1 April 2016
EMA/271022/2016
Procedure Management and Committees Support Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Renvela

sevelamer

Procedure no: EMEA/H/C/000993/P46/023

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Introduction 3
1.1. Steps taken for the assessment 5
2. Assessment of the post-authorisation measure PAM EMEA/H/C/993/P46 023 5
3. Rapporteur's overall conclusion 12

1. Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:

The application concerns the clinical study named ***"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" or SVCARB07609 / DRI12793***.

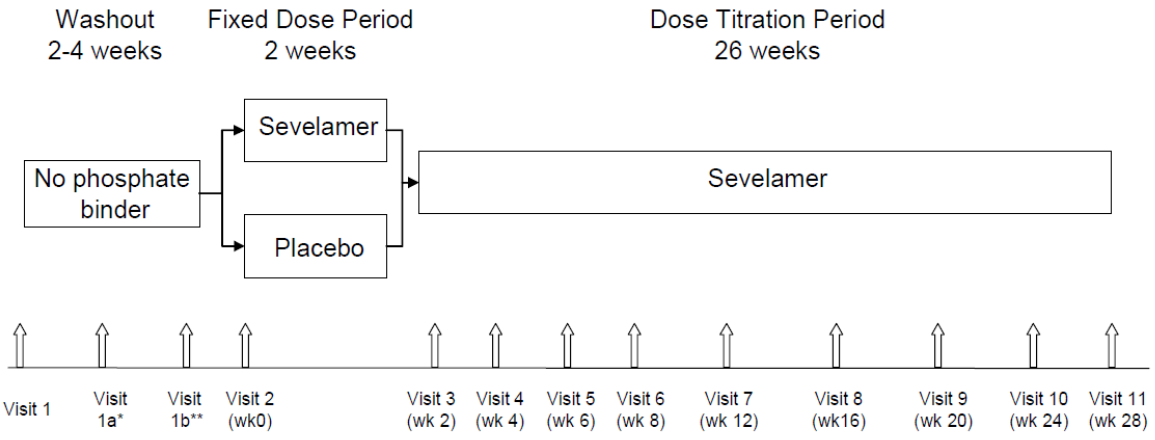
This was a phase 2, multicenter study, conducted in 23 sites in the US and 6 in Europe (EU) under the EudraCT n° 2011-002329-23. The EU participating countries were France, Germany, Lithuania and Poland. It started on May 11th, 2012 and was completed on June 16th, 2015. This trial was conducted with Renvela® in the context of the Pediatric Research Equity Act (PREA) in the USA and was not part of a Pediatric Investigational Plan (PIP) in the EU.

The results of this paediatric study are submitted pursuant to article 46 as a stand-alone' submission. A variation (e.g. category C.1.4 or C.1.6) to update the Renvela Product Information with the pediatric information will be submitted at a later stage.

This was a multicenter Phase 2 study with a 2-week, randomized (in a 1:1 ratio), placebo-controlled, fixed dose period followed by a 6-Month, single-arm, open-label, dose titration period. The study was divided into 3 periods: a 2 to 4-week phosphate binder Washout Period, a 2-week randomized, double-blind, placebo-controlled, fixed dose period and a 26-week open-label, sevelamer carbonate dose titration period.

The Objectives were to evaluate in hyperphosphatemic pediatric patients with chronic kidney disease (CKD) the safety and tolerability of sevelamer carbonate and the efficacy of sevelamer carbonate on the control of serum phosphorus.

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

Criteria for inclusion:

1. The patient has CKD requiring dialysis or CKD not on dialysis with an estimated GFR <60 mL/min/1.73 m2 based on central laboratory results and

2. The patient has a serum phosphorus level greater than the age appropriate upper limit of normal based on central laboratory results (according to the guidelines from the National Kidney foundation Am J Kidney Dis 2009):

- Patients taking phosphate binder(s) at screening: at or between Visit 1a and Visit 1b,

- Patients not taking phosphate binder(s) at screening: at Visit 1.

Sevelamer carbonate (during the Fixed Dose period (FDP) and the Dose titration period (DTP)) was used orally three times per day (TID) with meals and/or snacks. as a:

• Powder for oral suspension supplied as 0.8 g sachets.

• Tablets supplied as 800 mg tablets

For patients with a screening BSA <1.2 m2: 0.8 g (800 mg) sachets of powder for oral suspension.

For patients with a screening BSA ≥1.2 m2: 0.8 g (800 mg) sachets of powder for oral suspension or 0.8 g (800 mg) tablets depending on patient preference:

-FDP: either the tablet or powder formulation depending on patient preference, however the formulation dispensed at the beginning of the FDP had to be maintained throughout the FDP,

-DTP: either the tablet or powder formulation, however a mixture of tablets and powder was not allowed at the same time. The formulation dispensed at each study visit was to be maintained until the next study visit. The formulation might be changed at a subsequent study visit.

Placebo - only during the FDP**:** Matching placebo was provided as 0.8 g (800 mg) powder for oral suspension or, as an alternative for patients with a screening BSA ≥1.2 m2, 0.8 g (800 mg) tablets.

No placebo was administered during the DTP.

During the FDP, the dose of blinded sevelamer carbonate or placebo was based on the patient's screening BSA category (<0.75, ≥0.75 to <1.2, ≥1.2 m2).

Table 2 - Fixed dose period dosing

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

*If a child eats less than 3 meals/snacks per day, sevelamer carbonate or placebo should only be given with meals/snacks and not on an empty stomach. For example, if the patient's screening BSA is ≥0.75 to <1.2 m^2 and eats 2 meals/snacks per day that patient will take 0.8 g BID with meals.

The DTP was open-labelled: all patients received sevelamer carbonate. The starting dose of sevelamer carbonate during the DTP was to be the same as the IMP dose prescribed during the FDP. However, if the patient's serum phosphorus at Visit 3/Week 2 (end of the FDP) was below the age-defined lower limit of normal, the sevelamer carbonate dose was to be decreased or temporarily interrupted.

The dose of sevelamer carbonate might be increased or decreased every 2 weeks for 6 weeks and then every 4 weeks, as necessary, to achieve a serum phosphorus level within the age appropriate normal values based on central laboratory results or, until, based on the Investigator's opinion, the administered dose was the maximum that the patient could practically take or tolerate with meals. Dose titration increases or decreases were to be based on screening BSA category.

Criteria for evaluation:

Primary efficacy endpoint: Change from baseline (Visit 2 [Week 0]) to Visit 3 (Week 2) in serum phosphorus

Secondary efficacy endpoint: Change from baseline (Visit 2 [Week 0]) to Visit 11/ET (Week 28/ET) in serum phosphorus

Safety was evaluated on the basis of Adverse Events (AEs) and changes from Baseline in laboratory parameters and vital signs.

All AEs were classified as either Pre-Treatment AEs (PTAEs) or Treatment-Emergent AEs (TEAEs) as follows:

- PTAEs are events which start prior to the date of first dose of study drug.

- TEAEs are events with start dates on or after the date of first dose of study drug.

1.1. Steps taken for the assessment

Submission date:	20/01/2016
Start of procedure:	02/02/2016
CHMP Rapporteur's preliminary assessment report circulated on:	07/03/2016
CHMP Rapporteur's updated assessment report circulated on:	23/03/2016
CHMP opinion:	01/04/2016

2. Assessment of the post-authorisation measure PAM EMEA/H/C/993/P46 023

Population characteristics:

A total of 101 patients were randomized in the trial: 50 patients to receive sevelamer carbonate and 51 patients to receive placebo. One patient, randomized to sevelamer carbonate, did not take any dose of the study medication (patient not treated) and was discontinued from the study by the Investigator (physician's decision), due to noncompliance, and was not included in the safety set. This patient is considered as discontinued prior to being treated.

• Safety set included 100 patients (99.0%): 49 patients (98%) in sevelamer carbonate and 51 (100%) in placebo.

• FAS-FDP included 97 patients (96.0%): 48 patients (96%) on sevelamer carbonate and 49 patients (96.1%) on placebo.

• The PPS-FDP included 47 patients (46.5%): 24 patients (48.0%) on sevelamer carbonate and 23 patients (45.1%) on placebo. Fifty patients (49.5%) were excluded from the PPS-FDP - of the 50 excluded patients, 48 patients (24 on sevelamer carbonate and 24 on placebo) were excluded due to compliance with study treatment less than 70%.

The Full Analysis Set-DTP included 95 patients (94.1%): 46 patients (92.0%) were on sevelamer carbonate in the FDP ("sevelamer carbonate group") and 49 patients (96.1%) were on placebo in the FDP ("placebo group").

A total of 66 patients (65.3%) completed the study (FDP and DTP): 31 patients (62.0%) in the "sevelamer carbonate group" (patients who were on sevelamer carbonate in the FDP) and 35 patients (68.6%) in the "placebo group" (patients who were on placebo in the FDP).

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

Four patients (4.0%) discontinued due to an AE: 3 patients on the sevelamer carbonate (1 patient in the FDP and 2 patients in the DTP [both in the sevelamer carbonate group]) and 1 patient on placebo (who discontinued in the FDP).

The mean age was 14.1 (SD 2.93) years, 74% were adolescents (13 -18 years).

Overall, in the safety set, there were 63 males (63.0%) and 37 females (37.0%).

The mean screening BSA (m2) was 1.52 (SD 0.352) (BSA ≥1.2 in 86 patients [86.0%]; BSA ≥0.75 to <1.2 in 14 patients [14.0%]; no patients had BSA <0.75.

The mean qualifying serum phosphorus (mg/dL) was 7.19 (SD 1.987): (7.22 [SD 2.073] in the in the sevelamer carbonate group and 7.15 [SD 1.920] mg/dL in the placebo group).

The most common primary cause of CKD overall and in both groups was glomerulopathy (29 patients (29.0%): 17 patients [34.7%] in sevelamer carbonate group and 12 patients [23.5%] in the placebo group).

Overall, 77 patients [77.0%] were on dialysis: 35 patients [71.4%] in the sevelamer carbonate group and 42 patients [82.4%] in the placebo group and the mean duration of dialysis treatment was 1.59 (SD 2.178) years. In total, 54 patients [70.1%] were on hemodialysis (22 patients [62.9%] in the sevelamer carbonate group and 32 patients [76.2%] in the placebo group).

A total of 81 patients (81.0%) were taking phosphate binder at the screening visit: (42 patients [85.7%] in the sevelamer carbonate group and 39 patients [76.5%] in the placebo group. In total, 53 patients [65.4%] were taking sevelamer-based binder (similar across the groups) and 36 patients [44.4%] were taking a calcium-based binder (20 patients [47.6%] in sevelamer carbonate and 16 patients [41.0%] in placebo).

Overall, 72 patients [72.0%] were using vitamin D therapy upon entry to the study (36 patients in each group).

A total of 20 patients (20.0%) had a history of renal transplant (8 patients [16.3%] in the sevelamer carbonate group and 12 patients [23.5%] in the placebo group.

Median duration of exposure was the same for both groups in the FDP (15 days) and the DTP (183.5 days in the sevelamer carbonate group and 183 days the placebo group).

Mean drug compliance in the FDP was slightly higher in patients on sevelamer carbonate (71%) compared with patients on placebo (68%) while in the DTP, it was higher in the placebo group (77%) compared with the sevelamer carbonate group (71%). In the FDP, the median prescribed daily dose was 4.8 g for both groups and the mean prescribed daily dose was similar as well (4.41 [SD 0.896] g) in sevelamer carbonate compared with 4.31 [SD 1.096] g in placebo). In the DTP, the median and the mean prescribed daily dose were higher in the sevelamer carbonate group compared with the placebo group (median: 7.01 g versus 6.42 g and mean: 7.09 [SD 2.312] g versus 6.54 [SD 2.306] g for sevelamer carbonate and placebo, respectively).

FAS-FDP and FAS-DTP were consistent with the safety set.

CHMP comment: The included population is small and mostly adolescent and in hemodialysis. Therefore, a discontinuation of the study population of 33.7% is high. Although, 15.8% who discontinued were transplanted during the study period, 4% of the patients discontinued because of adverse events.

Efficacy results:

Primary efficacy endpoint:

Sevelamer carbonate significantly reduced serum phosphorus through Week 2 by an LS Mean difference of -0.90 (SD 0.270) mg/dL compared to placebo (p=0.001). Mean change from Baseline to Week 2 was -0.87 (SD 1.649) mg/dL in sevelamer carbonate and 0.04 (SD 1.478) mg/dL in placebo.

The confirmatory analysis conducted on the PPS-FDP supported the FAS-FDP result (LS Mean difference of -1.15 (SD 0.407) mg/dL in sevelamer carbonate compared to placebo [p=0.007]). Mean change from Baseline to Week 2 was -0.90 (SD 1.714) mg/dL in sevelamer carbonate and 0.25 (SD 1.654) mg/dL in placebo. The PPS-FDP population was 49% of the FAS-FDP population for each treatment group.

Results of subgroup analysis in FAS-FDP and PPS-FDP were consistent with results of primary efficacy analysis except for the subgroup with mean qualifying serum phosphorus <7.0 mg/dL, where a slight increase in mean serum phosphorus was observed at Week 2 in sevelamer carbonate (mean change from baseline: 0.05 [SD 1.097] mg/dL in FAS-FDP and 0.03 [SD 1.250] mg/dL in PPS-FDP). With respect to the subgroup with mean qualifying (baseline) serum phosphorus <7.0 mg/dL, an efficacy trend based on median change (-0.10 mg/dL in FAS-FDP, -0.25 mg/dL in PPS-FDP) suggested the presence of outliers. Indeed, the two patients with the lowest serum phosphorus levels at baseline (both values were in the low-normal range, relationship to dialysis confirmed in one patient) showed the largest increases in serum phosphorus at the end of the FDP.

Secondary efficacy endpoint:

Sevelamer carbonate significantly reduced serum phosphorus through Week 28/ET: the mean change from baseline to Week 28/ET was -1.18 (SD 2.122) mg/dL (p<0.0001).

Additional analysis:

Analysis of serum phosphorus levels over time clearly showed a decrease in serum phosphorus level during treatment with sevelamer carbonate. The most pronounced decrease in mean phosphorus level from baseline was achieved at the end of the first two weeks of active treatment. Results of analysis in

FAS-FDP showed that the mean change from baseline was -0.87 (SD 1.649) mg/dL at Week 2 in patients on sevelamer carbonate in the FDP and -0.77 (SD 1.592) mg/dL at Week 4 in patients on placebo in the FDP. At the end of treatment the mean change from baseline was -0.94 (SD 2.116) mg/dL at Week 28 and -1.17 (SD 2.184) mg/dL at Week 28/ET in patients who were on sevelamer carbonate in the FDP and -1.12 (SD 1.840) mg/dL at Week 28 and -1.19 (SD 1.981) mg/dL at Week 28/ET in patients who were on placebo in the FDP.

Changes observed in serum phosphorus measured over time in FAS-DTP were consistent with that observed in FAS-FDP.

The analysis in PPS-FDP also clearly showed a decrease in serum phosphorus level during treatment with sevelamer carbonate with the most pronounced decrease achieved at the end of the first two weeks of active treatment (mean change from baseline of -0.90 (SD 1.714) mg/dL at Week 2 in patients on sevelamer carbonated in the FDP and of -1.18 (SD 1.589) mg/dL at Week 4 in patients on placebo in the FDP. However, to the end of treatment, the mean phosphorus level slightly increased in patients on sevelamer carbonate in the FDP (mean change from baseline of -0.42 [SD 2.292] mg/dL at Week 28 and -0.85 [SD 2.410] mg/dL at the last study visit [Week 28/ET]). Similarly, in patients on placebo in the FDP, the mean phosphorus level slightly increased at Week 28 (mean change from baseline of -0.75 [SD 1.775] mg/dL) while at the last study visit [Week 28/ET] this increase was not observed (mean change from baseline of -1.23 [SD 2.205] mg/dL).

Sensitivity analysis:

All efficacy analyses conducted on the PPS-FDP served as the sensitivity analyses.

Ad hoc analysis:

An ad hoc analysis in the FAS-FDP showed that at Week 2, 4 patients in each group (8.3% in sevelamer carbonate and 8.2% in placebo) achieved a serum phosphorus level within their age-appropriate normal ranges. A similar result (2 patients [8.3%] in sevelamer carbonate and 2 patients [8.7%] in placebo) was observed in the PPS-FDP. At the last study visit (Week 28/ET), overall 26 patients (27.4%) had a serum phosphorus level within their age-appropriate normal ranges. A similar percentage (28.4% [19 patients]) was observed at Week 28.

CHMP's comment: The most pronounced decrease in mean phosphorus level from baseline was achieved at the end of the first two weeks of active treatment. Therefore the study met its primary endpoint. However, to the end of treatment, the mean phosphorus level slightly increased in patients on sevelamer carbonate and in patients on placebo in the FDP. Although the long term efficacy is not convincing and needs further investigation, the study met its secondary efficacy endpoint.

Safety results:

PTAEs:

A total of 65 PTAEs occurred in 36 patients (36.0%): 20 patients (20%) experienced PTAEs reported with mild severity, 13 patients (13.0%) experienced PTAEs of moderate severity and 3 patients (3.0%) of severe severity.

PTAEs were most frequently reported for the MedDRA SOC of Gastrointestinal disorders (11 events in 8 patients [8.0%]) and Infections and infestations (10 events in 9 patients [9.0%]). The most frequent PTAE was vomiting (4 events in 4 patients [4.0%]) followed by nausea and upper respiratory tract

infection (3 events in 3 patients [3.0%] for each term) and hypertension (3 events in 2 patients [2.0%]). In total there were 5 pre-treatment SAEs in 4 patients (4.0%) reported with the following PTs: abdominal pain, peritonitis, shunt occlusion, renal impairment, and hypertension.

TEAEs:

FDP: A total of 70 TEAEs occurred in 39 patients (39.0%): 34 in 19 patients (38.8%) on sevelamer carbonate and 36 in 20 patients (39.2%) on placebo. Most of these TEAEs were mild in severity (47 events in 30 patients (30.0%): 24 in 15 patients on sevelamer carbonate and 23 in 15 patients on placebo). Four TEAEs in 2 patients (2.0%) were reported with severe severity (1 event in patient on sevelamer carbonate and 3 events in 1 patient on placebo). TEAEs in sevelamer carbonate were most frequently reported for the MedDRA SOC of Injury, poisoning and procedural complications (5 events in 5 patients [10.2%] versus 2 events in 2 patients [3.9%] on placebo) while in placebo for the MedDRA SOC of Gastrointestinal disorders (11 events in 7 patients [13.7%] versus 4 events in 4 patients [8.2%] on sevelamer carbonate). Other common MedDRA SOCs in sevelamer carbonate were: Gastrointestinal disorders and Nervous system disorders (4 events in 4 patients [8.2%] in each SOC), Musculoskeletal and connective tissue disorders and Vascular disorders (4 events in 3 patients [6.1%] in each of the last 2 SOCs). The most frequent TEAE in sevelamer carbonate was hypertension (3 events in 2 patients [4.1%] versus 0 in placebo). The most frequent TEAE in placebo was vomiting (4 events in 3 patients [5.9%] versus 0 in sevelamer carbonate).

Four TEAEs in 2 patients (4.1%) on sevelamer carbonate reported as related or possibly related to study drug included: hyperphosphataemia, abdominal pain, ocular hyperaemia, and muscle spasms.

DTP: Overall 525 TEAEs occurred in 77 patients (77.0%): 253 in 35 patients (71.4%) in the sevelamer carbonate group and 272 in 42 patients (82.4%) in the placebo group.

313 events in 69 patients (69.0%) were mild in severity and 43 events in 20 patients (20.0%) were severe. TEAEs were most frequently reported for the MedDRA SOC of Gastrointestinal disorders (112 events in 42 patients [42.0%]).

Other common MedDRA SOCs were: General disorders and administration site conditions (76 events in 33 patients [33.0%]), Infections and infestations (71 events in 42 patients [42.0%]) and Nervous system disorders (37 events in 27 patients [27.0%]).

The most frequent TEAEs were: vomiting (29 events in 20 patients [20.0%]), abdominal pain and nausea (21 events in 15 patients [15.0%] for each term), pyrexia (25 events in 19 patients [19.0%]), headache (19 events in 17 patients [17.0%]), hypotension (14 events in 9 patients [9.0%]), abdominal pain upper (13 events in 9 patients [9.0%]), upper respiratory tract infection (12 events in 12 patients [12.0%]), and diarrhoea (11 events in 9 patients [9.0%]) and hypertension (11 events in 7 patients [7.0%]). Most of the 22 TEAEs in 13 patients [13.0%] reported as related or possibly related occurred in the MedDRA SOC of Gastrointestinal disorders (15 events in 8 patients [8.0%]) with nausea (5 events), constipation (3 events), vomiting and abdominal pain upper (2 events for each term) reported most frequently.

SAE:

FDP: 6 SAEs occurred in 5 patients (5.0%): a higher number of SAEs was reported in sevelamer carbonate (5 SAEs in 4 patients [8.2%]) compared with placebo (1 SAE in 1 patient [2.0%]). 5 SAEs occurring in sevelamer carbonate included: hypertension (2 events), device occlusion, peritonitis, and hyperkalaemia.

DTP: Overall 79 SAEs occurred in 31 patients (31.0%): 44 events in 17 patients in the sevelamer carbonate group and 35 events in 14 patients in the placebo group. 38 events in 18 patients (18.0%) were reported with severe severity. SAEs were most frequently reported for the MedDRA SOC of Infections and infestations (19 events in 12 patients [12.0%]).

Other common MedDRA SOCs were: General disorders and administration site conditions (13 events in 8 patients [8.0%]), Gastrointestinal disorders (8 events in 7 patients [7.0%]), Injury, poisoning and procedural complications (7 events in 4 patients [4.0%]) and Metabolism and nutrition disorders and Vascular disorders (6 events in 5 patients [5.0%] for each term).The most frequent (3 and 4 events) SAEs included: abdominal pain (3 events in 3 patients [3.0%]), device malfunction (3 events in 2 patients [2.0%]), renal impairment (4 events in 1 patient [1.0%]) and pyrexia (4 events in 3 patients [3.0%]). Four SAEs were reported as related or possibly related to study drug [constipation (2 events), gastritis and post procedural constipation].

Death: there were no deaths in the study.

CHMP comment: Adverse events are similar in all groups.

AE leading to discontinuation:

FDP: 2 events: 1 in patient on sevelamer carbonate (hyperphosphatemia) and 1 in patient on placebo (blood phosphorus increased).

DTP: 3 events including 2 reported as SAE: septic shock, varicella zoster virus infection, and chronic kidney disease.

CHMP comment: no comments

Laboratory:

Mean serum calcium and calcium (adjusted for albumin) remained essentially unchanged with sevelamer carbonate at Week 2 but increased by 0.15 mg/dL and 0.11 mg/dL respectively at Week 28 and 0.16 mg/dL and 0.11 mg/dL respectively at Week 28/ET.

Mean serum calcium x phosphorus product decreased with sevelamer carbonate by -8.63 mg2/dL2 at Week 2. At Week 28 and at Week 28/ET the mean change from baseline was -9.60 mg2/dL2 and -10.94 mg2/dL2, respectively.

Median serum iPTH increased with sevelamer carbonate to the end of treatment (mean change from baseline of 52.40 pg/mL at Week 28 and of 51.10 pg/mL at Week 28/ ET).

Mean total cholesterol decreased with sevelamer carbonate by -18.0 mg/dL at Week 2. The Mean change from baseline to the end of treatment was -24.8 mg/dL (at Week 28) and -20.8 mg/dL (at Week 28/ET). LDL-cholesterol decreased with sevelamer carbonate by 19.9 mg/dL at Week 2. Mean change from baseline to the end of treatment was -22.9 mg/dL (at Week 28) and -20.4 mg/dL (at Week 28/ET). Mean serum HDL-cholesterol remained essentially unchanged with sevelamer carbonate during this study. The non-meaningful changes were observed in triglycerides with sevelamer carbonate. The decreases in serum lipids in this study are consistent with the reductions in the serum lipids found in studies of adult patients with sevelamer carbonate and sevelamer hydrochloride.

A small, non-clinically meaningful increase (0.57 mEq/L) in mean serum bicarbonate was observed with sevelamer carbonate at Week 2 and to the end of treatment (mean change from baseline of 0.55 mEq/L at Week 28 and of 0.39 mEq/L at the last study visit [Week 28/ET]). A small, non-clinically meaningful decrease (-0.2 mEq/L) in mean serum chloride was observed with sevelamer carbonate at Week 2 and to the end of treatment (mean change from baseline of -1.1 mEq/L at Week 28 and of -1.0 mEq/L at Week 28/ET). The laboratory results did not show changes consistent with metabolic acidosis.

No clinically meaningful changes were observed in the measured glucose, creatinine, BUN, albumin, bilirubin, ALT, AST, and ALP overtime from baseline to the last study visit.

Overall, small but clinically non meaningful changes were reported in the measured serum hematology parameters.

The mean Vitamin A level was decreased with sevelamer carbonate by -61.4 ng/mL at Week 28 and -27.2 ng/mL at Week 28/ET.

The mean Vitamin E level was decreased with sevelamer carbonate by -0.45 µg/mL at Week 28 and -0.37 µg/mL at Week 28/ET.

A small non-clinically meaningful increase was observed in mean 25-Hydroxyvitamin D level with sevelamer carbonate at Week 28 (mean change from baseline of 0.68 ng/mL) and essentially no change at Week 28/ET (mean change from baseline of -0.03 ng/mL).

Mean 1, 25-Dihydroxyvitamin D level was decreased with sevelamer carbonate (mean change from baseline of -6.36 pg/mL at Week 28 and -3.64 pg/mL at Week 28/ET). 72.0% of patients were using vitamin D therapy upon entry to the study. There were modifications in vitamin D therapy during the sevelamer carbonate treatment period. There was one TEAE: vitamin D decreased (of mild severity) and two TEAEs: vitamin D deficiency (one of mild and one of moderate severity) reported in 3 patients in the DTP. None was reported as related or possibly related to the study drug.

Results of prothrombin time and international normalized ratio (INR) showed small non-clinically meaningful changes with sevelamer carbonate at Week 28 (mean change from baseline -0.21 sec for prothrombin time and -0.01 for INR) and at the last study visit (Week 28/ET) (mean change from baseline 0.13 sec for prothrombin time and 0.03 for INR). Overall, there were no clinically meaningful changes in any of the laboratory parameters including serum chemistry, hematology, coagulation and vitamins.

CHMP comment: no comments

Vital signs:

There were no remarkable changes in vital signs including, heart rate, blood pressure (systolic and diastolic), and temperature during study treatment.

CHMP comment: no comments

3. Rapporteur's overall conclusion

The majority of pediatric patients in this study were adolescent and on dialysis, and all had elevated age appropriate serum phosphorus levels at screening.

The study met its primary and secondary efficacy endpoints, although the secondary endpoint needs consideration and therefore more long term follow up studies are required.

The majority of the AEs were mild or moderate and assessed as not related to sevelamer carbonate. AEs were most frequently reported as Gastrointestinal disorders.

The benefit/risk ratio is positive in adolecents with CKD or in hemaodialysis.

Additional comments

Clinical Efficacy

The following issues were identified which would need to be addressed at the time of a variation application.

Patient disposition:

- Discontinuation of patients was high (34%). The timing of discontinuation and patient characteristics (potential for selection?) are unknown and need to be presented.

- Of the 50 excluded patients from the FAS-FDP, 48 patients (24 on sevelamer carbonate and 24 on placebo) were excluded due to compliance with study treatment less than 70%. The company is requested to clarify the reason for non-compliance with study treatment (could it for instance include discontinuing the study due to a kidney transplant?).

Pre-treatment:

- About 80% of patients already received phosphate binders at screening, 65% of which used a sevelamer-based binder. The applicant is requested to specify the dose and type of prior sevelamer-binder. Further, the serum phosphorus levels at screening visit (mean, range, etc) and % within normal range for all patients on prior P-binder should be compared to the serum phosphorus levels and % responders at the end of the FDP and DTP for the entire group and for the subgroup of patients that remained in the study at the end of FDP and end of DTP separately. Any discrepancies should be discussed.

Clinical efficacy:

- There was no a priori/predefined cut-off level for a clinical relevant treatment effect for the primary endpoint change from baseline in serum P over 2 weeks (FDP). The clinical relevance of the treatment effect should be further substantiated. This should include the change in serum P and % of patients reaching serum P within normal ranges.

- The effect was predominantly seen in patients with a baseline serum P of ≥ 7 mg/dL (mean change: -1.95 mg/dL, 95%CI: -2.64, -1.27) and not < 7 mg/dL (mean change: 0.05 [SD 1.097] mg/dL 95% CI: -0.39, 0.49), both constituting 50% of the patient population. The applicant is requested to provide the results of the primary analysis for the overall population and stratified for baseline serum P excluding the patients with baseline serum P levels in the normal range or below as these are not the intended target population.

- There appears to be a discrepancy between the results based on responder analyses and change in mean serum P. Mean serum phosphorus levels decreased with Renvela, but not placebo, during the two week placebo-controlled fixed dose period, whereas serum phosphorus levels appeared to remain stable over time during the open-label titration period. At the same time, the ad hoc responder analyses showed that 8% in both placebo and sevelamer treated groups achieved a serum phosphorus level within their age-appropriate normal ranges during the placebo-controlled phase which increased to 27.4% at the end of the open-label period. The applicant is requested to clarify the observed discrepancies.

PAM fulfilled (all commitments fulfilled) - No further action required

In view of the available data regarding the clinical study named **"*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*" or SVCARB07609 / DRI12793** the MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. This should be provided without any delay and no later than 60 days after the receipt of these conclusions.