Office of Clinical Pharmacology
Integrated Review

NDA or BLA Number	22127/S-015 and 22318/S-008
Link to EDR	Application 022127 - Sequence 0091 - 0091 (550) 05/26/2016 SUPPL-15 (Efficacy) /Multiple Categories/Subcategories
Submission Date	26th May 2016
Submission Type	Efficacy Supplement
Brand Name	Renvela®
Generic Name	Sevelamer Carbonate
Dosage Form and Strength	0.8 g, 1.6 g Sevelamer Carbonate/ Tablet or Packet for suspension
Route of Administration	Oral
Proposed Indication	Control of serum phosphorus in pediatric patients (6 years of age and older (b) (4) with chronic kidney disease on dialysis
Applicant	Genzyme Corporation
Associated IND	None
OCP Review Team	Ju-Ping Lai, Ph.D., Sudharshan Hariharan, Ph.D.

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1. EXECUTIVE SUMMARY

Renvela® (sevelamer carbonate) is a phosphate binder indicated for the control of serum phosphorus in adult patients with chronic kidney disease on dialysis. Renvela Tablets (NDA 22-127) and Renvela Oral Suspension (NDA 22-318) were approved in October 2007 and August 2009, respectively. The present submission is an efficacy supplement submitted by Genzyme Corporation on May 26, 2016 to propose an update on the USPI of Renvela based on a newly completed pediatric study which also serves as a completion of a post-marketing requirement (PMR) study and was intended to fulfil the PMR.

The submitted study report is the first pediatric study which provides information on efficacy, safety and tolerability for the use of a phosphate binder in the pediatric population. If approved, the indication will be extended to pediatrics with specific dosing instructions along with safety/clinical experience for the use of sevelamer in pediatric populations.

The review primarily focuses on (i) appropriateness of starting dose and titration increments for pediatric patients scaled based on body surface area, (ii) treatment effect in pediatrics when compared to adults, and (iii) efficacy findings in certain subgroups.

1.1 Recommendations

The Office of Clinical Pharmacology, Division of Clinical Pharmacology I, has reviewed the information submitted. This NDA is considered approvable from a clinical pharmacology perspective provided an agreement is reached on the Agency's proposed labeling recommendations. Key review issues with specific recommendations and comments are summarized below:

Review Issues	Recommendations and Comments
Supportive evidence of effectiveness	Evidence of effectiveness in pediatrics is demonstrated by statistically significant reductions in serum phosphorous in the sevelamer group when compared to placebo in the fixed-dosing period. The treatment effect is similar between adults and pediatrics. Further, patients on placebo who switched to active treatment following the fixed-dosing period showed significant reductions in serum phosphorous.
General dosing instructions	The recommended starting dose is 0.8 g or 1.6 g taken orally with meals based on BSA category. Doses can be titrated by 0.4 g or 0.8 g based on BSA at 2-week intervals as needed to achieve target levels. Extrapolating adult dosing to pediatrics by scaling based on body size (e.g., body surface area as in this case) appears to be appropriate and is justified based on the efficacy results from this

	study.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Intrinsic and extrinsic factors are not expected to impact either the availability of sevelamer carbonate or its ability to bind phosphate in the gastrointestinal tract. No dosing instruction is needed for subgroups.
Labeling	Dosing for pediatric patients provided in section 2
Bridge between the "to-be-marketed" and clinical trial formulations	Both Renvela Tablets and Oral Suspension are approved products by FDA.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Sevelamer carbonate is a non-absorbable, insoluble, anion exchange resin. Hence, conventional absorption, distribution, metabolism and elimination (ADME) aspects do not apply.

Sevelamer carbonate was developed as a pharmaceutical alternative to sevelamer hydrochloride (Renagel®). Sevelamer carbonate is an anion exchange resin, with the same polymeric structure as sevelamer hydrochloride, in which carbonate replaces chloride as the counter-ion. While the counter-ions differ for the two salts, the polymer itself, the active moiety involved in phosphate binding, is the same[1].

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

For adult patients, the approved starting dose is 0.8 g or 1.6 g administered orally three times per day with meals based on baseline serum phosphorus levels. Titration is by increments of 0.8 g per meal in two week intervals as needed to obtain serum phosphorus target.

For pediatric patients with hyperphosphatemia, the proposed starting dose is 0.8 g or 1.6 g taken orally with meals based on BSA category. Dose can be titrated as needed to achieve target levels at two-week intervals by 0.4 g or 0.8 g based on BSA category (Table 1).

Table 1: Recommended starting dosage and titration increment based on pediatric patient's body surface area (m^2)

[1] USPI of Renvela

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

2.2.2 Therapeutic individualization

The general dosing instructions, along with the proposed strategy to titrate based on serum phosphorus levels address the need for therapeutic individualization.

2.3 Outstanding Issues

While the PMR issued was to study pediatric patients from birth to < 19 years old, no patients younger than 6 years of age were enrolled in the study. Due to lack of clinical experience in patients from birth to < 6 years old, the label will be restricted to use in pediatric patients older than 6 years of age.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology agrees with the proposed dosing by the applicant. The following labeling concepts will be included in the final package insert:

- Starting dose based on BSA category in pediatric patients 6 years and older.
- Dose to be titrated at ~ 2 week intervals based on serum phosphorus assessment as necessary with the goal of controlling serum phosphorus within the target range.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

The current submission is a pediatric study report under PMR upon approval of Renvela Tablets and Oral Suspension indicated for the control of serum phosphorus in patients with chronic kidney disease on dialysis. Key regulatory history related to this submission is provided in the table below:

Table 2: Regulatory history

Dates	Key regulatory history
10/19/2007	Approval of Renvela Tablets (NDA 22127) included PMR for a deferred pediatric study.
8/12/2009	Approval of Renvela Powder for oral suspension (NDA 22318) included PMR for a deferred pediatric study.

1/21/2016	Submission of a Clinical Study Report for Protocol SVCARB007609 intended to fulfill the PREA requirement.
5/18/2016	Submission of electronic copies of the trial's datasets in response to an informational request by the Agency.
5/26/2016	Submission of Prior Approval Labeling Supplement which includes proposed labeling for the pediatric population based on the PMR study.

In the adult program, the ability of sevelamer to control serum phosphorus in CKD patients on dialysis was predominantly determined from the effects of the hydrochloride salt to bind phosphate. As provided in the USPI of Renvela, sevelamer hydrochloride significantly decreased mean serum phosphorus by ~2.1 mg/dL in CKD patients on hemodialysis who were hyperphosphatemic (serum phosphorus > 5.5 mg/dL) based on one of the clinical trials (Table 3)[2].

Table 3: Mean serum phosphorus (mg/dL) at baseline and change from baseline to end of treatment

	Sevelamer HCl (N=94)	**Active Control (N=98)**
Phosphorus Baseline	7.5	7.3
Change from Baseline at Endpoint	-2.1	-1.8

3.2 General Pharmacological and Pharmacokinetic Characteristics

- Sevelamer carbonate is a polymeric amine that binds phosphate. It is a non-absorbable, insoluble, anion exchange resin. Hence, conventional pharmacokinetic evaluation does not apply.
- Mechanism of action: The USPI of Renvela states that the amines in sevelamer carbonate exist in a protonated form in the intestine and interact with phosphate molecules through ionic and hydrogen bonding. By binding phosphate in the gastrointestinal tract and decreasing absorption, sevelamer carbonate lowers the phosphate concentration in the serum (serum phosphorus).

[2] USPI of Renvela

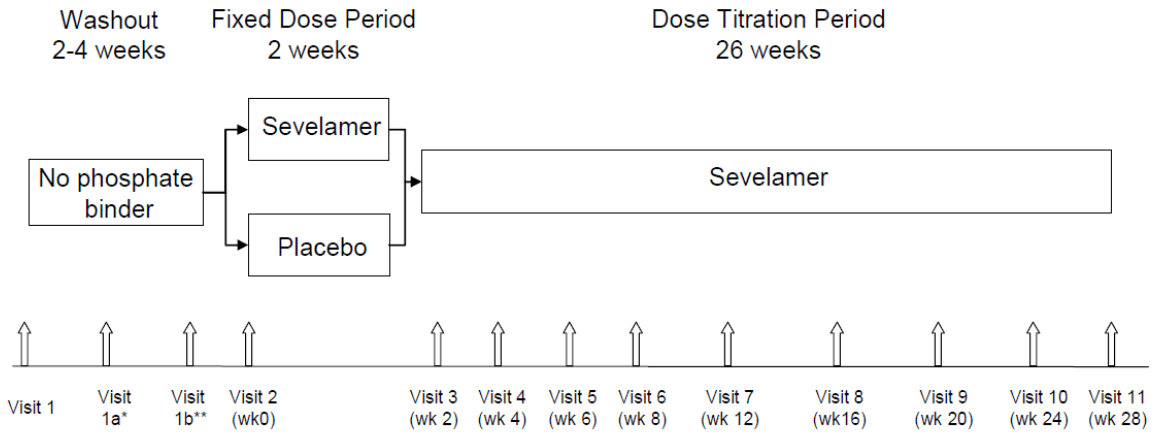
3.3 Clinical Pharmacology Questions

3.3.1 Does the clinical pharmacology information provide supportive evidence of effectiveness?

Yes. The data from study SVCARB007609 provides evidence of effectiveness of sevelamer carbonate in reducing serum phosphorus levels in pediatric patients 6 years of age and older with hyperphosphatemia.

Study SVCARB007609 is 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.

Figure 1: Study Design



Source: Study report SVCARB007609-DRI12793, Figure 1, page 16

The study consists of a washout period for 2-4 weeks followed by randomization to sevelamer or placebo receiving fixed doses for 2 weeks and subsequently 26 week dose titration period for all patients. The primary endpoint is change from Week 0 to Week 2 in serum phosphorus and the secondary endpoint is change from Week 0 to Week 28 in serum phosphorus.

The serum phosphorus levels measured over time is shown in Figure 2 below. Results of the primary and secondary endpoints are provided in Tables 4 and 5 below.

Figure 2: Mean serum phosphorus (mg/dL) measured over the course of the study

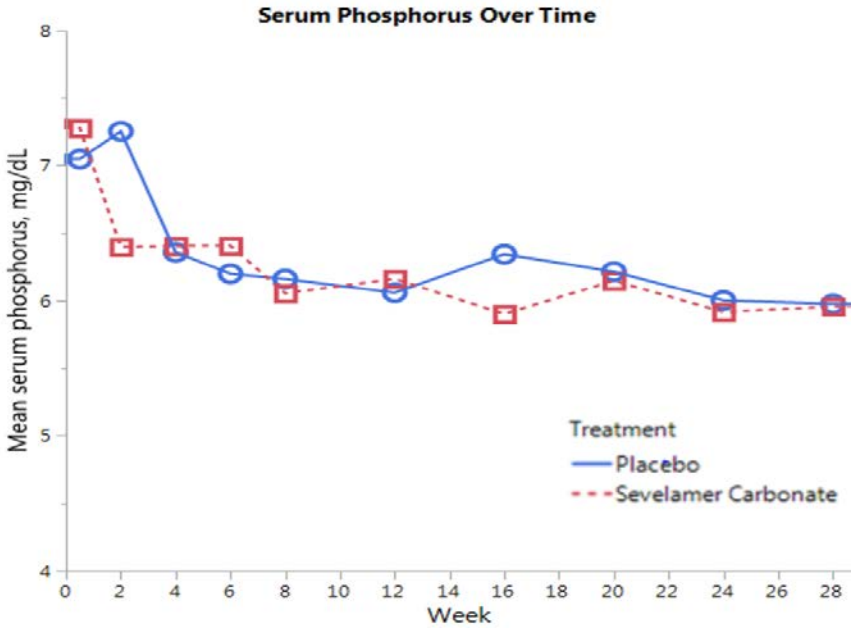


Table 4: Primary Endpoint Analyses: Change in serum phosphorus from baseline to Week 2

Time point	**Change from baseline serum phosphate (mg/dL) (Mean ± SD)**		**LS Mean Difference (Mean ± SE)**
	Placebo (N=49)	**Sevelamer (N=48)**	
Baseline	7.20±1.84	7.20±2.09	**-0.90 ± 0.270 (p=0.001)**
Week 2	0.04±1.478	-0.87±1.649	

Table 5: Secondary Endpoint Analyses: Change in serum phosphorus from baseline to Week 28/ET

Time point	**Change from baseline serum phosphate (mg/dL) (Mean ± SD)**	**LS Mean Difference (Mean ± SD)**
	Sevelamer (N=95)	
Baseline	7.16±1.94	**-1.18 ± 2.12 (p<0.0001)**
Week 28/ET	5.98±1.74	

Both primary and secondary endpoints showed statistical significant effect in reducing serum phosphorus levels.

Subgroup results:

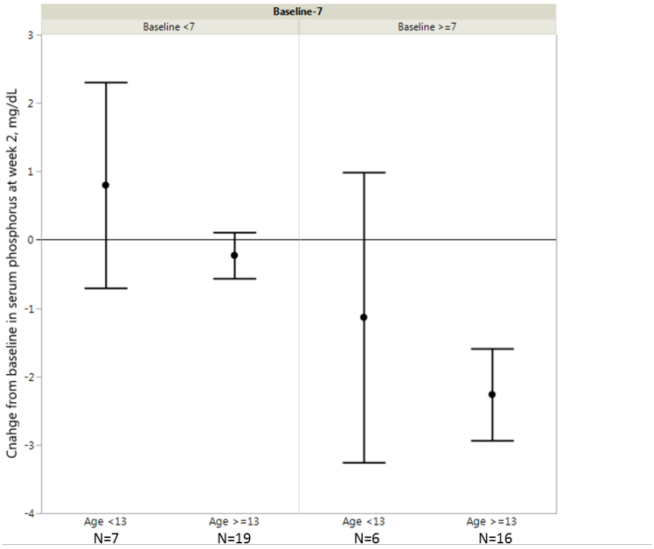
Efficacy results by subgroups, age (6-13/>13 y), baseline phosphorous (<7/≥7 mg/dL) and dialysis status (yes/no) are shown in Table 6. When grouped by these categories there seemed to be no treatment effect in younger pediatric patients (6-13 y), patients with lower baseline serum phosphorous (<7 mg/dL) and patients not undergoing dialysis. The dialysis subgroup results are not discussed further in the review. Since the adult clinical experience is primarily in CKD patients undergoing dialysis which is also the labeled population, the pediatric indication, if approved, is expected to be restricted to dialysis patients only. Moreover, patients on dialysis represented 77% of the study population and the subgroup finding in non-dialysis group is confounded by low baseline values.

Table 6: Treatment effect of sevelamer by subgroups: baseline serum phosphorus, age and dialysis status. Data shown are at week 2 (end of fixed-dose period).

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	0.30 (0.29)	0.06 (0.32)	0.24 (0.44) (-0.63, 1.10)
	≥7	9.07 (1.47) n=22	8.53 (1.36) n=26	-1.72 (0.33)	-0.14 (0.29)	-1.58 (0.42) (-2.42, -0.75)
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)

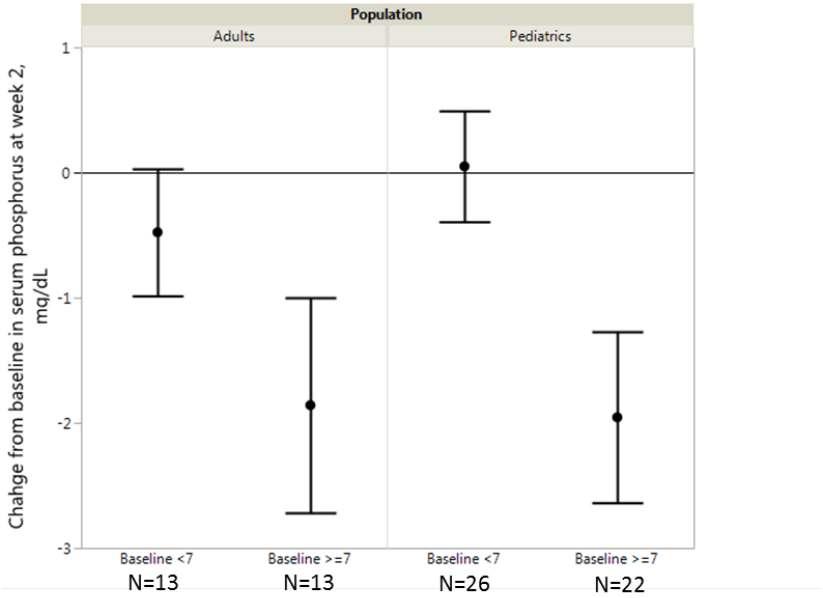
The subgroup results observed in younger patients (6-13 y) and low baseline serum phosphorous (<7 mg/dL) should be interpreted with caution due to low sample size as they are not powered to detect a statistically significant change. Nevertheless, when treatment effect for sevelamer is further sub-divided by the categories of age and baseline serum phosphorous, the baseline effect seems to be a predominant driver of the results than age (Figure 3). In the lower baseline group, no treatment effect is seen regardless of age whereas in the higher baseline group, both age groups show a trend for treatment effect with larger effect observed in older group. This is also supported by the fact that 26% (7/27) of the patients had baseline serum phosphorous values in the normal range in the younger subgroup (6-13 y) when compared to 4% (3/74) of the patients within the normal range in the higher age group (>13 y).

Figure 3: Treatment effect by subgroups: baseline P (≥7) and age (≥13). Data represented as mean ± 95% CI.



Interestingly, baseline serum phosphorous also affected the treatment effect of sevelamer in adults (Figure 4). The treatment effect in adults is lower in patients with baseline serum phosphorous <7 mg/dL when compared to patients with baseline serum phosphorous >7 mg/dL. This observation is also consistent for other binders where baseline is a significant predictor of treatment effect (please refer to clinical pharmacology review for NDA 205739 Patiromer dated on 7/23/2015). These observations suggest that the baseline effect is not a new finding for the pediatric program. Moreover, the baseline effect might not be of significant concern as patients with low baseline values may not need a large treatment effect to reach their treatment goal.

Figure 4: Comparison of baseline effect between pediatrics and adults after fixed dose for 2 weeks. Data represented as mean ± 95% CI.



Treatment compliance was evaluated in an attempt to see if it could explain any of the subgroup findings. Compliance was calculated by the following formula:

Treatment Compliance (%) = 100 x (Total Number of Tablets/Sachets Taken)/(Total Number of Tablets/Sachets Prescribed).

However, the proportion of non-compliant patients is similar between the groups as shown in Tables 7 and 8.

Table 7: Numbers and proportion of patients with < 70% compliance by baseline phosphorus

	High baseline	Low baseline
Non-compliant (<70%)	12/22 (55%)	12/26 (46%)

Table 8: Numbers and proportion of patients with < 70% compliance by age

	≥ 13y	< 13 y
Non-compliant (<70%)	17/35 (49%)	7/13 (54%)

3.3.2 Is the proposed general dosing regimen appropriate?

Yes. The proposed starting dose and titration scheme based on BSA category (table below) is appropriate.

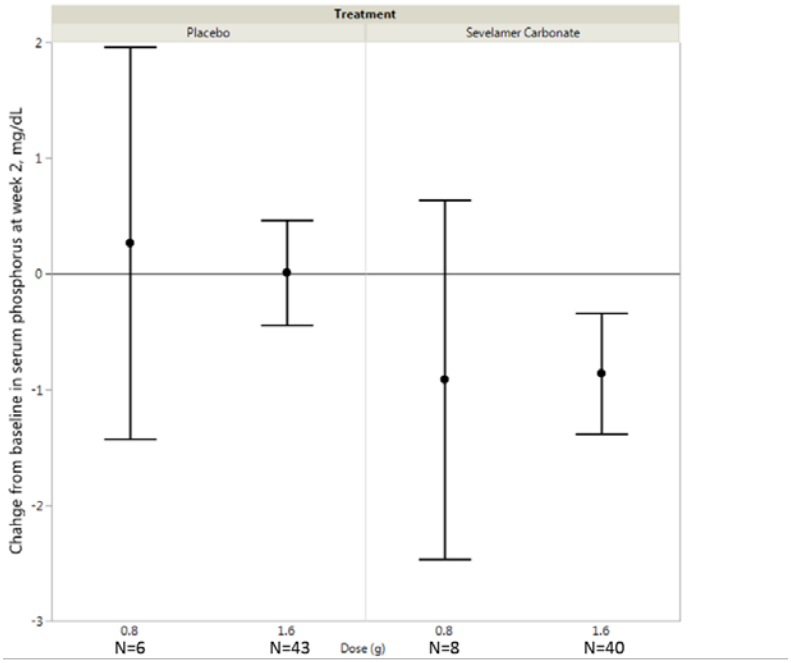
BSA (m^2)	Starting dose per meal/snack	Titration increases/decreases per dose
≥0.75 to <1.2	0.8 g	Titrate by 0.4 g
≥1.2	1.6 g	Titrate by 0.8 g

For dietary binders that are not systemically absorbed and which acts locally in the GI tract, extrapolation of efficacy from adults to pediatrics by scaling the adult doses based on an index of body size (e.g., body surface area or body weight) seems a reasonable approach. The current study utilized BSA based scaling for deriving doses. To evaluate the appropriateness of the starting dose and titration scheme, a comparison of the drug effect between pediatrics and adults was conducted.

Starting dose:

The treatment effect is evaluated by the change of serum phosphorus from baseline to the end of fixed dose period. As seen from Figure 5, both doses 0.8 g and 1.6 g resulted in similar reductions in change from baseline serum phosphorous when compared to placebo, further justifying that scaling the adult dose based on BSA is a viable approach.

Figure 5: Similar effect size in pediatrics received 0.8 or1.6 g. Data represented as mean ± 95% CI.

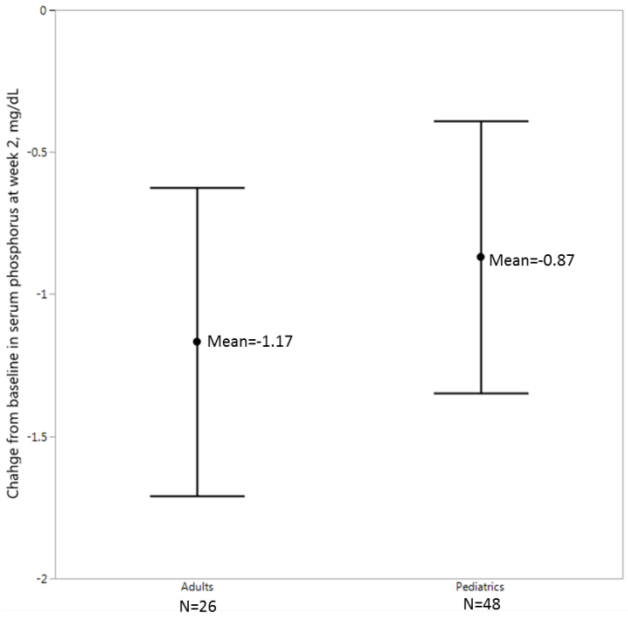


Moreover, the effect sizes are similar between pediatrics (-0.87 mg/dL) and adults[3] (-1.17 mg/dL) (Figure 6) following administration of fixed doses of sevelamer for 2 weeks. The doses used in adults were 1.6 g sevelamer three times daily with meals while the doses used in the

[3] Data comes from a Phase 2 dose ranging study with fixed dose of sevelamer in NDA 205109

pediatrics were based on BSA as described previously. This comparison supports the starting dose in the pediatric study which provides a similar treatment effect to that seen in adults.

Figure 6: Comparison of treatment effect between pediatrics and adults following administration of fixed dose for 2 weeks. Data represented as mean ± 95% CI.



Titration increment:

The titration increment steps evaluated in the study was 0.8 g or 0.4 g TID based on BSA. However, it is noted that the treatment effect is smaller in pediatric patients at the end of titration period when compared to adults (Table 9). When looking at how the doses were titrated during the titration phase in the pediatric study, it was found that ~68 % of the patients had at least two incidents where the dose was not titrated when the serum phosphorus level was outside of the normal range >0.3 mg/dL. Based on this information, it is possible that the small effect size observed at the end of titration period might be because that the titration was not carried out aggressively as per protocol specification possibly due to an added tolerability concern in pediatric patients. Since there is no dose-response information available in the pediatric program to justify the evaluated titration increments, it is only reasonable to assume that titration increment steps can also be scaled based on BSA from adult doses as was the approach for the starting dose which seemed appropriate.

Table 9: Comparison of effect size between pediatrics and adults at the end of treatment

	Change from baseline serum phosphate (mg/dL)	
	Pediatrics (N=95)	Adults (N=94)
Baseline	7.2	7.5
End of treatment	-1.2	-2.1

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

Intrinsic and extrinsic factors are not expected to impact either the availability of sevelamer carbonate or its ability to bind phosphate in the gastrointestinal tract.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Sevelamer carbonate is not expected to have systemic absorption. As a locally acting drug in the gastrointestinal tract, sevelamer has the potential to interact with other co-administered medications in GI. However, this drug-drug interaction (DDI) liability had been addressed in the adult program previously. Furthermore, it is not expected that pediatric patients would exhibit different drug interaction risk than adults.

Mixing with food other than water

Sevelamer carbonate is to be taken with meals to serve as a dietary phosphate binder. In the pediatric clinical study, sevelamer was administered by mixing with water. However, there is a possibility for sevelamer to be administered with dairy products such as milk, cheese and yogurt to the pediatric patients. At the time of this review, Office of Pharmaceutical Quality (OPQ) is evaluating the appropriateness and possible impact of mixing sevelamer carbonate powder with food other than water.

From clinical pharmacology perspective, it is noted that milk and dairy products contain high amount of phosphorus, for example, ~247 mg/cup skim milk, ~356 mg/cup skim plain yogurt.[4] The recommended phosphorus intake for patients at stages 3 and 4 of CKD is ~800-1000 mg per day[5] (~276-333 mg per meal). Sevelamer, as we know, will bind to dietary phosphorous if mixed with milk or other dairy products. This may not be a problem if milk or dairy products are part of the regular meal to supplement for daily intake of phosphorous. However, if dairy products are administered (only for purposes of mixing) in addition to regular dietary phosphorous intake in a meal, then there might be a potential impact of this clinical practice on efficacy.

3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

The products sevelamer carbonate tablets and powder for suspension are approved as Renvela by the FDA and are commercially available.

[4] United States Department of Agriculture, Agricultural Research Service, USDA Food Composition Databases
[5] KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease

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11/01/2016

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