per Protocol Set (PPS) included all FAS-evaluable patients with no significant protocol deviations, as determined by a blinded review by appropriate clinical and statistical personnel prior to data analysis. Factors that were considered in determining PPS evaluability included:

- Compliance differences between treatment periods (i.e., at least 30% difference in compliance)
- Entry criteria violation
- Proscribed medication usage
- Completed less than 3 weeks treatment in either treatment period
- Other significant protocol deviations

The primary assessment of phosphorus control equivalence was conducted using the PPS.

Demographics:

Demographics and baseline characteristics were summarized overall and by treatment sequence for all analysis sets. Treatment sequences were compared using Fisher's exact test for categorical data and the Wilcoxon rank sum test for continuous data. Categorical summaries were presented for gender, ethnicity and smoking status. Continuous summaries were presented for age and baseline assessments of weight, height, and body mass index (BMI). Age in years was calculated as $((\text{Date of informed consent} - \text{Date of birth}) + 1)/365.25$. Baseline weight and height measurements were captured at Week 0. BMI was calculated as weight in kilograms divided by square of height in meters. The weight measurement captured at Week -4 was listed only.

Medical history findings at Screening were tabulated by body system, both overall and by treatment sequence for all analysis sets. Renal history findings at Screening were summarized overall and by treatment sequence for all analysis sets. Treatment sequences were compared using Fisher's exact test for categorical data and the Wilcoxon rank sum test for continuous data. Categorical summaries were provided for primary cause of end stage renal disease, dialysis schedule, current phosphate binder use, previous parathyroidectomy, use of vitamin D, and kidney transplant. Continuous summary statistics were reported for length of time on dialysis. Length of time on dialysis in years was calculated as $((\text{Date of informed consent} - \text{Date of dialysis start}) + 1)/365.25$.

Compliance:

Percent compliance was calculated as the number of tablets/sachets taken in the period (estimated by subtracting the number of tablets/sachets returned from the number dispensed) divided by the total number of tablets/sachets prescribed in the period, and multiplied by 100.

Efficacy Analysis:

Primary Efficacy Analysis:

The effects of powder and tablet dosing on the control of serum phosphorus was determined using equivalence testing. The time-weighted average of the serum phosphorus assessments during the last two weeks of each treatment regimen (mean of non-missing assessments from Weeks 3, 3a, 4, and 4a for Treatment Period 1 and mean of non-missing assessments from Weeks 7, 7a, 8, and 8a for Treatment Period 2) was used to give a more accurate assessment of phosphorus control than would be attained by a single point reading. Measurements prior to Week 3 for Treatment Period 1 and prior to Week 7 for Treatment Period 2 were not carried forward for efficacy assessment.

Equivalence was assessed using natural-log transformed time-weighted mean serum phosphorus data. Least squares means for each treatment and the mean squared error from a 2x2 analysis of variance (ANOVA) with a random subject effect and fixed sequence, period, and treatment effects were used to derive the 90% confidence interval for the difference between powder (test) and tablet (reference) data on the log scale. Back transformation to the original scale yielded an estimate of the ratio (test/reference) and corresponding 90% confidence interval which was the basis of a 5% Two One-Sided Test (TOST) equivalence test. This test required that the 90% confidence interval for the ratio was within the interval (0.80, 1.25). If the sequence effect was significant ($p\text{-value} \leq 0.05$), then equivalence inferences were to be drawn from the Treatment Period 1 results.

The primary analysis was performed on the PPS to minimize the degree of bias in the equivalence testing. A FAS analysis was performed as a confirmatory analysis.

Secondary Efficacy Analyses are not reviewed here.

Additional Analyses: Serum phosphorus, calcium (albumin-adjusted), and calcium-phosphorus product levels at Screening, at Week -4 (after the 2-week washout), the change from Screening to Week -4, and at Week 0 were summarized overall and by treatment sequence among PPS, FAS, and Safety Set patients. Within treatment regimen changes were assessed using the Wilcoxon signed rank test.

Protocol Amendment:

There was one protocol amendment, dated May 8, 2006, that was made to increase the number of potential patients that could be considered for the study. A summary of the main changes is given below:

- The number of patients to be screened was changed from approximately 35 to approximately 75 due to a higher than anticipated screening failure rate.
- Sevelamer hydrochloride did not need to be the primary phosphate binder in those patients taking combination therapy before entry into the study.
- Study entry limits of iPTH and serum phosphorus levels measured at the local laboratory were increased due to the variation between local and central laboratory analyses, which meant that

some patients may not be considered eligible by the local analysis and would therefore not be screened.

- Change in sponsor study personnel.

Disposition of Patients:

A total of 75 individual patients were screened for this study of whom 1 patient was re-screened (and is counted twice in pre-randomization disposition data), giving an overall count of 76 patients. Of the screened patients, 34 (44.7%) patients did not enter the Run-In Period: 26 (34.2%) patients were screen failures before the Run-In Period, 4 (5.3%) patients wished to withdraw, 2 (2.6%) patients discontinued due to an AE, and 2 (2.6%) patients withdrew for “other” reasons. The most common reason for screen failure for entry into the Run-In Period was serum phosphorus levels below the required range (i.e., < 5.5 mg/dL [< 1.76 mmol/L]) which was reported for 17 of the 26 screen failure patients.

A total of 42 patients entered the Run-In Period, of whom 11 (14.5%) patients were not randomized: 7 (9.2%) patients were screen failures during the Run-In Period, 1 (1.3%) patient was non-compliant and 3 (3.9%) patients withdrew for “other” reasons. The most common reasons for screen failure during the Run-In Period were high iPTH levels (i.e., > 800 pg/mL) in 3 patients, and high phosphorus levels (i.e., > 6.5 mg/dL [> 2.08 mmol/L]) in 2 patients. In addition, of the 3 patients in the “other” category, the primary reason for withdrawal was noted to be high iPTH levels in 1 patient and high phosphorus levels in the other 2 patients.

Thirty-one patients were randomized to study treatment: 17 to the sevelamer carbonate powder/sevelamer hydrochloride tablet sequence (sequence 1) and 14 to the sevelamer hydrochloride tablet/sevelamer carbonate powder sequence (sequence 2). Of the 31 patients who entered Treatment Period 1, 3 (9.7%) patients discontinued: 1 (3.2%) patient discontinued due to an AE and 2 (6.5%) patients wished to withdraw. The 3 patients who discontinued during Treatment Period 1 were randomized to treatment sequence 1, and therefore discontinued during sevelamer carbonate powder treatment.

A total of 28 patients entered Treatment Period 2: 14 patients from sequence 1 and 14 patients from sequence 2. During Treatment Period 2, 4 (12.9%) patients discontinued: 1 (3.2%) patient discontinued due to an AE and 3 (9.7%) patients wished to withdraw. One of the patients (Patient 0521) who chose to withdraw from the study also had an AE leading to discontinuation, but “patient wishes to withdraw” was cited as the primary reason for withdrawal. The 4 patients who discontinued during Treatment Period 2 were randomized to treatment sequence 2, and therefore discontinued during sevelamer carbonate powder treatment. Overall, a total of 24 (77.4%) of the 31 randomized patients completed Treatment Period 2: 14/17 (82.4%) patients randomized to sequence 1 and 10/14 (71.4%) patients randomized to sequence 2. All patients who completed Treatment Period 2 also completed the Follow-up visit. The patient disposition overall and by treatment sequence is presented in the following table.

Table 5: Patient Disposition (N, %) by Randomized Sequence Group

Patient Category	Overall (N=76)	Sequence 1 Carbonate powder/ Hydrochloride tablets (N=17)	Sequence 2 Hydrochloride tablets/ Carbonate powder (N=14)
Screened Patients	76 [†]		
Patients Who Did Not Enter Run-In Period	34 (44.7)		
Screen failure before Run-In Period	26 (34.2)		
Adverse event	2 (2.6)		
Wishes to withdraw	4 (5.3)		
Other	2 (2.6)		
Patients Entered Run-In Period	42 (55.3)		
Non-Randomised Patients Among Run-In Patients	11 (14.5)		
Screen failure during the Run-In Period	7 (9.2)		
Non-compliant	1 (1.3)		
Other	3 (3.9)		
Randomised Patients	31 (40.8)	17	14
Discontinued Study Drug During Treatment Period 1	3 (9.7)	3 (17.6)	0
Adverse event	1 (3.2)	1 (5.9)	0
Wishes to withdraw	2 (6.5)	2 (11.8)	0
Completed Treatment Period 1	28 (90.3)	14 (82.4)	14 (100.0)
Discontinued Study Drug During Treatment Period 2	4 (12.9)	0	4 (28.6)
Adverse event	1 (3.2)	0	1 (7.1)
Wishes to withdraw	3 (9.7)	0	3 (21.4)
Completed Treatment Period 2	24 (77.4)	14 (82.4)	10 (71.4)
Discontinued Prior to Follow-up Visit	0	0	0
Completed Follow-up Visit	24 (77.4)	14 (82.4)	10 (71.4)

[†] 75 individual patients were screened and of these, 1 patient was re-screened.

Note: percentage values for Screening and Run-In Periods are based on number of screened patients (N=76). Percentage values for randomized treatment periods are based on the number of randomized patients, either overall or in each treatment sequence, as appropriate.

Protocol Deviations:

There were 7 major protocol deviations among 4 patients (Patients 0101, 0306, 0310 and 0311). Three of the 4 patients were included in the PPS as the protocol deviations were not expected to impact the equivalence assessment between treatment regimens. The exception was Patient 0310 who was excluded from the PPS as the patient failed to have at least 3 weeks of treatment in both randomized treatment periods.

Patients 0306, 0310 and 0311 each had one major deviation relating to the dose of sevelamer hydrochloride during the Run-In Period. All 3 patients had serum phosphorus levels at Visit 3 which according to the study protocol required an increase in the dose of study medication. In each case, the investigator preferred that the patient remained on their existing dose of sevelamer hydrochloride, either because they had only been on the dose for only 4 days before the Visit 3 sample was taken (Patients 0310 and 0311) or because the patient had experienced severe stomach cramps following previous dose escalations (Patient 0306).

Patient 0101 had 4 major protocol deviations. Three of the major deviations related to missed

study visits and therefore no blood samples being taken at Visits 3 and 4 during Run-In and Visit 11 during Treatment Period 1. The fourth major deviation in Patient 0101 was an error in the study medication issued to the patient during Treatment Period 1: the patient was randomized to receive sevelamer carbonate powder during Treatment Period 1 but at Visit 10, the research nurse prescribed sevelamer hydrochloride tablets in error, and therefore the cross-over in study medication occurred approximately 3 weeks earlier than scheduled (should have been at Visit 13).

Data Sets Analyzed:

The Safety Set included all randomized patients who received at least one dose of randomized study medication. Thirty-one patients were randomized and treated, and therefore there are 31 patients in the Safety Set.

The FAS included all randomized patients with at least one post-baseline assessment of serum phosphorus. All but 1 patient (Patient 0907) in the Safety Set had post-baseline serum phosphorus data, and therefore there are 30 patients in the FAS.

The PPS included all FAS-evaluable patients with no significant protocol deviations. Nine patients were excluded from the FAS, and therefore the PPS includes 21 patients. The following table presents patient evaluability overall and by treatment sequence.

Table 6: Patient Evaluability

Analysis Set Reason for exclusion	Overall (N=31) n (%)	Sequence 1	Sequence 2
		Carbonate powder/ Hydrochloride tablets (N=17) n (%)	Hydrochloride tablets/Carbonate powder (N=14) n (%)
Randomised	31 (100)	17 (100)	14 (100)
Never received study medication	0	0	0
Included in the Safety Set	31 (100)	17 (100)	14 (100)
No post-baseline phosphorus assessments	1 (3)	1 (6)	0
Included in the Full Analysis Set	30 (97)	16 (94)	14 (100)
At least 30% difference in compliance between treatment periods	3 (10)	1 (6)	2 (14)
Entry criteria violation	0	0	0
Proscribed medication usage	0	0	0
Less than 3 weeks on study treatment in both treatment periods	6 (19)	2 (12)	4 (29)
Included in the Per Protocol Set	21 (68)	13 (77)	8 (57)

Reviewer's comments:

From the above table it is noted that only a few patients were evaluated in this study.

In the Safety Set, all 31 patients received sevelamer carbonate powder treatment and 28 patients received sevelamer hydrochloride tablet treatment. In the FAS, all 30 patients received sevelamer carbonate powder treatment and 28 patients received sevelamer hydrochloride tablet treatment, and all 21 patients in the PPS received both treatment regimens.

Of the 9 FAS patients excluded from the PPS, 6 patients (0310, 0520, 0521, 0522, 0803, and 0903) failed to have at least 3 weeks of treatment in both treatment periods, and 3 patients

(0503, 0505 and 0509) had a differential compliance of at least 30% between randomized treatment periods as the reason for exclusion.

The 6 patients excluded from the PPS for having insufficient treatment duration in both randomized treatment periods all failed to complete at least 3 weeks treatment with sevelamer carbonate powder. Two of the 6 patients (0522 and 0803) withdrew from the study during treatment with sevelamer carbonate powder and never entered the sevelamer hydrochloride tablet randomized treatment period. The remaining 4 patients (0310, 0520, 0521, and 0903) completed the sevelamer hydrochloride tablet randomized treatment period and subsequently withdrew from the study before completing at least 3 weeks treatment with sevelamer carbonate powder.

Of the 3 patients with a differential compliance of at least 30% between randomized treatment periods, Patients 0503 and 0505 had lower compliance during treatment with sevelamer carbonate powder, whereas Patient 0509 had lower compliance during treatment with sevelamer hydrochloride tablets.

It should be noted that Patient 0604 was retained in the PPS even though the difference in compliance between treatment periods was >30%. During Treatment Period 2, the patient had taken sevelamer hydrochloride tablets remaining from their Run-In Period rather than the sevelamer hydrochloride tablets prescribed for the randomized treatment period. Therefore, based on the study drug supply returned at the end of Treatment Period 2, it appeared that the patient had a low compliance. However, the investigator noted that the patient had good compliance and was therefore kept in the PPS. In addition, Patients 0106, 0311, and 0502 were retained in the PPS even though they had missing compliance data from Treatment Period 2 (drug return data were missing) because there was no other evidence of noncompliance.

Demographics:

The following table displays the demographics and baseline characteristics for the Safety Set (N=31). There were no statistically significant differences between the treatment sequences in demographic characteristics.

Twenty-one (68%) patients were male and 10 (32%) patients were female, with a mean age of 53 years. The majority of patients were Caucasian (71%), with Asians (19%) and Blacks (10%) comprising the rest of the population. The mean weight was 76 kg (n=30), the mean height was 170 cm (n=23), and the mean BMI was 26 kg/m² (n=23).

Results for the PPS and FAS were generally similar to those of the Safety. The most notable difference between the Safety Set and the PPS was in the proportion of Caucasian (71% in the Safety Set and 81% in the PPS) and Asian patients (19% in the Safety Set compared with 5% in the PPS) in each analysis population. These differences were not considered to have any impact on the outcome of the efficacy analyses.

Table 7: Patient Demographics and Baseline Characteristics (Safety Set)

Demographic Characteristic	Safety Set (N=31)
Age (years)	
Mean ± SD	52.9 ± 13.2
Median (range)	51 (27-80)
Gender, n (%)	
Male	21 (68)
Female	10 (32)
Ethnicity, n (%)	
Caucasian	22 (71)
Black	3 (10)
Hispanic	0
Asian	6 (19)
Weight (kg) at Week 0 (n=30)	
Mean ± SD	75.9 ± 19.9
Median (range)	72.2 (43.7-140.3)
Height (cm) at Week 0 (n=23)	
Mean ± SD	170.3 ± 13.3
Median (range)	171 (150-198)
BMI (kg/m ²) at Week 0 (n=23)	
Mean ± SD	25.7 ± 5.8
Median (range)	24.1 (19.3-39.6)
Smoker, n (%)	
Yes	5 (16)
No	26 (84)

SD= Standard deviation

Renal History:

Renal history is presented in the following table. There were no statistically significant differences between the treatment sequences in renal history characteristics. The most common primary causes of CKD were glomerulonephritis (26%), diabetes (13%) and “other” causes (42%). Of the 13 patients with “other” cited as the primary cause, the etiology of CKD was recorded as unknown in 5 patients, IgA nephropathy in 2 patients and renovascular disease, reflux nephropathy, road traffic accident, hereditary nephritis, Goodpasture syndrome, and Alport’s syndrome in 1 patient each. Eight (26%) patients in the Safety Set had previously undergone a kidney transplant and 4 (13%) patients had a parathyroidectomy (3 total and 1 partial). The median time on dialysis was 4.4 years.

The majority of patients (81%) were on vitamin D at study entry. All randomized patients were taking sevelamer hydrochloride as a pre-study phosphate binder, either alone (58%), in combination with calcium phosphate binders (36%), or in combination with other metal phosphate binders (7%); 1 patient was taking sevelamer hydrochloride in combination with aluminum and 1 patient was taking sevelamer hydrochloride in combination with magnesium carbonate.

Table 8: Renal History (Safety Set)

Parameter	Safety Set (N=31)
Primary Cause of End Stage Renal Disease, n (%)	
Hypertension	1 (3)
Glomerulonephritis	8 (26)
Diabetes	4 (13)
Pyelonephritis	1 (3)
Polycystic Kidneys	2 (7)
Interstitial Nephritis	1 (3)
Congenital	1 (3)
Other	13 (42)
Previous Kidney Transplant, n (%)	
No	23 (74)
Yes	8 (26)
Previous Parathyroidectomy, n (%)	
No	27 (87)
Yes	4 (13)
Currently on Vitamin D, n (%)	
No	6 (19)
Yes	25 (81)
Time on Dialysis (years)	
Mean ± SD	7.2 ± 8.0
Median (range)	4.4 (0.2-30.3)
Pre-Study Phosphate Binder, n (%)	
Sevelamer Hydrochloride	18 (58)
Sevelamer Hydrochloride and Calcium	11 (36)
Other	2 (7)

Medical History:

Reflective of the extent of chronic illness in the patient population, more than half of the patients in the overall Safety Set (N=31) reported prior or current disorders or abnormalities in the following body systems: genitourinary/renal (30 patients, 97%), metabolic/endocrine/nutritional (27 patients, 87%), hematopoietic (27 patients, 87%), cardiovascular (27 patients, 87%), gastrointestinal/hepatic (21 patients, 68%), and musculoskeletal (19 patients, 61%). In general, the prior and current disorders were similar between the two treatment sequences.

Concomitant Medications During the Randomized Treatment Periods:

During the randomized treatment periods, all 31 (100%) patients in the Safety Set took a concomitant medication. The drug categories with the most frequent (> 25%) concomitant medications are presented in the following table.

Table 9: Most Frequent Concomitant Medications Taken During Randomized Treatment

Therapeutic Class	Sevelamer Carbonate Powder (N=31) n (%)	Sevelamer Hydrochloride Tablets (N=28) n (%)
Other anti-anaemic preparations	29 (94)	26 (93)
Vitamin D and analogues	26 (84)	22 (79)
Platelet aggregation inhibitors excl. heparin	19 (61)	17 (61)
Proton pump inhibitors	15 (48)	13 (46)
HMG CoA reductase inhibitors	13 (42)	11 (39)
Beta blocking agents, selective	9 (29)	10 (36)
Dihydropyridine derivatives	9 (29)	9 (32)
ACE inhibitors, plain	9 (29)	8 (29)
Anilides	9 (29)	8 (29)
Multivitamins, plain	8 (26)	7 (25)

During the randomized treatment periods, 16 (52%) patients began new medications, or stopped or had changes in existing medications during treatment with sevelamer carbonate powder and 11 (39%) patients during treatment with sevelamer hydrochloride tablets. The concomitant medications changes were similar between treatment regimens and generally similar to the medication changes made during the Run-In Period.

In the Safety Set, the drug categories with the most frequent concomitant medication changes (at least 10%) were penicillins with extended spectrum, changed by 3 (10%) patients during sevelamer carbonate treatment and 1 (4%) patient during sevelamer hydrochloride treatment, and vitamin D and analogues that were changed by 3 (10%) patients during sevelamer carbonate powder treatment and no patients during sevelamer hydrochloride tablet treatment.

During the randomized treatment periods, mean percent compliance of the Safety Set and the FAS was similar between the sevelamer carbonate and sevelamer hydrochloride regimens: 81% for sevelamer carbonate powder and 83% for sevelamer hydrochloride tablets in both analysis sets.

Analysis of Efficacy:

The primary efficacy analysis was performed on the PPS to minimize the degree of bias in the equivalence testing. A FAS analysis was performed as a confirmatory analysis.

In the PPS, the mean serum phosphorus was 5.0 ± 1.5 mg/dL (1.6 ± 0.5 mmol/L) during sevelamer carbonate powder treatment and 5.2 ± 1.1 mg/dL (1.7 ± 0.4 mmol/L) during sevelamer hydrochloride tablet treatment. For assessing phosphorus equivalence, the treatment response across sequences was pooled since the 2x2 ANOVA model sequence p-value was not significant ($p=0.932$). The geometric least squares mean ratio (sevelamer carbonate powder/sevelamer hydrochloride tablets) was 0.95 with a corresponding 90% confidence interval of 0.87-1.03. The confidence interval is within the interval of 0.80-1.25, indicating that sevelamer carbonate powder and sevelamer hydrochloride tablets are equivalent in controlling serum phosphorus. The results of a confirmatory analysis conducted with the FAS were similar as shown in the following table.

Table 10: Serum Phosphorus Time-Weighted Averages (PPS and FAS)

Analysis Set	Sevelamer Carbonate Powder mean \pm SD	Sevelamer Hydrochloride Tablets mean \pm SD	Geometric LS Mean Ratio	90% CI of Ratio
Serum phosphorus (mg/dL)				
Per Protocol Set (N=21)	5.0 ± 1.5 (n=21)	5.2 ± 1.1 (n=21)	0.95	0.87-1.03
Full Analysis Set (N=30)	5.0 ± 1.5 (n=25)	5.1 ± 1.1 (n=28)	0.96	0.88-1.05
Serum phosphorus (mmol/L)				
Per Protocol Set (N=21)	1.6 ± 0.5 (n=21)	1.7 ± 0.4 (n=21)	0.95	0.87-1.03
Full Analysis Set (N=30)	1.6 ± 0.5 (n=25)	1.7 ± 0.4 (n=28)	0.96	0.88-1.05

SD = Standard deviation

Statistical Reviewer's comment:

It is notable that the drop-outs were relatively high in carbonate powder group in both periods, 17.6% (3/17) and 28.6% (4/14) in period 1 and period 2, respectively (Table 10). The reviewer conducted a sensitivity analysis using a worse-case imputation method for missing data: a maximum phosphate value of the period was assigned to the missing values. The result is comparable with the one excluding missing values. However, the conclusion of efficacy is still a concern given a small study with high drop-outs.

Serum Phosphorus During Screening/Washout and Run-In:

Prior to the randomized treatment periods, patients entered a 2-week Screening/Washout period followed by a 4-week sevelamer hydrochloride Run-In Period. The mean serum phosphorus at Screening in the PPS was 5.0 ± 1.0 mg/dL (1.6 ± 0.3 mmol/L). At the end of the Washout period (Week -4), mean serum phosphorus levels had increased significantly (mean change 2.7 ± 2.1 mg/dL [0.9 ± 0.7 mmol/L]; $p < 0.001$) to 7.6 ± 1.8 mg/dL (2.5 ± 0.6 mmol/L) confirming the hyperphosphatemic nature of the study population. Serum phosphorus levels subsequently decreased during the 4-week sevelamer hydrochloride Run-In Period and at the start of the randomized treatment period (Week 0), the mean value was 5.0 ± 1.2 mg/dL (1.6 ± 0.4 mmol/L) and comparable to Screening levels. The change in serum phosphorus during the Screening/Washout and Run-In Period in the FAS and Safety Set was similar to that observed for the PPS.

Handling of Dropouts or Missing Data:

The primary efficacy measure was the time-weighted average of the serum phosphorus assessments for the non-missing assessments (scheduled and unscheduled) from the last two weeks in each treatment regimen because this methodology can accommodate the varying number of assessments that could arise during the two week period and the varying intervals between assessments. Missing data were not imputed and measurements were not carried forward.

Interim Analyses:

No interim analyses were performed.

Efficacy Conclusions:

Sevelamer carbonate powder and sevelamer hydrochloride tablets, each dosed TID with meals, are equivalent in controlling serum phosphorus in patients with CKD on HD.

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Table 11: Summary of Analysis Populations

	Overall	Sevelamer Carbonate Powder QD	Sevelamer Hydrochloride Tablets TID
Randomised	217	144	73
Never Received Study treatment	4 (1.8%)	3 (2.1%)	1 (1.4%)
Safety Set	213	141	72
No post-dosing phosphorus assessments	0 (0%)	0 (0%)	0 (0%)
Included in Full Analysis Set	213	141	72
Less than 8 weeks of treatment	26 (12.2%)	21 (14.9%)	5 (6.9%)
Compliance (< 70%)	37 (17.4%)	23 (16.3%)	14 (19.4%)
Inclusion or exclusion criteria violation	1 (0.5%)	0 (0%)	1 (1.4%)
Use of proscribed medication	0 (0%)	0 (0%)	0 (0%)
Other significant protocol violation	1 (0.5%)	0 (0%)	1 (1.4%)
Per-Protocol Set	148	97	51

Demographics:

The demographic characteristics were similar between treatment groups. The majority of patients in both groups were male (62% and 58% in the sevelamer carbonate powder QD group and sevelamer hydrochloride tablet TID group, respectively) and African American (54% in both groups). The mean age was just under 60 years old for both groups (57 and 59 years in the sevelamer carbonate powder QD group and sevelamer hydrochloride tablet TID group, respectively). Results for the FAS and PPS were similar to those of the Safety Set.

Table 12: Patient Demographics-Safety Set

Parameter	Sevelamer Carbonate Powder QD (N=141)	Sevelamer Hydrochloride Tablet TID (N=72)	P-Value*
Race [N (%)]			0.254
African American	76 (53.9)	39 (54.2)	
White	59 (41.8)	32 (44.4)	
Other	6 (4.3)	1 (1.4)	
Age (years)			0.254
Mean ± SD	56.7 ± 14.2	59.0 ± 13.8	
Median (Range)	58.0 (20-85)	59.5 (27-82)	
Gender [N (%)]			0.659
Male	87 (61.7)	42 (58.3)	
Female	54 (38.3)	30 (41.7)	
History of Diabetes [N (%)]			> 0.999
Yes	79 (56.0)	40 (55.6)	
No	62 (44.0)	32 (44.4)	
Post-Dialysis Weight (lbs)			0.658
Mean ± SD	186.7 ± 47.3	187.8 ± 57.4	
Median (Range)	185.0 (60-339)	178.0 (65-364)	
Height (inches)			0.639
Mean ± SD	67.5 ± 4.1	67.1 ± 5.1	
Median (Range)	68.0 (56.0-75.9)	67.0 (45.7-75.2)	
Body Mass Index (lbs/inches ²)			0.907
Mean ± SD	28.8 ± 6.8	29.4 ± 8.4	
Range	28.2 (10.8-53.9)	28.9 (10.5-54.2)	
Stratification Criteria [N (%)]			0.959
Cinacalcet Use and iPTH ≤ 400 pg/mL (400 ng/L)	34 (24.1)	15 (20.8)	
Cinacalcet Use and iPTH > 400 pg/mL (400 ng/L)	12 (8.5)	6 (8.3)	
No cinacalcet use and iPTH ≤ 400 pg/mL (400 ng/L)	77 (54.6)	42 (58.3)	
No cinacalcet use and iPTH > 400 pg/mL (400 ng/L)	18 (12.8)	9 (12.5)	

*Fisher's Exact Test for categorical variables and Wilcoxon Rank Sum Test for continuous variables.

Renal History:

Renal history was similar between treatment groups. The three most common primary causes of chronic kidney disease as assigned by the Investigators were diabetes (40% and 35% in the sevelamer carbonate powder QD group and sevelamer hydrochloride tablet TID group, respectively), hypertension (29% and 33% in the sevelamer carbonate powder QD group and sevelamer hydrochloride tablet TID group, respectively), and other causes (16% and 21% in the

sevelamer carbonate powder QD group and sevelamer hydrochloride tablet TID group, respectively). The majority of patients were currently receiving vitamin D (85% for both treatment groups). Patients had been on dialysis for a mean of 44 months in the sevelamer carbonate QD group and 53 months in the sevelamer hydrochloride tablet TID group. There was a statistically significant difference between the treatment groups in time on dialysis ($p=0.048$), but this difference was not considered clinically meaningful. Results for the FAS and PPS were similar to those of the Safety Set except in the PPS there was no statistically significant difference between the treatment groups in time on dialysis.

Table 13: Renal History-Safety Set

Parameter	Sevelamer Carbonate Powder QD (N=141)	Sevelamer Hydrochloride Tablet TID (N=72)	P-Value*
Primary Cause of Chronic Renal Failure [N (%)]			0.511
Hypertension	41 (29.1)	24 (33.3)	
Glomerulonephritis	15 (10.6)	4 (5.6)	
Diabetes	57 (40.4)	25 (34.7)	
Pyelonephritis	0 (0)	0 (0)	
Polycystic Kidneys	2 (1.4)	3 (4.2)	
Hydronephrosis	0 (0)	0 (0)	
Interstitial Nephritis	3 (2.1)	1 (1.4)	
Other	23 (16.3)	15 (20.8)	
Time on Dialysis (months)			0.048
Mean \pm SD	44.4 \pm 45.0	52.6 \pm 43.9	
Median (Range)	30.9 (3.0 - 320.1)	39.9 (2.9-233.3)	
Vitamin D Use at Screening [N (%)]			> 0.999
No	21 (14.9)	11 (15.3)	
Yes	120 (85.1)	61 (84.7)	
Previous Parathyroidectomy [N (%)]			0.381
No	136 (96.5)	71 (98.6)	
Partial Parathyroidectomy	4 (2.8)	0 (0)	
Total Parathyroidectomy	1 (0.7)	1 (1.4)	

*Fisher's Exact Test for categorical variables and Wilcoxon Rank Sum Test for continuous variables.

Medical History:

Reflective of the extent of chronic illness in the patient population, more than half of the patients in the Safety Set reported clinically significant history in the following body systems: cardiovascular (98.6%), renal (97.7%), endocrine/metabolic (95.3%), hematological conditions (92.5%), gastrointestinal (85.9%), musculoskeletal (83.6%), respiratory (66.7%), head, eyes, ears, nose, and throat (HEENT) (66.2%), neurological (58.7%), urological/reproductive (55.9%), allergies (51.2%) and dermatologic (50.2%). There were no statistically significant differences between the treatment groups in medical history. Results for the FAS and PPS were similar to those of the Safety Set.

Prior Medications:

All patients (100%) had taken at least one prior medication. The most common classes of prior medication (> 25% of patients) were vitamins (98%), antianemic preparations (97%), antithrombotic agents (81%), all other therapeutic products (68%), antacids (55%), beta blockers (52%), lipid reducing agents (52%), agents acting on the renin-angiotension system (50%), analgesics (46%), calcium channel blockers (41%), diabetes drugs (40%), mineral supplements (40%), thyroid therapy (38%), antihypertensives (33%), and psycholeptics (25%). The percentage of patients using prior medications was similar between treatment groups with the exception (> 10% difference between treatment groups) of analgesics: 50% in the sevelamer carbonate powder QD group and 38% in the sevelamer hydrochloride tablet TID group.

Concomitant Medications:

During the randomized treatment period, all (100%) patients in the Safety Set took at least one concomitant medication. The drug categories with the most frequent (> 25%) concomitant medications are presented in the following table. The most frequent categories of concomitant medications were vitamins, antianemic preparations, and antithrombotic agents. The percentage of patients using concomitant medications was similar between treatment groups with the exception (> 10 % difference between the treatment groups) of antibacterials (33% for the sevelamer carbonate powder QD group and 49% for the sevelamer hydrochloride tablet TID group) and cardiac therapy (26% for the sevelamer carbonate powder QD group and 39% for the sevelamer hydrochloride tablet TID group). The results for the PPS are similar.

Table 14: Most Frequent (>25 %) Concomitant Medications Taken During Randomized Treatment Period-Safety Set

Therapeutic Class	Sevelamer Carbonate Powder QD (N=141) (%)	Sevelamer Hydrochloride Tablet TID (N=72) (%)
Vitamins	98	100
Antianaemic Preparations	96	99
Antithrombotic Agents	84	89
Analgesics	62	53
Antacids	56	62
Serum Lipid Reducing Agents	56	49
Beta Blocking Agents	53	58
Agents Acting on the Renin-Angiotension System	49	58
Calcium Channel Blockers	45	39
Thyroid Therapy	43	38
Diabetes Drugs	41	40
Psycholeptics	38	29
Antihypertensives	36	38
Antibacterials	33	49
Vaccines	30	39
Blood Substitutes	29	33
Cardiac Therapy	26	39
Laxatives	21	29

Dialysate Bath Bicarbonate Concentration:

In the Safety Set, the mean baseline bicarbonate concentration in the dialysate bath was 37.0 mEq/L and 36.7 mEq/L for the sevelamer carbonate powder QD and sevelamer hydrochloride tablet TID groups, respectively. The mean bicarbonate concentration at Week 24/ET was 36.9 mEq/L and 36.8 mEq/L for the sevelamer carbonate powder QD and sevelamer hydrochloride tablet TID groups, respectively. There was no statistically significant change in dialysate bath bicarbonate concentration within groups and no statistically significant difference in the change in bicarbonate concentration between groups.

Dietary Evaluation:

For the PPS, dietary intake parameters pre-treatment and late during the randomized treatment period (Weeks 22 to 24) are presented in the following table. For most dietary parameters, there were slight decreases in the sevelamer carbonate powder QD group and slight increases in the sevelamer hydrochloride tablet TID group. There were, however, no statistically significant changes from baseline in dietary intake within treatment groups and no statistically significant

differences in the change in dietary intake between the treatment groups. These results suggest that the efficacy results were not influenced by dietary changes. The results for the Safety Set and FAS are similar except that there was a statistically significant increase in dietary calcium intake in the sevelamer carbonate powder QD group ($+76.6 \pm 269.9$ mg/day, $p=0.031$ for both Safety Set and FAS). The change in dietary calcium was statistically different between the treatment groups ($p=0.049$).

Table 15: Dietary Intake-PPS

Parameter	Sevelamer Carbonate Powder QD (N=97) [mean \pm SD]	Sevelamer Hydrochloride Tablet TID (N=51) [mean \pm SD]	P-value*
Phosphorus (mg/day)			0.185
Pre-treatment washout	798.5 \pm 239.1	783.9 \pm 278.6	
Late treatment	825.2 \pm 231.4	761.0 \pm 311.3	
Change from Pre-treatment washout to Late treatment	34.4 \pm 237.9	-43.1 \pm 243.9	
P-Value [^]	0.515	0.384	
Calcium (mg/day)			0.071
Pre-treatment washout	417.6 \pm 165.7	435.8 \pm 297.1	
Late treatment	457.8 \pm 179.4	373.4 \pm 179.9	
Change from Pre-treatment washout to Late treatment	-42.0 \pm 228.9	-69.0 \pm 264.4	
P-Value [^]	0.103	0.267	
Vitamin D (mcg/day)			0.457
Pre-treatment washout	3.5 \pm 3.6	3.6 \pm 3.0	
Late treatment	3.1 \pm 1.9	3.2 \pm 3.3	
Change from Pre-treatment washout to Late treatment	-0.8 \pm 4.0	-0.5 \pm 4.1	
P-Value [^]	0.677	0.209	
Energy (kcal/day)			0.485
Pre-treatment washout	1411.0 \pm 433.2	1338.1 \pm 436.4	
Late treatment	1471.0 \pm 557.5	1286.7 \pm 518.6	
Change from Pre-treatment washout to Late treatment	82.9 \pm 548.5	-50.0 \pm 294.7	
P-Value [^]	0.863	0.411	
Total Protein (g/day)			0.285
Pre-treatment washout	61.8 \pm 18.8	62.7 \pm 22.7	
Late treatment	63.1 \pm 18.5	59.9 \pm 24.1	
Change from Pre-treatment washout to Late treatment	1.1 \pm 18.0	-4.4 \pm 20.8	
P-Value [^]	0.480	0.397	
Parameter	Sevelamer Carbonate Powder QD (N=97) [mean \pm SD]	Sevelamer Hydrochloride Tablet TID (N=51) [mean \pm SD]	P-value*
Cholesterol (mg/day)			0.193
Pre-treatment washout	267.5 \pm 182.1	300.6 \pm 162.5	
Late treatment	302.2 \pm 185.9	269.4 \pm 153.5	
Change from Pre-treatment washout to Late treatment	25.0 \pm 188.8	-37.3 \pm 161.0	
P-Value [^]	0.446	0.310	
Total Carbohydrate (g/day)			0.963
Pre-treatment washout	167.1 \pm 63.9	150.0 \pm 57.6	
Late treatment	168.0 \pm 83.4	151.6 \pm 71.6	
Change from Pre-treatment washout to Late treatment	10.1 \pm 87.1	3.9 \pm 45.7	
P-Value [^]	0.629	0.823	
Fat (g/day)			0.149
Pre-treatment washout	55.7 \pm 20.2	55.0 \pm 20.5	
Late treatment	61.5 \pm 27.2	49.7 \pm 21.3	
Change from Pre-treatment washout to Late treatment	4.7 \pm 27.7	-5.4 \pm 14.9	
P-Value [^]	0.637	0.079	

*P-value is from Wilcoxon Rank Sum test

[^]P-value is from Wilcoxon Signed Rank test

Note: The number of observations varies in the statistics shown. Please refer to the end of text tables for details.

Measurements of Treatment Compliance:

During the randomized treatment period, mean percent compliance in the Safety Set and the FAS was similar between groups (86% for sevelamer carbonate powder QD group and 85% for sevelamer hydrochloride tablet TID group, respectively). Patients with <70% compliance during the treatment period were excluded from the PPS. The mean percent compliance in the PPS set was also similar between treatment groups (90% for sevelamer carbonate powder QD group and 91% for sevelamer hydrochloride tablet TID group).

Change in Serum Phosphorus:

In the PPS, the mean serum phosphorus pre-washout was 5.2 ± 1.1 mg/dL (1.68 ± 0.37 mmol/L) for the sevelamer carbonate powder QD group and 5.3 ± 1.0 mg/dL (1.72 ± 0.32 mmol/L) for the

sevelamer hydrochloride tablet TID group. Following the two week phosphate binder washout (Week 0), the mean serum phosphorus 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 confirming that this population was hyperphosphatemic. 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 (both $p < 0.001$) 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 both 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 comparable, thus confirming these findings. The following table presents the change from baseline to Week 24/ET for serum phosphorus for both the PPS and the FAS.

Table 16: Change in Serum Phosphorus

	Sevelamer Carbonate Powder QD [mean \pm SD]	Sevelamer Hydrochloride Tablets TID [mean \pm SD]	2-sided 95% CI†
Serum Phosphorus (mg/dL)			
Per Protocol Set	N=97	N=51	
Pre-washout	5.2 \pm 1.1	5.3 \pm 1.0	
Baseline	7.3 \pm 1.3	7.6 \pm 1.3	
Week 24/ET	5.3 \pm 1.4	4.6 \pm 1.0	
Change	-2.0 \pm 1.8	-2.9 \pm 1.3	0.39, 1.50
P-value [^]	< 0.001	< 0.001	
Full Analysis Set	N=141	N=72	
Pre-washout	5.3 \pm 1.1	5.3 \pm 1.0	
Baseline	7.3 \pm 1.4	7.4 \pm 1.3	
Week 24/ET	5.4 \pm 1.4	4.9 \pm 1.2	
Change	-1.9 \pm 1.7	-2.5 \pm 1.6	0.19, 1.12
P-value [^]	< 0.001	< 0.001	
Serum Phosphorus (mmol/L)			
Per Protocol Set	N=97	N=50	
Pre-washout	1.68 \pm 0.37	1.72 \pm 0.32	
Baseline	2.36 \pm 0.43	2.45 \pm 0.41	
Week 24/ET	1.71 \pm 0.45	1.50 \pm 0.32	
Change	-0.66 \pm 0.57	-0.96 \pm 0.42	0.12, 0.48
P-value [^]	< 0.001	< 0.001	
Full Analysis Set	N=141	N=72	
Pre-washout	1.70 \pm 0.36	1.72 \pm 0.31	
Baseline	2.34 \pm 0.44	2.39 \pm 0.41	
Week 24/ET	1.73 \pm 0.46	1.58 \pm 0.38	
Change	-0.61 \pm 0.54	-0.82 \pm 0.50	0.06, 0.36
P-value [^]	< 0.001	< 0.001	

[^]P-value is from Wilcoxon Signed Rank Test

† 95% CI on difference = sevelamer carbonate powder QD – sevelamer hydrochloride tablet TID. If upper confidence bound is < 1 then non-inferiority was to be concluded.

A post-hoc analysis was performed to understand the serum phosphorus results across dose level. The following table presents the change in serum phosphorus by average prescribed dose. The change in serum phosphorus in the 2.4 to 4.8 g group was similar for both sevelamer carbonate powder QD and sevelamer hydrochloride tablet TID groups. In the sevelamer hydrochloride tablet TID group, the change in serum phosphorus was greater at higher doses. In the sevelamer carbonate powder QD group there was no dose response.

Table 17: Serum Phosphorus by Average Prescribed Dose

Dose Groups (g/day)	Sevelamer Carbonate Powder QD	Sevelamer Hydrochloride Tablet TID
Serum Phosphorus (mg/dL)		
2.4-4.8		
N	23	10
Mean Change	-2.13	-2.18
≥ 4.8-9.6		
N	44	25
Mean Change	-2.09	-2.93
>9.6		
N	29	13
Mean Change	-1.75	-3.51
Serum Phosphorus (mmol/L)		
2.4-4.8		
N	23	10
Mean Change	-0.69	-0.70
≥ 4.8-9.6		
N	44	25
Mean Change	-0.68	-0.95
>9.6		
N	29	13
Mean Change	-0.56	-1.13

Time Weighted Average of Serum Phosphorus;

In the PPS, the mean time weighted (excluding the first month of treatment) 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 statistically significantly different between treatment groups ($p=0.021$). Likewise, in the FAS, the mean time weighted serum phosphorus was 5.4 ± 1.0 mg/dL (1.75 ± 0.32 mmol/L) for the sevelamer carbonate powder QD group and 5.0 ± 0.8 mg/dL (1.60 ± 0.25 mmol/L) for the sevelamer hydrochloride tablet TID group. The time weighted average was significantly different between treatment groups ($p=0.001$).

Table 18: Time Weighted Average for Serum Phosphorus

	Sevelamer Carbonate Powder QD [mean ± SD]	Sevelamer Hydrochloride Tablets TID [mean ± SD]	P-Value [#]
Serum Phosphorus (mg/dL)			
Per Protocol Set			0.021
n	N=97	N=51	
Mean	5.3 ± 0.9	4.9 ± 0.7	
Full Analysis Set			0.001
n	N=141	N=72	
Mean	5.4 ± 1.0	5.0 ± 0.8	
Serum Phosphorus (mmol/L)			
Per Protocol Set			0.023
n	N=97	N=51	
Mean	1.70 ± 0.30	1.59 ± 0.24	
Full Analysis Set			0.001
n	N=141	N=72	
Mean	1.75 ± 0.32	1.60 ± 0.25	

*P-value is from Wilcoxon Rank Sum Test

Serum Phosphorus Responders:

The percentage of patients responding to therapy [serum phosphorus between 3.5 and 5.5 mg/dL (1.13 and 1.78 mmol/L), inclusive] at each time point is summarized by treatment group in the following table. At the different time points, the percentage of patients responding to treatment ranged from 45.8% to 59.4% in the sevelamer carbonate powder QD group and from 33.3% to 74.5% in the sevelamer hydrochloride tablet TID group. The percentage of patients with a serum phosphorus response was similar between the treatment groups for the first 6 weeks of treatment, but was higher in the sevelamer hydrochloride tablet TID group thereafter. At Week 24/ET, the percentage of serum phosphorus responders in the sevelamer hydrochloride tablet TID group (73%) was higher than in the sevelamer carbonate powder QD group (56%) and approached

statistical significance ($p=0.052$). The results for the FAS are similar for the sevelamer carbonate powder QD group (54%), but the percent response was lower for the sevelamer hydrochloride tablet TID group (64%, $p=0.189$).

Table 19: Serum Phosphorus Responders at Each Time point-PPS

	Sevelamer Carbonate Powder QD (N=97) n (%)	Sevelamer Hydrochloride Tablets TID (N=51) n (%)	P-Value*
Baseline	3 (3.1)	2 (3.9)	
Week 2	44 (45.8)	17 (33.3)	
Week 4	50 (54.3)	27 (54.0)	
Week 6	49 (52.1)	27 (55.1)	
Week 8	53 (55.2)	33 (66.0)	
Week 12	57 (59.4)	35 (70.0)	
Week 16	53 (58.2)	36 (73.5)	
Week 20	48 (54.5)	34 (70.8)	
Week 24	48 (56.5)	35 (74.5)	
Week 24/ET	54 (55.7)	37 (72.5)	0.052

*P-value is from Fisher's Exact Test

Calcium-Phosphorus Product:

The following table presents the change from baseline to Week 24/ET for calcium (albumin-adjusted)-phosphorus product for the FAS. There were statistically significant reductions from baseline in serum calcium-phosphorus product in both the sevelamer carbonate powder QD group and the sevelamer hydrochloride tablet TID group. Between group comparison indicated that the change in serum calcium-phosphorus product was significantly different between treatment groups with greater decreases demonstrated with sevelamer hydrochloride treatment ($p=0.008$).

Table 20: Change in Calcium-Phosphorus Product-Full Analysis Set

	Sevelamer Carbonate Powder QD (N=141) [mean \pm SD]	Sevelamer Hydrochloride Tablets TID (N=72) [mean \pm SD]	P-Value*
Calcium-Phosphorus Product (mg^2/dL^2)			
Baseline	65.1 \pm 13.3	67.0 \pm 13.2	
Week 24/ET	49.4 \pm 13.7	45.9 \pm 13.0	
Change	-15.7 \pm 15.6	-21.0 \pm 16.2	0.008
P-value^	< 0.001	< 0.001	
Calcium-Phosphorus Product (mmol^2/L^2)			
Baseline	5.25 \pm 1.07	5.40 \pm 1.06	
Week 24/ET	3.98 \pm 1.10	3.70 \pm 1.05	
Change	-1.27 \pm 1.25	-1.70 \pm 1.30	0.007
P-value^	< 0.001	< 0.001	

*P-value is from Wilcoxon Rank Sum Test for the change

^P-value is from Wilcoxon Signed Rank Test

Handling of Dropouts or Missing Data:

No missing or invalid observations were imputed. The last on treatment efficacy measure was carried forward to represent the Week 24/ET measurement for patients who terminated from the study prior to Week 24 and had at least one post-washout efficacy measurement. The use of the term Week 24/ET indicates that if patients were withdrawn and/or no measurement was available at Week 24 that the final measured valued was carried forward to Week 24/ET.

Use of an “Efficacy Subset” of Patients:

The primary efficacy analysis of the primary efficacy parameter was conducted using the PPS as this is appropriate for non-inferiority testing. The FAS was used as a confirmatory assessment of non-inferiority. The analysis of all other efficacy endpoints is presented using the FAS as this is generally recommended per ICH E.9. However, data are displayed for the secondary endpoints using both the FAS and PPS.

Efficacy Conclusions:

Sevelamer carbonate powder for oral suspension when dosed once per day with the largest meal is not non-inferior compared to sevelamer hydrochloride tablets when dosed three times per day with meals based on the primary efficacy analysis of a change from baseline in serum phosphorus levels at Week 24/ET among the PPS.

6.1.5 Clinical Microbiology

NA

6.1.6 Efficacy Conclusions

The non-inferiority of sevelamer carbonate has not been established in study GD3-199-301. The equivalence of sevelamer carbonate powder and sevelamer hydrochloride tablets in study SVCARB00205 is questionable because of a small study with high drop-outs. Although the efficacy of sevelamer carbonate powder is inconclusive in this NDA, the efficacy of sevelamer carbonate tablets has been previously demonstrated in NDA 22,127.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This Safety Review is essentially from a Summary of Clinical Safety in Amendment 2 submitted July 30, 2008.

A total of 31 patients were randomized and received at least one dose of sevelamer carbonate powder in Study SVCARB00205. A similar proportion of patients experienced adverse events (AE) on both sevelamer carbonate powder (32.3%) and sevelamer hydrochloride tablets (42.9%). Adverse events were reported by system organ classes (SOCs). During both treatment regimens the majority of AEs occurred as a single event in single patients. The frequency of treatment related AEs was low. A total of 4 events in 3 (9.7%) patients were considered by the Investigator to be treatment related. All treatment related AEs were reported with sevelamer carbonate powder and included 2 events of nausea, 1 event of constipation, and 1 event of vomiting. One severe AE (chest pain) was reported during sevelamer carbonate powder treatment and no severe AEs were reported during sevelamer hydrochloride tablet treatment. No patients died during the period from Screening through the end of the 1-week Follow-up Period.

In Study GD3-199-301, a total of 141 patients received sevelamer carbonate powder once a day (QD) and 72 patients received sevelamer hydrochloride tablets three times a day (TID) for up to 24 weeks. A similar proportion of sevelamer carbonate powder QD patients (87.9%) and sevelamer hydrochloride tablet TID patients (91.7%) experienced adverse events. In both treatment groups, the highest frequency of treatment emergent AEs were gastrointestinal disorders which included nausea, diarrhea, vomiting, constipation, and upper abdominal pain. Treatment related nausea and vomiting were more common during sevelamer carbonate powder QD treatment than during sevelamer hydrochloride tablet TID treatment. In general, SAEs during sevelamer carbonate powder QD and sevelamer hydrochloride tablets TID treatment were similar. The majority were assessed by the Investigator as not related to study treatment. A higher percentage of sevelamer carbonate powder QD patients discontinued due to an AE (12.0% of patients on sevelamer carbonate powder QD; 5.6% patients on sevelamer hydrochloride tablets TID). In the sevelamer carbonate powder QD group, the majority of AEs leading to discontinuation were treatment related upper gastrointestinal disorders. The nature of the reasons for discontinuation suggest that the palatability of the powder formulation being dosed QD may have contributed to lower tolerability of sevelamer carbonate powder QD compared with TID dosing with sevelamer hydrochloride tablets.

7.1.1 Deaths

7.1.1.1 Study SVCARB00205

No patients died during the period from Screening through the end of the 1-week Follow-up Period. During the 30-day post-completion period, one patient experienced a Serious Adverse Event (SAE) of a brain stem hemorrhage with death. The death was considered secondary to preexisting conditions and assessed as not related to sevelamer carbonate powder by the Investigator.

7.1.1.2 Study GD3-199-301

A total of 2 (1.4%) sevelamer carbonate powder QD patients and 4 (5.6%) sevelamer hydrochloride tablet TID patients died during the randomized treatment period. The following table provides a list of the patients who died during the treatment period. All treatment-emergent deaths were assessed as not related to the study treatment by the Investigators. The causes of death were all consistent with the patients' underlying renal disease and chronic kidney disease (CKD) status.

Table 21: Patient Deaths in Study GD3-199-301

Treatment Group	Patient ID	Cause of Death	Relationship to Study Treatment
Sevelamer carbonate powder QD	505113	Cardiac arrest, cause unknown	Not Related
	516116	Withdrawal of renal replacement therapy	Not Related
Sevelamer hydrochloride tablets TID	505121	Cardiac arrest, cause unknown	Not Related
	508132	Septic shock	Not Related
		Staphylococcal pneumonia	Not Related
		Hypertensive cardiovascular disease	Not Related
	510118	Septicaemia	Not Related
	514108	Intracranial bleed	Not Related

One additional patient died approximately 10 weeks after discontinuing from the study. This event was reported even though it occurred after the 30-day follow-up period. This patient was a 75 year old female with CKD on hemodialysis with a medical history significant for diabetes mellitus, hypertension, congestive heart failure, and a history of smoking. The patient was randomized to sevelamer carbonate powder QD, but discontinued from the study due to a prolonged hospitalization for congestive heart failure. Approximately 10 weeks later the patient died. The primary cause of death was reported as cardiopulmonary arrest. The relationship between sevelamer carbonate powder and the adverse event cardiopulmonary arrest was reported as not related by the Investigator.

7.1.2 Other Serious Adverse Events

7.1.2.1 Study SVCARB00205

The frequency of serious adverse events (SAEs) was low in both treatment regimens. No SAEs were considered by the Investigator to be related to study treatment. Three patients discontinued during sevelamer carbonate powder treatment and no patients discontinued during sevelamer hydrochloride tablet treatment. Three of the four events leading to discontinuation were non-serious AEs and were Gastrointestinal Disorders. A small, but statistically significant, increase in serum bicarbonate and decrease in serum chloride levels were observed during the treatment with sevelamer carbonate powder. These changes were not observed during treatment with sevelamer hydrochloride tablets.

Reviewer's comment:

The increase in serum bicarbonate and decrease in serum chloride levels is interesting as the Sponsor in NDA 22-127 (Renvela, sevelamer carbonate) stated that the carbonate formula was being developed in order that serum blood levels for chloride and bicarbonate did not have to be monitored as often as with the hydrochloride formula.

In Study SVCARB00205, the frequency of SAEs was low in each treatment regimen during the randomized treatment periods: 2 events in 2 (6.5%) patients during sevelamer carbonate powder TID treatment and 2 events in 1 (3.6%) patient during sevelamer hydrochloride tablet TID treatment. The following table displays all treatment emergent SAEs that occurred during the randomized treatment periods.

Table 22: Serious Adverse Events During the Randomized Treatment Periods (Safety Set)

System Organ Class Preferred Term	Sevelamer Carbonate Powder TID (N=31)		Sevelamer Hydrochloride Tablets TID (N=28)	
	Events N	Patients n (%)	Events N	Patients n (%)
Any SAE	2	2 (6.5)	2	1 (3.6)
General Disorders and Administration Site Conditions	1	1 (3.2)	2	1 (3.6)
Chest pain	1	1 (3.2)	0	0
Catheter related complication	0	0	2	1 (3.6)
Infections and Infestations	1	1 (3.2)	0	0
Catheter sepsis	1	1 (3.2)	0	0

The SAEs of catheter-related complication (both events in one individual patient) and catheter sepsis were considered by the Investigator to be of moderate intensity and not related to study treatment. The SAE of chest pain was considered by the Investigator to be of severe intensity and unlikely related to study treatment; the patient was discontinued from the study due to this event.

SAEs starting or worsening during the randomized treatment periods were also analyzed for the following demographic subgroups: males and females, Blacks and other races, < 65 years of age and ≥ 65 years of age. Interpretation of the data is limited due to the low frequency of SAEs during the study and the small number of patients in these subgroups. In general, the results showed that the SAEs occurring during the study were not influenced by gender, race or age.

7.1.2.2 Study GD3-199-301

In Study GD3-199-301, a higher percentage of patients in the sevelamer hydrochloride tablet TID group experienced SAEs. 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 were similar during sevelamer carbonate powder QD and sevelamer hydrochloride tablets TID treatment. In both treatment groups, the highest frequency of treatment emergent SAEs were 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 also Cardiac Disorders [17 SAEs in 9 (6.4%) of sevelamer carbonate powder QD patients and 16 SAEs in 9 (12.5%) sevelamer hydrochloride tablet TID patients]. SAEs occurring in ≥ 2% of patients are provided in the following table.

Table 23: Serious Adverse Events Occurring in ≥ 2% (Safety Set)

System Organ Class Preferred Term	Sevelamer Carbonate Powder QD (N=141)		Sevelamer Hydrochloride Tablets TID (N=72)	
	Events N	Patients n (%)	Events N	Patients n (%)
Any SAE	85	33 (23.4)	72	28 (38.9)
Cardiac Disorders	17	9 (6.4)	16	9 (12.5)
Cardiac Failure Congestive	7	5 (3.5)	7	4 (5.6)
Coronary Artery Disease	1	1 (0.7)	3	3 (4.2)
Atrial Fibrillation	3	3 (2.1)	1	1 (1.4)
Infections and Infestations	19	15 (10.6)	12	11 (15.3)
Pneumonia	6	6 (4.3)	3	3 (4.2)
Injury, Poisoning and Procedural Complications	5	4 (2.8)	7	6 (8.3)
Arteriovenous Fistula Thrombosis	3	2 (1.4)	5	4 (5.6)
Metabolism and Nutrition Disorders	12	8 (5.7)	5	3 (4.2)
Hyperkalaemia	5	4 (2.8)	2	2 (2.8)
Hypoglycaemia	1	1 (0.7)	2	2 (2.8)
Respiratory, Thoracic and Mediastinal Disorders	8	8 (5.7)	3	3 (4.2)
Pulmonary oedema	3	3 (2.1)	1	1 (1.4)
Surgical and Medical Procedures	2	2 (1.4)	3	3 (4.2)
Arteriovenous Fistula Operation	0	0 (0)	2	2 (2.8)
Vascular Disorders	4	4 (2.8)	11	7 (9.7)
Hypertension	1	1 (0.7)	2	2 (2.8)

The most frequently reported (> 4% patients) SAEs were cardiac failure congestive [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].

The majority of treatment emergent SAEs were assessed by the Investigator as not related to the study treatment. One patient experienced an SAE (probable fecal impaction) considered possibly related to sevelamer hydrochloride. The patient, a 54 year old female with CKD on hemodialysis with a medical history significant for constipation, abdominal surgery including Cesarean-section and tubal ligation, hypertension, coronary atherosclerosis, and type II diabetes mellitus was randomized to sevelamer hydrochloride, two 800 mg tablets TID with meals. Approximately 15 weeks after beginning the study treatment, the patient presented to the Emergency Department with a five day history of abdominal pain and abdominal distension without bowel movements. An abdominal x-ray showed considerable stool in the rectal vault, consistent with probable fecal impaction. No evidence of mass or obstruction was observed. The patient was treated with enemas and ketorolac tromethamine, recovered without sequelae and was discharged. Sevelamer hydrochloride was continued. The relationship between sevelamer hydrochloride and the adverse event of probable fecal impaction was reported as possible by the Investigator.

SAEs that occurred during the randomized treatment periods were also analyzed for the following subgroups: males, females, African Americans, Non-African American, < 65 years of age, and ≥ 65 years of age. In general, the SAEs seen within each gender, race and age group were similar and consistent with the analysis of the overall population.

The majority of treatment-emergent AEs were mild or moderate in intensity. The percent of patients experiencing treatment related AEs was greater in the sevelamer carbonate powder QD group. 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. Two patients experienced treatment related AEs that were severe in intensity. One patient who experienced severe diarrhea in the sevelamer carbonate powder group and one patient who experienced severe hypocalcemia in the sevelamer hydrochloride tablet group were assessed as treatment related by the Investigator.

Table 24: Treatment Emergent Adverse Events in >2% of Patients (Safety Set)

System Organ Class Preferred Term	Sevelamer Carbonate Powder QD (N=141)		Sevelamer Hydrochloride Tablets TID (N=72)	
	Events N	Patients n (%)	Events N	Patients n (%)
Any Treatment related Adverse Event	72	43 (30.5)	26	13 (18.1)
Gastrointestinal Disorders	58	32 (22.7)	18	8 (11.1)
Diarrhoea	17	12 (8.5)	5	4 (5.6)
Nausea	18	14 (9.9)	4	2 (2.8)
Vomiting	8	8 (5.7)	1	1 (1.4)
Constipation	1	1 (0.7)	4	4 (5.6)
Stomach Discomfort	5	3 (2.1)	1	1 (1.4)
General Disorders and Administration Site Conditions	6	6 (4.3)	0	0 (0)
Oral Administration Complication	6	6 (4.3)	0	0 (0)
Investigations	2	2 (1.4)	3	2 (2.8)
Carbon Dioxide Decreased	1	1 (0.7)	3	2 (2.8)
Metabolism and Nutrition Disorders	5	5 (3.5)	4	3 (4.2)
Hypocalcaemia	1	1 (0.7)	3	2 (2.8)

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Study SVCARB00205

The following table presents an overview of the patients with treatment emergent adverse events, treatment emergent severe adverse events and related treatment emergent adverse events in Study SVCARB00205.

Table 25: Overview of Treatment Emergent Adverse Events (Safety Set)

	Sevelamer Carbonate Powder TID (N=31) n (%)	Sevelamer Hydrochloride Tablets TID (N=28) n (%)
Any Treatment Emergent AEs	10 (32.3)	12 (42.9)
Treatment Emergent Severe AEs	1 (3.2)	0
Related Treatment Emergent AEs	3 (9.7)	0

Treatment Emergent Adverse Events in Study SVCARB00205:

The overall frequency of AEs that occurred during the randomized treatment periods was similar between both treatment regimens: 21 events in 10 (32.3%) patients during treatment with sevelamer carbonate powder and 26 events in 12 (42.9%) patients during treatment with sevelamer hydrochloride tablets as shown in the following table.

Table 26: Summary of All Cause Treatment Emergent AEs that Occurred in $\geq 5\%$ (Safety Set)

System Organ Class	Sevelamer Carbonate Powder TID (N=31)		Sevelamer Hydrochloride Tablets TID (N=28)	
	Events N	Patients n (%)	Events N	Patients n (%)
Any AE	21	10 (32.3)	26	12 (42.9)
Gastrointestinal Disorders	5	4 (12.9)	4	3 (10.7)
Skin and Subcutaneous Tissue Disorders	2	2 (6.5)	2	2 (7.1)
Infections and Infestations	2	2 (6.5)	1	1 (3.6)
Investigations	2	2 (6.5)	1	1 (3.6)
Vascular Disorders	2	2 (6.5)	1	1 (3.6)
General Disorders and Administration Site Conditions	1	1 (3.2)	5	4 (14.3)
Musculoskeletal and Connective Tissue Disorders	1	1 (3.2)	4	3 (10.7)
Surgical and Medical Procedures	1	1 (3.2)	3	3 (10.7)

In both treatment regimens, the most frequent events were Gastrointestinal Disorders, with 5 events in 4 (12.9%) patients during treatment with sevelamer carbonate powder, and 4 events in 3 (10.7%) patients during treatment with sevelamer hydrochloride tablets. AEs occurred more frequently during sevelamer hydrochloride tablet treatment than during sevelamer carbonate powder treatment for General Disorders and Administration Site Conditions (14.3% vs. 3.2%).

In general, AEs were reported in both treatment regimens. The majority of AEs occurred as single events in single patients. The AE reported in more than one patient during sevelamer carbonate powder treatment was nausea (2 events in 2 [6.5%] patients). The events reported in more than one patient during sevelamer hydrochloride tablet treatment were fatigue and arteriovenous fistula operation, each reported as 2 events in 2 (7.1%) patients.

AEs that occurred during the randomized treatment periods were also analyzed for the following demographic subgroups: males and females, Blacks and other races, and < 65 years of age and ≥ 65 years of age. Interpretation this data is limited because of the small number of patients in some of the subgroups, but in general, the results showed that AEs occurring during the study were not influenced by gender, race or age.

Treatment Related Adverse Events:

During the randomized treatment periods, a total of 4 events in 3 (9.7%) patients were considered by the Investigator to be treatment related to sevelamer carbonate powder. All were Gastrointestinal Disorders which included nausea (2 events in 2 [6.5%] patients), constipation (1 event in 1 [3.2%] patient) and vomiting (1 event in 1 [3.2%] patient). All treatment related AEs were of mild or moderate intensity. No treatment related AEs were reported during treatment with sevelamer hydrochloride tablets during the randomized treatment periods.

7.1.3.2 Study GD3-199-301

The following table presents an overview the patients with treatment emergent adverse events, treatment emergent severe adverse events and related treatment emergent adverse events in Study GD3-199-301.

Table 27: Overview of Patients with Treatment Emergent Adverse Events (Safety Set)

	Sevelamer Carbonate Powder QD (N=141) n (%)	Sevelamer Hydrochloride Tablets TID (N=72) n (%)
Any Treatment Emergent AEs	124 (87.9)	66 (91.7)
Treatment Emergent Severe AEs	22 (15.6)	19 (26.4)
Related Treatment Emergent AEs	43 (30.5)	13 (18.1)

Treatment Emergent Adverse Events:

The percentage 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. The most frequently occurring AEs (≥ 10% of randomized patients in either treatment group, are presented in the following table.

Table 28: Summary of All Cause AEs in $\geq 10\%$ of Patients (Safety Set)

System Organ Class	Sevelamer Carbonate Powder QD (N = 141)		Sevelamer Hydrochloride Tablets TID (N = 72)	
	Events N	Patients n (%)	Events N	Patients n (%)
Any Adverse Event	723	124 (87.9)	430	66 (91.7)
Gastrointestinal Disorders	147	66 (46.8)	75	35 (48.6)
Cardiac Disorders	30	19 (13.5)	23	12 (16.7)
Musculoskeletal and Connective Tissue Disorders	73	47 (33.3)	34	21 (29.2)
Injury, Poisoning, and Procedural Complications	66	44 (31.2)	55	32 (44.4)
Infections and Infestations	77	43 (30.5)	36	28 (38.9)
General Disorders and Administrative Site Conditions	63	37 (26.2)	48	27 (37.5)
Nervous System Disorders	41	29 (20.6)	27	18 (25.0)
Respiratory, Thoracic and Mediastinal Disorders	53	29 (20.6)	24	18 (25.0)
Metabolism and Nutrition Disorders	33	24 (17.0)	19	16 (22.2)
Vascular Disorders	28	22 (15.6)	31	20 (27.8)
Skin and Subcutaneous Tissue Disorders	24	21 (14.9)	19	14 (19.4)
Investigations	22	11 (7.8)	16	12 (16.7)

In general, there was a similar incidence of AEs in the sevelamer carbonate powder QD and sevelamer hydrochloride tablet TID treatment groups. In both treatment groups, the highest frequency of treatment emergent AEs occurred in the 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: nausea (37 events in 30 [21.3%] sevelamer carbonate powder QD patients and 11 events in 8 [11.1%] sevelamer hydrochloride tablet TID patients), diarrhea (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 powder QD patients and 19 events in 13 [18.1%] sevelamer hydrochloride tablet TID patients).

The following differences between treatment groups were noted. A higher number of patients on sevelamer carbonate powder QD experienced muscle spasms and urinary tract infections compared to patients on sevelamer hydrochloride tablets TID. Twenty eight events of muscle spasms occurred in 20 [14.2%] sevelamer carbonate powder QD patients and 9 events occurred in 4 [5.6%] sevelamer hydrochloride tablet TID patients. The events of muscle spasms in general, constituted muscle cramps during dialysis. Eleven events of urinary tract infection occurred in 10 [7.1%] sevelamer carbonate powder QD patients and 3 events occurred in 2 [2.8%] sevelamer hydrochloride tablet TID patients. Patients who experienced urinary tract infections had a history of urinary tract infections or pre-existing conditions that pre-disposed patients to develop a urinary tract infection.

A higher number of patients on sevelamer hydrochloride tablets TID experienced arteriovenous fistula thrombosis compared to patients on sevelamer carbonate powder QD. A total of 12 events occurred in 8 [5.7%] sevelamer carbonate powder QD patients and 19 events

occurred in 13 [18.1%] sevelamer hydrochloride tablet TID patients. However, when all of the similar medical concepts in the Injury, Poisoning and Procedural Complications are evaluated as a whole, there was no difference between the treatment regimens with regard to arteriovenous fistula problems.

Treatment-emergent AEs were also analyzed for the following subgroups: males, females, African Americans, Non-African Americans, < 65 years of age, and ≥ 65 years of age. Differences in frequency between subgroups were noted for the following adverse events: muscle spasms, oral administration complication, nausea, vomiting, stomach discomfort, and constipation. In depth review of these adverse events revealed that patients who experienced these adverse events had a medical history of the event or a pre-existing condition that pre-disposed them to the event. Furthermore, the events were all mild or moderate in intensity, and the majority of patients recovered without treatment, intervention or discontinuation of study medication. Thus, the analysis of AEs by subgroup did not identify any new safety issues and indicates that AEs reported during the study were not influenced by gender, race or age.

Treatment Related Adverse Events in Study GD3-199-301:

The percent of patients experiencing treatment related AEs was greater in the sevelamer carbonate powder QD group. 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. Two patients experienced treatment related AEs that were severe in intensity. One patient who experienced severe diarrhea in the sevelamer carbonate powder group and one patient who experienced severe hypocalcaemia in the sevelamer hydrochloride tablet group were assessed as treatment related by the Investigator. A summary of the treatment related AEs occurring in > 2% patients is in the following table.

Table 29: Treatment Emergent Adverse Events Occurring in >2% (Safety Set)

System Organ Class Preferred Term	Sevelamer Carbonate Powder QD (N=141)		Sevelamer Hydrochloride Tablets TID (N=72)	
	Events N	Patients n (%)	Events N	Patients n (%)
Any Treatment related Adverse Event	72	43 (30.5)	26	13 (18.1)
Gastrointestinal Disorders	58	32 (22.7)	18	8 (11.1)
Diarrhoea	17	12 (8.5)	5	4 (5.6)
Nausea	18	14 (9.9)	4	2 (2.8)
Vomiting	8	8 (5.7)	1	1 (1.4)
Constipation	1	1 (0.7)	4	4 (5.6)
Stomach Discomfort	5	3 (2.1)	1	1 (1.4)
General Disorders and Administration Site Conditions	6	6 (4.3)	0	0 (0)
Oral Administration Complication	6	6 (4.3)	0	0 (0)
Investigations	2	2 (1.4)	3	2 (2.8)
Carbon Dioxide Decreased	1	1 (0.7)	3	2 (2.8)
Metabolism and Nutrition Disorders	5	5 (3.5)	4	3 (4.2)
Hypocalcaemia	1	1 (0.7)	3	2 (2.8)

Treatment related AEs were most frequently seen with Gastrointestinal Disorders. The most frequently occurring (> 4% patients) treatment related AEs were diarrhea (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 events in 4 [5.6%] sevelamer hydrochloride tablet TID patients). The most frequently occurring (>4% patients) treatment related to the SOC General Disorders and Administrative Site Conditions was: oral administration complication (6 events in 6 [4.3%] sevelamer carbonate powder QD patients and no events in the sevelamer hydrochloride tablet TID patients).

Treatment emergent AEs possibly or probably related to the study drug were also analyzed for the following subgroups: males, females, African Americans, Non-African Americans, < 65 years of age, and ≥ 65 years of age. Differences in frequency between subgroups were noted for the following treatment related adverse events: oral administration complication, nausea, vomiting, and constipation. In-depth review of these AEs revealed that patients who experienced these adverse events had a medical history of the event or a pre-existing condition that pre-disposed them to the event. The events were all mild or moderate in intensity, and the majority of patients recovered without sequelae. The analysis of treatment related AEs by subgroup did not identify any new safety issues and indicate that AEs reported during this study were not influenced by gender, race or age.

7.1.4 Other Search Strategies

NA

7.1.5 Common Adverse Events

NA

7.1.6 Less Common Adverse Events

NA

7.1.7 Laboratory Findings

There were no clinically significant changes in safety laboratory measures during sevelamer carbonate treatment in SVCARB00205. However, statistically significant increases in serum bicarbonate and decreases in serum chloride levels were observed during treatment with sevelamer carbonate in this Study.

In Study GD3-199-301, individual patient changes that were assessed as clinically significant by the Investigator were captured as AEs and as SOC Investigations. The percent of patients experiencing AEs in the SOC Investigations was greater in the sevelamer hydrochloride tablet TID group. A total of 11 (7.8%) sevelamer carbonate powder QD patients and 12 (16.7%) sevelamer hydrochloride tablet TID patients experienced an AE coded to the SOC Investigations. Treatment emergent AEs in the SOC Investigations that were assessed as treatment-related by the Investigators included: blood parathyroid hormone increased (sevelamer carbonate powder

QD: 1 patient and sevelamer hydrochloride tablet TID: 0 patients) and carbon dioxide decreased (sevelamer carbonate powder QD: 1 patient; sevelamer hydrochloride tablet TID: 2 patients).

7.1.8 Vital Signs

In both Studies SVCARB00205 and GD3-199-301, there were no clinical or statistical changes in vital signs during the clinical trials.

7.1.10 Immunogenicity

NA

7.1.11 Human Carcinogenicity

NA

7.1.12 Special Safety Studies

Clinical studies of sevelamer carbonate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There have been no reports of patient abuse or dependence on sevelamer carbonate tablets or powder. Sevelamer carbonate is not absorbed and not metabolized. There is no reasonable mechanism by which sevelamer carbonate use is likely to be associated with addictive properties and therefore the potential for drug abuse is exceedingly low.

7.1.14 Human Reproduction and Pregnancy Data

The safety of sevelamer carbonate (powder or tablets) has not been established in pregnant or lactating women. Requirements for vitamins and other nutrients are increased in pregnancy. The effect of sevelamer on the absorption of vitamins and other nutrients has not been studied in pregnant women.

7.1.15 Assessment of Effect on Growth

NA

7.1.16 Overdose Experience

Sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, has been given to normal healthy volunteers in doses of up to 14 grams per day for eight days with no adverse effects. In CKD patients, the maximum average actual daily dose of sevelamer

carbonate studied was 14 grams/day (both TID and QD). There are no reports of over dosage with sevelamer carbonate (powder or tablets) or sevelamer hydrochloride in patients. Since sevelamer carbonate is not absorbed, the risk of systemic toxicity is low.

7.1.17 Postmarketing Experience

Renagel® (sevelamer hydrochloride), was approved in the United States on October 30, 1998 for capsules (NDA 20-926) and July 12, 2000 for tablets (NDA 21-179). The estimated US patient exposure to Renagel is greater than _____patient-years. Renagel is currently approved for marketing in over 55 countries. Post marketing safety surveillance of sevelamer hydrochloride has been ongoing since initial approval of sevelamer hydrochloride in 1998. Renvela® Tablets (sevelamer carbonate), contain the same active moiety as sevelamer hydrochloride and were approved for marketing on October 19, 2007. Marketing began in March, 2008.

b(4)

The most frequent post-marketing adverse event for sevelamer hydrochloride is hyperphosphatemia. Successful control of serum phosphorus in this patient population is multifactorial, including reduction in dietary intake of phosphate, inhibition of intestinal phosphate absorption with phosphate binders, and removal of phosphate with dialysis. An ongoing evaluation of all reported cases of hyperphosphatemia received spontaneously for sevelamer hydrochloride, including the patient's prior phosphate binder and phosphorus levels, the patient's sevelamer hydrochloride dosage regimen and phosphorus levels, and patient compliance with diet and medication, has not revealed any new product or safety related issues.

Other commonly reported spontaneous adverse events for patients on sevelamer hydrochloride included nausea, diarrhea, vomiting, constipation, flatulence, dyspepsia, headache, dyspnea and hypertension. These events were observed in clinical trials with sevelamer hydrochloride, are described in the product labeling and are considered expected (labeled) adverse events. Events of nausea, vomiting, flatulence, and dyspepsia were seen in patients during sevelamer carbonate treatment and are also listed in the product labeling.

Pruritus, abdominal pain and rash are other adverse events that were seen during clinical trials with sevelamer hydrochloride and were frequently reported during post-marketing experience with sevelamer hydrochloride. These three terms are described as postmarketing experience in the current Renagel and Renvela labels.

Reports of intestinal obstruction, intestinal perforation and ileus for patients on sevelamer hydrochloride have been rare. An in depth review of these gastrointestinal event reports received for patients on sevelamer hydrochloride revealed there was no dose relationship, and that age and treatment duration varied. Patient medical histories were complicated and may have contributed to the events. Due to the nature of post-marketing reporting, details regarding sevelamer hydrochloride therapy, clinical diagnosis and medical history were limited, which complicated the review of these reports. A comprehensive review of post-marketing reports of ileus, intestinal obstruction and intestinal perforation revealed that complex co-morbidities and concomitant medications often contributed to the event. The current Renagel and Renvela labels describe the risk of intestinal obstruction, intestinal perforation, and ileus during sevelamer therapy.

Deaths and serious adverse events reported for patients on sevelamer hydrochloride were rare, were reported across system organ classes, and were consistent with patients' underlying renal disease.

7.2 Adequacy of Patient Exposure and Safety Assessments

With the post-marketing experience and prior clinical trials for both sevelamer hydrochloride and sevelamer carbonate, there is adequate patient exposure and safety assessments.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Overall, common adverse events experienced were not unexpected and were consistent with patients' underlying renal disease and CKD status. The adverse events experienced during sevelamer carbonate powder treatment and sevelamer carbonate tablet treatment were similar in nature. In summary, the safety profile of sevelamer carbonate powder is similar to the established safety profile of sevelamer carbonate tablets and sevelamer hydrochloride. This has been shown in the sevelamer carbonate and sevelamer hydrochloride tablet studies and the sevelamer hydrochloride post-marketing safety profile.

7.4 General Methodology

NA

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Renagel and Renvela are given three times a day as stated in their labels. In this NDA, Study SVCARB00205 was for sevelamer carbonate powder to be utilized also three times a day.

..... Therefore, we recommend that should the powder be approved, it should be dosed three times a day.

b(4)

8.2 Drug-Drug Interactions

Six drugs were evaluated with sevelamer hydrochloride: digoxin, warfarin, enalapril, metoprolol, ciprofloxacin, and iron. In these studies, sevelamer hydrochloride was found to have no effect on the bioavailability of digoxin, warfarin, metoprolol, enalapril or iron. However, the bioavailability of ciprofloxacin was decreased by approximately 50% when co-administered with sevelamer hydrochloride.

In addition, during post-marketing experience, very rare cases of increased TSH levels have been reported in patients coadministered sevelamer hydrochloride and levothyroxine. The current sevelamer hydrochloride and sevelamer carbonate tablet labels recommend that when administering an oral medication where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, the medication should be administered at least one hour before or three hours after sevelamer (carbonate or hydrochloride), or the physician should consider monitoring blood levels of the drug. The current labels also recommend closer monitoring of TSH levels in patients receiving both levothyroxine and sevelamer carbonate.

8.3 Special Populations

Clinical studies of sevelamer carbonate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8.4 Pediatrics

As there are currently no phosphate binders that are indicated for pediatric dialysis patients, an active control would not be useful for comparison of safety and efficacy. In general, children below age 2 tend to be on phosphate supplements and it is rare that these children need a binder. In addition, children 0-1 year of age is a very small population which would be difficult to recruit and maintain in a clinical study.

The Sponsor proposes to study patients ~~18~~ 18 years of age. Sevelamer carbonate powder when mixed with water provides a liquid formulation (suspension) that should facilitate administration of this powder to children.

8.5 Advisory Committee Meeting

NA

b(4)

8.6 Literature Review

NA

8.7 Postmarketing Risk Management Plan

NA

8.8 Other Relevant Materials

NA

9 OVERALL ASSESSMENT

9.1 Conclusions

In 1998 Renagel (sevelamer hydrochloride) was approved in the United States for the control of hyperphosphatemia in adult patients on hemodialysis. In 2007 a new formula of sevelamer where the counterion was changed from chloride to carbonate was approved (NDA 22-127). In this NDA the Sponsor has submitted a change in the tablet form of sevelamer carbonate to a powder form for patients unable to swallow _____ . The Sponsor has submitted two clinical studies comparing the powder formula to sevelamer hydrochloride tablets. The study comparing the powder formula three times a day is small but somewhat efficacious. Utilizing the powder once a day in a larger study did not prove to be efficacious. In the label the Sponsor has recommended only the three times a day dosing. The safety profile of the powder formula appears to be similar the previous sevelamer studies, causing primarily gastrointestinal side effects. Certainly there is a need for a powder formula for some patients _____ therefore these reviewers recommend that the new powder be approved for three times a day dosing.

b(4)

9.2 Recommendation on Regulatory Action

Approval

9.3 Recommendation on Postmarketing Actions

None

9.4 Labeling Review

The label is essentially acceptable as the Sponsor has included only three times a day dosing. The label will be reviewed in future with the review team.

Clinical and Statistical Review
Gail Moreschi, MD, MPH, and Ququan Liu, MD, MS
NDA 22-318
Sevelamer carbonate powder; Renvela

9.5 Comments to Applicant

None

10 APPENDICES

10.1 Review of Individual Study Reports

NA

10.2 Line-by-Line Labeling Review

NA

Clinical and Statistical Review
Gail Moreschi, MD, MPH, and Ququan Liu, MD, MS
NDA 22-318
Sevelamer carbonate powder; Renvela

REFERENCES

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/s/

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CLINICAL and STATISTICAL REVIEW

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Reviewers Names Gail Moreschi, M.D., M.P.H.
Ququan Liu, M.D., M.S.
Review Completion Date December 1, 2008

Established Name Sevelamer carbonate
(Proposed) Trade Name Renvela
Therapeutic Class Phosphate binder
Applicant Genzyme

Priority Designation S

Formulation Powder for Oral Suspension **b(4)**
Dosing Regimen tid, —
Indication Hyperphosphatemia
Intended Population Patients on dialysis

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1 EXECUTIVE SUMMARY

In 1998 Renagel (sevelamer hydrochloride) was approved in the United States for the control of hyperphosphatemia in adult patients on hemodialysis. In 2007 a new formula of sevelamer where the counterion was changed from chloride to carbonate was approved (NDA 22-127). In this NDA the Sponsor has submitted a change in the tablet form of sevelamer carbonate to a powder form for patients unable to swallow. The Sponsor has submitted two clinical studies comparing the powder formula to sevelamer hydrochloride tablets. The study comparing the powder formula three times a day is small but somewhat efficacious. Utilizing the powder once a day in a larger study did not prove to be efficacious. In the label the Sponsor has recommended only the three times a day dosing. The safety profile of the powder formula appears to be similar the previous sevelamer studies, causing primarily gastrointestinal side effects. Certainly there is a need for a powder formula for some patients, therefore these reviewers recommend that the new powder be approved for three times a day dosing.

b(4)

b(4)

1.1 Recommendation on Regulatory Action

Approval

1.2 Recommendation on Postmarketing Actions

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The Sponsor has submitted two clinical studies to demonstrate the safety and efficacy of sevelamer carbonate powder.

1.3.2 Efficacy

Although a small study, the three times a day dosing of the new powder formula appears to be efficacious. The once a day dosing study with the largest meal did not show efficacy.

1.3.3 Safety

This new sevelamer carbonate powder formula appears to have the same safety profile as has been shown with sevelamer over the years since its first approval. Gastrointestinal side effects remain a problem.

1.3.4 Dosing Regimen and Administration

The powder will be given three times a day. Each individual powder sachet will be mixed with _____ of water. The patient is instructed to drink the mixture within 30 minutes of preparation.

b(4)

1.3.5 Drug-Drug Interactions

Six drugs were evaluated with sevelamer hydrochloride: digoxin, warfarin, enalapril, metoprolol, ciprofloxacin, and iron. In these studies, sevelamer hydrochloride was found to have no effect on the bioavailability of digoxin, warfarin, metoprolol, enalapril or iron. However, the bioavailability of ciprofloxacin was decreased by approximately 50% when co-administered with sevelamer hydrochloride.

1.3.6 Special Populations

This new formula is intended for patients unable to swallow _____

b(4)

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Sevelamer hydrochloride (Renagel®) has been on the market since 1998 to treat hyperphosphatemia in patients with chronic renal disease (CKD) on hemodialysis. In 2007 the Sponsor changed the ion from hydrochloride to carbonate in order to decrease the frequency of monitoring serum chloride and bicarbonate. In this NDA the formula has been changed from a tablet to a powder formula.

2.2 Currently Available Treatment for Indications

There are three FDA approved phosphate binders: Renagel® (sevelamer hydrochloride), PhosLo (calcium acetate), and Fosrenol (lanthanum carbonate). This will be the first powder formula.

2.3 Availability of Proposed Active Ingredient in the United States

NA

2.4 Important Issues With Pharmacologically Related Products

NA

2.5 Presubmission Regulatory Activity

NA

2.6 Other Relevant Background Information

NA

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

This review is not currently available and will be submitted separately.

3.2 Animal Pharmacology/Toxicology

This review is not currently available and will be submitted separately.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The Sponsor has submitted two clinical studies for this NDA.

4.2 Tables of Clinical Studies

Table 1: Clinical Studies

Study ID	Number of Study Centres Location(s)	Study Start Enrolment Status, Date Total Enrolment/ Enrolment Goal	Design Control Type	Study & Control Drugs Dose and Regimen	Primary Study Objective	Subjects/ Arm Treated/ Completed	Duration	Gender M/F Mean Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint
SV-CARB00205	7 sites in the United Kingdom	Started: 31 Jan 2006 Completed: 21 Mar 2007 Screened: 75 enrolled/ 75 planned Randomised: 31 enrolled/ 24 planned	Randomised, open-label, cross-over	Sevelamer carbonate powder for oral suspension 800 mg sachets Sevelamer hydrochloride 800 mg tablets The binder dose at the end of the sevelamer hydrochloride run-in was replaced gran per gran by study drug. The dose was to be maintained throughout the treatment periods. Both to be taken orally TID with meals. Mean actual dose (Safety Set) Sevelamer carbonate: 5.9 = 2.7 g/day Sevelamer hydrochloride: 6.5 = 3.3 g/day	Compare the safety and efficacy of sevelamer carbonate powder with sevelamer hydrochloride tablets, each dosed TID	Treated: 31 (31 patients received sevelamer carbonate powder and 28 patients received sevelamer hydrochloride tablets) Completed both treatments: 24	15 weeks: 2-week washout period; 4-week sevelamer hydrochloride run-in period; two 4-week randomised treatment periods; 1-week follow-up period.	68% 32% 53 years (27-80 years)	Haemodialysis patients	Time weighted average of serum phosphorus
GD3-199-301	29 sites in the United States	Started: 27 Jan 06 Completed: 16 Mar 07 Screened: 396 enrolled/280 planned Randomised: 217 (144 sevelamer carbonate powder QD, 73 sevelamer hydrochloride tablets TID) enrolled/ 207 (138 sevelamer carbonate powder QD, 69 sevelamer hydrochloride tablets TID) planned	Randomised, open-label, parallel	Sevelamer carbonate powder for oral suspension 2.4 g sachets Sevelamer hydrochloride 800 mg tablets The starting dose was 4.8 g/day of either sevelamer carbonate powder or sevelamer hydrochloride tablets. The dose was to be titrated to reach a serum phosphorus level of ≥ 3.5 and ≤ 5.5 mg/dL (≥ 1.13 and ≤ 1.76 mmol/L). Sevelamer carbonate powder was to be taken QD with the largest meal. Sevelamer hydrochloride tablets were to be taken TID with meals. Mean actual dose (Safety Set) Sevelamer carbonate powder dosed QD: 6.2 = 2.6 g/day Sevelamer hydrochloride tablets dosed TID: 6.7 = 3.0 g/day	Compare the safety and efficacy of sevelamer carbonate powder dosed QD with the largest meal to sevelamer hydrochloride tablets dosed TID with meals	Sevelamer carbonate powder QD: 141 treated/ 93 completed Sevelamer hydrochloride tablets TID: 72 treated/ 62 completed	26 weeks: 2-week washout period, 24-week randomised treatment period	61% 39% 58 years (20-85 years)	Haemodialysis patients	Change in serum phosphorus

4.3 Review Strategy

The Sponsor has submitted two clinical studies which were reviewed. This was a joint review between the medical and the statistical reviewers.

4.4 Data Quality and Integrity

It was determined by the review team that a DSI inspection was not required.

4.5 Compliance with Good Clinical Practices

The submitted clinical trials were conducted in accordance with good ethical standards.

4.6 Financial Disclosures

There are no questions raised as to the integrity of the data.

5 CLINICAL PHARMACOLOGY

This review is not currently available and will be submitted separately.

5.1 Pharmacokinetics

5.2 Pharmacodynamics

5.3 Exposure-Response Relationships

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Renagel (sevelamer hydrochloride) was approved in the United States in 1998 for the control of hyperphosphatemia in adult patients on hemodialysis (HD). Renvela (sevelamer carbonate, NDA 22-127) was recently approved in the tablet form. Sevelamer carbonate was developed as an alternate salt form to the original sevelamer hydrochloride; carbonate is an alternative counterion to chloride. Since both salts have the same polymeric structure, a similar efficacy and safety profile should be seen. In this NDA sevelamer carbonate has a new formulation, a powder form, for those who are unable to swallow _____ **b(4)**

6.1.1 Methods

The Sponsor has submitted 2 clinical studies utilizing the powder formulation which will be reviewed individually as they have different study designs. The first study SVCARB00205 is with the usual three times a day dosing. The second study GD3-199-301 was done with a once a day dosing with the largest meal. In both studies the comparator was sevelamer hydrochloride.

6.1.2 General Discussion of Endpoints

The reduction of serum phosphate has been the accepted endpoint for the treatment of hyperphosphatemia in the adult patient with chronic renal failure (CKD) on hemodialysis (HD).

6.1.3 Study Design

The two studies will be presented separately here because of the differences in their individual study designs.

6.1.3.1 SVCARB00205

Study title: A randomized, cross-over study to demonstrate equivalence of sevelamer carbonate powder and sevelamer hydrochloride tablets dosed three times per day in hemodialysis patients

Study Centers: Patients were enrolled at 7 centers in the United Kingdom (UK).

Study Dates: January 31, 2006 to March 21, 2007

Objectives:

Primary Objectives in hyperphosphatemic chronic kidney disease (CKD) patients on hemodialysis (HD):

1. To demonstrate equivalence of sevelamer carbonate powder to sevelamer hydrochloride tablets dosed three times a day (TID) with meals, on control of serum phosphorus levels.
2. To evaluate the safety and tolerability of sevelamer carbonate powder compared to sevelamer hydrochloride tablets dosed TID with meals.

Secondary Objectives in hyperphosphatemic CKD patients on HD, to compare the effects of sevelamer carbonate powder to sevelamer hydrochloride tablets when dosed TID with meals on:

1. Serum calcium-phosphorus product.
2. Serum lipid profile (total cholesterol, high density lipoprotein [HDL] cholesterol, low density lipoprotein [LDL] cholesterol, and triglycerides).

These secondary objectives will not be reviewed in this NDA.

Study Design:

This was a Phase 3, multi-center, open-label, randomized, cross-over study of sevelamer carbonate powder dosed TID with meals versus sevelamer hydrochloride tablets dosed TID with meals in hyperphosphatemic CKD patients on HD. The study consisted of 6 periods: a 2-week

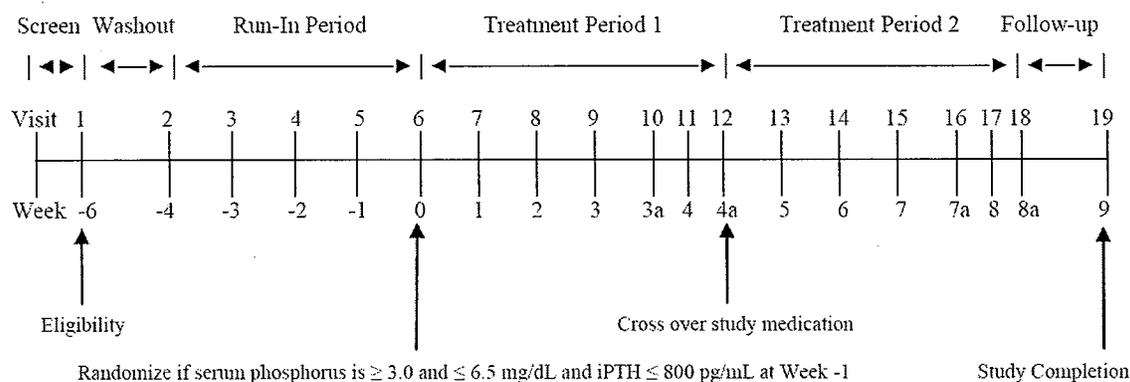
Screening and Washout Period, a 4-week sevelamer hydrochloride tablet Run-In Period, a 4-week Treatment Period (Treatment Period 1), a second 4-week Treatment Period (Treatment Period 2 when the alternative study medication was taken), and a Follow-up visit 1 week after the last study treatment visit.

At Screening, patients had to be taking sevelamer hydrochloride alone or as combination therapy (e.g., using sevelamer hydrochloride and calcium, or metal phosphate binders concomitantly). Patients who fulfilled the entry criteria were asked to discontinue their current phosphate binder(s) and enter a 2-week Washout Period. At the end of the Washout Period, patients who were hyperphosphatemic (serum phosphorus ≥ 5.5 mg/dL or ≥ 1.76 mmol/L) continued into the 4-week Run-In Period. Each patient's binder dose taken prior to the Washout Period was replaced with an equivalent number of 800 mg tablets of sevelamer hydrochloride (not to exceed a total daily dose of 14.4 g or 18 x 800 mg tablets). Patients had weekly visits during the Run-In Period. The dose of sevelamer hydrochloride tablets could be adjusted if necessary at Visits 3 and 4 (Weeks -3 and -2) to keep serum phosphorus levels within a target level of 3.5 and 5.5 mg/dL (1.12 and 1.76 mmol/L), inclusive, by increasing or decreasing by 1 x 800 mg tablet TID (2.4 g/day).

Patients who were eligible to continue into the treatment period were to maintain the dose of the study drug that was last prescribed during the Run-In Period for the remainder of the study. At Baseline (Visit 6, Week 0), eligible patients were randomly assigned to one of two treatment sequences:

- sevelamer carbonate powder dosed TID with meals for four weeks followed by sevelamer hydrochloride tablets dosed TID with meals for four weeks
- sevelamer hydrochloride tablets dosed TID with meals for four weeks followed by sevelamer carbonate powder dosed TID with meals for four weeks.

Figure 1: Study Design



The prescribed dose during the two randomized treatment periods was individualized based on the final sevelamer hydrochloride tablet dose prescribed at the end of the Run-In Period prior to randomization. Patients had weekly study visits for the first 2 weeks and 2 study visits during

each of the last 2 weeks of Treatment Period 1. During Treatment Period 2, patients previously assigned to sevelamer hydrochloride tablets were crossed-over to sevelamer carbonate powder and those previously assigned to sevelamer carbonate powder were crossed-over to sevelamer hydrochloride tablets for an additional 4 weeks of treatment. Patients had weekly study visits for the first 2 weeks and 2 study visits during each of the last 2 weeks of Treatment Period 2. At the end of Treatment Period 2, study medication was discontinued and patients were instructed to return to their pre-study phosphate binder medication. Patients returned for a Follow-up visit 7 days later.

The study was open-label due to the practical considerations involved in blinding patients to study medication assignment (powder vs. tablet).

The Inclusion Criteria included:

Taking sevelamer hydrochloride alone (e.g. not using other types of phosphate binders concomitantly) or on combination therapy (e.g. using sevelamer hydrochloride and calcium containing, or metal phosphate binders concomitantly) not exceeding a total daily binder dose of 14.4 g. for at least 60 days prior to screening.

Had the following documented local laboratory measurements:

- a) Two most recent consecutive serum phosphorus measurements that were ≥ 3.0 and ≤ 7.0 g/dL (≥ 0.96 and ≤ 2.26 mmol/L) within 60 days of screening.
- b) A most recent intact PTH (iPTH) measurement ≤ 900 pg/mL (≤ 99 pmol/L) within 90 days of screening.
- c) A most recent serum calcium (adjusted for albumin) measurement within normal range defined by the local laboratory within 60 days of screening.

If patient was on vitamin D replacement or receiving calcimimetic therapy, the patient must be at a stable dose for at least one month prior to screening and was willing to maintain the same dose throughout the duration of the study, except for safety reasons.

The Exclusion Criteria included patients that had active dysphagia, swallowing disorders, bowel obstruction, or severe gastrointestinal motility disorders.

Treatments:

During the Run-In Period, patients received sevelamer hydrochloride at a dose based on their most recently prescribed phosphate binder dose prior to the Washout Period. The dose of study drug that was last taken during the Run-In Period was to be used throughout the randomized cross-over treatment periods.

During the randomized treatment periods, patients received either sevelamer carbonate powder or sevelamer hydrochloride tablets according to the randomization assignment. Patients were randomized on a 1:1 basis to one of the following two treatment sequences:

- Sevelamer carbonate 800 mg powder TID for four weeks followed by sevelamer hydrochloride 800 mg tablets TID for four weeks.

- Sevelamer hydrochloride 800 mg tablets TID for four weeks followed by sevelamer carbonate 800 mg powder TID for four weeks.

All study medication was taken orally. Patients were instructed to thoroughly mix each individual sevelamer carbonate powder 800 mg sachet with 20 mL of water. A measuring cup was provided to patients to ensure the appropriate volume of water was used. Patients were instructed to drink the mixture within 30 minutes of preparation. Multiple sachets may have been mixed at once, as long as the appropriate amount of water was used (i.e., 1 sachet = 20 mL of water, 2 sachets = 40 mL of water, etc.). No additional preparation was required for sevelamer hydrochloride tablets.

Patients were randomized within each site on a 1:1 basis in blocks of 4 to one of the two treatment sequences. Dose titration, by increasing or decreasing by 1 x 800 mg tablet TID (2.4 g/day), was permitted during the Run-In Period at Visits 3 and 4 (Weeks -3 and -2) to keep serum phosphorus levels within a target range of 3.5 and 5.5 mg/dL (1.12 and 1.76 mmol/L) inclusive. The patient's final dose of sevelamer hydrochloride at the end of the Run-In Period was then to be used during both randomized treatment periods.

Table 2: Schedule of Study Events

	Screening / Start of washout	RUN-IN TREATMENT PERIOD					TREATMENT PERIOD 1			TREATMENT PERIOD 2		
	Visit 1 (Week -6)	Visit 2 (Week -4)	Visit 3 (Week -3)	Visit 4 (Week -2)	Visit 5 (Week -1)	Visit 6 (Week 0) BASELINE	Visits 7, 8, 9, 10, 11 (Weeks 1, 2, 3, 3a, 4)	Visit 12 (Week 4a)	Visits 13, 14, 15, 16, 17 (Weeks 5, 6, 7, 7a, 8)	Visit 18/ET (Week 8a)	Visit 19 Follow-up (Week 9)	
Describe Study and Obtain Informed Consent	√											
Review Inclusion & Exclusion	√	√				√						
Assign Patient Number	√											
Review Medical and Renal History and prior medications	√											
Review two consecutive local lab serum phosphorus values within 60 days of screening	√											
Review most recent iPTH within 90 days of screening	√											
Review most recent CA (adjusted for albumin) value within 60 days of screening	√											
Record Height						√						
Physical Exam (including Vital Signs and weight)		√				√		√		√		
Serum human chorionic gonadotrophin	√											
Serum phosphorus, calcium (albumin-adjusted), albumin, calcium (albumin-adjusted) phosphorus product	√	√	√	√	√	√	√	√	√	√		
Serum glucose, creatinine, chloride and bicarbonate						√		√		√		
Serum sodium, potassium, BUN	√	√				√		√		√		
Serum iPTH					√	√	√	√		√		
Serum 25-Vit D and 1,25-Vit D						√		√		√		
Serum Lipid Profile						√		√		√		

	Screening / Start of washout	RUN-IN TREATMENT PERIOD					TREATMENT PERIOD 1			TREATMENT PERIOD 2		
	Visit 1 (Week -6)	Visit 2 (Week -4)	Visit 3 (Week -3)	Visit 4 (Week -2)	Visit 5 (Week -1)	Visit 6 (Week 0) BASELINE	Visits 7, 8, 9, 10, 11 (Weeks 1, 2, 3, 3a, 4)	Visit 12 (Week 4a)	Visits 13, 14, 15, 16, 17 (Weeks 5, 6, 7, 7a, 8)	Visit 18/ET (Week 8a)	Visit 19 Follow-up (Week 9)	
Serum Electrolytes: Phospho	√	√				√		√		√		
Local Phosphorus	√	√				√		√		√		
Serum Calcium	√	√				√		√		√		
Discontinue phosphate binder treatment	√					√		√		√		
Randomize Patient						√		√		√		
Dispense Sevelamer Hydrochloride 800 Run-In		√										
Dispense study drug per randomization assignment for Treatment Period 1						√		√		√		
Dispense study drug per randomization assignment for Treatment Period 2												
Perform Study Drug Assessability				√		√	√	√	√	√		
Discontinue Study Drug						√		√		√		
Continue Medications and A/E Assessments							Continuous Monitoring					

*Doing accountability at Visits 9 and 18 only.

Efficacy Measurements:

For the primary efficacy parameter, blood samples were measured for serum phosphorus at Weeks 3, 3a, 4, 4a (Treatment Period 1) and Weeks 7, 7a, 8, and 8a (Treatment Period 2). For the secondary efficacy parameters, blood samples were measured for serum calcium-phosphorus product at Weeks 3, 3a, 4, 4a (Treatment Period 1) and Weeks 7, 7a, 8, and 8a (Treatment Period 2) See the above Table 2.

For lipid parameters (total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides), blood samples were measured at Week 4a for Treatment Period 1 and Week 8a for Treatment Period 2. Blood samples taken for analysis on the same day as HD were taken just prior to the start of dialysis. However, these secondary endpoints will not be reviewed here.

6.1.3.2 Study GD3-199-301

Study Title: 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

Study Centers: 29 sites in the United States participated in the trial. One site screened patients but did not enroll any patients.

Study Dates: January 27, 2006 to March 19, 2007

Objectives:

Primary objectives in chronic kidney disease (CKD) patients on hemodialysis 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 hemodialysis, 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).

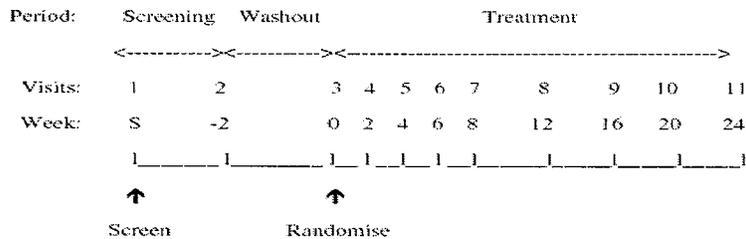
These secondary objectives will not be reviewed here.

Study Design:

This was a randomized, parallel, open-label study in CKD patients on HD to evaluate the safety and efficacy of sevelamer carbonate powder, dosed QD with the largest meal, compared to sevelamer hydrochloride tablets dosed TID with meals. The study consisted of three periods: a

two week screening period, a two-week phosphate binder washout period, and a 24-week randomized treatment period.

Figure 2: Study Schematic



During the Screening Period, patients were screened for eligibility. 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 randomized (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 randomized 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 ≤ 1.76 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).

Inclusion Criteria included:

Had the following documented local laboratory measurements:

- a. Two most recent consecutive serum phosphorus measurements that were ≥ 3.0 and ≤ 6.5 mg/dL (≥ 0.97 and ≤ 2.10 mmol/L) within 60 days of screening
- b. A most recent iPTH measurement ≤ 800 pg/mL (≤ 800 ng/L) within 90 days of screening

Had the following central laboratory measurements:

- a. A serum phosphorus measurement > 5.5 mg/dL (1.78 mmol/L) at randomization (Week 0)
- b. A serum iPTH measurement ≤ 800 pg/mL (≤ 800 ng/L) at screening

Exclusion Criteria included:

Active bowel obstruction, dysphagia, swallowing disorder, or severe gastrointestinal (GI) motility disorders

Treatment:

During the randomized treatment periods, patients received either sevelamer carbonate powder or sevelamer hydrochloride tablets according to the randomization assignment. The patients were randomized in a 2:1 fashion (in favor of carbonate powder) to one of two treatments: sevelamer carbonate powder dosed QD with the largest meal or sevelamer hydrochloride tablets dosed TID with meals. The starting dose was 4.8 g of either sevelamer hydrochloride tablets or sevelamer carbonate powder. Sevelamer carbonate powder (Genzyme Corporation) was supplied as 2.4 g sachets provided in 30 count boxes. TUMS® Regular 500 mg tablets, containing 200 mg elemental calcium were provided in the event that an evening calcium supplement was needed.

Patients were instructed to thoroughly mix each individual sevelamer carbonate powder 2.4 g packet with 2 ounces (oz) of cold water. Patients were instructed to drink the mixture immediately, and not longer than 30 minutes after preparation. If the mixture was not taken immediately after preparation, the patients were instructed to stir the mixture again prior to drinking. Patients were permitted to mix multiple packets at once, as long as the appropriate amount of water was used (i.e. 1 packet = 2 oz. of water, 2 packets = 4 oz. of water, 3 packets = 6 oz. of water, etc.).

Once the Week 0 labs were available, eligible patients were randomized [stratified by screening iPTH ≤ 400 or > 400 pg/mL (≤ 400 or > 400 ng/L) and cinacalcet treatment at Week 0] to one of two treatment groups in a 2:1 fashion in favor of sevelamer carbonate powder:

1. sevelamer carbonate powder dosed QD with the largest meal or
2. sevelamer hydrochloride tablets dosed TID with meals.

Patients with higher PTH levels are likely to have higher levels of phosphorus and can be more difficult to treat. Cinacalcet treatment may result in more effective treatment of hyperparathyroidism and be associated with lower serum phosphorus levels. Therefore, the stratification by PTH and cinacalcet was an attempt to balance the number of patients with severe hyperparathyroidism and cinacalcet use in each group.

The starting dose of 4.8 grams/day for both sevelamer carbonate powder and sevelamer hydrochloride tablets was selected based on the approved dosing instructions for sevelamer hydrochloride tablets. Those instructions recommend a starting dose of 800 to 1600 mg, administered as one to two 800 mg tablets with each meal for a total daily dose 2.4 to 4.8 grams/day. The sevelamer hydrochloride dosing instructions also state that the dose should be titrated until an acceptable phosphorus level is reached. Therefore, dose titration was also suggested for sevelamer carbonate powder and sevelamer hydrochloride tablets in this study.

Patients were instructed to take sevelamer carbonate powder once a day with the largest meal. This was recommended so that sevelamer carbonate would be present in the gastrointestinal tract at the same time as the meal with the greatest phosphate intake.

The starting dose was 4.8 g daily of either sevelamer hydrochloride tablets or sevelamer carbonate powder. The study treatment dose was to be titrated up or down in increments of 2.4 g daily at Visits 4, 5, 6, 7, 8, 9 and 10 (Weeks 2, 4, 6, 8, 12, 16, 20) to reach a target serum phosphorus level of ≥ 3.5 and ≤ 5.5 mg/dL (≥ 1.13 and ≤ 1.78 mmol/L).

Sevelamer hydrochloride tablets were to be taken TID with meals. Sevelamer carbonate powder was to be taken QD with the largest meal. The study was open-label as it was not possible to blind the patients to study treatment assignment due to the different formulations and dosing regimens.

Therapy for hyperparathyroidism may have been started, stopped or titrated every four weeks (Weeks 4, 8, 12, 16, and 20) to reach a target serum iPTH of ≥ 150 and ≤ 300 pg/mL (≥ 150 and ≤ 300 ng/L). Cinacalcet may have been 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. The Investigator retrieved unused study drug at each visit and performed drug accountability.

Table 3: Assessment and Procedures to be Performed at Each Study Visit

	Visit 1 (Screening)	Visit 2 (Week -2)	Visit 3 (Week 0)	Visit 4 (Week 2)	Visit 5 (Week 4)	Visit 6 (Week 6)	Visit 7 (Week 8)	Visit 8 (Week 12)	Visit 9 (Week 16)	Visit 10 (Week 20)	Visit 11/ET (Week 24/ET)
Describe Study and Obtain Informed Consent	√										
Review Inclusion/Exclusion Criteria	√		√								
Assign Patient Number	√										
Review Medical and Renal History	√										
Review two most recent local lab phosphorus values within 60 days of screening and iPTH within 90 days of screening	√										
Physical Exam (including vital signs)	√										√
Serum Chemistry Profile		√ ¹	√ ²	√ ¹	√ ¹	√ ¹	√ ²				
Serum hCG (Women of Child bearing Potential)	√										
Serum iPTH	√	√	√		√		√	√	√	√	√
C-reactive protein			√								√
Serum 25-OH D and 1,25-OH D			√								√
Serum Lipid Profile (TC, LDL, TG, HDL)			√								√
Serum Haematology Profile ³			√								√
Serum Storage Sample			√								√
Randomize Patient			√								
Dispense Study Drug			√ ⁶	√	√	√	√	√	√	√	
Perform Study Drug Accountability			√	√	√	√	√	√	√	√	√
USC 24-hour dietary recall	√ ⁴	√ ⁵						√ ⁵			√ ⁵
Questionnaire		√ ⁷									
AE Assessment											
Concomitant Medications/Therapies											

¹ Chemistry profile at Visit 2, 4, 5, 6, 7, 8, 9 and 10; Serum phosphorus, calcium (adjusted for albumin), albumin, chloride, bicarbonate and calcium-phosphorus product.

² Chemistry profile at Visit 3 and 11/ET: Serum phosphorus, calcium (adjusted for albumin), albumin, calcium-phosphorus product, bicarbonate, chloride, uric acid, sodium, potassium, glucose, BUN, liver function tests (ALT and AST) and creatinine.

³ Haematology profile includes: CBC with differential, platelet count, clotting factors (PT, PTT).

⁴ Review the patient dietary summary and fax patient information to USC.

⁵ On three randomly selected days during the 2-week washout period, mid-way through treatment, and the last 2 weeks of treatment, dietary recalls will be performed by USC.

⁶ Once the laboratory results are available from Visit 3(Week 0), a two-week supply of study drug will be provided to eligible patients at their next clinic visit.

⁷ Patient Satisfaction Questionnaire is to be completed at Week -2 (+/- 2 weeks) and Week 12 (+/- 2 weeks)

The Statistical Plan was submitted January 26, 2007, after the commencement of this study.

Sample Size Consideration:

The sample size was evaluated with respect to the primary efficacy parameter of the study, the change from baseline to Week 24/ET in serum phosphorus. A total of 165 evaluable subjects (2:1 randomization: 110 sevelamer carbonate powder QD, 55 sevelamer hydrochloride tablet TID) were required to achieve 90% power based on a two group student's t-test with a one-sided 2.5% type I error rate for a noninferiority margin of 1 mg/dL (non-inferiority would be concluded if powder QD provides serum phosphorus reduction that is statistically significantly greater than that associated with tablets TID minus 1 mg/dL). Approximately 207 subjects were randomized to one of the two treatment groups to account for anticipated exclusions from the per-protocol populations.

Analysis Populations:

Safety Set (SS): This population consists of all randomized subjects who received at least one dose of study medication.

Full Analysis Set (FAS): This population consists of the subset of the Safety Set with any post-dosing phosphorus assessments.

Per Protocol Set (PPS): This population consists of the subset of the FAS with no major protocol violations as determined by a review prior to database lock.

Study Treatment: Percent compliance, starting prescribed daily dose, ending prescribed daily dose, average prescribed daily dose, average actual dose and duration of study drug were presented by treatment group. Wilcoxon rank sum tests were used to test the difference between the treatment groups for SS, FAS, and PPS populations.

Treatment duration was calculated using the following formula:

$$\text{Duration (weeks)} = (\text{Last Date of Dosing} - \text{First Date of Dosing} + 1) / 7.$$

Treatment compliance was calculated overall as follows:

$$\text{Compliance} = \frac{(\text{Number of Packets Dispensed} - \text{Number of Packets Returned}) \times 100}{(\text{powder}) \text{ Number of Prescribed Packets}}$$

$$\text{Compliance} = \frac{(\text{Number of Tablets Dispensed} - \text{Number of Tablets Returned}) \times 100}{(\text{tablets}) \text{ Number of Prescribed Tablets}}$$

Efficacy Analysis:

The analysis of efficacy endpoints included tabulations of findings at each timepoint and the change from baseline to each post-baseline time point. The final row displayed the change from baseline to Week 24/ET. Data was not carried forward for these analyses with the exception of the Week 24/ET timepoint. Efficacy analysis was done for FAS and PPS populations.

Primary Efficacy Parameter: The primary efficacy analysis was an assessment of non-inferiority with respect to a change from baseline in serum phosphorus levels at Week 24/final among the

Per-Protocol Set. A Full Analysis Set analysis was performed as a confirmatory analysis. Specifically, a two-sided 95% confidence interval was estimated for the difference in serum phosphorus change between treatment groups (diff = sevelamer carbonate powder QD - sevelamer hydrochloride tablets TID). If the upper confidence bound is less than 1 mg/dL, then non-inferiority will be concluded. Serum phosphorus results at each assessment timepoint were tabulated by treatment group.

Demographics:

Patient demographics including age, race, ethnicity, gender, history of diabetes, post-dialysis weight, body mass index (BMI), height and stratification criteria [iPTH \leq 400 pg/mL (\leq 400 ng/L) versus $>$ 400 pg/mL ($>$ 400 ng/L) at Screening and use of cinacalcet at baseline (Week 0)] was summarized by treatment group and overall. Comparability of treatment groups was assessed using Fisher's exact tests for categorical variables and the Wilcoxon rank sum test for continuous variables.

Renal History:

Renal history including primary cause of end stage renal disease (ESRD), time on dialysis, vitamin D use at screening, and history of parathyroidectomy was summarized by treatment group and overall. Comparability of treatment groups was assessed using Fisher's exact tests for categorical variables and the Wilcoxon rank sum test for continuous variables.

Medical History:

The number and percentage of patients reporting a medical history for each body system was summarized by treatment group and overall. Fisher's exact test was used to test for differences between the two treatment groups.

Efficacy Analysis:

The analysis of efficacy endpoints includes tabulations of findings at each time point and the change from baseline to each post-baseline time point. Data was not carried forward for these analyses with the exception of the Week 24/ET time point. Efficacy analyses were done for the FAS and PPS populations.

Primary Efficacy Analysis:

The primary efficacy analysis was an assessment of non-inferiority with respect to change from baseline in serum phosphorus levels at Week 24/final among the PPS. A FAS analysis was performed as a confirmatory analysis. Specifically, a two-sided 95% confidence interval was estimated for the difference in 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 concluded. Serum phosphorus results at each assessment time point were tabulated by treatment group.

Sub-group analyses for the primary efficacy endpoint were also performed separately within the following randomization strata 1) serum iPTH \leq 400 and $>$ 400 pg/mL [\leq 400 and $>$ 400 ng/L]

and 2) cinacalcet use at Week 0. No non-inferiority assessment was made among these subgroups.

Disposition of Patients:

Patients were enrolled at 29 study centers. One site (515) screened, but did not enroll any patients. The first patient signed informed consent on January 27, 2006, and the last patient completed the last visit on March 19, 2007.

A total of 396 patients were screened for this study and of these, 179 patients were screen failures. The most frequent cause of screen failure was exclusionary laboratory measurement: 130 (72.6%) patients. Two hundred and seventeen patients were randomized: 144 were assigned to sevelamer carbonate powder QD and 73 were assigned to sevelamer hydrochloride tablets TID, reflecting the 2:1 randomization design. Four [3 (2.1%) sevelamer carbonate powder QD patients; 1 (1.4%) sevelamer hydrochloride tablet TID patient] of the randomized patients never received study treatment. A total of 62 [51 (35.4%) sevelamer carbonate powder QD patients; 11 (15.1%) sevelamer hydrochloride tablet TID patients] discontinued from the study prematurely. The most frequent causes of discontinuation were adverse event [18 (12.5%) sevelamer carbonate powder QD patients; 4 (5.5%) sevelamer hydrochloride tablet TID patients] and withdrawn consent [18 (12.5%) sevelamer carbonate powder QD patients; 2 (2.7%) sevelamer hydrochloride tablet TID patients]. A higher proportion of sevelamer carbonate powder patients discontinued due to an adverse event or consent withdrawn than sevelamer hydrochloride patients. One hundred and fifty five patients completed the study: 93 (64.6%) sevelamer carbonate powder QD patients and 62 (84.9%) sevelamer hydrochloride tablet TID patients.

Table 4: Patient Disposition by Treatment Group

	Overall	Sevelamer Carbonate Powder QD	Sevelamer Hydrochloride Tablet TID
Screened	396		
Screen Failures			
Withdrawal of Consent Prior to Visit 2 or Visit 3	12 (6.7)		
Exclusionary Medical or Medication History	17 (9.5)		
Exclusionary Laboratory Measurement	130 (72.6)		
Adverse Experience	5 (2.8)		
Other	15 (8.4)		
Randomised Patients	217	144	73
Never Received Study treatment	4 (1.8)	3 (2.1)	1 (1.4)
Discontinued Prematurely			
Adverse Experience	22 (10.1)	18 (12.5)	4 (5.5)
Failure to Comply with Protocol Requirements	4 (1.8)	4 (2.8)	0 (0)
Withdrew Consent	20 (9.2)	18 (12.5)	2 (2.7)
Lost to Follow-up	2 (0.9)	1 (0.7)	1 (1.4)
Death	3 (1.4)	1 (0.7)	2 (2.7)
Other	11 (5.1)	9 (6.3)	2 (2.7)
Completed Study	155 (71.4)	93 (64.6)	62 (84.9)

Two additional sevelamer carbonate powder QD and two additional sevelamer hydrochloride tablet TID patients died during the course of the study. These deaths were not specified as the primary cause of early termination and thus are not included in this table.

Reviewer's comment:

It is interesting to note that the powder formulation given once a day had more drop-outs as this formulation is being developed for the patients' convenience.

Protocol Deviations

There were 5 major protocol deviations among 4 patients (Patients 503111, 505104, 506101 and 522108). Patient 503111 experienced a prolonged hospitalization _____ . During this hospitalization, the patient did not take sevelamer hydrochloride. The prolonged hospitalization also resulted in the final study visit being more than 5 weeks delayed. Patient 505104 had their dose of sevelamer hydrochloride increased to 16.8 g/day (greater than allowed per protocol) on August 10, 2006. The dose was reduced to within protocol specifications (14.4 g/day) on October 4, 2006. Patient 506101 returned 519 sevelamer hydrochloride tablets at the end of study visit. The study site believed the patient's nursing home gave her their supply of sevelamer hydrochloride instead of the patient's study treatment. Patient 522108 received hemodialysis 4 times per week rather than three times per week as specified by the protocol due to interdialytic weight gain.

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6.1.4 Efficacy Findings

6.1.4.1 Study SVCARB00205

Primary Efficacy Variable:

The primary efficacy measure was a time-weighted average of the serum phosphorus assessments during the last two weeks of each treatment regimen (mean of non-missing assessments from Weeks 3, 3a, 4, and 4a for Treatment Period 1 and mean of non-missing assessments from Weeks 7, 7a, 8, and 8a for Treatment Period 2). Blood samples taken for analysis on the same day as HD were taken just prior to the start of dialysis.

Statistical Methods

Categorical variables were described using frequencies and percents. Continuous variables were described by the number of patients with non-missing assessments, mean, standard deviation, median, minimum, and maximum. All tests were two-sided and were performed at the 5% significance level unless otherwise specified.

The original randomization envelope for Site 02 was misplaced and the randomization envelope originally intended for Site 05 was used instead (as Site 05 was not used to recruit any patients). Therefore, patients enrolled at Site 02 were assigned patient identification numbers designated for Site 05 (0501, etc) and appear as such in the patient data listings.

Analysis Populations:

All patients were administered their treatment assignments in accordance with their randomized sequence assignments. Therefore, for each analysis population, patients were analyzed according to their randomized sequence.

Safety Set:

The Safety Set included all randomized patients who were treated with at least one dose of randomized study medication.

Full Analysis Set:

The Full Analysis Set (FAS) included the subset of Safety Set-evaluable patients with at least one post-baseline assessment of serum phosphorus. A confirmatory assessment of phosphorus control equivalence was conducted using the FAS.

Per Protocol Set:

The Per Protocol Set (PPS) included all FAS-evaluable patients with no significant protocol deviations, as determined by a blinded review by appropriate clinical and statistical personnel prior to data analysis. Factors that were considered in determining PPS evaluability included:

- Compliance differences between treatment periods (i.e., at least 30% difference in compliance)
- Entry criteria violation
- Proscribed medication usage
- Completed less than 3 weeks treatment in either treatment period
- Other significant protocol deviations

The primary assessment of phosphorus control equivalence was conducted using the PPS.

Demographics:

Demographics and baseline characteristics were summarized overall and by treatment sequence for all analysis sets. Treatment sequences were compared using Fisher's exact test for categorical data and the Wilcoxon rank sum test for continuous data. Categorical summaries were presented for gender, ethnicity and smoking status. Continuous summaries were presented for age and baseline assessments of weight, height, and body mass index (BMI). Age in years was calculated as $((\text{Date of informed consent} - \text{Date of birth}) + 1)/365.25$. Baseline weight and height measurements were captured at Week 0. BMI was calculated as weight in kilograms divided by square of height in meters. The weight measurement captured at Week -4 was listed only.

Medical history findings at Screening were tabulated by body system, both overall and by treatment sequence for all analysis sets. Renal history findings at Screening were summarized overall and by treatment sequence for all analysis sets. Treatment sequences were compared using Fisher's exact test for categorical data and the Wilcoxon rank sum test for continuous data. Categorical summaries were provided for primary cause of end stage renal disease, dialysis schedule, current phosphate binder use, previous parathyroidectomy, use of vitamin D, and kidney transplant. Continuous summary statistics were reported for length of time on dialysis. Length of time on dialysis in years was calculated as $((\text{Date of informed consent} - \text{Date of dialysis start}) + 1)/365.25$.

Compliance:

Percent compliance was calculated as the number of tablets/sachets taken in the period (estimated by subtracting the number of tablets/sachets returned from the number dispensed) divided by the total number of tablets/sachets prescribed in the period, and multiplied by 100.

Efficacy Analysis:

Primary Efficacy Analysis:

The effects of powder and tablet dosing on the control of serum phosphorus was determined using equivalence testing. The time-weighted average of the serum phosphorus assessments during the last two weeks of each treatment regimen (mean of non-missing assessments from Weeks 3, 3a, 4, and 4a for Treatment Period 1 and mean of non-missing assessments from Weeks 7, 7a, 8, and 8a for Treatment Period 2) was used to give a more accurate assessment of phosphorus control than would be attained by a single point reading. Measurements prior to Week 3 for Treatment Period 1 and prior to Week 7 for Treatment Period 2 were not carried forward for efficacy assessment.

Equivalence was assessed using natural-log transformed time-weighted mean serum phosphorus data. Least squares means for each treatment and the mean squared error from a 2x2 analysis of variance (ANOVA) with a random subject effect and fixed sequence, period, and treatment effects were used to derive the 90% confidence interval for the difference between powder (test) and tablet (reference) data on the log scale. Back transformation to the original scale yielded an estimate of the ratio (test/reference) and corresponding 90% confidence interval which was the basis of a 5% Two One-Sided Test (TOST) equivalence test. This test required that the 90% confidence interval for the ratio was within the interval (0.80, 1.25). If the sequence effect was significant ($p\text{-value} \leq 0.05$), then equivalence inferences were to be drawn from the Treatment Period 1 results.

The primary analysis was performed on the PPS to minimize the degree of bias in the equivalence testing. A FAS analysis was performed as a confirmatory analysis.

Secondary Efficacy Analyses are not reviewed here.

Additional Analyses: Serum phosphorus, calcium (albumin-adjusted), and calcium-phosphorus product levels at Screening, at Week -4 (after the 2-week washout), the change from Screening to Week -4, and at Week 0 were summarized overall and by treatment sequence among PPS, FAS, and Safety Set patients. Within treatment regimen changes were assessed using the Wilcoxon signed rank test.

Protocol Amendment:

There was one protocol amendment, dated May 8, 2006, that was made to increase the number of potential patients that could be considered for the study. A summary of the main changes is given below:

- The number of patients to be screened was changed from approximately 35 to approximately 75 due to a higher than anticipated screening failure rate.
- Sevelamer hydrochloride did not need to be the primary phosphate binder in those patients taking combination therapy before entry into the study.
- Study entry limits of iPTH and serum phosphorus levels measured at the local laboratory were increased due to the variation between local and central laboratory analyses, which meant that

some patients may not be considered eligible by the local analysis and would therefore not be screened.

- Change in sponsor study personnel.

Disposition of Patients:

A total of 75 individual patients were screened for this study of whom 1 patient was re-screened (and is counted twice in pre-randomization disposition data), giving an overall count of 76 patients. Of the screened patients, 34 (44.7%) patients did not enter the Run-In Period: 26 (34.2%) patients were screen failures before the Run-In Period, 4 (5.3%) patients wished to withdraw, 2 (2.6%) patients discontinued due to an AE, and 2 (2.6%) patients withdrew for “other” reasons. The most common reason for screen failure for entry into the Run-In Period was serum phosphorus levels below the required range (i.e., < 5.5 mg/dL [< 1.76 mmol/L]) which was reported for 17 of the 26 screen failure patients.

A total of 42 patients entered the Run-In Period, of whom 11 (14.5%) patients were not randomized: 7 (9.2%) patients were screen failures during the Run-In Period, 1 (1.3%) patient was non-compliant and 3 (3.9%) patients withdrew for “other” reasons. The most common reasons for screen failure during the Run-In Period were high iPTH levels (i.e., > 800 pg/mL) in 3 patients, and high phosphorus levels (i.e., > 6.5 mg/dL [> 2.08 mmol/L]) in 2 patients. In addition, of the 3 patients in the “other” category, the primary reason for withdrawal was noted to be high iPTH levels in 1 patient and high phosphorus levels in the other 2 patients.

Thirty-one patients were randomized to study treatment: 17 to the sevelamer carbonate powder/sevelamer hydrochloride tablet sequence (sequence 1) and 14 to the sevelamer hydrochloride tablet/sevelamer carbonate powder sequence (sequence 2). Of the 31 patients who entered Treatment Period 1, 3 (9.7%) patients discontinued: 1 (3.2%) patient discontinued due to an AE and 2 (6.5%) patients wished to withdraw. The 3 patients who discontinued during Treatment Period 1 were randomized to treatment sequence 1, and therefore discontinued during sevelamer carbonate powder treatment.

A total of 28 patients entered Treatment Period 2: 14 patients from sequence 1 and 14 patients from sequence 2. During Treatment Period 2, 4 (12.9%) patients discontinued: 1 (3.2%) patient discontinued due to an AE and 3 (9.7%) patients wished to withdraw. One of the patients (Patient 0521) who chose to withdraw from the study also had an AE leading to discontinuation, but “patient wishes to withdraw” was cited as the primary reason for withdrawal. The 4 patients who discontinued during Treatment Period 2 were randomized to treatment sequence 2, and therefore discontinued during sevelamer carbonate powder treatment. Overall, a total of 24 (77.4%) of the 31 randomized patients completed Treatment Period 2: 14/17 (82.4%) patients randomized to sequence 1 and 10/14 (71.4%) patients randomized to sequence 2. All patients who completed Treatment Period 2 also completed the Follow-up visit. The patient disposition overall and by treatment sequence is presented in the following table.

Table 5: Patient Disposition (N, %) by Randomized Sequence Group

Patient Category	Overall (N=76)	Sequence 1 Carbonate powder/ Hydrochloride tablets (N=17)	Sequence 2 Hydrochloride tablets/ Carbonate powder (N=14)
Screened Patients	76 [†]		
Patients Who Did Not Enter Run-In Period	34 (44.7)		
Screen failure before Run-In Period	26 (34.2)		
Adverse event	2 (2.6)		
Wishes to withdraw	4 (5.3)		
Other	2 (2.6)		
Patients Entered Run-In Period	42 (55.3)		
Non-Randomised Patients Among Run-In Patients	11 (14.5)		
Screen failure during the Run-In Period	7 (9.2)		
Non-compliant	1 (1.3)		
Other	3 (3.9)		
Randomised Patients	31 (40.8)	17	14
Discontinued Study Drug During Treatment Period 1	3 (9.7)	3 (17.6)	0
Adverse event	1 (3.2)	1 (5.9)	0
Wishes to withdraw	2 (6.5)	2 (11.8)	0
Completed Treatment Period 1	28 (90.3)	14 (82.4)	14 (100.0)
Discontinued Study Drug During Treatment Period 2	4 (12.9)	0	4 (28.6)
Adverse event	1 (3.2)	0	1 (7.1)
Wishes to withdraw	3 (9.7)	0	3 (21.4)
Completed Treatment Period 2	24 (77.4)	14 (82.4)	10 (71.4)
Discontinued Prior to Follow-up Visit	0	0	0
Completed Follow-up Visit	24 (77.4)	14 (82.4)	10 (71.4)

[†] 75 individual patients were screened and of these, 1 patient was re-screened.

Note: percentage values for Screening and Run-In Periods are based on number of screened patients (N=76).

Percentage values for randomized treatment periods are based on the number of randomized patients, either overall or in each treatment sequence, as appropriate.

Protocol Deviations:

There were 7 major protocol deviations among 4 patients (Patients 0101, 0306, 0310 and 0311). Three of the 4 patients were included in the PPS as the protocol deviations were not expected to impact the equivalence assessment between treatment regimens. The exception was Patient 0310 who was excluded from the PPS as the patient failed to have at least 3 weeks of treatment in both randomized treatment periods.

Patients 0306, 0310 and 0311 each had one major deviation relating to the dose of sevelamer hydrochloride during the Run-In Period. All 3 patients had serum phosphorus levels at Visit 3 which according to the study protocol required an increase in the dose of study medication. In each case, the investigator preferred that the patient remained on their existing dose of sevelamer hydrochloride, either because they had only been on the dose for only 4 days before the Visit 3 sample was taken (Patients 0310 and 0311) or because the patient had experienced severe stomach cramps following previous dose escalations (Patient 0306).

Patient 0101 had 4 major protocol deviations. Three of the major deviations related to missed

study visits and therefore no blood samples being taken at Visits 3 and 4 during Run-In and Visit 11 during Treatment Period 1. The fourth major deviation in Patient 0101 was an error in the study medication issued to the patient during Treatment Period 1: the patient was randomized to receive sevelamer carbonate powder during Treatment Period 1 but at Visit 10, the research nurse prescribed sevelamer hydrochloride tablets in error, and therefore the cross-over in study medication occurred approximately 3 weeks earlier than scheduled (should have been at Visit 13).

Data Sets Analyzed:

The Safety Set included all randomized patients who received at least one dose of randomized study medication. Thirty-one patients were randomized and treated, and therefore there are 31 patients in the Safety Set.

The FAS included all randomized patients with at least one post-baseline assessment of serum phosphorus. All but 1 patient (Patient 0907) in the Safety Set had post-baseline serum phosphorus data, and therefore there are 30 patients in the FAS.

The PPS included all FAS-evaluable patients with no significant protocol deviations. Nine patients were excluded from the FAS, and therefore the PPS includes 21 patients. The following table presents patient evaluability overall and by treatment sequence.

Table 6: Patient Evaluability

Analysis Set Reason for exclusion	Overall (N=31) n (%)	Sequence 1 Carbonate powder/ Hydrochloride tablets (N=17) n (%)	Sequence 2 Hydrochloride tablets/Carbonate powder (N=14) n (%)
Randomized	31 (100)	17 (100)	14 (100)
Never received study medication	0	0	0
Included in the Safety Set	31 (100)	17 (100)	14 (100)
No post-baseline phosphorus assessments	1 (3)	1 (6)	0
Included in the Full Analysis Set	30 (97)	16 (94)	14 (100)
At least 30% difference in compliance between treatment periods	3 (10)	1 (6)	2 (14)
Entry criteria violation	0	0	0
Proscribed medication usage	0	0	0
Less than 3 weeks on study treatment in both treatment periods	6 (19)	2 (12)	4 (29)
Included in the Per Protocol Set	21 (68)	13 (77)	8 (57)

Reviewer's comments:

From the above table it is noted that only a few patients were evaluated in this study.

In the Safety Set, all 31 patients received sevelamer carbonate powder treatment and 28 patients received sevelamer hydrochloride tablet treatment. In the FAS, all 30 patients received sevelamer carbonate powder treatment and 28 patients received sevelamer hydrochloride tablet treatment, and all 21 patients in the PPS received both treatment regimens.

Of the 9 FAS patients excluded from the PPS, 6 patients (0310, 0520, 0521, 0522, 0803, and 0903) failed to have at least 3 weeks of treatment in both treatment periods, and 3 patients

(0503, 0505 and 0509) had a differential compliance of at least 30% between randomized treatment periods as the reason for exclusion.

The 6 patients excluded from the PPS for having insufficient treatment duration in both randomized treatment periods all failed to complete at least 3 weeks treatment with sevelamer carbonate powder. Two of the 6 patients (0522 and 0803) withdrew from the study during treatment with sevelamer carbonate powder and never entered the sevelamer hydrochloride tablet randomized treatment period. The remaining 4 patients (0310, 0520, 0521, and 0903) completed the sevelamer hydrochloride tablet randomized treatment period and subsequently withdrew from the study before completing at least 3 weeks treatment with sevelamer carbonate powder.

Of the 3 patients with a differential compliance of at least 30% between randomized treatment periods, Patients 0503 and 0505 had lower compliance during treatment with sevelamer carbonate powder, whereas Patient 0509 had lower compliance during treatment with sevelamer hydrochloride tablets.

It should be noted that Patient 0604 was retained in the PPS even though the difference in compliance between treatment periods was >30%. During Treatment Period 2, the patient had taken sevelamer hydrochloride tablets remaining from their Run-In Period rather than the sevelamer hydrochloride tablets prescribed for the randomized treatment period. Therefore, based on the study drug supply returned at the end of Treatment Period 2, it appeared that the patient had a low compliance. However, the investigator noted that the patient had good compliance and was therefore kept in the PPS. In addition, Patients 0106, 0311, and 0502 were retained in the PPS even though they had missing compliance data from Treatment Period 2 (drug return data were missing) because there was no other evidence of noncompliance.

Demographics:

The following table displays the demographics and baseline characteristics for the Safety Set (N=31). There were no statistically significant differences between the treatment sequences in demographic characteristics.

Twenty-one (68%) patients were male and 10 (32%) patients were female, with a mean age of 53 years. The majority of patients were Caucasian (71%), with Asians (19%) and Blacks (10%) comprising the rest of the population. The mean weight was 76 kg (n=30), the mean height was 170 cm (n=23), and the mean BMI was 26 kg/m² (n=23).

Results for the PPS and FAS were generally similar to those of the Safety. The most notable difference between the Safety Set and the PPS was in the proportion of Caucasian (71% in the Safety Set and 81% in the PPS) and Asian patients (19% in the Safety Set compared with 5% in the PPS) in each analysis population. These differences were not considered to have any impact on the outcome of the efficacy analyses.

Table 7: Patient Demographics and Baseline Characteristics (Safety Set)

Demographic Characteristic	Safety Set (N=31)
Age (years)	
Mean ± SD	52.9 ± 13.2
Median (range)	51 (27-80)
Gender, n (%)	
Male	21 (68)
Female	10 (32)
Ethnicity, n (%)	
Caucasian	22 (71)
Black	3 (10)
Hispanic	0
Asian	6 (19)
Weight (kg) at Week 0 (n=30)	
Mean ± SD	75.9 ± 19.9
Median (range)	72.2 (43.7-140.3)
Height (cm) at Week 0 (n=23)	
Mean ± SD	170.3 ± 13.3
Median (range)	171 (150-198)
BMI (kg/m ²) at Week 0 (n=23)	
Mean ± SD	25.7 ± 5.8
Median (range)	24.1 (19.3-39.6)
Smoker, n (%)	
Yes	5 (16)
No	26 (84)

SD= Standard deviation

Renal History:

Renal history is presented in the following table. There were no statistically significant differences between the treatment sequences in renal history characteristics. The most common primary causes of CKD were glomerulonephritis (26%), diabetes (13%) and “other” causes (42%). Of the 13 patients with “other” cited as the primary cause, the etiology of CKD was recorded as unknown in 5 patients, IgA nephropathy in 2 patients and renovascular disease, reflux nephropathy, road traffic accident, hereditary nephritis, Goodpasture syndrome, and Alport’s syndrome in 1 patient each. Eight (26%) patients in the Safety Set had previously undergone a kidney transplant and 4 (13%) patients had a parathyroidectomy (3 total and 1 partial). The median time on dialysis was 4.4 years.

The majority of patients (81%) were on vitamin D at study entry. All randomized patients were taking sevelamer hydrochloride as a pre-study phosphate binder, either alone (58%), in combination with calcium phosphate binders (36%), or in combination with other metal phosphate binders (7%); 1 patient was taking sevelamer hydrochloride in combination with aluminum and 1 patient was taking sevelamer hydrochloride in combination with magnesium carbonate.

Table 8: Renal History (Safety Set)

Parameter	Safety Set (N=31)
Primary Cause of End Stage Renal Disease, n (%)	
Hypertension	1 (3)
Glomerulonephritis	8 (26)
Diabetes	4 (13)
Pyelonephritis	1 (3)
Polycystic Kidneys	2 (7)
Interstitial Nephritis	1 (3)
Congenital	1 (3)
Other	13 (42)
Previous Kidney Transplant, n (%)	
No	23 (74)
Yes	8 (26)
Previous Parathyroidectomy, n (%)	
No	27 (87)
Yes	4 (13)
Currently on Vitamin D, n (%)	
No	6 (19)
Yes	25 (81)
Time on Dialysis (years)	
Mean ± SD	7.2 ± 8.0
Median (range)	4.4 (0.2-30.3)
Pre-Study Phosphate Binder, n (%)	
Sevelamer Hydrochloride	18 (58)
Sevelamer Hydrochloride and Calcium	11 (36)
Other	2 (7)

Medical History:

Reflective of the extent of chronic illness in the patient population, more than half of the patients in the overall Safety Set (N=31) reported prior or current disorders or abnormalities in the following body systems: genitourinary/renal (30 patients, 97%), metabolic/endocrine/nutritional (27 patients, 87%), hematopoietic (27 patients, 87%), cardiovascular (27 patients, 87%), gastrointestinal/hepatic (21 patients, 68%), and musculoskeletal (19 patients, 61%). In general, the prior and current disorders were similar between the two treatment sequences.

Concomitant Medications During the Randomized Treatment Periods:

During the randomized treatment periods, all 31 (100%) patients in the Safety Set took a concomitant medication. The drug categories with the most frequent (> 25%) concomitant medications are presented in the following table.

Table 9: Most Frequent Concomitant Medications Taken During Randomized Treatment

Therapeutic Class	Sevelamer Carbonate Powder (N=31) n (%)	Sevelamer Hydrochloride Tablets (N=28) n (%)
Other anti-anaemic preparations	29 (94)	26 (93)
Vitamin D and analogues	26 (84)	22 (79)
Platelet aggregation inhibitors excl. heparin	19 (61)	17 (61)
Proton pump inhibitors	15 (48)	13 (46)
HMG CoA reductase inhibitors	13 (42)	11 (39)
Beta blocking agents, selective	9 (29)	10 (36)
Dihydropyridine derivatives	9 (29)	9 (32)
ACE inhibitors, plain	9 (29)	8 (29)
Anilides	9 (29)	8 (29)
Multivitamins, plain	8 (26)	7 (25)

During the randomized treatment periods, 16 (52%) patients began new medications, or stopped or had changes in existing medications during treatment with sevelamer carbonate powder and 11 (39%) patients during treatment with sevelamer hydrochloride tablets. The concomitant medications changes were similar between treatment regimens and generally similar to the medication changes made during the Run-In Period.

In the Safety Set, the drug categories with the most frequent concomitant medication changes (at least 10%) were penicillins with extended spectrum, changed by 3 (10%) patients during sevelamer carbonate treatment and 1 (4%) patient during sevelamer hydrochloride treatment, and vitamin D and analogues that were changed by 3 (10%) patients during sevelamer carbonate powder treatment and no patients during sevelamer hydrochloride tablet treatment.

During the randomized treatment periods, mean percent compliance of the Safety Set and the FAS was similar between the sevelamer carbonate and sevelamer hydrochloride regimens: 81% for sevelamer carbonate powder and 83% for sevelamer hydrochloride tablets in both analysis sets.

Analysis of Efficacy:

The primary efficacy analysis was performed on the PPS to minimize the degree of bias in the equivalence testing. A FAS analysis was performed as a confirmatory analysis.

In the PPS, the mean serum phosphorus was 5.0 ± 1.5 mg/dL (1.6 ± 0.5 mmol/L) during sevelamer carbonate powder treatment and 5.2 ± 1.1 mg/dL (1.7 ± 0.4 mmol/L) during sevelamer hydrochloride tablet treatment. For assessing phosphorus equivalence, the treatment response across sequences was pooled since the 2x2 ANOVA model sequence p-value was not significant ($p=0.932$). The geometric least squares mean ratio (sevelamer carbonate powder/sevelamer hydrochloride tablets) was 0.95 with a corresponding 90% confidence interval of 0.87-1.03. The confidence interval is within the interval of 0.80-1.25, indicating that sevelamer carbonate powder and sevelamer hydrochloride tablets are equivalent in controlling serum phosphorus. The results of a confirmatory analysis conducted with the FAS were similar as shown in the following table.

Table 10: Serum Phosphorus Time-Weighted Averages (PPS and FAS)

Analysis Set	Sevelamer Carbonate Powder mean \pm SD	Sevelamer Hydrochloride Tablets mean \pm SD	Geometric LS Mean Ratio	90% CI of Ratio
Serum phosphorus (mg/dL)				
Per Protocol Set (N=21)	5.0 ± 1.5 (n=21)	5.2 ± 1.1 (n=21)	0.95	0.87-1.03
Full Analysis Set (N=30)	5.0 ± 1.5 (n=25)	5.1 ± 1.1 (n=28)	0.96	0.88-1.05
Serum phosphorus (mmol/L)				
Per Protocol Set (N=21)	1.6 ± 0.5 (n=21)	1.7 ± 0.4 (n=21)	0.95	0.87-1.03
Full Analysis Set (N=30)	1.6 ± 0.5 (n=25)	1.7 ± 0.4 (n=28)	0.96	0.88-1.05

SD = Standard deviation

Statistical Reviewer's comment:

It is notable that the drop-outs were relatively high in carbonate powder group in both periods, 17.6% (3/17) and 28.6% (4/14) in period 1 and period 2, respectively (Table 10). The reviewer conducted a sensitivity analysis using a worse-case imputation method for missing data: a maximum phosphate value of the period was assigned to the missing values. The result is comparable with the one excluding missing values. However, the conclusion of efficacy is still a concern given a small study with high drop-outs.

Serum Phosphorus During Screening/Washout and Run-In:

Prior to the randomized treatment periods, patients entered a 2-week Screening/Washout period followed by a 4-week sevelamer hydrochloride Run-In Period. The mean serum phosphorus at Screening in the PPS was 5.0 ± 1.0 mg/dL (1.6 ± 0.3 mmol/L). At the end of the Washout period (Week -4), mean serum phosphorus levels had increased significantly (mean change 2.7 ± 2.1 mg/dL [0.9 ± 0.7 mmol/L]; $p < 0.001$) to 7.6 ± 1.8 mg/dL (2.5 ± 0.6 mmol/L) confirming the hyperphosphatemic nature of the study population. Serum phosphorus levels subsequently decreased during the 4-week sevelamer hydrochloride Run-In Period and at the start of the randomized treatment period (Week 0), the mean value was 5.0 ± 1.2 mg/dL (1.6 ± 0.4 mmol/L) and comparable to Screening levels. The change in serum phosphorus during the Screening/Washout and Run-In Period in the FAS and Safety Set was similar to that observed for the PPS.

Handling of Dropouts or Missing Data:

The primary efficacy measure was the time-weighted average of the serum phosphorus assessments for the non-missing assessments (scheduled and unscheduled) from the last two weeks in each treatment regimen because this methodology can accommodate the varying number of assessments that could arise during the two week period and the varying intervals between assessments. Missing data were not imputed and measurements were not carried forward.

Interim Analyses:

No interim analyses were performed.

Efficacy Conclusions:

Sevelamer carbonate powder and sevelamer hydrochloride tablets, each dosed TID with meals, are equivalent in controlling serum phosphorus in patients with CKD on HD.

6.1.4.2 Study GD3-199-301

Table 11: Summary of Analysis Populations

	Overall	Sevelamer Carbonate Powder QD	Sevelamer Hydrochloride Tablets TID
Randomised	217	144	73
Never Received Study treatment	4 (1.8%)	3 (2.1%)	1 (1.4%)
Safety Set	213	141	72
No post-dosing phosphorus assessments	0 (0%)	0 (0%)	0 (0%)
Included in Full Analysis Set	213	141	72
Less than 8 weeks of treatment	26 (12.2%)	21 (14.9%)	5 (6.9%)
Compliance (< 70%)	37 (17.4%)	23 (16.3%)	14 (19.4%)
Inclusion or exclusion criteria violation	1 (0.5%)	0 (0%)	1 (1.4%)
Use of proscribed medication	0 (0%)	0 (0%)	0 (0%)
Other significant protocol violation	1 (0.5%)	0 (0%)	1 (1.4%)
Per-Protocol Set	148	97	51

Demographics:

The demographic characteristics were similar between treatment groups. The majority of patients in both groups were male (62% and 58% in the sevelamer carbonate powder QD group and sevelamer hydrochloride tablet TID group, respectively) and African American (54% in both groups). The mean age was just under 60 years old for both groups (57 and 59 years in the sevelamer carbonate powder QD group and sevelamer hydrochloride tablet TID group, respectively). Results for the FAS and PPS were similar to those of the Safety Set.

Table 12: Patient Demographics-Safety Set

Parameter	Sevelamer Carbonate Powder QD (N=141)	Sevelamer Hydrochloride Tablet TID (N=72)	P-Value*
Race [N (%)]			0.254
African American	76 (53.9)	39 (54.2)	
White	59 (41.8)	32 (44.4)	
Other	6 (4.3)	1 (1.4)	
Age (years)			0.254
Mean ± SD	56.7 ± 14.2	59.0 ± 13.8	
Median (Range)	58.0 (20-85)	59.5 (27-82)	
Gender [N (%)]			0.659
Male	87 (61.7)	42 (58.3)	
Female	54 (38.3)	30 (41.7)	
History of Diabetes [N (%)]			> 0.999
Yes	79 (56.0)	40 (55.6)	
No	62 (44.0)	32 (44.4)	
Post-Dialysis Weight (lbs)			0.658
Mean ± SD	186.7 ± 47.3	187.8 ± 57.4	
Median (Range)	185.0 (60-339)	178.0 (65-364)	
Height (inches)			0.639
Mean ± SD	67.5 ± 4.1	67.1 ± 5.1	
Median (Range)	68.0 (56.0-75.9)	67.0 (45.7-75.2)	
Body Mass Index (lbs/inches ²)			0.907
Mean ± SD	28.8 ± 6.8	29.4 ± 8.4	
Range	28.2 (10.8-53.9)	28.9 (10.5-54.2)	
Stratification Criteria [N (%)]			0.959
Cinacalcet Use and iPTH ≤ 400 pg/mL (400 ng/L)	34 (24.1)	15 (20.8)	
Cinacalcet Use and iPTH > 400 pg/mL (400 ng/L)	12 (8.5)	6 (8.3)	
No cinacalcet use and iPTH ≤ 400 pg/mL (400 ng/L)	77 (54.6)	42 (58.3)	
No cinacalcet use and iPTH > 400 pg/mL (400 ng/L)	18 (12.8)	9 (12.5)	

*Fisher's Exact Test for categorical variables and Wilcoxon Rank Sum Test for continuous variables.

Renal History:

Renal history was similar between treatment groups. The three most common primary causes of chronic kidney disease as assigned by the Investigators were diabetes (40% and 35% in the sevelamer carbonate powder QD group and sevelamer hydrochloride tablet TID group, respectively), hypertension (29% and 33% in the sevelamer carbonate powder QD group and sevelamer hydrochloride tablet TID group, respectively), and other causes (16% and 21% in the

sevelamer carbonate powder QD group and sevelamer hydrochloride tablet TID group, respectively). The majority of patients were currently receiving vitamin D (85% for both treatment groups). Patients had been on dialysis for a mean of 44 months in the sevelamer carbonate QD group and 53 months in the sevelamer hydrochloride tablet TID group. There was a statistically significant difference between the treatment groups in time on dialysis ($p=0.048$), but this difference was not considered clinically meaningful. Results for the FAS and PPS were similar to those of the Safety Set except in the PPS there was no statistically significant difference between the treatment groups in time on dialysis.

Table 13: Renal History-Safety Set

Parameter	Sevelamer Carbonate Powder QD (N=141)	Sevelamer Hydrochloride Tablet TID (N=72)	P-Value*
Primary Cause of Chronic Renal Failure [N (%)]			0.511
Hypertension	41 (29.1)	24 (33.3)	
Glomerulonephritis	15 (10.6)	4 (5.6)	
Diabetes	57 (40.4)	25 (34.7)	
Pyelonephritis	0 (0)	0 (0)	
Polycystic Kidneys	2 (1.4)	3 (4.2)	
Hydronephrosis	0 (0)	0 (0)	
Interstitial Nephritis	3 (2.1)	1 (1.4)	
Other	23 (16.3)	15 (20.8)	
Time on Dialysis (months)			0.048
Mean \pm SD	44.4 \pm 45.0	52.6 \pm 43.9	
Median (Range)	30.9 (3.0 – 320.1)	39.9 (2.9–233.3)	
Vitamin D Use at Screening [N (%)]			> 0.999
No	21 (14.9)	11 (15.3)	
Yes	120 (85.1)	61 (84.7)	
Previous Parathyroidectomy [N (%)]			0.381
No	136 (96.5)	71 (98.6)	
Partial Parathyroidectomy	4 (2.8)	0 (0)	
Total Parathyroidectomy	1 (0.7)	1 (1.4)	

*Fisher's Exact Test for categorical variables and Wilcoxon Rank Sum Test for continuous variables.

Medical History:

Reflective of the extent of chronic illness in the patient population, more than half of the patients in the Safety Set reported clinically significant history in the following body systems: cardiovascular (98.6%), renal (97.7%), endocrine/metabolic (95.3%), hematological conditions (92.5%), gastrointestinal (85.9%), musculoskeletal (83.6%), respiratory (66.7%), head, eyes, ears, nose, and throat (HEENT) (66.2%), neurological (58.7%), urological/reproductive (55.9%), allergies (51.2%) and dermatologic (50.2%). There were no statistically significant differences between the treatment groups in medical history. Results for the FAS and PPS were similar to those of the Safety Set.

Prior Medications:

All patients (100%) had taken at least one prior medication. The most common classes of prior medication (> 25% of patients) were vitamins (98%), antianemic preparations (97%), antithrombotic agents (81%), all other therapeutic products (68%), antacids (55%), beta blockers (52%), lipid reducing agents (52%), agents acting on the renin-angiotension system (50%), analgesics (46%), calcium channel blockers (41%), diabetes drugs (40%), mineral supplements (40%), thyroid therapy (38%), antihypertensives (33%), and psycholeptics (25%). The percentage of patients using prior medications was similar between treatment groups with the exception (> 10% difference between treatment groups) of analgesics: 50% in the sevelamer carbonate powder QD group and 38% in the sevelamer hydrochloride tablet TID group.

Concomitant Medications:

During the randomized treatment period, all (100%) patients in the Safety Set took at least one concomitant medication. The drug categories with the most frequent (> 25%) concomitant medications are presented in the following table. The most frequent categories of concomitant medications were vitamins, antianemic preparations, and antithrombotic agents. The percentage of patients using concomitant medications was similar between treatment groups with the exception (> 10 % difference between the treatment groups) of antibacterials (33% for the sevelamer carbonate powder QD group and 49% for the sevelamer hydrochloride tablet TID group) and cardiac therapy (26% for the sevelamer carbonate powder QD group and 39% for the sevelamer hydrochloride tablet TID group). The results for the PPS are similar.

Table 14: Most Frequent (>25 %) Concomitant Medications Taken During Randomized Treatment Period-Safety Set

Therapeutic Class	Sevelamer Carbonate Powder QD (N=141) (%)	Sevelamer Hydrochloride Tablet TID (N=72) (%)
Vitamins	98	100
Antianaemic Preparations	96	99
Antithrombotic Agents	84	89
Analgesics	62	53
Antacids	56	62
Serum Lipid Reducing Agents	56	49
Beta Blocking Agents	53	58
Agents Acting on the Renin-Angiotension System	49	58
Calcium Channel Blockers	45	39
Thyroid Therapy	43	38
Diabetes Drugs	41	40
Psycholeptics	38	29
Antihypertensives	36	38
Antibacterials	33	49
Vaccines	30	39
Blood Substitutes	29	33
Cardiac Therapy	26	39
Laxatives	21	29

Dialysate Bath Bicarbonate Concentration:

In the Safety Set, the mean baseline bicarbonate concentration in the dialysate bath was 37.0 mEq/L and 36.7 mEq/L for the sevelamer carbonate powder QD and sevelamer hydrochloride tablet TID groups, respectively. The mean bicarbonate concentration at Week 24/ET was 36.9 mEq/L and 36.8 mEq/L for the sevelamer carbonate powder QD and sevelamer hydrochloride tablet TID groups, respectively. There was no statistically significant change in dialysate bath bicarbonate concentration within groups and no statistically significant difference in the change in bicarbonate concentration between groups.

Dietary Evaluation:

For the PPS, dietary intake parameters pre-treatment and late during the randomized treatment period (Weeks 22 to 24) are presented in the following table. For most dietary parameters, there were slight decreases in the sevelamer carbonate powder QD group and slight increases in the sevelamer hydrochloride tablet TID group. There were, however, no statistically significant changes from baseline in dietary intake within treatment groups and no statistically significant

differences in the change in dietary intake between the treatment groups. These results suggest that the efficacy results were not influenced by dietary changes. The results for the Safety Set and FAS are similar except that there was a statistically significant increase in dietary calcium intake in the sevelamer carbonate powder QD group ($+76.6 \pm 269.9$ mg/day, $p=0.031$ for both Safety Set and FAS). The change in dietary calcium was statistically different between the treatment groups ($p=0.049$).

Table 15: Dietary Intake-PPS

Parameter	Sevelamer Carbonate Powder QD (N=97) [mean ± SD]	Sevelamer Hydrochloride Tablet TID (N=51) [mean ± SD]	P-value*
Phosphorus (mg/day)			0.185
Pre-treatment washout	798.5 ± 239.1	783.9 ± 278.6	
Late treatment	825.2 ± 231.4	761.0 ± 311.3	
Change from Pre-treatment washout to Late treatment	34.4 ± 237.9	-43.1 ± 243.9	
P-Value^	0.515	0.384	
Calcium (mg/day)			0.071
Pre-treatment washout	417.6 ± 165.7	435.8 ± 297.1	
Late treatment	457.8 ± 179.4	373.4 ± 179.9	
Change from Pre-treatment washout to Late treatment	42.0 ± 228.9	-69.0 ± 264.4	
P-Value^	0.103	0.267	
Vitamin D (mcg/day)			0.457
Pre-treatment washout	3.5 ± 3.6	3.6 ± 3.0	
Late treatment	3.1 ± 1.9	3.2 ± 3.3	
Change from Pre-treatment washout to Late treatment	-0.8 ± 4.0	-0.5 ± 4.1	
P-Value^	0.677	0.209	
Energy (kcal/day)			0.485
Pre-treatment washout	1411.0 ± 433.2	1338.1 ± 436.4	
Late treatment	1471.0 ± 557.5	1286.7 ± 518.6	
Change from Pre-treatment washout to Late treatment	82.9 ± 548.5	-50.0 ± 294.7	
P-Value^	0.863	0.411	
Total Protein (g/day)			0.285
Pre-treatment washout	61.8 ± 18.8	62.7 ± 22.7	
Late treatment	63.1 ± 18.5	59.9 ± 24.1	
Change from Pre-treatment washout to Late treatment	1.1 ± 18.0	-4.4 ± 20.8	
P-Value^	0.480	0.397	
Parameter	Sevelamer Carbonate Powder QD (N=97) [mean ± SD]	Sevelamer Hydrochloride Tablet TID (N=51) [mean ± SD]	P-value*
Cholesterol (mg/day)			0.193
Pre-treatment washout	267.5 ± 182.1	300.6 ± 162.5	
Late treatment	302.2 ± 185.9	269.4 ± 153.5	
Change from Pre-treatment washout to Late treatment	25.0 ± 188.8	-37.3 ± 161.0	
P-Value^	0.446	0.310	
Total Carbohydrate (g/day)			0.963
Pre-treatment washout	167.1 ± 63.9	150.0 ± 57.6	
Late treatment	168.0 ± 83.4	151.6 ± 71.6	
Change from Pre-treatment washout to Late treatment	10.1 ± 87.1	3.9 ± 45.7	
P-Value^	0.629	0.833	
Fat (g/day)			0.149
Pre-treatment washout	55.7 ± 20.2	55.0 ± 20.5	
Late treatment	61.5 ± 27.2	49.7 ± 21.3	
Change from Pre-treatment washout to Late treatment	4.7 ± 27.7	-5.4 ± 14.9	
P-Value^	0.637	0.079	

*P-value is from Wilcoxon Rank Sum test

^ P-value is from Wilcoxon Signed Rank test

Note: The number of observations varies in the statistics shown. Please refer to the end of text tables for details.

Measurements of Treatment Compliance:

During the randomized treatment period, mean percent compliance in the Safety Set and the FAS was similar between groups (86% for sevelamer carbonate powder QD group and 85% for sevelamer hydrochloride tablet TID group, respectively). Patients with <70% compliance during the treatment period were excluded from the PPS. The mean percent compliance in the PPS set was also similar between treatment groups (90% for sevelamer carbonate powder QD group and 91% for sevelamer hydrochloride tablet TID group).

Change in Serum Phosphorus:

In the PPS, the mean serum phosphorus pre-washout was 5.2 ± 1.1 mg/dL (1.68 ± 0.37 mmol/L) for the sevelamer carbonate powder QD group and 5.3 ± 1.0 mg/dL (1.72 ± 0.32 mmol/L) for the

sevelamer hydrochloride tablet TID group. Following the two week phosphate binder washout (Week 0), the mean serum phosphorus 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 confirming that this population was hyperphosphatemic. 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 (both $p < 0.001$) 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 both 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 comparable, thus confirming these findings. The following table presents the change from baseline to Week 24/ET for serum phosphorus for both the PPS and the FAS.

Table 16: Change in Serum Phosphorus

	Sevelamer Carbonate Powder QD [mean \pm SD]	Sevelamer Hydrochloride Tablets TID [mean \pm SD]	2-sided 95% CI†
Serum Phosphorus (mg/dL)			
Per Protocol Set	N=97	N=51	
Pre-washout	5.2 \pm 1.1	5.3 \pm 1.0	
Baseline	7.3 \pm 1.3	7.6 \pm 1.3	
Week 24/ET	5.3 \pm 1.4	4.6 \pm 1.0	
Change	-2.0 \pm 1.8	-2.9 \pm 1.3	0.39, 1.50
P-value [^]	< 0.001	< 0.001	
Full Analysis Set	N=141	N=72	
Pre-washout	5.3 \pm 1.1	5.3 \pm 1.0	
Baseline	7.3 \pm 1.4	7.4 \pm 1.3	
Week 24/ET	5.4 \pm 1.4	4.9 \pm 1.2	
Change	-1.9 \pm 1.7	-2.5 \pm 1.6	0.19, 1.12
P-value [^]	< 0.001	< 0.001	
Serum Phosphorus (mmol/L)			
Per Protocol Set	N=97	N=50	
Pre-washout	1.68 \pm 0.37	1.72 \pm 0.32	
Baseline	2.36 \pm 0.43	2.45 \pm 0.41	
Week 24/ET	1.71 \pm 0.45	1.50 \pm 0.32	
Change	-0.66 \pm 0.57	-0.96 \pm 0.42	0.12, 0.48
P-value [^]	< 0.001	< 0.001	
Full Analysis Set	N=141	N=72	
Pre-washout	1.70 \pm 0.36	1.72 \pm 0.31	
Baseline	2.34 \pm 0.44	2.39 \pm 0.41	
Week 24/ET	1.73 \pm 0.46	1.58 \pm 0.38	
Change	-0.61 \pm 0.54	-0.82 \pm 0.50	0.06, 0.36
P-value [^]	< 0.001	< 0.001	

[^]P-value is from Wilcoxon Signed Rank Test

† 95% CI on difference = sevelamer carbonate powder QD – sevelamer hydrochloride tablet TID. If upper confidence bound is < 1 then non-inferiority was to be concluded.

A post-hoc analysis was performed to understand the serum phosphorus results across dose level. The following table presents the change in serum phosphorus by average prescribed dose. The change in serum phosphorus in the 2.4 to 4.8 g group was similar for both sevelamer carbonate powder QD and sevelamer hydrochloride tablet TID groups. In the sevelamer hydrochloride tablet TID group, the change in serum phosphorus was greater at higher doses. In the sevelamer carbonate powder QD group there was no dose response.

Table 17: Serum Phosphorus by Average Prescribed Dose

Dose Groups (g/day)	Sevelamer Carbonate Powder QD	Sevelamer Hydrochloride Tablet TID
Serum Phosphorus (mg/dL)		
2.4-4.8		
N	23	10
Mean Change	-2.13	-2.18
≥ 4.8-9.6		
N	44	25
Mean Change	-2.09	-2.93
>9.6		
N	29	13
Mean Change	-1.75	-3.51
Serum Phosphorus (mmol/L)		
2.4-4.8		
N	23	10
Mean Change	-0.69	-0.70
≥ 4.8-9.6		
N	44	25
Mean Change	-0.68	-0.95
>9.6		
N	29	13
Mean Change	-0.56	-1.13

Time Weighted Average of Serum Phosphorus;

In the PPS, the mean time weighted (excluding the first month of treatment) 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 statistically significantly different between treatment groups ($p=0.021$). Likewise, in the FAS, the mean time weighted serum phosphorus was 5.4 ± 1.0 mg/dL (1.75 ± 0.32 mmol/L) for the sevelamer carbonate powder QD group and 5.0 ± 0.8 mg/dL (1.60 ± 0.25 mmol/L) for the sevelamer hydrochloride tablet TID group. The time weighted average was significantly different between treatment groups ($p=0.001$).

Table 18: Time Weighted Average for Serum Phosphorus

	Sevelamer Carbonate Powder QD [mean ± SD]	Sevelamer Hydrochloride Tablets TID [mean ± SD]	P-Value*
Serum Phosphorus (mg/dL)			
Per Protocol Set			0.021
n	N=97	N=51	
Mean	5.3 ± 0.9	4.9 ± 0.7	
Full Analysis Set			0.001
n	N=141	N=72	
Mean	5.4 ± 1.0	5.0 ± 0.8	
Serum Phosphorus (mmol/L)			
Per Protocol Set			0.023
n	N=97	N=51	
Mean	1.70 ± 0.30	1.59 ± 0.24	
Full Analysis Set			0.001
n	N=141	N=72	
Mean	1.75 ± 0.32	1.60 ± 0.25	

*P-value is from Wilcoxon Rank Sum Test

Serum Phosphorus Responders:

The percentage of patients responding to therapy [serum phosphorus between 3.5 and 5.5 mg/dL (1.13 and 1.78 mmol/L), inclusive] at each time point is summarized by treatment group in the following table. At the different time points, the percentage of patients responding to treatment ranged from 45.8% to 59.4% in the sevelamer carbonate powder QD group and from 33.3% to 74.5% in the sevelamer hydrochloride tablet TID group. The percentage of patients with a serum phosphorus response was similar between the treatment groups for the first 6 weeks of treatment, but was higher in the sevelamer hydrochloride tablet TID group thereafter. At Week 24/ET, the percentage of serum phosphorus responders in the sevelamer hydrochloride tablet TID group (73%) was higher than in the sevelamer carbonate powder QD group (56%) and approached

statistical significance ($p=0.052$). The results for the FAS are similar for the sevelamer carbonate powder QD group (54%), but the percent response was lower for the sevelamer hydrochloride tablet TID group (64%, $p=0.189$).

Table 19: Serum Phosphorus Responders at Each Time point-PPS

	Sevelamer Carbonate Powder QD (N=97) n (%)	Sevelamer Hydrochloride Tablets TID (N=51) n (%)	P-Value*
Baseline	3 (3.1)	2 (3.9)	
Week 2	44 (45.8)	17 (33.3)	
Week 4	50 (54.3)	27 (54.0)	
Week 6	49 (52.1)	27 (55.1)	
Week 8	53 (55.2)	33 (66.0)	
Week 12	57 (59.4)	35 (70.0)	
Week 16	53 (58.2)	36 (73.5)	
Week 20	48 (54.5)	34 (70.8)	
Week 24	48 (56.5)	35 (74.5)	
Week 24/ET	54 (55.7)	37 (72.5)	0.052

*P-value is from Fisher's Exact Test

Calcium-Phosphorus Product:

The following table presents the change from baseline to Week 24/ET for calcium (albumin-adjusted)-phosphorus product for the FAS. There were statistically significant reductions from baseline in serum calcium-phosphorus product in both the sevelamer carbonate powder QD group and the sevelamer hydrochloride tablet TID group. Between group comparison indicated that the change in serum calcium-phosphorus product was significantly different between treatment groups with greater decreases demonstrated with sevelamer hydrochloride treatment ($p=0.008$).

Table 20: Change in Calcium-Phosphorus Product-Full Analysis Set

	Sevelamer Carbonate Powder QD (N=141) [mean \pm SD]	Sevelamer Hydrochloride Tablets TID (N=72) [mean \pm SD]	P-Value*
Calcium-Phosphorus Product (mg^2/dL^2)			
Baseline	65.1 \pm 13.3	67.0 \pm 13.2	
Week 24/ET	49.4 \pm 13.7	45.9 \pm 13.0	
Change	-15.7 \pm 15.6	-21.0 \pm 16.2	0.008
P-value^	< 0.001	< 0.001	
Calcium-Phosphorus Product (mmol^2/L^2)			
Baseline	5.25 \pm 1.07	5.40 \pm 1.06	
Week 24/ET	3.98 \pm 1.10	3.70 \pm 1.05	
Change	-1.27 \pm 1.25	-1.70 \pm 1.30	0.007
P-value^	< 0.001	< 0.001	

*P-value is from Wilcoxon Rank Sum Test for the change

^P-value is from Wilcoxon Signed Rank Test

Handling of Dropouts or Missing Data:

No missing or invalid observations were imputed. The last on treatment efficacy measure was carried forward to represent the Week 24/ET measurement for patients who terminated from the study prior to Week 24 and had at least one post-washout efficacy measurement. The use of the term Week 24/ET indicates that if patients were withdrawn and/or no measurement was available at Week 24 that the final measured valued was carried forward to Week 24/ET.

Use of an “Efficacy Subset” of Patients:

The primary efficacy analysis of the primary efficacy parameter was conducted using the PPS as this is appropriate for non-inferiority testing. The FAS was used as a confirmatory assessment of non-inferiority. The analysis of all other efficacy endpoints is presented using the FAS as this is generally recommended per ICH E.9. However, data are displayed for the secondary endpoints using both the FAS and PPS.

Efficacy Conclusions:

Sevelamer carbonate powder for oral suspension when dosed once per day with the largest meal is not non-inferior compared to sevelamer hydrochloride tablets when dosed three times per day with meals based on the primary efficacy analysis of a change from baseline in serum phosphorus levels at Week 24/ET among the PPS.

6.1.5 Clinical Microbiology

NA

6.1.6 Efficacy Conclusions

The non-inferiority of sevelamer carbonate has not been established in study GD3-199-301. The equivalence of sevelamer carbonate powder and sevelamer hydrochloride tablets in study SVCARB00205 is questionable because of a small study with high drop-outs. Although the efficacy of sevelamer carbonate powder is inconclusive in this NDA, the efficacy of sevelamer carbonate tablets has been previously demonstrated in NDA 22,127.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This Safety Review is essentially from a Summary of Clinical Safety in Amendment 2 submitted July 30, 2008.

A total of 31 patients were randomized and received at least one dose of sevelamer carbonate powder in Study SVCARB00205. A similar proportion of patients experienced adverse events (AE) on both sevelamer carbonate powder (32.3%) and sevelamer hydrochloride tablets (42.9%). Adverse events were reported by system organ classes (SOCs). During both treatment regimens the majority of AEs occurred as a single event in single patients. The frequency of treatment related AEs was low. A total of 4 events in 3 (9.7%) patients were considered by the Investigator to be treatment related. All treatment related AEs were reported with sevelamer carbonate powder and included 2 events of nausea, 1 event of constipation, and 1 event of vomiting. One severe AE (chest pain) was reported during sevelamer carbonate powder treatment and no severe AEs were reported during sevelamer hydrochloride tablet treatment. No patients died during the period from Screening through the end of the 1-week Follow-up Period.

In Study GD3-199-301, a total of 141 patients received sevelamer carbonate powder once a day (QD) and 72 patients received sevelamer hydrochloride tablets three times a day (TID) for up to 24 weeks. A similar proportion of sevelamer carbonate powder QD patients (87.9%) and sevelamer hydrochloride tablet TID patients (91.7%) experienced adverse events. In both treatment groups, the highest frequency of treatment emergent AEs were gastrointestinal disorders which included nausea, diarrhea, vomiting, constipation, and upper abdominal pain. Treatment related nausea and vomiting were more common during sevelamer carbonate powder QD treatment than during sevelamer hydrochloride tablet TID treatment. In general, SAEs during sevelamer carbonate powder QD and sevelamer hydrochloride tablets TID treatment were similar. The majority were assessed by the Investigator as not related to study treatment. A higher percentage of sevelamer carbonate powder QD patients discontinued due to an AE (12.0% of patients on sevelamer carbonate powder QD; 5.6% patients on sevelamer hydrochloride tablets TID). In the sevelamer carbonate powder QD group, the majority of AEs leading to discontinuation were treatment related upper gastrointestinal disorders. The nature of the reasons for discontinuation suggest that the palatability of the powder formulation being dosed QD may have contributed to lower tolerability of sevelamer carbonate powder QD compared with TID dosing with sevelamer hydrochloride tablets.

7.1.1 Deaths

7.1.1.1 Study SVCARB00205

No patients died during the period from Screening through the end of the 1-week Follow-up Period. During the 30-day post-completion period, one patient experienced a Serious Adverse Event (SAE) of a brain stem hemorrhage with death. The death was considered secondary to preexisting conditions and assessed as not related to sevelamer carbonate powder by the Investigator.

7.1.1.2 Study GD3-199-301

A total of 2 (1.4%) sevelamer carbonate powder QD patients and 4 (5.6%) sevelamer hydrochloride tablet TID patients died during the randomized treatment period. The following table provides a list of the patients who died during the treatment period. All treatment-emergent deaths were assessed as not related to the study treatment by the Investigators. The causes of death were all consistent with the patients' underlying renal disease and chronic kidney disease (CKD) status.

Table 21: Patient Deaths in Study GD3-199-301

Treatment Group	Patient ID	Cause of Death	Relationship to Study Treatment
Sevelamer carbonate powder QD	505113	Cardiac arrest, cause unknown	Not Related
	516116	Withdrawal of renal replacement therapy	Not Related
Sevelamer hydrochloride tablets TID	505121	Cardiac arrest, cause unknown	Not Related
	508132	Septic shock	Not Related
		Staphylococcal pneumonia	Not Related
		Hypertensive cardiovascular disease	Not Related
	510118	Septicaemia	Not Related
514108	Intracranial bleed	Not Related	

One additional patient died approximately 10 weeks after discontinuing from the study. This event was reported even though it occurred after the 30-day follow-up period. This patient was a 75 year old female with CKD on hemodialysis with a medical history significant for diabetes mellitus, hypertension, congestive heart failure, and a history of smoking. The patient was randomized to sevelamer carbonate powder QD, but discontinued from the study due to a prolonged hospitalization for congestive heart failure. Approximately 10 weeks later the patient died. The primary cause of death was reported as cardiopulmonary arrest. The relationship between sevelamer carbonate powder and the adverse event cardiopulmonary arrest was reported as not related by the Investigator.

7.1.2 Other Serious Adverse Events

7.1.2.1 Study SVCARB00205

The frequency of serious adverse events (SAEs) was low in both treatment regimens. No SAEs were considered by the Investigator to be related to study treatment. Three patients discontinued during sevelamer carbonate powder treatment and no patients discontinued during sevelamer hydrochloride tablet treatment. Three of the four events leading to discontinuation were non-serious AEs and were Gastrointestinal Disorders. A small, but statistically significant, increase in serum bicarbonate and decrease in serum chloride levels were observed during the treatment with sevelamer carbonate powder. These changes were not observed during treatment with sevelamer hydrochloride tablets.

Reviewer's comment:

The increase in serum bicarbonate and decrease in serum chloride levels is interesting as the Sponsor in NDA 22-127 (Renvela, sevelamer carbonate) stated that the carbonate formula was being developed in order that serum blood levels for chloride and bicarbonate did not have to be monitored as often as with the hydrochloride formula.

In Study SVCARB00205, the frequency of SAEs was low in each treatment regimen during the randomized treatment periods: 2 events in 2 (6.5%) patients during sevelamer carbonate powder TID treatment and 2 events in 1 (3.6%) patient during sevelamer hydrochloride tablet TID treatment. The following table displays all treatment emergent SAEs that occurred during the randomized treatment periods.

Table 22: Serious Adverse Events During the Randomized Treatment Periods (Safety Set)

System Organ Class Preferred Term	Sevelamer Carbonate Powder TID (N=31)		Sevelamer Hydrochloride Tablets TID (N=28)	
	Events N	Patients n (%)	Events N	Patients n (%)
Any SAE	2	2 (6.5)	2	1 (3.6)
General Disorders and Administration Site Conditions	1	1 (3.2)	2	1 (3.6)
Chest pain	1	1 (3.2)	0	0
Catheter related complication	0	0	2	1 (3.6)
Infections and Infestations	1	1 (3.2)	0	0
Catheter sepsis	1	1 (3.2)	0	0

The SAEs of catheter-related complication (both events in one individual patient) and catheter sepsis were considered by the Investigator to be of moderate intensity and not related to study treatment. The SAE of chest pain was considered by the Investigator to be of severe intensity and unlikely related to study treatment; the patient was discontinued from the study due to this event.

SAEs starting or worsening during the randomized treatment periods were also analyzed for the following demographic subgroups: males and females, Blacks and other races, < 65 years of age and ≥ 65 years of age. Interpretation of the data is limited due to the low frequency of SAEs during the study and the small number of patients in these subgroups. In general, the results showed that the SAEs occurring during the study were not influenced by gender, race or age.

7.1.2.2 Study GD3-199-301

In Study GD3-199-301, a higher percentage of patients in the sevelamer hydrochloride tablet TID group experienced SAEs. 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 were similar during sevelamer carbonate powder QD and sevelamer hydrochloride tablets TID treatment. In both treatment groups, the highest frequency of treatment emergent SAEs were 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 also Cardiac Disorders [17 SAEs in 9 (6.4%) of sevelamer carbonate powder QD patients and 16 SAEs in 9 (12.5%) sevelamer hydrochloride tablet TID patients]. SAEs occurring in ≥ 2% of patients are provided in the following table.

Table 23: Serious Adverse Events Occurring in ≥ 2% (Safety Set)

System Organ Class Preferred Term	Sevelamer Carbonate Powder QD (N=141)		Sevelamer Hydrochloride Tablets TID (N=72)	
	Events N	Patients n (%)	Events N	Patients n (%)
Any SAE	85	33 (23.4)	72	28 (38.9)
Cardiac Disorders	17	9 (6.4)	16	9 (12.5)
Cardiac Failure Congestive	7	5 (3.5)	7	4 (5.6)
Coronary Artery Disease	1	1 (0.7)	3	3 (4.2)
Atrial Fibrillation	3	3 (2.1)	1	1 (1.4)
Infections and Infestations	19	15 (10.6)	12	11 (15.3)
Pneumonia	6	6 (4.3)	3	3 (4.2)
Injury, Poisoning and Procedural Complications	5	4 (2.8)	7	6 (8.3)
Arteriovenous Fistula Thrombosis	3	2 (1.4)	3	4 (5.6)
Metabolism and Nutrition Disorders	12	8 (5.7)	5	3 (4.2)
Hyperkalaemia	5	4 (2.8)	2	2 (2.8)
Hypoglycaemia	1	1 (0.7)	2	2 (2.8)
Respiratory, Thoracic and Mediastinal Disorders	8	8 (5.7)	3	3 (4.2)
Pulmonary oedema	3	3 (2.1)	1	1 (1.4)
Surgical and Medical Procedures	2	2 (1.4)	3	3 (4.2)
Arteriovenous Fistula Operation	0	0 (0)	2	2 (2.8)
Vascular Disorders	4	4 (2.8)	11	7 (9.7)
Hypertension	1	1 (0.7)	2	2 (2.8)

The most frequently reported (> 4% patients) SAEs were cardiac failure congestive [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].

The majority of treatment emergent SAEs were assessed by the Investigator as not related to the study treatment. One patient experienced an SAE (probable fecal impaction) considered possibly related to sevelamer hydrochloride. The patient, a 54 year old female with CKD on hemodialysis with a medical history significant for constipation, abdominal surgery including Cesarean-section and tubal ligation, hypertension, coronary atherosclerosis, and type II diabetes mellitus was randomized to sevelamer hydrochloride, two 800 mg tablets TID with meals. Approximately 15 weeks after beginning the study treatment, the patient presented to the Emergency Department with a five day history of abdominal pain and abdominal distension without bowel movements. An abdominal x-ray showed considerable stool in the rectal vault, consistent with probable fecal impaction. No evidence of mass or obstruction was observed. The patient was treated with enemas and ketorolac tromethamine, recovered without sequelae and was discharged. Sevelamer hydrochloride was continued. The relationship between sevelamer hydrochloride and the adverse event of probable fecal impaction was reported as possible by the Investigator.

SAEs that occurred during the randomized treatment periods were also analyzed for the following subgroups: males, females, African Americans, Non-African American, < 65 years of age, and ≥ 65 years of age. In general, the SAEs seen within each gender, race and age group were similar and consistent with the analysis of the overall population.

The majority of treatment-emergent AEs were mild or moderate in intensity. The percent of patients experiencing treatment related AEs was greater in the sevelamer carbonate powder QD group. 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. Two patients experienced treatment related AEs that were severe in intensity. One patient who experienced severe diarrhea in the sevelamer carbonate powder group and one patient who experienced severe hypocalcemia in the sevelamer hydrochloride tablet group were assessed as treatment related by the Investigator.

Table 24: Treatment Emergent Adverse Events in >2% of Patients (Safety Set)

System Organ Class Preferred Term	Sevelamer Carbonate Powder QD (N=141)		Sevelamer Hydrochloride Tablets TID (N=72)	
	Events N	Patients n (%)	Events N	Patients n (%)
Any Treatment related Adverse Event	72	43 (30.5)	26	13 (18.1)
Gastrointestinal Disorders	58	32 (22.7)	18	8 (11.1)
Diarrhoea	17	12 (8.5)	5	4 (5.6)
Nausea	18	14 (9.9)	4	2 (2.8)
Vomiting	8	8 (5.7)	1	1 (1.4)
Constipation	1	1 (0.7)	4	4 (5.6)
Stomach Discomfort	5	3 (2.1)	1	1 (1.4)
General Disorders and Administration Site Conditions	6	6 (4.3)	0	0 (0)
Oral Administration Complication	6	6 (4.3)	0	0 (0)
Investigations	2	2 (1.4)	3	2 (2.8)
Carbon Dioxide Decreased	1	1 (0.7)	3	2 (2.8)
Metabolism and Nutrition Disorders	5	5 (3.5)	4	3 (4.2)
Hypocalcaemia	1	1 (0.7)	3	2 (2.8)

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Study SVCARB00205

The following table presents an overview of the patients with treatment emergent adverse events, treatment emergent severe adverse events and related treatment emergent adverse events in Study SVCARB00205.

Table 25: Overview of Treatment Emergent Adverse Events (Safety Set)

	Sevelamer Carbonate Powder T1D (N=31) n (%)	Sevelamer Hydrochloride Tablets T1D (N=28) n (%)
Any Treatment Emergent AEs	10 (32.3)	12 (42.9)
Treatment Emergent Severe AEs	1 (3.2)	0
Related Treatment Emergent AEs	3 (9.7)	0

Treatment Emergent Adverse Events in Study SVCARB00205:

The overall frequency of AEs that occurred during the randomized treatment periods was similar between both treatment regimens: 21 events in 10 (32.3%) patients during treatment with sevelamer carbonate powder and 26 events in 12 (42.9%) patients during treatment with sevelamer hydrochloride tablets as shown in the following table.

Table 26: Summary of All Cause Treatment Emergent AEs that Occurred in $\geq 5\%$ (Safety Set)

System Organ Class	Sevelamer Carbonate Powder T1D (N=31)		Sevelamer Hydrochloride Tablets T1D (N=28)	
	Events N	Patients n (%)	Events N	Patients n (%)
Any AE	21	10 (32.3)	26	12 (42.9)
Gastrointestinal Disorders	5	4 (12.9)	4	3 (10.7)
Skin and Subcutaneous Tissue Disorders	2	2 (6.5)	2	2 (7.1)
Infections and Infestations	2	2 (6.5)	1	1 (3.6)
Investigations	2	2 (6.5)	1	1 (3.6)
Vascular Disorders	2	2 (6.5)	1	1 (3.6)
General Disorders and Administration Site Conditions	1	1 (3.2)	5	4 (14.3)
Musculoskeletal and Connective Tissue Disorders	1	1 (3.2)	4	3 (10.7)
Surgical and Medical Procedures	1	1 (3.2)	3	3 (10.7)

In both treatment regimens, the most frequent events were Gastrointestinal Disorders, with 5 events in 4 (12.9%) patients during treatment with sevelamer carbonate powder, and 4 events in 3 (10.7%) patients during treatment with sevelamer hydrochloride tablets. AEs occurred more frequently during sevelamer hydrochloride tablet treatment than during sevelamer carbonate powder treatment for General Disorders and Administration Site Conditions (14.3% vs. 3.2%).

In general, AEs were reported in both treatment regimens. The majority of AEs occurred as single events in single patients. The AE reported in more than one patient during sevelamer carbonate powder treatment was nausea (2 events in 2 [6.5%] patients). The events reported in more than one patient during sevelamer hydrochloride tablet treatment were fatigue and arteriovenous fistula operation, each reported as 2 events in 2 (7.1%) patients.

AEs that occurred during the randomized treatment periods were also analyzed for the following demographic subgroups: males and females, Blacks and other races, and < 65 years of age and ≥ 65 years of age. Interpretation this data is limited because of the small number of patients in some of the subgroups, but in general, the results showed that AEs occurring during the study were not influenced by gender, race or age.

Treatment Related Adverse Events:

During the randomized treatment periods, a total of 4 events in 3 (9.7%) patients were considered by the Investigator to be treatment related to sevelamer carbonate powder. All were Gastrointestinal Disorders which included nausea (2 events in 2 [6.5%] patients), constipation (1 event in 1 [3.2%] patient) and vomiting (1 event in 1 [3.2%] patient). All treatment related AEs were of mild or moderate intensity. No treatment related AEs were reported during treatment with sevelamer hydrochloride tablets during the randomized treatment periods.

7.1.3.2 Study GD3-199-301

The following table presents an overview the patients with treatment emergent adverse events, treatment emergent severe adverse events and related treatment emergent adverse events in Study GD3-199-301.

Table 27: Overview of Patients with Treatment Emergent Adverse Events (Safety Set)

	Sevelamer Carbonate Powder QD (N=141) n (%)	Sevelamer Hydrochloride Tablets TID (N=72) n (%)
Any Treatment Emergent AEs	124 (87.9)	66 (91.7)
Treatment Emergent Severe AEs	22 (15.6)	19 (26.4)
Related Treatment Emergent AEs	43 (30.5)	13 (18.1)

Treatment Emergent Adverse Events:

The percentage 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. The most frequently occurring AEs (≥ 10% of randomized patients in either treatment group, are presented in the following table.

Table 28: Summary of All Cause AEs in $\geq 10\%$ of Patients (Safety Set)

System Organ Class	Sevelamer Carbonate Powder QD (N = 141)		Sevelamer Hydrochloride Tablets TID (N = 72)	
	Events N	Patients n (%)	Events N	Patients n (%)
Any Adverse Event	723	124 (87.9)	430	66 (91.7)
Gastrointestinal Disorders	147	66 (46.8)	75	35 (48.6)
Cardiac Disorders	30	19 (13.5)	23	12 (16.7)
Musculoskeletal and Connective Tissue Disorders	73	47 (33.3)	34	21 (29.2)
Injury, Poisoning, and Procedural Complications	66	44 (31.2)	55	32 (44.4)
Infections and Infestations	77	43 (30.5)	36	28 (38.9)
General Disorders and Administrative Site Conditions	63	37 (26.2)	48	27 (37.5)
Nervous System Disorders	41	29 (20.6)	27	18 (25.0)
Respiratory, Thoracic and Mediastinal Disorders	53	29 (20.6)	24	18 (25.0)
Metabolism and Nutrition Disorders	33	24 (17.0)	19	16 (22.2)
Vascular Disorders	28	22 (15.6)	31	20 (27.8)
Skin and Subcutaneous Tissue Disorders	24	21 (14.9)	19	14 (19.4)
Investigations	22	11 (7.8)	16	12 (16.7)

In general, there was a similar incidence of AEs in the sevelamer carbonate powder QD and sevelamer hydrochloride tablet TID treatment groups. In both treatment groups, the highest frequency of treatment emergent AEs occurred in the 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: nausea (37 events in 30 [21.3%] sevelamer carbonate powder QD patients and 11 events in 8 [11.1%] sevelamer hydrochloride tablet TID patients), diarrhea (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 powder QD patients and 19 events in 13 [18.1%] sevelamer hydrochloride tablet TID patients).

The following differences between treatment groups were noted. A higher number of patients on sevelamer carbonate powder QD experienced muscle spasms and urinary tract infections compared to patients on sevelamer hydrochloride tablets TID. Twenty eight events of muscle spasms occurred in 20 [14.2%] sevelamer carbonate powder QD patients and 9 events occurred in 4 [5.6%] sevelamer hydrochloride tablet TID patients. The events of muscle spasms in general, constituted muscle cramps during dialysis. Eleven events of urinary tract infection occurred in 10 [7.1%] sevelamer carbonate powder QD patients and 3 events occurred in 2 [2.8%] sevelamer hydrochloride tablet TID patients. Patients who experienced urinary tract infections had a history of urinary tract infections or pre-existing conditions that pre-disposed patients to develop a urinary tract infection.

A higher number of patients on sevelamer hydrochloride tablets TID experienced arteriovenous fistula thrombosis compared to patients on sevelamer carbonate powder QD. A total of 12 events occurred in 8 [5.7%] sevelamer carbonate powder QD patients and 19 events

occurred in 13 [18.1%] sevelamer hydrochloride tablet TID patients. However, when all of the similar medical concepts in the Injury, Poisoning and Procedural Complications are evaluated as a whole, there was no difference between the treatment regimens with regard to arteriovenous fistula problems.

Treatment-emergent AEs were also analyzed for the following subgroups: males, females, African Americans, Non-African Americans, < 65 years of age, and ≥ 65 years of age. Differences in frequency between subgroups were noted for the following adverse events: muscle spasms, oral administration complication, nausea, vomiting, stomach discomfort, and constipation. In depth review of these adverse events revealed that patients who experienced these adverse events had a medical history of the event or a pre-existing condition that pre-disposed them to the event. Furthermore, the events were all mild or moderate in intensity, and the majority of patients recovered without treatment, intervention or discontinuation of study medication. Thus, the analysis of AEs by subgroup did not identify any new safety issues and indicates that AEs reported during the study were not influenced by gender, race or age.

Treatment Related Adverse Events in Study GD3-199-301:

The percent of patients experiencing treatment related AEs was greater in the sevelamer carbonate powder QD group. 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. Two patients experienced treatment related AEs that were severe in intensity. One patient who experienced severe diarrhea in the sevelamer carbonate powder group and one patient who experienced severe hypocalcaemia in the sevelamer hydrochloride tablet group were assessed as treatment related by the Investigator. A summary of the treatment related AEs occurring in > 2% patients is in the following table.

Table 29: Treatment Emergent Adverse Events Occurring in >2% (Safety Set)

System Organ Class Preferred Term	Sevelamer Carbonate Powder QD (N=141)		Sevelamer Hydrochloride Tablets TID (N=72)	
	Events N	Patients n (%)	Events N	Patients n (%)
Any Treatment related Adverse Event	72	43 (30.5)	26	13 (18.1)
Gastrointestinal Disorders	58	32 (22.7)	18	8 (11.1)
Diarrhoea	17	12 (8.5)	5	4 (5.6)
Nausea	18	14 (9.9)	4	2 (2.8)
Vomiting	8	8 (5.7)	1	1 (1.4)
Constipation	1	1 (0.7)	4	4 (5.6)
Stomach Discomfort	5	3 (2.1)	1	1 (1.4)
General Disorders and Administration Site Conditions	6	6 (4.3)	0	0 (0)
Oral Administration Complication	6	6 (4.3)	0	0 (0)
Investigations	2	2 (1.4)	3	2 (2.8)
Carbon Dioxide Decreased	1	1 (0.7)	3	2 (2.8)
Metabolism and Nutrition Disorders	5	5 (3.5)	4	3 (4.2)
Hypocalcaemia	1	1 (0.7)	3	2 (2.8)

Treatment related AEs were most frequently seen with Gastrointestinal Disorders. The most frequently occurring (> 4% patients) treatment related AEs were diarrhea (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 events in 4 [5.6%] sevelamer hydrochloride tablet TID patients). The most frequently occurring (>4% patients) treatment related to the SOC General Disorders and Administrative Site Conditions was: oral administration complication (6 events in 6 [4.3%] sevelamer carbonate powder QD patients and no events in the sevelamer hydrochloride tablet TID patients).

Treatment emergent AEs possibly or probably related to the study drug were also analyzed for the following subgroups: males, females, African Americans, Non-African Americans, < 65 years of age, and \geq 65 years of age. Differences in frequency between subgroups were noted for the following treatment related adverse events: oral administration complication, nausea, vomiting, and constipation. In-depth review of these AEs revealed that patients who experienced these adverse events had a medical history of the event or a pre-existing condition that predisposed them to the event. The events were all mild or moderate in intensity, and the majority of patients recovered without sequelae. The analysis of treatment related AEs by subgroup did not identify any new safety issues and indicate that AEs reported during this study were not influenced by gender, race or age.

7.1.4 Other Search Strategies

NA

7.1.5 Common Adverse Events

NA

7.1.6 Less Common Adverse Events

NA

7.1.7 Laboratory Findings

There were no clinically significant changes in safety laboratory measures during sevelamer carbonate treatment in SVCARB00205. However, statistically significant increases in serum bicarbonate and decreases in serum chloride levels were observed during treatment with sevelamer carbonate in this Study.

In Study GD3-199-301, individual patient changes that were assessed as clinically significant by the Investigator were captured as AEs and as SOC Investigations. The percent of patients experiencing AEs in the SOC Investigations was greater in the sevelamer hydrochloride tablet TID group. A total of 11 (7.8%) sevelamer carbonate powder QD patients and 12 (16.7%) sevelamer hydrochloride tablet TID patients experienced an AE coded to the SOC Investigations. Treatment emergent AEs in the SOC Investigations that were assessed as treatment-related by the Investigators included: blood parathyroid hormone increased (sevelamer carbonate powder

QD: 1 patient and sevelamer hydrochloride tablet TID: 0 patients) and carbon dioxide decreased (sevelamer carbonate powder QD: 1 patient; sevelamer hydrochloride tablet TID: 2 patients).

7.1.8 Vital Signs

In both Studies SVCARB00205 and GD3-199-301, there were no clinical or statistical changes in vital signs during the clinical trials.

7.1.10 Immunogenicity

NA

7.1.11 Human Carcinogenicity

NA

7.1.12 Special Safety Studies

Clinical studies of sevelamer carbonate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There have been no reports of patient abuse or dependence on sevelamer carbonate tablets or powder. Sevelamer carbonate is not absorbed and not metabolized. There is no reasonable mechanism by which sevelamer carbonate use is likely to be associated with addictive properties and therefore the potential for drug abuse is exceedingly low.

7.1.14 Human Reproduction and Pregnancy Data

The safety of sevelamer carbonate (powder or tablets) has not been established in pregnant or lactating women. Requirements for vitamins and other nutrients are increased in pregnancy. The effect of sevelamer on the absorption of vitamins and other nutrients has not been studied in pregnant women.

7.1.15 Assessment of Effect on Growth

NA

7.1.16 Overdose Experience

Sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, has been given to normal healthy volunteers in doses of up to 14 grams per day for eight days with no adverse effects. In CKD patients, the maximum average actual daily dose of sevelamer

carbonate studied was 14 grams/day (both TID and QD). There are no reports of over dosage with sevelamer carbonate (powder or tablets) or sevelamer hydrochloride in patients. Since sevelamer carbonate is not absorbed, the risk of systemic toxicity is low.

7.1.17 Postmarketing Experience

Renagel® (sevelamer hydrochloride), was approved in the United States on October 30, 1998 for capsules (NDA 20-926) and July 12, 2000 for tablets (NDA 21-179). The estimated US patient exposure to Renagel is greater than _____ patient-years. Renagel is currently approved for marketing in over 55 countries. Post marketing safety surveillance of sevelamer hydrochloride has been ongoing since initial approval of sevelamer hydrochloride in 1998. Renvela® Tablets (sevelamer carbonate), contain the same active moiety as sevelamer hydrochloride and were approved for marketing on October 19, 2007. Marketing began in March, 2008.

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The most frequent post-marketing adverse event for sevelamer hydrochloride is hyperphosphatemia. Successful control of serum phosphorus in this patient population is multifactorial, including reduction in dietary intake of phosphate, inhibition of intestinal phosphate absorption with phosphate binders, and removal of phosphate with dialysis. An ongoing evaluation of all reported cases of hyperphosphatemia received spontaneously for sevelamer hydrochloride, including the patient's prior phosphate binder and phosphorus levels, the patient's sevelamer hydrochloride dosage regimen and phosphorus levels, and patient compliance with diet and medication, has not revealed any new product or safety related issues.

Other commonly reported spontaneous adverse events for patients on sevelamer hydrochloride included nausea, diarrhea, vomiting, constipation, flatulence, dyspepsia, headache, dyspnea and hypertension. These events were observed in clinical trials with sevelamer hydrochloride, are described in the product labeling and are considered expected (labeled) adverse events. Events of nausea, vomiting, flatulence, and dyspepsia were seen in patients during sevelamer carbonate treatment and are also listed in the product labeling.

Pruritus, abdominal pain and rash are other adverse events that were seen during clinical trials with sevelamer hydrochloride and were frequently reported during post-marketing experience with sevelamer hydrochloride. These three terms are described as postmarketing experience in the current Renagel and Renvela labels.

Reports of intestinal obstruction, intestinal perforation and ileus for patients on sevelamer hydrochloride have been rare. An in depth review of these gastrointestinal event reports received for patients on sevelamer hydrochloride revealed there was no dose relationship, and that age and treatment duration varied. Patient medical histories were complicated and may have contributed to the events. Due to the nature of post-marketing reporting, details regarding sevelamer hydrochloride therapy, clinical diagnosis and medical history were limited, which complicated the review of these reports. A comprehensive review of post-marketing reports of ileus, intestinal obstruction and intestinal perforation revealed that complex co-morbidities and concomitant medications often contributed to the event. The current Renagel and Renvela labels describe the risk of intestinal obstruction, intestinal perforation, and ileus during sevelamer therapy.

Deaths and serious adverse events reported for patients on sevelamer hydrochloride were rare, were reported across system organ classes, and were consistent with patients' underlying renal disease.

7.2 Adequacy of Patient Exposure and Safety Assessments

With the post-marketing experience and prior clinical trials for both sevelamer hydrochloride and sevelamer carbonate, there is adequate patient exposure and safety assessments.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Overall, common adverse events experienced were not unexpected and were consistent with patients' underlying renal disease and CKD status. The adverse events experienced during sevelamer carbonate powder treatment and sevelamer carbonate tablet treatment were similar in nature. In summary, the safety profile of sevelamer carbonate powder is similar to the established safety profile of sevelamer carbonate tablets and sevelamer hydrochloride. This has been shown in the sevelamer carbonate and sevelamer hydrochloride tablet studies and the sevelamer hydrochloride post-marketing safety profile.

7.4 General Methodology

NA

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Renagel and Renvela are given three times a day as stated in their labels. In this NDA, Study SVCARB00205 was for sevelamer carbonate powder to be utilized also three times a day.

Therefore, we recommend that should the powder be approved, it should be dosed three times a day.

b(4)

8.2 Drug-Drug Interactions

Six drugs were evaluated with sevelamer hydrochloride: digoxin, warfarin, enalapril, metoprolol, ciprofloxacin, and iron. In these studies, sevelamer hydrochloride was found to have no effect on the bioavailability of digoxin, warfarin, metoprolol, enalapril or iron. However, the bioavailability of ciprofloxacin was decreased by approximately 50% when co-administered with sevelamer hydrochloride.

In addition, during post-marketing experience, very rare cases of increased TSH levels have been reported in patients coadministered sevelamer hydrochloride and levothyroxine. The current sevelamer hydrochloride and sevelamer carbonate tablet labels recommend that when administering an oral medication where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, the medication should be administered at least one hour before or three hours after sevelamer (carbonate or hydrochloride), or the physician should consider monitoring blood levels of the drug. The current labels also recommend closer monitoring of TSH levels in patients receiving both levothyroxine and sevelamer carbonate.

8.3 Special Populations

Clinical studies of sevelamer carbonate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8.4 Pediatrics

As there are currently no phosphate binders that are indicated for pediatric dialysis patients, an active control would not be useful for comparison of safety and efficacy. In general, children below age 2 tend to be on phosphate supplements and it is rare that these children need a binder. In addition, children 0-1 year of age is a very small population which would be difficult to recruit and maintain in a clinical study.

The Sponsor proposes to study patients \geq 18 years of age. Sevelamer carbonate powder when mixed with water provides a liquid formulation (suspension) that should facilitate administration of this powder to children.

8.5 Advisory Committee Meeting

NA

8.6 Literature Review

NA

8.7 Postmarketing Risk Management Plan

NA

8.8 Other Relevant Materials

NA

9 OVERALL ASSESSMENT

9.1 Conclusions

In 1998 Renagel (sevelamer hydrochloride) was approved in the United States for the control of hyperphosphatemia in adult patients on hemodialysis. In 2007 a new formula of sevelamer where the counterion was changed from chloride to carbonate was approved (NDA 22-127). In this NDA the Sponsor has submitted a change in the tablet form of sevelamer carbonate to a powder form for patients unable to swallow. The Sponsor has submitted two clinical studies comparing the powder formula to sevelamer hydrochloride tablets. The study comparing the powder formula three times a day is small but somewhat efficacious. Utilizing the powder once a day in a larger study did not prove to be efficacious. In the label the Sponsor has recommended only the three times a day dosing. The safety profile of the powder formula appears to be similar the previous sevelamer studies, causing primarily gastrointestinal side effects. Certainly there is a need for a powder formula for some patients. therefore these reviewers recommend that the new powder be approved for three times a day dosing.

b(4)

b(4)

9.2 Recommendation on Regulatory Action

Approval

9.3 Recommendation on Postmarketing Actions

None

9.4 Labeling Review

The label is essentially acceptable as the Sponsor has included only three times a day dosing. The label will be reviewed in future with the review team.

Clinical and Statistical Review
Gail Moreschi, MD, MPH, and Ququan Liu, MD, MS
NDA 22-318
Sevelamer carbonate powder; Renvela

9.5 Comments to Applicant

None

10 APPENDICES

10.1 Review of Individual Study Reports

NA

10.2 Line-by-Line Labeling Review

NA

REFERENCES

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/s/

Gail Moreschi
12/1/2008 12:16:03 PM
MEDICAL OFFICER