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Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Overall the efficacy of sevelamer is demonstrated in pediatric patients with chronic kidney disease (CKD). However, the data suggest that sevelamer had no (or small) effect in the patients with baseline serum phosphorus <7 mg/dL, which is quite in contrast with the effect in the patients with baseline serum phosphorus ≥ 7 mg/dL (p value for the treatment by stratum interaction is very small). The lack of treatment effect in this patient subgroup cannot be explained by outliers and the interpretation for the result is complicated by the inclusion of subjects with normal phosphorus levels at baseline in the study. Thus the efficacy in the patients with baseline serum phosphorus <7 mg/dL seems inconclusive and this finding may be worthy warning in the labeling.

1.2 Brief Overview of Clinical Studies

This sNDA includes a deferral of pediatric study granted as a postmarketing commitment when Renvela was approved on October 19, 2007. The study (SVCARB007609 (DRI12793)) is entitled “ 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 (CKD)”. A labeling revision for pediatrics is proposed.

1.3 Statistical Issues and Findings

Overall the efficacy of sevelamer appears to be demonstrated in pediatric patients with CKD. A sensitivity analysis of primary endpoint, using a dichotomized baseline serum phosphorus (<7 vs. ≥ 7 mg/dL) as a covariate, suggests that the treatment effect is different across baseline serum phosphorus strata (p=0.0007 for the interaction of treatment by baseline phosphorus) and there is no treatment effect shown in the patients with baseline serum phosphorus <7 mg/dL (0.12 (-0.81, 1.05), difference and 95% CI on LS mean change from baseline). Baseline serum phosphorus is a stratification factor used in the randomization and the data seem to confirm that the treatment effect is different across strata. The lack of efficacy in the stratum of baseline serum phosphorus <7 mg/dL cannot be explained by outliers-- patients received dialysis and had elevated serum phosphorus levels at screening, low-normal values at baseline, and elevated values at the end of the fixed dose period, explained by the sponsor. The interpretation for the results is complicated by the inclusion of subjects (9%, 9/97) with normal phosphorus levels at baseline in the study. Thus the efficacy in the patients with baseline serum phosphorus <7 mg/dL seems inconclusive.

2. INTRODUCTION

2.1 Overview

In chronic kidney disease the homeostatic system for maintaining physiological phosphorus balance is altered by the progressive loss of functioning nephrons. Failure to control hyperphosphatemia may be associated with debilitating sequelae and increased mortality. Studies in children with CKD have also demonstrated an association between hyperphosphatemia and CKD-associated vasculopathy and impairment of linear growth. A major component of hyperphosphatemia

management is the use of phosphate binders to decrease the intestinal absorption of dietary phosphorus.

No phosphate binders have been approved for use in children. Sevelamer hydrochloride is approved for patients on dialysis, but studies in pediatric CKD patients suggest that sevelamer hydrochloride may not be optimal for use in pediatric patients who are vulnerable to acid-base imbalance. Sevelamer carbonate (Renvela®) was developed as a pharmaceutical alternative to sevelamer hydrochloride (Renagel®), it has equivalent phosphate binding properties to sevelamer hydrochloride and no adverse impact on acid-base balance.

This clinical study was to evaluate the safety and efficacy of sevelamer carbonate in pediatric CKD patients.

2.2 Data Sources

The sponsor's SAS datasets were stored in the directories of the Center's electronic document room: <\\CDSESUB1\evsprod\NDA022127\0088> and <\\CDSESUB1\evsprod\NDA022318\0071>.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

A consistent result of the primary efficacy analysis can be generated from both raw and derived data.

3.2 Evaluation of Efficacy

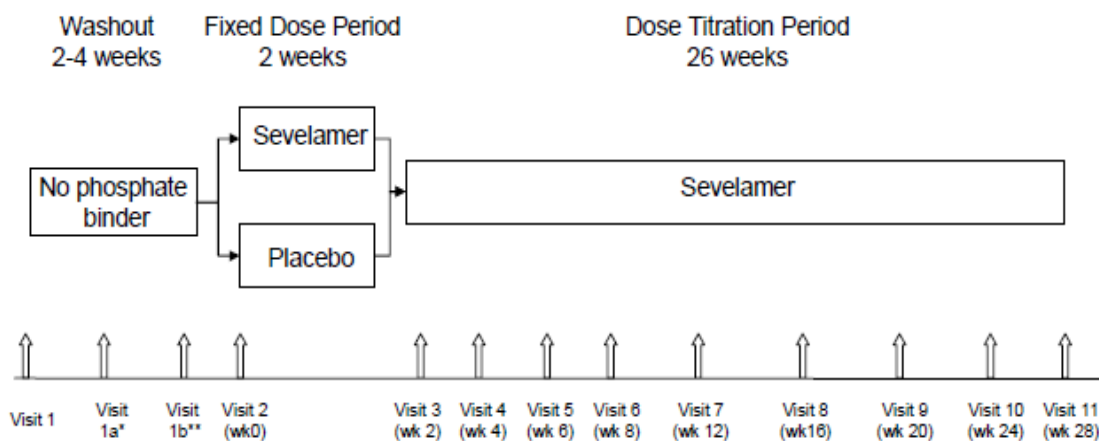
3.2.1 Primary Study Objective

The primary objective of this study was to evaluate the efficacy of sevelamer carbonate on the control of serum phosphorus and to evaluate the safety and tolerability of sevelamer carbonate in hyperphosphatemic pediatric patients with CKD.

3.2.2 Study Design

This was a phase 2, multicenter study with a 2-week, randomized, placebo-controlled, fixed dose period followed by a 6-month, single-arm, open-label, dose titration period with sevelamer carbonate in hyperphosphatemic pediatric patients with CKD. The study consisted of 3 periods of washout, fixed dose period (FDP) and dose titration period (DTP) as shown in Figure 1:

Figure 1 Overview of 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

Eligible patients taking a phosphate binder at screening were to enter the Washout Period, in which the phosphate binder was to be discontinued for 2 to 4 weeks depending on the serum phosphorus levels. Once the patient's blood serum phosphorus level was greater than the age-appropriate upper limit of normal (ULN), patients who met all other eligibility criteria proceeded to the FDP. Patients, not taking phosphate binder at screening, with a serum phosphorus greater than their age-appropriate ULN and satisfying all eligibility criteria, were to directly proceed to the FDP.

At visit 2, patients meeting all entry criteria, were randomized in a 1:1 ratio, stratified by screening body surface area (BSA) (<1.2 versus ≥ 1.2 m²) and qualifying serum phosphorus (<7.0 versus ≥ 7.0 mg/dL), to receive either blinded sevelamer carbonate or placebo during the 2-week FDP. Following the FDP, patients were to proceed to the open-label DTP during which all patients were to receive sevelamer carbonate for additional 26 weeks.

3.2.3 Efficacy Measures and Analyses

- 1) Primary Efficacy Endpoint: Change from baseline (Visit 2 (Week 0)) to Visit 3 (Week 2) in serum phosphorus.
- 2) Secondary Efficacy Endpoint: Change from baseline (Visit 2 (Week 0)) to Visit 11/ET (Week 28/ET) in serum phosphorus.
- 3) Statistical Analysis Methodology

- Sample size determination: 100 evaluable patients (50 per group) will provide 80% power to detect a difference of 0.75 mg/dL (0.24 mmol/L) in mean change from Baseline to Week 2 between treatment groups with a standard deviation of 1.32 mg/dL (0.43 mmol/L) for the

change from Baseline, using analysis of covariance (ANCOVA) modeling, two-sided 5% type I error.

- Analysis of primary efficacy endpoint: The primary endpoint was analyzed by an analysis of covariance (ANCOVA) with baseline phosphorus and screening BSA as covariates and a fixed effect of treatment in the full analysis set – fixed dose period. Significance of treatment difference was to be declared if the p-value was ≤ 0.05 . If data for the primary time point (Week 2) was missing, the last non-missing post-baseline observation taken prior to Visit 3 (Week 2) was used instead.
- Analyses of secondary efficacy endpoint: The secondary endpoint was summarized descriptively by treatment group and overall. If a patient randomized to placebo dropped out prior to entering the DTP, that patient did not contribute to the end of treatment summary since the intent of that summary was to characterize the change from baseline in serum phosphorus for patients on sevelamer carbonate. Therefore, Visit 11/ET (Week 28/ET) represented the last on-treatment value for a patient randomized to sevelamer carbonate and the last on-treatment value after Visit 3 for a patient randomized to placebo. Wilcoxon signed rank tests were used to assess the changes within a treatment group.

If data for Visit 11 (Week 28) was missing, the last non-missing post-baseline observation taken prior to Visit 11 (Week 28) was used instead. For patients randomized to placebo who discontinued prior to entering the DTP, a missing value was not to be imputed.

- Subgroup analysis: Change from baseline to Visit 3 (Week 2) in serum phosphorus was summarized by treatment group for screening BSA (<1.2 versus $\geq 1.2 m^2$) and baseline serum phosphorus (<7.0 versus ≥ 7.0 mg/dL [<2.26 versus ≥ 2.26 mmol/L]) subgroups. No significance testing between treatment groups was performed within these subgroups.
- Sensitivity analysis: All efficacy analyses conducted on the PPS-FDP served as the sensitivity analyses.
- Handling of dropouts or missing data:
The primary efficacy endpoint will be evaluated at Visit 3 (Week 2). If data for that time point is missing, the last non-missing post-baseline observation taken prior to Visit 3 (Week 2) will be used.

The secondary efficacy endpoint will be evaluated at Visit 11/ET (Week 28/ET). If data for Visit 11(Week 28) is missing, the last non-missing post-baseline observation taken prior to Visit 11 (Week 28) will be used. For patients randomized to placebo who discontinue prior to entering the Dose Titration Period, a missing value will not be imputed since the intent of that summary is to characterize the change from baseline in serum phosphorus for patients on sevelamer carbonate.

Baseline is defined as the Visit 2 (Week 0) measurement taken prior to study drug start. If data for that time point is missing, the latest off-treatment value (Visit 1 for patients not

taking a phosphate binder at Screening or Visit 1a/1b for patients taking a phosphate binder at Screening) will be used.

3.2.4 Patient Disposition, Demographic and Baseline Characteristics

1) Patient Disposition and Study Completion/Withdrawal Information

A total of 128 patients enrolled at 29 study centers (23 sites in USA and 6 in Europe) were screened, and 101 patients were randomized to sevelamer carbonate (n=50) and placebo (n=51). A total of 100 patients were treated (received at least one dose of study medication).

A total of 66 patients (65.3%, 66/101) completed the study (FDP and DTP): 31 patients (62.0%, 31/50) in the “sevelamer carbonate group” (patients who were on sevelamer carbonate in the FDP) and 35 patients (68.6%, 35/51) in the “placebo group” (patients who were on placebo in the FDP).

Overall, 34 treated patients (33.7%, 34/101) discontinued from the entire study: 18 patients (36.0%, 18/50) in the sevelamer carbonate group and 16 patients (31.4%, 16/51) in the placebo group. The main reason for discontinuation in both groups was kidney transplant (16 patients (15.8%, 16/101), 8 patients in each group)). (Table 1)

Table 1 Patient Disposition, All Randomized Analysis Set

	Placebo (N = 51) n (%)	Sevelamer Carbonate (N = 50) n (%)	Total (N = 101) n (%)
Randomized	51 (100.0)	50 (100.0)	101 (100.0)
Treated	51 (100.0)	49 (98.0)	100 (99.0)
Discontinued Prior to Being Treated	0	1 (2.0)	1 (1.0)
Physician Decision**	0	1 (2.0)	1 (1.0)
Discontinued After Being Treated	16 (31.4)	18 (36.0)	34 (33.7)
Adverse Event	1 (2.0)	3 (6.0)	4 (4.0)
Lost to Follow-up	0	0	0
Pregnancy	0	0	0
Study Terminated by Sponsor	0	0	0
Death	0	0	0
Withdrawal by Subject	2 (3.9)	4 (8.0)	6 (5.9)
Physician Decision	5 (9.8)	3 (6.0)	8 (7.9)
Other*	8 (15.7)	8 (16.0)	16 (15.8)
<i>Kidney transplant</i>	<i>8 (15.7)</i>	<i>8 (16.0)</i>	<i>16 (15.8)</i>
Completed	35 (68.6)	31 (62.0)	66 (65.3)

Note: The denominator for percentages is the number of randomized patients in each treatment group.

Note: Treated refers to a patient taking at least one dose of study drug.

Note: *Mainly Kidney transplant.

(Source: Sponsor’s Table 6, confirmed by the reviewer’s analysis)

***Reviewer's Comments:** *Missing data seems to be extensive (33.7%, 34/101). The main reason for discontinuation in both groups was kidney transplant (16 patients (15.8%, 16/101). However kidney transplant for most patients seemed to occur in the later time of the study—DTP and patients stayed in study longer (the shortest time was Week 8). Only one patients received kidney transplants in the FDP and had serum phosphorus measurement at Week 2 (primary efficacy time point), no value was imputed for the primary efficacy analysis.*

The next leading reason for discontinuation was physician decision (7.9%, 8/101), mainly because of non-compliance. Again all these drop-outs occurred in the later time of the study_DTP (the earliest was Week 12), no value was imputed for the primary efficacy analysis.

2) Patient Demographic and Baseline Characteristics

The demographic and baseline characteristics were similar in both treatment arms. Most subjects (63.0%) were males. The mean age was 14.1 years (13.9 years in the sevelamer carbonate group and 14.3 years in the placebo group). The planned enrollment goal-- $\geq 20\%$ enrolled subjects were <13 years old, was achieved: 26.0% were <13 years old and 74.0% were adolescents (13-18 years). Near half of the patients (54%) were Whites and 35.0% were Blacks.

No patient had a BSA <0.75 . Most patients (86%) had a BSA ≥ 1.2 , and less patients (14%) had a BSA ≥ 0.75 to <1.2 .

Half of the patients (n=50, 50.0%) had a qualifying serum phosphorus level <7.0 mg/dL (26 patients (53.1%) in the sevelamer group and 24 patients (47.1%) in the placebo group), and half (n=50, 50.0%) had ≥ 7.0 mg/dL (23 patients (46.9%) in the sevelamer carbonate group and (27 patients (52.9%) in the placebo group) (Table 2).

Table 2 Patient Demographic and Baseline Characteristics

	Placebo (N = 51)	Sevelamer Carbonate (N = 49)	Total (N = 100)
Age (years)			
N	51	49	100
Mean (SD)	14.3 (3.11)	13.9 (2.75)	14.1 (2.93)
Median	15.0	14.0	15.0
Age Categories (years), n (%)			
N	51	49	100
0-12	13 (25.5)	13 (26.5)	26 (26.0)
13-18	38 (74.5)	36 (73.5)	74 (74.0)

Sex, n (%)			
N	51	49	100
Male	33 (64.7)	30 (61.2)	63 (63.0)
Female	18 (35.3)	19 (38.8)	37 (37.0)
Race, n (%)			
N	51	49	100
American Indian or Alaska Native	0	1 (2.0)	1 (1.0)
Asian	1 (2.0)	1 (2.0)	2 (2.0)
Black	19 (37.3)	16 (32.7)	35 (35.0)
Native Hawaiian or Other Pacific Islander	0	0	0
White	27 (52.9)	27 (55.1)	54 (54.0)
Multiple	0	0	0
Not Reported	0	2 (4.1)	2 (2.0)
Unknown	4 (7.8)	2 (4.1)	6 (6.0)
Ethnicity, n (%)			
N	51	49	100
Hispanic or Latino	9 (17.6)	11 (22.4)	20 (20.0)
Not Hispanic or Latino	41 (80.4)	38 (77.6)	79 (79.0)
Not Reported	0	0	0
Unknown	1 (2.0)	0	1 (1.0)
Screening BSA (m ²)			
N	51	49	100
Mean (SD)	1.56 (0.394)	1.47 (0.299)	1.52 (0.352)
Median	1.50	1.50	1.50
Screening BSA Categories (m ²), n (%)			
N	51	49	100
< 0.75	0	0	0
>=0.75 - <1.2	6 (11.8)	8 (16.3)	14 (14.0)
>=1.2	45 (88.2)	41 (83.7)	86 (86.0)
Qualifying Serum Phosphorus (mg/dL)			
N	51	49	100
Mean (SD)	7.15 (1.920)	7.22 (2.073)	7.19 (1.987)
Median	7.10	6.70	6.90
Qualifying Serum Phosphorus Level (mg/dL), n (%)			
N	51	49	100
< 7.0	24 (47.1)	26 (53.1)	50 (50.0)
>=7.0	27 (52.9)	23 (46.9)	50 (50.0)

(Source: The sponsor's Table 8, confirmed by the reviewer's analysis)

3.2.5 Sponsor's Primary Efficacy Results

1. Primary efficacy endpoint analysis:

Sevelamer reduces serum phosphorus. The Mean change from baseline to Week 2 (Visit 3) in serum phosphorus is -0.87 for the sevelamer group and 0.04 for the placebo group, and the mean difference of -0.90 between the two groups is statistically significant (p=0.001) (Table 3).

Table 3 Serum Phosphorus (mg/dL) Change from Baseline to Week 2, Full Analysis Set, FDP

Mean Baseline (SD)		LS Mean Change from Baseline (SD)*		Difference on LS Mean Change from Baseline (SD) P-value (95% CI)
Sevelamer	Placebo	Sevelamer	Placebo	
N=48	N=49			
7.20 (2.09)	7.20 (1.84)	-0.87(1.65)	0.04 (1.48)	-0.90 (0.27) 0.001 (-1.44, -0.37)

*Adjust for baseline phosphorus and body surface area
(Source: Sponsor's Table 14, confirmed by the reviewer's analysis)

2. Subgroup Analysis:

The subgroup analysis of primary endpoint by screening BSA (< 1.2 vs. $\geq 1.2 m^2$) and mean qualifying baseline serum phosphorus (< 7 vs. ≥ 7 mg/dL) were summarized descriptively, but no formal statistical test was conducted. The results were consistent with the primary efficacy analysis, trending numerically in favor of sevelamer, except for the subgroup with qualifying baseline serum phosphorus < 7.0 mg/dL (Table 4).

Table 4 Subgroup Analyses by BSA & Baseline Phosphorus

		Mean Baseline (SD)		Mean Change from Baseline (SD)*	
		Sevelamer	Placebo	Sevelamer	Placebo
Body Surface Area (m^2)	< 1.2 (n=14)	7.49 (1.57)	7.42 (2.95)	-0.91 (1.86)	0.27 (1.62)
	≥ 1.2 (n=83)	7.15 (2.19)	7.17 (1.68)	-0.86 (1.63)	0.01 (1.48)
Baseline Phosphorus (mg/dL)	< 7 (n=49)	5.63 (0.91)	5.69 (0.89)	0.05 (1.20)	0.18 (1.51)
	≥ 7 (n=48)	9.07 (1.47)	8.53 (1.36)	-1.95 (1.54)	-0.08 (1.47)

*A sign of "-" indicates a reduction in serum phosphorus
(Source: CSR 10.1.2.1, confirmed by the reviewer's analysis)

3.2.6 Sponsor's Secondary Efficacy Results

1. Secondary efficacy endpoint analysis:

The mean differences in serum phosphorus between baseline and Week 28 (Visit 11) were statistically significant for both groups combined (-1.18 (SD 2.122) mg/dL ($p < 0.0001$)) and

individually (-1.23 (SD 2.206) mg/dL (p=0.0010)) in the sevelamer carbonate group and -1.13 (SD 2.06) mg/dL (p=0.0001) in the placebo group (Table 5).

Table 5 Serum Phosphorus (mg/dL) Change from Baseline to Week 28, Full Analysis Set-DTP

Statistics	Sevelamer N=46	Placebo N=49	Combined N=95
Mean Baseline (SD)	7.28 (2.10)	7.05 (1.80)	7.16 (1.94)
Mean at Week 28 (SD)	6.04 (1.88)	5.92 (1.61)	5.98 (1.74)
Mean Change from Baseline (SD)	-1.23 (2.21)	-1.13 (2.06)	-1.18 (2.12)
P-value (Wilcoxon Signed Rank)	0.001	0.0001	<0.0001

(Source: Sponsor's Table 18, confirmed by the reviewer's analysis)

**Reviewer comment: There was no pre-specified plan to control the overall type I error for the secondary endpoint analysis.*

3.2.7 Reviewer's Results

1. Sensitivity Efficacy analysis:

- 1) A sensitivity analysis of primary endpoint, using a dichotomized baseline serum phosphorus (<7 vs. ≥7 mg/dL, a stratification factor used in randomization) as a covariate, suggests that that the treatment effect is different across baseline serum phosphorus strata (p=0.0007 for the interaction of treatment by baseline phosphorus) and the efficacy does not seem to be established in the patients with baseline serum phosphorus <7 mg/dL (0.12 (-0.81, 1.05) for LS mean difference and 95% CI) (Table 6).

Table 6 Sensitivity Analysis of Primary Endpoint, FDP

Baseline phosphorus (mg/dL)	Mean Baseline		LS Mean Change from Baseline*		Difference on LS Mean Change from Baseline (SD) (95% CI)
	Sevelamer (SD)	Placebo (SD)	Sevelamer (SD)	Placebo (SD)	
<7 (n=49)	5.63 (0.91)	5.69 (0.89)	0.33 (0.35)	0.21 (0.33)	0.12 (0.44) (-0.81, 1.05)
≥7	9.07 (1.47)	8.53 (1.36)	-1.92 (0.38)	0.26 (0.34)	-2.17 (0.46)

(n=48)					(-3.09, -1.26)
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*Adjust for baseline serum phosphorus, body surface area
(Source: The reviewer's analysis)

- 2) For the finding of lack of efficacy in the patients with baseline serum phosphorus <7 mg/dL, (b) (4) a small treatment effect found in the sevelamer group (median change -0.10 mg/dL) in the patients with qualifying (baseline) serum phosphorus <7.0 mg/dL suggests the presence of outliers. In particular, the two patients (SVCARB07609/8013-0002 and SVCARB07609/8019-0001) with the lowest serum phosphorus levels at baseline had the largest increases in serum phosphorus at the end of the FDP. (b) (4) this reviewer conducted a sensitivity analysis excluding those two patients. However, the significance of the result is unchanged (Table 7).

Table 7 Sensitivity Analysis of Primary Endpoint, Excluding Outlier, FDP

Baseline phosphorus (mg/dL)	Mean Baseline		LS Mean Change from Baseline*		Difference on LS Mean Change from Baseline (SD) (95% CI)
	Sevelamer (SD)	Placebo (SD)	Sevelamer (SD)	Placebo (SD)	
<7 (n=47)	5.79 (0.67)	5.69 (0.91)	0.10 (0.34)	0.20 (0.31)	0.10 (0.45) (-0.80, 1.00)
≥7 (n=48)	9.07 (1.47)	8.53 (1.36)	-1.86 (0.36)	0.29 (0.32)	-2.16 (0.46) (-3.03, -1.07)

*Adjust for baseline serum phosphorus, body surface area
(Source: The reviewer's analysis)

- 3) It noted that some patients (9%, 9/97) had normal serum phosphorus (≤5.8 mg/dL (ULN)) for age 6 to 13 years old, and ≤4.5 mg/dL (ULN) for age 13 to 18 years old) at baseline. All nine patients (14%) were in the subgroup of baseline serum phosphorus <7 mg/dL and 64% (7/11) of them were at the young age group of 6-13 years old (Table 8). An analysis excluding those patients was conducted and the result remains the same (Table 9).

Table 8 Distribution of Patients by Baseline Phosphorus, Age and Upper Limit of Normal (ULN)

Baseline Phosphorus (mg/dL)	Age (Year)	Phosphorus ULN	# of Patients
<7	=>6 to <13 (n=11)	≤5.8 mg/dL (ULN)	7*
		>5.8 mg/dL (ULN)	4
	=>13 to 18 (n=38)	≤4.5 mg/dL (ULN)	2*
		>4.5 mg/dL (ULN)	36

≥7	=>6 to <13 (n=15)	=<5.8 mg/dL (ULN)	0
		>5.8 mg/dL (ULN)	15
	=>13 to 18 (n=33)	=<4.5 mg/dL (ULN)	0
		>4.5 mg/dL (ULN)	33

(Source: The reviewer's analysis)

Table 9 Sensitivity Analysis of Primary Endpoint, Excluding Patients with Normal Baseline Phosphorus, FDP

Baseline phosphorus (mg/dL)	Mean Baseline		LS Mean Change from Baseline*		Difference on LS Mean Change from Baseline (SD) (95% CI)
	Sevelamer (SD)	Placebo (SD)	Sevelamer (SD)	Placebo (SD)	
<7 (n=42)	6.0 (0.57)	5.89 (0.76)	0.18 (0.38)	0.25 (0.36)	-0.10 (0.48) (-1.03, 0.89)
≥7 (n=46)	9.07 (1.47)	8.53 (1.36)	-1.87 (0.36)	0.40 (0.33)	-2.27 (0.46) (-3.18, -1.35)

*Adjust for baseline serum phosphorus, body surface area
(Source: The reviewer's analysis)

3.2.8 Conclusions

Overall the efficacy of sevelamer carbonate seems to be demonstrated in pediatric CKD patients. However, the sensitivity analyses of primary endpoint suggest that the treatment effect is not shown in the patients with baseline serum phosphorus <7 mg/dL. The lack of efficacy in this subgroup cannot be explained by outliers. The further investigation is limited due to a small number of patients in the subgroup.

3.3 Evaluation of Safety

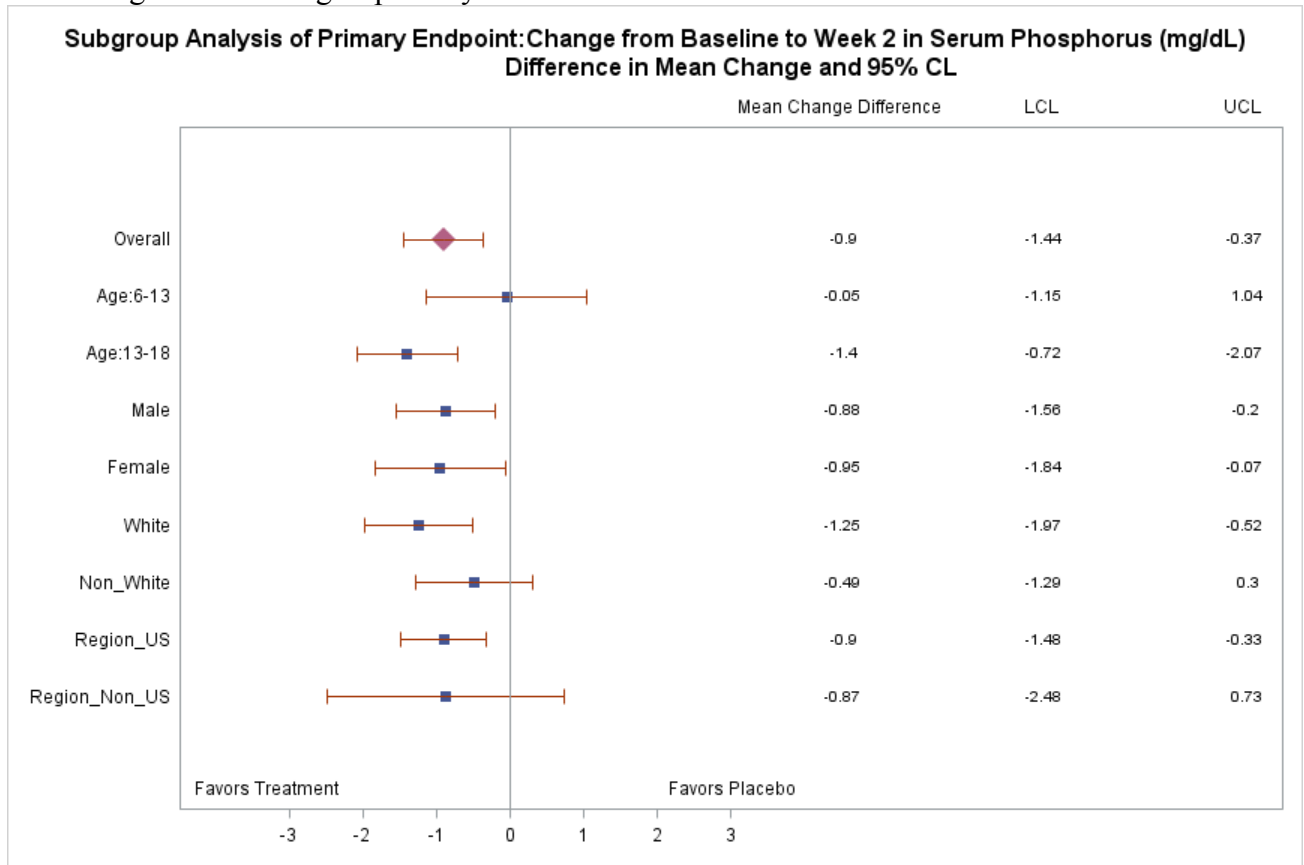
Please refer to Dr. Smith's review for safety assessment.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Exploratory subgroup analyses of primary endpoint were performed on age, gender, race and geographic region. Most patients were 13-18 years old (73%), males (63%), whites (54%) and recruited in the U.S (89%). The numerical results generally trended in favor of sevelamer except in the small subgroup of younger patients who were 6-13 years old (27%) (Figure 2).

Figure 2 Subgroup Analysis 1

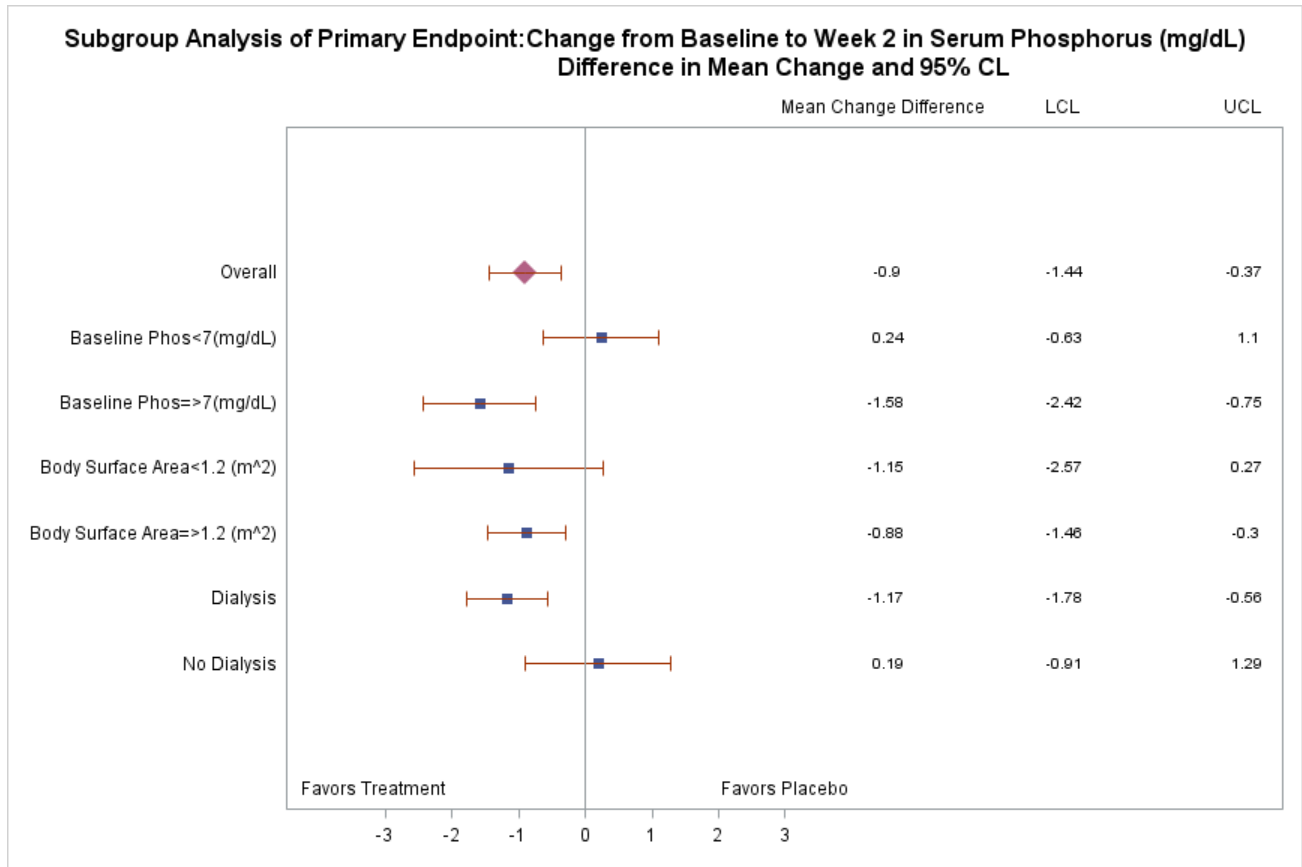


(Source: The reviewer’s analysis)

4.2 Other Special/Subgroup Populations

Exploratory subgroup analyses of primary endpoint were performed on dialysis status, baseline serum phosphorus and body surface area. The numerical results trended in favor of sevelamer, except in the subgroups of patients with serum baseline phosphorus < 7 mg/dL and patients who had no dialysis (Figure 3).

Figure 3 Subgroup Analysis 2



(Source: The reviewer’s analysis)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Overall the efficacy of sevelamer appears to be demonstrated in pediatric patients with CKD. A sensitivity analysis of primary endpoint, using a dichotomized baseline serum phosphorus (<7 vs. ≥7 mg/dL) as a covariate, suggests that the treatment effect is different across baseline serum phosphorus strata (p=0.0007 for the interaction of treatment by baseline phosphorus) and there is no treatment effect shown in the patients with baseline serum phosphorus <7 mg/dL (0.12 (-0.81, 1.05), difference and 95% CI on LS mean change from baseline). Baseline serum phosphorus is a stratification factor used in the randomization and the data seem to confirm that the treatment effect is different across strata. The lack of efficacy in the stratum of baseline serum phosphorus <7 mg/dL cannot be explained by outliers and the interpretation for the result is complicated by the inclusion of subjects (9%, 9/97) with normal phosphorus levels at baseline in the study. Thus the efficacy in the patients with baseline serum phosphorus <7 mg/dL seems inconclusive.

5.2 Conclusions and Recommendations

Overall the efficacy of sevelamer is demonstrated in pediatric patients with CKD. However, the data suggest that sevelamer had no (or small) effect in the patients with baseline serum phosphorus <7 mg/dL, which is quite in contrast with the effect in the patients with baseline serum phosphorus \geq 7 mg/dL (p value for the treatment by stratum interaction is very small). The lack of treatment effect in this patient subgroup cannot be explained by outliers and the interpretation for the result is complicated by the inclusion of subjects with normal phosphorus levels at baseline in the study. Thus the efficacy in the patients with baseline serum phosphorus <7 mg/dL seems inconclusive and this finding may be worthy warning in the labeling.

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/s/

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