CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22127 s015 and 22318 s008
Priority or Standard	Priority
Submit Date(s)	May 26, 2016
Received Date(s)	May 26, 2016
PDUFA Goal Date	November 25, 2016
Division / Office	Division of Cardiovascular and Renal Products/ODEI
Reviewer Name	Kimberly Smith
Review Completion Date	October 31, 2016
Established Name	sevelamer carbonate
Trade Name	Renvela
Therapeutic Class	phosphate binder
Applicant	Genzyme/Sanofi
Formulation(s)	tablet, powder for oral suspension
Dosing Regimen	For patients with a body surface area (BSA) of ≥0.75 to <1.2 m^2, start at 0.8 g per meal/snack and titrate by 0.4 g per dose every 2 weeks as needed based on serum phosphorus levels; For patients with a BSA of ≥1.2 m^2, start at 1.6 g per meal/snack and titrate by 0.8 g per dose every 2 weeks as needed based on serum phosphorus levels
Indication(s)	(b) (4)
Intended Population(s)	Pediatric patients 6 years of age and older

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Sevelamer carbonate should be approved for the control of serum phosphorus in children 6 years of age and older with chronic kidney disease on dialysis.

1.2 Risk Benefit Assessment

Hyperphosphatemia is common in end-stage renal disease patients on dialysis and has been associated with secondary hyperparathyroidism, vascular, valvular, and other soft tissue calcification, cardiovascular disease, and death. Several phosphate binders are approved for use in adults with chronic kidney disease (CKD) on dialysis based on reductions in serum phosphorus. There are no data demonstrating that treatment effects on serum phosphorus levels predict effects on clinical outcomes.

Sevelamer carbonate is a phosphate binder that binds dietary phosphate in the gastrointestinal tract, thereby decreasing its absorption and lowing serum phosphorus levels. Sevelamer carbonate tablets and powder for oral solution were approved on October 19, 2007 (NDA 22127) and August 12, 2009 (NDA 22318), respectively, for the control of serum phosphorus in patients with chronic kidney disease on dialysis. Both approvals included a postmarketing requirement to conduct deferred pediatric studies under PREA in patients with CKD on dialysis aged <1 month to 16 years (NDA 22127) and aged 0 to 18 years (NDA 22318). On January 21, 2016, the applicant submitted the results of Study SVCARB07609 intended to satisfy the PREA requirements. On May 21, 2016, the applicant submitted a prior approval labeling supplement with proposed changes to pediatric labeling based on the study results.

Study SVCARB07609 included a 2-week, randomized, placebo-controlled, fixed-dose period followed by a 6-month, single-arm, open-label, dose-titration period. The primary objective was to investigate the efficacy and safety of sevelamer carbonate in hyperphosphatemic pediatric patients with chronic kidney disease. A total of 101 patients 6 to 18 years of age were randomized to sevelamer carbonate (n=50) or placebo (n=51) during the fixed-dose period. Most patients were 13 to 18 years of age (73%) and had a BSA ≥1.2 m^2 (84%). Approximately 78% of patients were CKD patients on dialysis. Although entry criteria permitted the enrollment of subjects less than 6 years of age, no subject below this age was enrolled in the study.

Sevelamer carbonate significantly reduced serum phosphorus through Week 2 (primary endpoint) by an LS Mean difference of -0.90 (SE 0.27) mg/dL compared to placebo (p=0.001). A similar treatment response was observed during the 6-month, open-label dose-titration period. Approximately 30% of subjects reached their target serum phosphorus. The results of the primary efficacy endpoint were consistent by BSA subgroup. In contrast, a treatment effect was not observed in subjects with a baseline serum phosphorus below 7 mg/dL, in subjects 6 to <13 years of age, or in subjects not on dialysis. Of note, baseline serum phosphorus was low in these three subgroups, suggesting that this factor may have played a role. In addition, interpretation of the efficacy findings in subjects 6 to <13 years of age is limited by the small number of subjects in this age category, the inclusion of subjects with normal phosphorus levels

at baseline (because of improvements in phosphorus levels from the screening to baseline measurement), and artificially low values in some subjects (as a result of post-dialysis blood draws).

Treatment-emergent adverse events were common, occurring in 40% of subjects during the fixed-dose period and 77% during the dose-titration period; however, the events were not unexpected for a pediatric dialysis population and were generally consistent with events observed in studies in adults.

In conclusion, study SVCARB07609 provides evidence of safety and effectiveness of sevelamer carbonate in pediatric patients 13 years of age and older with CKD on dialysis. Although a treatment effect on serum phosphorus was not observed in patients 6 to <13 years of age, it is reasonable to extrapolate efficacy to this population based on the mechanism of action of the drug and data in older patients, as the Agency has agreed to for pediatric phosphate binder programs initiated after this one. No subject below 6 years of age was enrolled; therefore, the safety and efficacy of sevelamer carbonate has not been established in pediatric patients below 6 years of age. A treatment effect was not observed in the subgroup of subjects not on dialysis; the indication should align with the indication in the adult population and be limited to patients with CKD on dialysis.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

Study SVCARB07609 was conducted in response to a post-marketing requirement to conduct deferred pediatric studies under PREA in patients with CKD on dialysis aged <1 month to 16 years (NDA 22127) and aged 0 to 18 years (NDA 22318). Although entry criteria permitted the enrollment of patients less than 6 years of age, no patient below this age was enrolled in the study. Five patients 3 to 5 years of age were screened, but none met the eligibility criteria. According to the applicant, recruitment of patients in this age group is extremely challenging because of the small size of the population. The applicant acted with due diligence to enroll subjects 0 to 5 years of age and, as such, the post-marketing requirement should be satisfied.

2 Introduction and Regulatory Background

Hyperphosphatemia is common in end-stage renal disease patients on dialysis. In observational studies of patients with CKD, hyperphosphatemia has been associated with secondary hyperparathyroidism, vascular, valvular, and other soft tissue calcification, and cardiovascular disease. In dialysis patients, hyperphosphatemia has also been associated with an increased risk of mortality. In pediatric patients with CKD, hyperphosphatemia and secondary hyperparathyroidism is also associated with growth retardation, skeletal maturation delay, and skeletal deformities. Several phosphate binders are approved for use in adults with CKD on dialysis based on reductions in serum phosphorus. There are no data in adult or pediatric patients demonstrating that treatment effects on serum phosphorus levels predict effects on clinical outcomes. See Section 2.5 for a discussion of the regulatory history.

2.1 Product Information

Sevelamer carbonate is a phosphate binder that binds dietary phosphate in the gastrointestinal tract, thereby decreasing its absorption and lowing serum phosphorus levels. The proposed indication is:

(b) (4)

The applicant is proposing starting doses and titration steps based on body surface area (BSA) as shown in Table 1. The dose may be titrated every 2 weeks as needed to achieve target serum phosphorus levels.

Table 1: Starting does and titration steps

BSA (m^2)	Starting dose per meal/snack	Titration increases/ decreases per dose
≥ 0.75 to < 1.2	0.8 g	Titrate by 0.4 g
≥ 1.2	1.6 g	Titrate by 0.8 g

2.2 Tables of Currently Available Treatments for Proposed Indications

Several phosphate binders are approved for use in adult patients on dialysis. None are approved for use in pediatric patients or in patients with chronic kidney disease not on dialysis.

2.3 Availability of Proposed Active Ingredient in the United States

Sevelamer hydrochloride capsules and tablets were approved on October 30, 1998 (NDA 20926) and July 12, 2000 (NDA 21179), respectively. Sevelamer carbonate tablets and powder for oral solution were approved for the control of serum phosphorus in patients with chronic kidney disease on dialysis on October 19, 2007 (NDA 22127) and August 12, 2009 (NDA 22318), respectively.

2.4 Important Safety Issues With Consideration to Related Drugs

Based on clinical studies of sevelamer hydrochloride and sevelamer carbonate in adults, the sevelamer carbonate label includes a Warning and Precaution for gastrointestinal adverse events including serious cases of dysphagia, bowel obstruction, and perforation. In addition, Section 5 recommends monitoring (b) (4) vitamins D, E, K, and folic acid levels. According to the label, adverse reactions are largely gastrointestinal and, for sevelamer hydrochloride, include vomiting (22%), nausea (20%), diarrhea (19%), dyspepsia (16%), abdominal pain (9%), flatulence (8%) and constipation (8%).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The sevelamer carbonate approvals included the following postmarketing requirements:

NDA 22127: Deferred pediatric study under PREA for the treatment of the control of serum phosphorus in patients with Chronic Kidney Disease (CKD) on dialysis in pediatric patients ages < 1 month to 16 years old. Final Report Submission: October 20, 2009

NDA 22318: Deferred pediatric study under PREA for the treatment of hyperphosphatemia and chronic kidney disease on dialysis in pediatric patients ages 0-18. Final Report Submission: December 31, 2011

The Agency issued a Written Request on January 16, 2009 for a 3-week placebo-controlled dose response phase in a hyperphosphatemic pediatric dialysis population, followed by an open-label titration and maintenance phase of at least 26 weeks, and a 2-week placebo-controlled randomized withdrawal phase. On December 29, 2009, the applicant notified the Agency that they did not intend to conduct the study outlined in the Written Request because of concerns with feasibility.

On February 2, 2010, the applicant submitted a synopsis for protocol SVCARB007609 intended to satisfy the PREA requirements. There were a number of interactions with the Agency regarding design of this study; a summary of key regulatory milestones, agreements and advice related to this protocol is provided in Table 2.

Table 2: Summary of key regulatory milestones, agreements, and advice

Source	Advice from Agency
February 2, 2010	- Sponsor submitted synopsis of protocol SVCARB007609 for a single-arm, open-label, dose titration study
June 29, 2010 Advice Letter	- Division noted study was unlikely to fulfill PREA requirement and recommended long-term, open-label period followed by 2-week, placebo-controlled withdrawal phase - Population could include pre-dialysis patients but need sufficient number on dialysis - Subjects must have hyperphosphatemia sufficient to assess the magnitude of phosphate control - Important to minimize variability of phosphate assessments during the withdrawal phase - Study should be powered to rule out a 0.75 mg/dL difference between treatment arms in the withdrawal phase
February 17, 2011 Advice Letter	- Division noted single-arm, open-label, dose titration study was unlikely to provide adequate dosing information and recommended a 2-week placebo-controlled, fixed-dose study with 6-month follow-up - In response to sponsor's request to reassess dates for PREA requirement, Division reiterated study completion date of December 31, 2011 - The Division of Pediatric and Maternal Health consulted at sponsor's request
August 12, 2011 Advice Letter	- Sponsor proposed 2-week, randomized, placebo-controlled, fixed-dose period followed by a 6-month, single-arm, dose titration period - Division stated the proposed design was "a generally reasonable approach to assessing the effectiveness of Renvela in children" - Reasonable to include subjects who do not require dialysis but

Source	Advice from Agency
	sponsor should "not expect this pre-dialysis experience will suffice to support a claim in pre-dialysis patients" - More interested in "the experience with prepubertal children, now only 20% of your study population"
April 9, 2013 Deferral Extension Denied Letter	- Division denied deferral extension request "because the delays, beginning with study design were within your control. The delays reflect neither complexity of trial design nor too small a patient population"
April 11, 2013	- Notification of Non-Compliance with PREA letter issued
January 21, 2016	- Sponsor submitted clinical study report for study SVCARB007609
April 18, 2016 Information Request Letter	- Division requested 1) clarification of trial population, 2) why the sponsor had not submitted proposed labeling revisions or submission of proposed labeling revisions, 3) electronic copies of the trial's datasets
May 18, 2016	- Applicant submitted trial datasets
May 26, 2016	- Applicant submitted Prior Approval Labeling Supplement

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was well organized and sufficiently complete to support review of the application.

3.2 Compliance with Good Clinical Practices

Protocol Deviations
Six subjects had major protocol deviations during the fixed-dose period: one (8026-0003) missed doses; one (8020-0005) was prescribed 2.4 g TID instead of 1.6 g TID; one (8027-0002) was prescribed 0.4 g TID instead of 1.6 g TID due to miscalculation of BSA and dose was increased once the deviation was detected; two (8014-0003; 8021-0004) received calcium carbonate administered other than as an evening calcium supplement; and one (8005-0001) received commercial sevelamer carbonate during the washout period. In addition, 48 subjects had a protocol deviation in the category "low compliance with study treatment" reflecting compliance with study treatment less than 70%.

3.3 Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators in study SVCARB07609. The applicant reported receiving complete financial disclosure statements from 111 of 122 (91%) clinical investigators who screened at least one patient. The

remaining 11 sub-investigators completed initial financial disclosure statements but not subsequent statements, despite at least two attempts by the applicant to obtain the information.

As shown in Table 3, none of the investigators were full or part-time employees of Genzyme/Sanofi. Three investigators reported disclosable financial interests as outlined in Table 4.

Table 3: Clinical investigator financial disclosure information for SVCARB07609

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 122		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 11		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

Table 4: Disclosable financial arrangements

Investigator	Center	Location	Rand. Subjects	Amount Disclosed	Disclosure
(b) (6)		USA	(b) (6)	>$25,000; Payment of only $10,438 confirmed	Spouse received >$25,000 as a pathology consultant for another Genzyme/Sanofi study
		USA		$31,962	Participation in clinical science meetings and speaker programs
		USA		$50,000	Renal fellowship award payment in 2008, before start of study.

The applicant addressed steps taken to minimize the potential for bias resulting from these interests and arrangements including the design of SVCARB07609 with a randomized, double-blind, placebo-controlled phase and primary endpoint based on a central laboratory parameter.

Reviewer's comment: Based on analyses conducted by the statistical reviewer, excluding the 13 (13%) subjects enrolled at sites (b) (6) *did not affect the efficacy results. It is unlikely that these financial arrangements could have biased the study findings.*

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The current and proposed labeling instructs that sevelamer carbonate powder should be reconstituted with water before ingestion. In response to information requests, the applicant provided the results of a study that evaluated the *in vitro* phosphate binding of sevelamer carbonate when mixed with various vehicles other than water (e.g., applesauce, scrambled eggs, yogurt). The Division of Biopharmaceutics is reviewing these data.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

No new preclinical pharmacology/toxicology studies were conducted in support of this sNDA. The pharmacology/toxicology team reviewed the excipients in the formulation to determine whether any might pose a safety issue for children down to 6 years of age (see review by Dr. Rama Dwivedi filed September 6, 2016). They concluded that no excipients in the formulation pose a safety issue.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Sevelamer carbonate is a non-absorbed polymer that exists in a protonated form in the intestine and binds phosphate molecules in the gastrointestinal tract through ionic and hydrogen bonding, thereby decreasing systemic absorption of phosphate.

4.4.2 Pharmacodynamics

See Section 6.1 for a discussion of treatment effects on serum phosphorus, the main pharmacodynamic effect.

4.4.3 Pharmacokinetics

Sevelamer carbonate is not systemically absorbed.

5 Sources of Clinical Data

In support of the proposed indication, the applicant submitted the results of study SVCARB07609 titled "A 2-Week, Randomized, Placebo-Controlled, Fixed-Dose Period Followed by a 6-Month, Single-Arm, Open-Label, Dose Titration Period Study to Investigate the Efficacy and Safety of Sevelamer Carbonate in Hyperphosphatemic Pediatric Patients with Chronic Kidney Disease." The study was conducted at 29 sites in the United States (23 sites) and Europe (6 sites in Germany, Lithuania, and Poland) between May 11, 2012 and June 16, 2015.

Initial Protocol and Amendments
The original protocol was issued on May 26, 2011 and was amended once on November 3, 2011. The description below is based on the original protocol with amendments as noted.

Study Design
Study SVCARB07609 included three periods: 1) a 2 to 4-week washout period for patients on phosphate binders at baseline, 2) a 2-week randomized, placebo-controlled, fixed-dose period (FDP), and 3) a single-arm, open-label, 26-week, dose-titration period (DTP).

Patients taking a phosphate binder at baseline started with a 2-week phosphate binder washout period. If serum phosphorus levels exceeded the age-appropriate upper limit of normal (Table 5) at the end of two weeks and other eligibility criteria were met, the subject was randomized. If serum phosphorus levels were less than the age-appropriate upper limit of normal after two weeks, subjects could remain off binders for an additional 2 weeks. If serum phosphorus and other eligibility criteria were met during or at the end of the two weeks, the subject could be randomized. Per protocol amendment 1, subjects who were screen failures based on serum phosphorus could be rescreened if at least 3 months had elapsed from the previous attempt. Subjects not on phosphate binders at baseline who met eligibility criteria could proceed directly to randomization.

Table 5: Protocol-specified normal serum phosphorus ranges by age

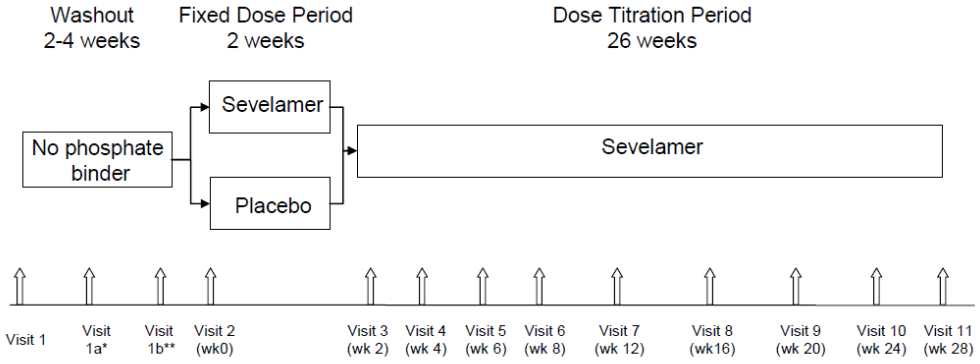
Age	Normal Range
0 to <6 months	5.2 to 8.4 mg/dL (1.68 to 2.71 mmol/L)
≥6 to <12 months	5.0 to 7.8 mg/dL (1.61 to 2.52 mmol/L)
≥1 to <6 years	4.5 to 6.5 mg/dL (1.45 to 2.10 mmol/L)
≥6 to <13 years	3.6 to 5.8 mg/dL (1.16 to 1.87 mmol/L)
≥13 to <20 years	2.3 to 4.5 mg/dL (0.74 to 1.45 mmol/L)

Source: Applicant, Protocol SVCARB07609, Table 1.

Subjects were randomized 1:1 to a fixed dose of sevelamer carbonate or placebo for 2 weeks (FDP). This was followed by a 6-month, single-arm, open-label period in which all subjects

received sevelamer carbonate and doses could be titrated to achieve age-specific normal serum phosphorus levels (DTP). An overview of the study design is shown in Figure 1.

Figure 1: Study design



*Patients taking phosphate binder(s) at Screening.
**Patients whose serum phosphorus is not greater than the age appropriate upper limit of normal Visit 1a

Source: Applicant, Protocol SVCARB07609.

Reviewer's comment: The serum phosphorus ranges specified in Table 5 reflect normal serum phosphorus values and are more stringent than the recommended treatment targets for patients with CKD on dialysis. According to the 2005 K/DOQI Clinical Practice Guidelines for Mineral Metabolism and Disease in Children with Chronic Kidney Disease, for children with CKD Stage 5 including those treated with hemodialysis or peritoneal dialysis, the serum levels of phosphorus should be maintained between 3.5 and 5.5 mg/dL during adolescence and between 4 and 6 mg/dL for children between the ages of 1-12 years. The 2009 KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment suggests "lowering elevated phosphorus levels toward the normal range," although the guideline notes this is suggested based on low quality evidence and does not specifically address targets in adults vs. pediatric patients. There are no data demonstrating that treating to achieve a particular serum phosphorus level improves clinical outcomes.

Objectives

In hyperphosphatemic pediatric patients with CKD to:

- Evaluate the safety and tolerability of sevelamer carbonate
- Evaluate the efficacy of sevelamer carbonate on the control of serum phosphorus

Population

Key Inclusion Criteria:

1. 0 to < 19 years old at Visit 1.
2. CKD requiring dialysis or CKD not on dialysis with an estimated GFR <60 mL/min/1.73m^2 based on central laboratory results.
    a. Taking phosphate binder(s) at Screening: At Visit 1a
    b. Taking phosphate binder(s) at Screening: At Visit 1
3. Serum phosphorus level greater than the age appropriate upper limit of normal based on central laboratory results (Table 1).
    a. Taking phosphate binder(s) at Screening: At or between Visit 1a and Visit 1b
    b. Not taking phosphate binder(s) at Screening: At Visit 1

4. If female with reproductive capacity, has a negative pregnancy test based on central laboratory results.

Enrollment required that at least 20% of subjects were less than 13 years of age and at least 70% were receiving dialysis.

Reviewer's comment: Study eligibility was based on a single serum phosphorus measurement above the age appropriate upper limit of normal.

Key Exclusion Criteria:

1. Active dysphagia, swallowing disorders or a predisposition to or current bowel obstruction, ileus or severe gastrointestinal motility disorder(s) including severe constipation, or major GI tract surgery.
2. Non-renal cause of hyperphosphatemia (added per protocol amendment 1).
3. History of, or active, ethanol or drug dependence or abuse, excluding tobacco use.
4. Requires continuous tube feeds. Patients requiring bolus tube feeds are not excluded.
5. Any evidence of active malignancy except for basal cell carcinoma of the skin. A history of malignancy is not an exclusion criterion.
6. Immunosuppressive medication for a functioning organ transplant.
7. Anti-arrhythmic medications for treatment of arrhythmias. Antiarrhythmic medications used for other indications are not excluded by this criterion.
8. Anti-seizure medications for treatment of seizures. Anti-seizure medications used for other indications are not excluded by this criterion.
9. Known allergy to sevelamer or any of its constituents.
10. Pregnant or breast-feeding, if female, or not willing to use birth control, if sexually active female patient with reproductive capacity.
11. In the opinion of the Investigator, does not require a phosphate binder.
12. In the opinion of the Investigator, has any clinically significant unstable medical condition.
13. In the opinion of the Investigator, is unable to adhere to the requirements of the study.

Study Procedures

Randomization

Eligible patients were randomized 1:1, stratified by screening BSA (<1.2 vs. ≥ 1.2 m^2) and the most recent central laboratory serum phosphorus level before the Visit 2/Week 0 visit (<7 vs. ≥ 7 mg/dL).

Blinding

The investigator, subject, and sponsor remained blinded to treatment assignment during the FDP. The DTP was open-label.

Trial Treatments

Subjects with a screening body surface area (BSA) <1.2 m^2 received sevelamer carbonate as powder for oral suspension in 0.8 g sachets. Subjects with a screening BSA ≥ 1.2 m^2 could choose to take either powder for oral suspension or 0.8 g tablets. Subjects randomized to placebo received matching powder or tablets.

Subjects or parents/guardians mixed the powder with water. The resulting oral suspension could be portioned to obtain 0.2 g increments and multiple packets could be used to obtain doses

higher than 0.8 g. Subjects were to drink the entire preparation within 30 minutes. Details were outlined in an "Investigational Product Handling Manual."

If subjects ate less than three meals or snacks per day, they were to skip the remaining doses (per protocol amendment 1). According to the protocol, the oral suspension could be administered via nasogastric or feeding tube.

Fixed-Dose Period:
During the FDP, the dose was based on BSA category at screening as shown in Table 6 and was taken up to thrice daily with meals and/or snacks. BSA was calculated using the Gehan & George equation.

Table 6: Fixed-dose period dosing

Screening BSA (m^2)	Dose	# Tablets/Sachets
<0.75	0.4 g TID	Half sachet TID
≥0.75 - <1.2	0.8 g TID	1 sachet TID
≥1.2	1.6 g TID	2 tablets or 2 sachets TID

Source: Applicant, Protocol SVCARB07609.

Dose Titration Period:
During the DTP, study drug dose could be changed every 2 weeks for 6 weeks then every 4 weeks based on the increments shown in Table 7 to achieve a serum phosphorus level within the age appropriate normal values based on central laboratory assessment or until, based on the Investigator's opinion, the administered dose is the maximum the patient can practically take or tolerate with meals. Study drug was to be up-titrated if serum phosphorus exceeded the age-appropriate upper limit of normal and could be temporarily interrupted and/or down-titrated if serum phosphorus was less than the age-appropriate lower limit of normal. Subjects who required less than 0.2 g TID were to be discontinued from study drug and, per protocol amendment 1, withdrawn from the study.

Table 7: Dose Titration Period Dosing

Screening BSA (m^2)	Starting dose	Titration increases/decreases
<0.75	0.4 g TID	Titrate up/down by 0.2g TID
≥0.75 - <1.2	0.8 g TID	Titrate up/down by 0.4g TID
≥1.2	1.6 g TID	Titrate up/down by 0.8g TID

Source: Applicant, Protocol SVCARB07609.

Rationale for Dose Selection:
According to the Clinical Study Report (CSR), the dose of sevelamer carbonate required in pediatric patients was expected to be less than that required in adults based on input from pediatricians caring for CKD patients and because dietary phosphate intake in children is less than adults. For subjects with a BSA <0.75 m^2, the starting and titration doses were 25% of adult doses. For subjects with a BSA ≥0.75 m^2 to <1.2 m^2, the starting and titration doses were 50% of adult doses. For subjects with a BSA of ≥1.2 m^2, doses were the same as adult doses.

Compliance
The investigator was to maintain records of investigational product used by each subject.

Concomitant Therapies
Throughout the study, subjects were to continue with their prescribed dietary recommendations and dialysis care. They were not permitted to use other phosphate binders or antacids containing aluminum, magnesium, or calcium (unless prescribed as an evening calcium supplement.) Use of vitamin D or calcimimetics was not specified.

Study Assessments
Subjects returned to the clinic for visits every two weeks through Week 8, then every 4 weeks through Week 28. Windows were specified for each visit, but visits occurring outside of these windows were not considered protocol violations.

Serum phosphorus, calcium, and albumin were assessed at each visit. Serum chemistries (sodium, potassium, glucose, BUN, creatinine, bicarbonate, chloride, AST, ALT, total bilirubin, alkaline phosphatase, and lipid panel) were assessed at Weeks 0, 2, and 28. A physical examination, vital signs, serum intact PTH, vitamin levels (vitamin A, vitamin E, 25-hydroxyvitamin D, 1,25-dihydroxy vitamin D), and hematology parameters were assessed at Weeks 0 and 28. Laboratory parameters were measured by a central laboratory.

Table 8: Schedule of Study Events

	Patients Not Taking Phosphate Binder(s) at Screening	Patients Taking Phosphate Binder(s) at Screening			All Patients									
	Screening	Screening	Washout Period		Fixed Dose Period		Dose Titration Period							
	Visit 1	Visit 1	Visit 1a[7]	Visit 1b[1,7]	Visit 2 (Wk 0)	Visit 3 (Wk 2)	Visit 4 (Wk 4)	Visit 5[7] (Wk 6)	Visit 6 (Wk 8)	Visit 7 (Wk 12)	Visit 8 (Wk 16)	Visit 9 (Wk 20)	Visit 10 (Wk 24)	Visit 11/ET (Wk 28/ET)
Describe Study/ Obtain Informed Consent	√	√												
Review Inclusion/Exclusion	√	√			√									
Review Demographics, Medical/Renal History	√	√												
Height and Weight	√	√												√
Beta-hCG, Serum creatinine[2]	√		√											
Serum phosphorus, calcium and albumin	√		√	√	√	√	√	√	√	√	√	√	√	√
Contact patient about Visit 2	√		√	√										
Randomization					√									
Chemistry Profile, Lipids[3]					√	√								√
Serum iPTH, Vitamins & Hematology[4]					√									√
Stored serum sample[8]					√									√
Physical Exam with Vitals					√									√
Dispense Study Drug					√	√	√		√	√	√	√	√	
Contact patient to adjust binder dose[5]						√	√	√	√	√	√	√	√	
AE Assessment[6]	Continuous Monitoring													
Concomitant Medications	Continuous Monitoring													

Reviewer's comment: The protocol did not specify the timing of blood draws relative to dialysis or with respect to the time of day. In an October 19, 2016 response to an information request, the applicant noted that it is typical to draw samples pre-dialysis and that in a "Questions & Answers log" addressing questions raised during the course of the study, the sponsor stated that study-related blood samples were to be drawn pre-dialysis. Case report forms did not collect the time of blood draws in relation to the timing of dialysis.

Subject Follow-up
A subject was considered "completed' when scheduled Visit 11 (Week 28) assessments had been completed. According to the protocol, discontinuation of treatment did not imply withdrawal from the study. Subjects who received at least one dose of study drug and withdrew from

treatment were asked to complete Visit 11/end of treatment assessments. The protocol specified that subjects who were to receive immunosuppressive therapy for a planned organ transplant were to discontinue study treatment and withdraw from the study.

Monitoring
A Data Monitoring Committee (DMC) periodically reviewed safety data.

Endpoints
The primary efficacy endpoint was change from Baseline (Visit 2/Week 0) to Visit 3 (Week 2) in serum phosphorus.

The secondary efficacy endpoint was change from Baseline to Visit 11/ET (Week 28/ET) in serum phosphorus. The secondary endpoint was "presented for descriptive purposes."

Statistical Analysis Plan
The statistical analysis plan was issued July 23, 2012.

Datasets:
Efficacy analyses used the Full Analysis Set (FAS), which was defined as all treated patients with a baseline phosphorus value and at least one post-baseline phosphorus assessment according to randomized treatment assignment. Analysis sets were defined for both the fixed-dose (FAS-FDP) and dose-titration (FAS-DTP) periods.

Safety analyses used the safety set, which included all enrolled patients who were treated with at least one dose of study drug.

Efficacy Analyses:
The primary efficacy endpoint was analyzed using an ANCOVA model with terms for baseline phosphorus, screening BSA, and treatment. The secondary endpoint was to be summarized descriptively by treatment group and overall. The Wilcoxin signed rank test was used to assess within-group changes.

Baseline for both endpoints was defined as the Visit 2/Week 0 measurement taken before the start of study drug. If the measurement was missing, baseline was defined as the last off-treatment value. If Week 2 or Week 28 data were missing, the last non-missing post-baseline observation was used. If a patient randomized to placebo dropped out before the dose titration period, that patient was excluded from the secondary efficacy analysis. Values from unscheduled visits could be used if values from scheduled visits were missing.

Reviewer's comments:
1. *As noted in the eligibility criteria, the qualifying serum phosphorus for purposes of study eligibility was obtained at Visit 1, 1a, or 1b, depending on whether a subject was on a phosphate binder and the duration of the washout period. Baseline was defined as the phosphorus value at Visit 2, which could occur up to 6 weeks after Visit 1.*
2. *Efficacy analyses were based on a single baseline and a single post-baseline serum phosphorus measurement.*

Adjustment for Multiplicity:
The primary efficacy analysis was to be analyzed at an alpha of 0.05. According to the protocol, other p-values were "presented for descriptive purposes; therefore, no adjustment for multiplicity is needed."

Subgroup Analyses:
The primary efficacy endpoint was to be summarized for subgroups based on screening BSA (<1.2 vs. ≥1.2m^2) and baseline serum phosphorus (<7.0 vs. ≥7.0 mg/dL).

Sample Size Calculations:
A sample size of 100 subjects, 50 per treatment group, was expected to provide 80% power at a two-sided alpha of 0.05 to detect a 0.75 mg/dL difference in mean change in serum phosphorus from baseline to Week 2 between treatment arms assuming a standard deviation of 1.32 mg/dL.

6 Review of Efficacy

6.1 Indication

The proposed indication is:

(b) (4)

6.1.1 Methods

In support of the proposed indication, the applicant submitted the results of Study SVCARB07609. See Section 5 for an overview of study design.

6.1.2 Demographics

Baseline demographics were similar between the two treatment arms (Table 9). Three quarters of subjects were 13 to 18 years of age, and no subjects were less than 6 years of age. Most subjects were enrolled in the United States.

Table 9: Baseline demographics

	Sevelamer (n=50) n (%)	**Placebo (n=51) n (%)**	**Total (n=101) n (%)**
Male	30 (61)	33 (65)	63 (62)
Age (mean [SD])	13.9 (2.7)	14.3 (3.1)	14 (2.9)
13 – 18 years	36 (72)	38 (75)	74 (73)
6 – 12 years	14 (28)	13 (25)	27 (27)
0 – 5 years	0	0	0
Race			
White	28 (56)	27 (53)	55 (55)
Black	16 (33)	19 (37)	35 (35)
Other	6 (12)	5 (10)	11 (11)
Country			
United States	42 (86)	46 (90)	88 (87)
Poland, Germany, Lithuania	7 (14)	5 (10)	12 (12)

Source: Clinical reviewer's analysis of *adsl.xpt.*

Reviewer's comment: According to an April 18, 2016 response to an information request, five patients 3 to 5 years of age were screened but none met inclusion criteria because phosphorus levels at the end of washout were within age appropriate normal ranges.

As shown in Table 10, most subjects were in the largest BSA category ≥1.2 m^2. The median baseline serum phosphorus was 7.0. Approximately 80% of subjects were on dialysis with two thirds of these subjects on hemodialysis. Approximately 80% of subjects were taking one or more phosphate binders at screening (~60% sevelamer and ~40% calcium carbonate or acetate).

Table 10: Baseline characteristics

	Sevelamer (n=50) n (%)	**Placebo (n=51) n (%)**	**Total (n=101) n (%)**
BSA (mean [SD])	1.5 (0.3)	1.6 (0.4)	1.5 (0.4)
≥1.2	42 (84)	45 (88)	42 (84)
≥0.75 to <1.2	8 (16)	6 (12)	14 (14)
<0.75	0	0	0
Serum phosphorus (mean [SD])	7.3 (2.1)	7.1 (1.9)	7.2 (2.0)
< 7.0	26 (52)	24 (47)	50 (50)
≥ 7.0	24 (48)	27 (53)	51 (50)
Dialysis	36 (72)	42 (82)	78 (78)
Hemodialysis	23 (46)	32 (63)	55 (55)
Peritoneal dialysis	13 (26)	10 (20)	23 (23)
Taking phosphate binder	43 (86)	39 (77)	82 (81)

Source: Clinical reviewer's analysis of *adsl.xpt, admh.xpt.*

6.1.3 Subject Disposition

Screening Period
Of 128 screened patients, 101 (79%) were eligible for randomization (Table 11). Most screen failures did not have a serum phosphorus level greater than the age appropriate upper limit of normal.

Table 11: Subject disposition – screening period

	Subjects n (%)
Subjects screened	128 (100)
Subjects eligible for randomization	101 (79)
Screen failures	27 (21)
Does not have a serum phosphorus level greater than the age appropriate upper limit of normal	18
Unable to adhere to requirements of study	4
Has an excluded gastrointestinal disorder	2
Does not have CKD requiring dialysis or with an eGFR <60 mL/min/1.73m^2	1
Uses anti-seizure medication	1
Has any clinically significant unstable condition	1

Source: Clinical reviewer's analysis of *adsl.xpt* and *ie.xpt.*

All randomized subjects were treated except one subject randomized to sevelamer who was reportedly non-compliant. This subject was excluded from both the FAS-FDP and FAS-DTP datasets. Because of missing post-baseline phosphorus values, one additional sevelamer and two placebo subjects were excluded from the FAS-FDP, and three additional sevelamer and two placebo subjects were excluded from the FAS-DTP dataset. Approximately two-thirds of subjects completed the study, defined as completing the Week 28 assessments. Nearly half of premature study drug discontinuations were for kidney transplant.

Table 12: Disposition by randomized treatment assignment

	Sevelamer n (%)	**Placebo n (%)**
Randomized	50 (100)	51 (100)
Treated	49 (98)	51 (100)
FAS-FDP	48 (96)	49 (96)
FAS-DTP	46 (92)	49 (96)
Completed study[1]	31 (62)	35 (69)
Discontinued from study	19 (38)	16 (31)
Other (kidney transplant)	8 (16)	8 (16)
Physician decision	4 (8)	5 (10)
Withdrawal by subject	4 (8)	2 (4)
Adverse event[2]	4 (8)	1 (2)
Not treated	1 (2)	0

Source: Clinical reviewer's analysis of *adsl.xpt* and *ds.xpt.*
[1]Defined as completing assessments scheduled for Week 28
[2]One subject in each arm discontinued treatment during the FDP, three additional subjects initially randomized to the sevelamer treatment arm discontinued during the open-label extension period.

Reviewer's comment: See Section 7.3.3 for a discussion of the adverse events leading to study drug discontinuation.

During the FDP, one subject in each treatment arm discontinued study drug. Both events related to elevated serum phosphorus ("hyperphosphatemia" and "blood phosphorus increased"; Source: Applicant, Appendix 16.2.7, Table 14.3.2.1.1).

During the DTP, three subjects discontinued study drug because of an adverse event (septic shock, varicella zoster infection, and chronic kidney disease).

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint was change from Baseline (Visit 2/Week 0) to Visit 3 (Week 2) in serum phosphorus. As shown in Table 13, serum phosphorus declined in the sevelamer arm but not the placebo arm with a least squares (LS) mean of the difference in the change from baseline between the treatment arms of -0.9 mg/dL (95% CI -1.44, -0.37; p=0.001).

Table 13: Primary efficacy analysis (FAS-FDP)

	Sevelamer (n=48)	Placebo (n=49)	LS mean difference (95 % CI; p-value)
Baseline phosphorus (mean [SD] mg/dL)	7.20 (2.1)	7.20 (1.8)	
Week 2 phosphorus (mean [SD] mg/dL)	6.34 (1.3)	7.24 (2.0)	
Mean change mg/dL	-0.87 (1.65)	0.04 (1.48)	-0.9 (-1.44, -0.37; 0.001)

Source: Clinical reviewer's analysis of *adsl.xpt, adlb.xpt.* Applicant, CSR, Table 14. Analysis confirmed by statistical reviewer.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary efficacy endpoint was change from Baseline to Visit 11/ET (Week 28/ET) in serum phosphorus. As previously noted, there was no pre-specified plan to control the overall type I error for the analysis of the secondary endpoint. In the FAS-DTP population, mean (SD) baseline serum phosphorus was 7.16 (1.9) mg/dL and mean (SD) Week 28 serum phosphorus was 5.98 (1.7) mg/dL resulting in a mean change from baseline of -1.18 mg/dL. (Source: Applicant, CSR, Table 18; Analysis confirmed by statistical reviewer.)

6.1.7 Subpopulations

Subgroup Analyses of Primary Efficacy Endpoint
As shown in Table 14, the results of the primary efficacy endpoint were consistent by BSA subgroup, but a treatment effect was not observed in subjects with a baseline serum phosphorus below 7 mg/dL, in subjects 6 to <13 years of age, or in subjects not on dialysis. Of note, subjects 6 to <13 years of age randomized to sevelamer had a mean baseline serum phosphorus nearly 1 mg/dL lower than subjects randomized to placebo. Subjects not on dialysis had a mean baseline serum phosphorus over 2 mg/dL lower than subjects on dialysis.

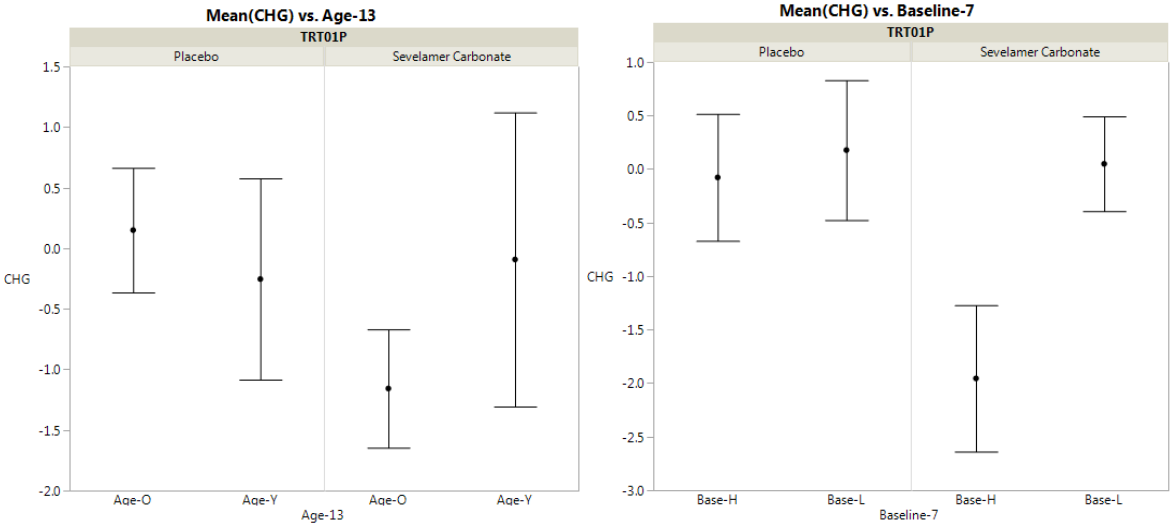
Table 14: Primary efficacy analysis by subgroups[1]

Subgroup		Mean Baseline		LS Mean Change from Baseline		Difference in LS mean change form baseline (SD) (95% CI)
		Sevelamer (SD)	Placebo (SD)	Sevelamer (SD)	Placebo (SD)	
Baseline phosphorus (mg/dL)	<7	5.63 (0.91) n=26	5.69 (0.89) n=23	0.06 (0.26)	0.17 (0.28)	-0.11 (0.38) (-0.87, 0.66)
	≥7	9.07 (1.47) n=22	8.53 (1.36) n=26	-1.98 (0.32)	-0.05 (0.30)	-1.93 (0.44) (-2.82, -1.04)
Age (years)	6 - <13	6.56 (1.88) n=13	7.55 (2.25) n=13	-0.18 (0.40)	-0.24 (0.43)	0.05 (0.55) (-1.04, 1.15)
	13 - 18	7.44 (2.14) n=35	7.07 (1.69) n=36	-1.24 (0.23)	0.16 (0.25)	-1.40 (0.34) (-2.07, -0.72)
Dialysis	Yes	7.84 (2.14) (n=34)	7.61 (1.71) (n=40)	-0.88 (0.23)	0.30 (0.21)	-1.17 (0.31) (-1.78, -0.56)
	No	5.66 (0.73) (n=14)	5.38 (1.25) (n=9)	-0.87 (0.36)	-1.06 (0.45)	0.19 (0.55) (-0.91, 1.29)
BSA (m^2)	<1.2	7.49 (1.57) (n=8)	7.42 (2.95) (n=6)	-0.79 (0.47)	0.36 (0.54)	-1.15 (0.71) (-2.57, 0.27)
	≥1.2	7.15 (2.19) (n=40)	7.17 (1.68) (n=43)	-0.88 (0.21)	-0.003 (0.20)	-0.88 (-1.46, 0.30)

Source: Analyses by statistical reviewer.
[1]Analysis adjusted for BSA and baseline phosphorus.

The above effect of age and baseline serum phosphorus is visually depicted in Figure 2. Of note, there was wide variability in treatment effect in all age groups, but more so in the younger subgroup.

Figure 2: Change in serum phosphorus by age (left) and baseline serum phosphorus (right)



Source: Clinical pharmacology reviewer.
Note: Age-O = ≥13 years, Age-Y = <13 years; Base-H = baseline serum phosphorus ≥7 mg/dL, Base-L = <7 mg/dL.

To explore the variation in treatment effect by baseline characteristics, the statistical reviewer conducted a regression analysis using change from baseline to Week 2 in serum phosphorus as the dependent variable and baseline serum phosphorus (<7 vs. >7 mg/dL), BSA, age (<13 vs. ≥ 13 years), and interaction terms of baseline phosphorus by treatment and age by treatment. As shown in Table 15, the p-values for baseline serum phosphorus alone and both interaction terms were <0.05, suggesting a strong effect of baseline serum phosphorus and age. An effect of treatment was observed with a p-value of 0.038 even after controlling for these variables.

Table 15: Regression Analysis of Primary Endpoint

Effect	F Value	Pr > F
Treatment	4.43	0.038
Age	0.81	0.369
Baseline Phosphorus	14.45	<0.001
Body Surface Area	0.01	0.911
Treatment * Age	4.90	0.029
Treatment * Baseline Phosphorus	10.20	0.002

Source: Analysis by statistical reviewer.

To explore whether poor adherence to prescribed study treatment may have contributed to the lack of treatment effect in subjects with a low baseline serum phosphorus or younger age, adherence was calculated by dividing the total number of tablets or sachets taken by the total number prescribed. Non-adherence, defined as taking <70% of the prescribed doses was common, but did not vary substantially by subgroup (Table 16).

Table 16: Non-adherence by baseline serum phosphorus and age

	Non-adherent n/N (%)
Baseline serum phosphorus	
<7 mg/dL	12/26 (46)
≥7 mg/dL	12/22 (55)
Age	
<13 years	7/13 (54)
>13 years	17/35 (49)

Source: Analyses by clinical pharmacology reviewer.

As noted previously, subjects 6 to <13 years of age randomized to sevelamer had a mean baseline serum phosphorus nearly 1 mg/dL lower than subjects randomized to placebo and there was wide variability in treatment effect in both treatment arms, but more so in the sevelamer arm. As shown in Table 17, seven (27%) subjects 6 to <13 years of age (2/13 [15%] placebo subjects and 5/13 [38%] sevelamer subjects) had a baseline serum phosphorus within the age-specific normal range at baseline. The applicant noted that two sevelamer subjects (8013-0002 and 8019-0001) had elevated serum phosphorus levels at screening, low-normal values at baseline, and elevated values at the end of the FDP (7.0/3.6/6.1 mg/dL and 7.9/3.7/7.2 mg/dL, respectively). The subjects were both receiving dialysis and the serum phosphorus values correlated with serum creatinine levels, suggesting a relationship to dialysis treatment. The applicant was able to confirm that the baseline sample was drawn after dialysis for subject 8019-0001.

Table 17: Subjects with baseline serum phosphorus < upper limit of normal (ULN)

Age	ULN Phosphorus	n/N (%)
6 to <13 years	≤ 5.8 mg/dL	7/26 (27)[1]
13 to 18 years	≤ 4.5 mg/dL	2/71 (3)[2]

Source: Clinical reviewer's analysis of *adlb.xpt*.
[1]Two placebo and five sevelamer carbonate subjects.
[2]One placebo and one sevelamer carbonate subject.

Reviewer's comment:

1. *As previously noted, the protocol did not specify the timing of phosphorus measurements relative to dialysis. Serum phosphorus values drawn immediately following dialysis will be low because dialysis removes intravascular phosphorus but levels rebound over time because of equilibration with extravascular phosphorus. As a result, post-dialysis serum phosphorus levels do not provide an accurate depiction of total body phosphorus stores.*
2. *Excluding the seven subjects 6 to <13 years of age with a normal baseline serum phosphorus from analyses would result in only eight subjects in the sevelamer carbonate arm and 11 in the placebo arm. This analysis is unlikely to be informative.*

Subgroup Analyses of Secondary Efficacy Endpoint

As shown in Table 18, a smaller treatment effect was observed over the DTP in subjects with a lower baseline serum phosphorus, subjects <13 years of age, and subjects not on dialysis. This is consistent with subgroup analyses of the primary efficacy endpoint.

Table 18: Secondary efficacy analysis by subgroup

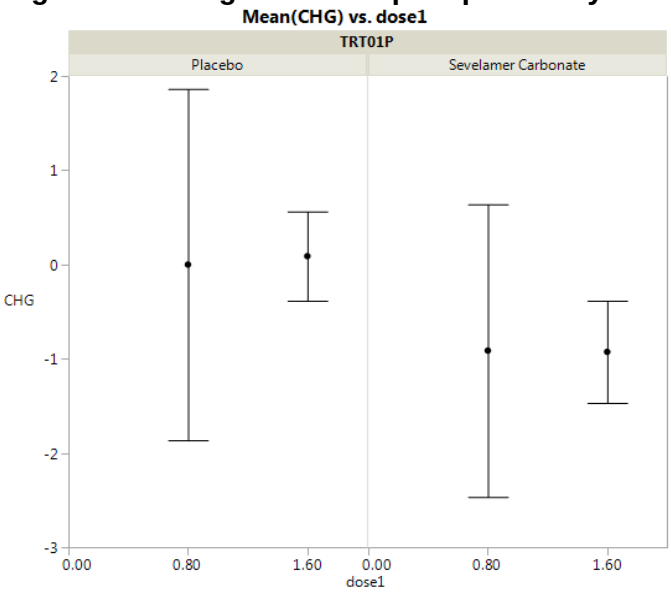
		n	Mean Baseline (SD)	Mean Change from Baseline (SD)
Baseline phosphorus (mg/dL)	<7	47	5.58 (0.97)	-0.19 (1.52)
	≥7	48	8.70 (1.31)	-2.15 (2.19)
Age (years)	<13	25	6.84 (1.81)	-0.36 (2.18)
	≥13	70	7.28 (1.99)	-1.47 (2.04)
Dialysis	Yes	72	7.68 (1.90)	-1.44 (2.27)
	No	23	5.55 (0.95)	-0.35 (1.28)
BSA (m^2)	<1.2	13	7.07 (1.66)	-0.90 (2.21)
	≥1.2	82	7.17 (1.99)	-1.22 (2.12)

Source: Analyses by statistical reviewer.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The applicant is proposing a starting dose of 0.8 g for patients with a BSA ≥0.75 to <1.2 m^2 and 1.6 g for patients with a BSA ≥1.2 m^2. As shown in Figure 4, serum phosphorus decreased a similar amount with both starting doses of sevelamer carbonate relative to placebo.

Figure 3: Change in serum phosphorus by starting dose.

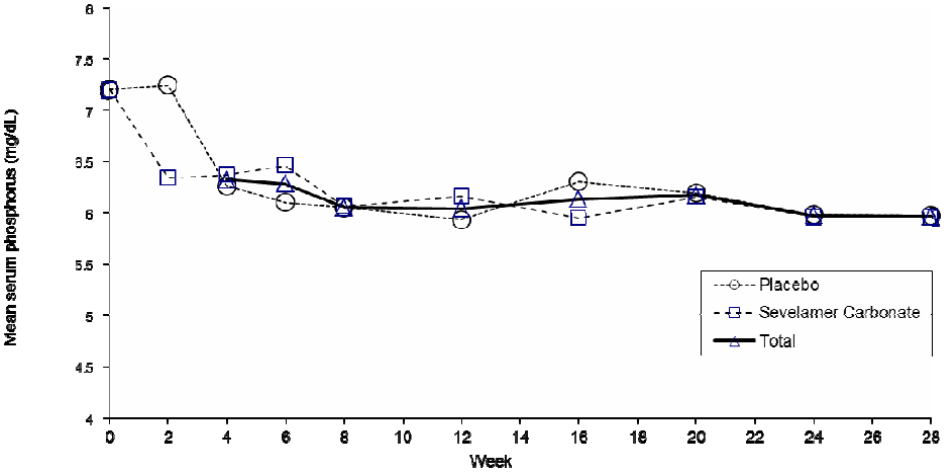


Source: Analyses by clinical pharmacology reviewer.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

During the open-label DTP, mean serum phosphorus remained stable at a reduced level through Week 28 (Figure 5).

Figure 4: Serum phosphorus over time – FAS-FDP



Source: Applicant, CSR, Figure 2.

6.1.10 Additional Efficacy Issues/Analyses

During the DTP, study drug was to be titrated to reach a serum phosphorus target of 3.6 to 5.8 mg/dL for subjects 6 to <13 years of age and 2.3 to 4.5 mg/dL for subjects ≥ 13 to 18 years of

age. Only 21% of subjects in the older age group were in the age-specific target range at Week 28/ET compared with 56% of subjects in the younger group.

Table 19: Subjects achieving serum phosphorus ≤ age-specific upper limit by Week 28/End of Treatment

	≤ Upper Limit of Target Range n/N (%)
Total	29/95 (31)
6 to <13 years	14/25 (56)
13 to 18 years	15/70 (21)

Source: Clinical reviewer's analysis of *adlb.xpt.*

Reviewer's comment: The clinical pharmacology reviewer noted several cases in which serum phosphorus values should have prompted an increase in study drug but the dose remained unchanged. This suggests that drug was not aggressively titrated during the dose titration phase, although the reasons for failure to titrate were not recorded.

7 Review of Safety

7.1 Methods

Study SVCARB07609 served as the primary source of safety data for the application. Safety analyses used the safety set, which included 100 enrolled patients who received at least one dose of study drug.

7.1.2 Categorization of Adverse Events

The applicant categorized AEs/SAEs by systemic organ class (SOC) and preferred term (PT) using MedDRA version 18. An SAE was defined as an event that resulted in death; was life-threatening; was a congenital anomaly/birth defect; required or prolonged hospitalization; resulted in persistent or significant disability/incapacity; or was a medically important event. AEs were collected until Week 28/End of Treatment visit. SAEs were collected up to 15 days after the Week 28/End of Treatment visit.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

During the FDP, the mean prescribed daily dose was 4.4 g/day (Table 20). During the DTP, the mean prescribed daily dose was 6.8 g/day with a maximum of 12.5 g/day. The maximum treatment duration was 223 days.

Table 20: Study drug exposure

	Sevelamer n=49	**Placebo N=51**
Fixed-Dose Period		
Treatment days – mean (SD)	14.6 (2.2)	14.4 (2.5)
– range	4-18	1-20
Prescribed daily dose (g) – mean (SD)	4.4 (0.9)	4.3 (1.1)
– range	2.4-4.8	1.2-7.2
Dose Titration Period		
Treatment days – mean (SD)	161.5 (54)	160.6 (54)
– range	13-216	8-223
Prescribed daily dose (g) – mean (SD)	7.1 (2.3)	6.5 (2.3)
– range	2.4-11.4	2.4-12.5

Source: Applicant, CSR, Table 14.3.1.1.1.

Reviewer's comment: The durations of the FDP and DTP exceed the protocol-specified durations in some cases. According to an April 18, 2016 response to an information request, this was the result of visit windows of 3 to 14 days. If a visit occurred late, subsequent visits were scheduled according to the standard duration between two visits, resulting in longer treatment durations.

7.2.2 Explorations for Dose Response

It is not possible to evaluate dose response because there was a single starting dose based on BSA.

7.2.4 Routine Clinical Testing

See Section 5 for detailed information on study assessments. In brief, subjects returned to the clinic for visits every two weeks through Week 8, then every 4 weeks through Week 28. Serum phosphorus, calcium, and albumin were assessed at each visit. Serum chemistries (sodium, potassium, glucose, BUN, creatinine, bicarbonate, chloride, AST, ALT, total bilirubin, alkaline phosphatase, and lipid panel) were assessed at Weeks 0, 2, and 28. A physical examination, vital signs, serum intact PTH, vitamin levels (vitamin A, vitamin E, 25-hydroxyvitamin D, 1,25 dihydroxy vitamin D), and hematology parameters were assessed at Weeks 0 and 28.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Based on clinical studies in adults, adverse events with this class are primarily gastrointestinal (e.g., vomiting, nausea, diarrhea, abdominal pain).

7.3 Major Safety Results

7.3.1 Deaths

No subjects died during the study.

7.3.2 Nonfatal Serious Adverse Events

During the FDP, five SAEs were reported in four (8%) sevelamer carbonate subjects and one SAE was reported in one (2%) placebo subject. Events in the sevelamer carbonate arm included hypertension in two subjects and device occlusion, peritonitis, and hyperkalemia in one subject each. The event in the placebo arm was viral gastroenteritis. (Source: Applicant, CSR, Tables 14.3.2.1.1 and 14.3.2.1.4) During the DTP, 79 SAEs were reported for 31 (31%) subjects (Table 21). The reported SAEs would not be considered unexpected events in a pediatric dialysis population.

Table 21: Serious adverse events occurring in ≥ 2 subjects during dose titration period

	Total n=100 n (%)
SAEs	79
Subjects with SAEs	31 (31)
Abdominal pain	3 (3)
Anemia	2 (2)
Constipation	2 (2)
Device malfunction	2 (2)
Bacteremia	2 (2)
Peritonitis	2 (2)
Upper respiratory tract infection	2 (2)
Urinary tract infection	2 (2)
Hyperkalemia	2 (2)
Hypocalcemia	2 (2)
Hypotension	2 (2)

Source: Applicant, CSR, Table 26.

The events of abdominal pain and constipation were as follows:

Subject 8010-0001 (abdominal pain, constipation): 18-year-old female with ESRD on hemodialysis and a history of constipation, vomiting, small bowel obstruction, and dyspepsia. She was randomized to sevelamer carbonate and started treatment on (b) (6). On (b) (6), the patient developed worsening constipation and was hospitalized for abdominal pain and shortness of breath. An abdominal CT did not show obstruction and an X-ray showed a distended, non-obstructed colon. She received docusate, senna, lactulose, and bisacodyl. Study drug was continued and the dose was increased per protocol because of high serum phosphorus levels. The event was reported as resolved on September 30, 2012. On (b) (6), the patient was again hospitalized for abdominal pain. An abdominal ultrasound showed a moderate amount of stool and air distending the colon without obstruction. No specific treatment was reported and the patient was scheduled for outpatient follow-up with gastroenterology.

Subject 8013-0005 (abdominal pain): 16 year-old female with ESRD on hemodialysis with a history of choledochal cyst s/p cystectomy. She was randomized to sevelamer carbonate and started treatment on (b) (6). On (b) (6), she was admitted to the hospital with fever and right-sided abdominal pain. She was treated with IV gentamicin and vancomycin and study drug was discontinued. The investigator reported that the event was related to her history of choledochal cystectomy.

Subject 8022-0002 (abdominal pain): 18 year-old female with ESRD on peritoneal dialysis and a history of constipation and nausea/vomiting. She was randomized to sevelamer carbonate on (b) (6). On (b) (6), she was admitted to the hospital with abdominal pain and peritonitis. She was treated with intraperitoneal antibiotics. On May 28, 2013, she was diagnosed with pelvic inflammatory disease from *Chlamydia trachomatis.*

Subject 8006-0001 (constipation): 16 year-old female with ESRD on hemodialysis with a history of constipation related to sacral agenesis. She was randomized to placebo on (b) (6). On (b) (6), she entered the open-label period and started sevelamer carbonate. On (b) (6), she was hospitalized for worsening constipation with nausea/vomiting since March 17, 2013. She had been treated as an outpatient by a gastroenterologist with senna, polyethylene glycol, and lactulose without a bowel movement in 3-4 weeks. She was treated for fecal impaction. Study drug was continued.

Reviewer's comment: Constipation and abdominal pain are known adverse reactions of sevelamer carbonate. Study drug may have contributed to the events of worsening constipation in subjects 8010-0001 and 8006-0001.

7.3.3 Dropouts and/or Discontinuations

During the FDP, one subject in each treatment arm discontinued study drug. Both events related to elevated serum phosphorus ("hyperphosphatemia" and "blood phosphorus increased"; Source: Applicant, Appendix 16.2.7, Table 14.3.2.1.1).

During the DTP, three subjects discontinued study drug because of an adverse event (septic shock, varicella zoster infection, and chronic kidney disease).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Approximately 40% of subjects in each treatment arm experienced a treatment-emergent adverse event during the 2-week FDP (Table 22). The only events occurring in at least two sevelamer carbonate subjects were headache and hypertension.

Table 22: Treatment-emergent adverse events occurring in ≥2 sevelamer carbonate subjects during fixed-dose period

	Sevelamer n=49 n(%)	Placebo n=51 n(%)
TEAEs	34	36
Subjects with TEAE	19 (39)	20 (39)
Headache	2 (4)	2 (4)
Hypertension	2 (4)	0

Source: Applicant, CSR, Table 14.3.2.1.2.

Adverse events were common during the DTP and generally reflected events that might be expected in a pediatric dialysis population (Table 23).

Table 23: Treatment-emergent adverse events occurring in >5% of subjects during dose-titration period

	Total n=100 n (%)
TEAEs	525
Subjects with TEAE	77 (77%)
Vomiting	20 (20)
Pyrexia	19 (19)
Headache	17 (17)
Nausea	15 (15)
Abdominal pain	15 (15)
Upper respiratory tract infection	12 (12)
Abdominal pain – upper	9 (9)
Diarrhea	9 (9)
Hypotension	9 (9)
Pain in extremity	8 (8)
Dizziness	7 (7)
Cough	7 (7)
Hypertension	7 (7)
Catheter site pain	6 (6)
Seasonal allergy	6 (6)
Nasopharyngitis	6 (6)

Source: Applicant, CSR, Table 14.3.2.2.2.

7.4.2 Laboratory Findings

The current sevelamer carbonate label includes Warnings and Precautions related to monitoring (b) (4) changes in fat soluble vitamin levels. As such, these laboratory parameters were evaluated in Study SVCARB07609.

(b) (4)

Changes in fat soluble vitamin levels by the end of the DTP are shown in Table 25. The differences were not statistically significant and it is not clear that the magnitude of the changes would be clinically meaningful.

Table 25: Changes in fat soluble vitamin levels

	Baseline	Week 28	Change from Baseline
Vitamin A	1173 (±458, n=94)	1089 (±414, n=68)	-61.4 (±446.5, n=64)
Vitamin E	11.8 (±4.2, n=98)	11.5 (±4.1, n=68)	-0.5 (±3.9, n=67)
25-OH Vitamin D	25.5 (±12.3, n=98)	24.7 (±11.5, n=67)	-0.7 (±11.1, n=66)

Source: Applicant, CSR, Section 11.4.1.8.

8 Postmarket Experience

See Section 9.1.

9 Appendices

9.1 Literature Review/References

Published Studies of Sevelamer in Pediatric Patients
Three small studies evaluating the efficacy of sevelamer hydrochloride in pediatric patients with CKD have been reported in the published literature (Table 26). The treatment effect after dose-titration ranged from -0.2 mg/dL in a study of patients with CKD not on dialysis (Gulati, 2010) to -1.3 to -1.5 mg/dL in two studies that mostly enrolled subjects on dialysis (Mahdavi, 2003; Pieper, 2006).

Table 26: Published efficacy and safety studies of sevelamer carbonate in pediatric patients

Study	Design	Sevelamer Dose	Study Population	N for Efficacy	Change in Phosphorus
Mahdavi 2003	6-month, single-arm, open-label period; single center	800 mg tid cc, titrated by 400 tid monthly to phos <6.5 mg/dL	17 patients: HD (3), PD (14); 2-11 yr (7), 12-19 yr (10)	12	-1.3 mg/dL (7.5 ± 2.2 to 6.2 ± 1.2 during first 8 weeks)
Pieper 2006	8-week, randomized, open-label crossover; 10 centers	Equal to dose administered before, titrated q2wk to phos <6.2 mg/dL for >2 yo	40 patients - 18 for efficacy analyses: HD (11), PD (6), or eGFR 20 to <60 (1)	18	-1.5 ± 1.6 mg/dL
Gulati 2010	12-week, randomized, open-label; single center	400 mg tid cc, titrated by 400 tid at 4 and 8 weeks to phos <5.5 mg/dL	11 sevelamer patients: CKD 3 (5) CKD 4 (6)	10	-0.2 mg/dL (6.2 mg/dL to 6.0 mg/dL)

Reported safety findings in these three studies included gastrointestinal adverse events (abdominal pain, nausea, vomiting, diarrhea, anorexia), changes in laboratory parameters (decreases in serum bicarbonate, cholesterol, calcium, and vitamin D levels; hypercalcemia), pruritis, muscle cramps, headache, and hyperparathyroidism.

Reviewer's comment: Interpretation of the efficacy findings in these studies is limited by their small size and exclusion of subjects from efficacy analyses. The safety findings are consistent with those previously reported.

Kim et.al. (2016) published a case report of a 17-year-old female on dialysis with a history of anoplasty and creation of a sigmoid conduit in infancy with a revision of the conduit 8 years prior to the reported event. Two months after starting sevelamer hydrochloride, she developed severe right lower quadrant abdominal pain, was found to have a stricture of the sigmoid colon, and underwent partial colectomy and colostomy. "Histopathologic examination showed colonic mucosal injury and characteristic "fish-scale"-like sevelamer hydrochloride crystals within the mucosa."

Reviewer's comment: The current sevelamer carbonate label includes a Warning and Precaution for serious cases of bowel obstruction and perforation.

References:

1. Gulati A, et.al. Short-term efficacy of sevelamer versus calcium acetate in patients with chronic kidney disease stage 3-4. International Urology and Nephrology, 2010. 42(4): p. 1055-1062.
2. KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney International, 2009. 76, Suppl 113: S1-130.
3. KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Children With Chronic Kidney Disease. American Journal of Kidney Diseases, 2005. 46(4), Suppl 1: S32-S38.
4. Kim J, et.al. Sevelamer crystals in the mucosa of the gastrointestinal tract in a teenager with end-stage renal disease. Pediatric Nephrology, 2016. 31(2): 339-341.
5. Mahdavi, et.al. Sevelamer hydrochloride: an effective phosphate binder in dialyzed children. Pediatric Nephrology, 2003. 18: 1260-1264.
6. Pieper A, Haffner D, Hoppe B, et al. A randomized crossover trial comparing sevelamer with calcium acetate in children with CKD. American Journal of Kidney Diseases, 2006. 47(4): 625-635.

9.2 Labeling Recommendations

- Study SVCARB07609 provides evidence of the safety and effectiveness of sevelamer carbonate in pediatric patients 13 years of age and older.
- For patients 6 to <13 years of age, efficacy may be extrapolated from data in older patients based on the mechanism of action of the drug.
- The safety and efficacy of sevelamer carbonate has not been established in pediatric patients below 6 years of age.

- The indication should be limited to patients with CKD on dialysis, consistent with the indication in adults.
- Section 14 of the label should describe the subgroup findings for patients with a lower baseline serum phosphorus, patients 6 to <13 years of age, and patients not on dialysis.

9.3 Advisory Committee Meeting

An advisory committee meeting was not held for this application.

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/s/

KIMBERLY A SMITH
10/31/2016

ALIZA M THOMPSON
10/31/2016