**MULTI-DISCIPLINARY COLLABORATIVE REVIEW**

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|---|---|
| Application Type: | Original New Drug Application (NDA) |
| Application Number: | (b) (4) |
| Priority or Standard: | Priority |
| Formulation: | (b) (4) |
| | |
| Application Type: | (b) (4) |
| Application Number: | 205109-009 |
| Priority or Standard: | Standard |
| Formulation: | (b) (4) |
| | |
| Submit Date: | January 7, 2021 |
| Received Date: | January 7, 2021 |
| PDUFA Goal Date: | July 7, 2021 |
| | |
| Division: | Division of Cardiology and Nephrology |
| Review Completion Date: | See Electronic Signature Date |
| | |
| Trade Name: | Velphoro |
| Established Name: | Ferric oxyhydroxide (as determined by the Agency) |
| Applicant: | Vifor Fresenius Medical Care Renal Pharma France |
| Proposed labeling changes: | Velphoro is indicated for the control of serum phosphorus levels (b) (4) |
| | |
| Regulatory Action: | (b) (4) |

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# 1. Executive Summary

## 1.1 Summary of Regulatory Action

Velphoro (ferric oxyhydroxide, PA21) is an iron-based phosphate binder that is approved as a chewable tablet for the control of serum phosphorus levels in adults with chronic kidney disease (CKD) on dialysis.

(b) (4)

(b) (4) the Applicant submitted the results of an open-label, randomized, active-controlled, multicenter study conducted in pediatric patients 2 to 17 years of age with hyperphosphatemia and advanced CKD (defined as an estimated glomerular filtration rate <30 mL/min/l.73 $m^2$ or CKD on dialysis). The study included a washout period for patients on a phosphate binder, a 10-week dose titration period, and a 24-week safety extension period. Given its mechanism of action, Velphoro, if administered at an appropriate dose, is expected to be effective in lowering serum phosphorus levels. As such, the goal of the study, from an FDA perspective, was to obtain information to support dosing and to assess safety and tolerability.

The study randomized a total of 85 patients to Velphoro (N=66) or an active control arm (N=19). The majority of these patients were on dialysis. Although entry criteria permitted the enrollment of patients less than 2 years of age, no patient below 2 years of age was enrolled. Most patients (65%) in the trial were 12 to 17 years of age; seven patients (9%) were 2 to <6 years of age.

Data supporting dosing

Because Velphoro acts locally in the intestinal tract, exposure matching cannot be used to extrapolate efficacy from adults to pediatric patients. Hence, to support extrapolation, Velphoro's effect on serum phosphorus was assessed via descriptive analyses. In the trial population as a whole, the treatment effect of Velphoro on serum phosphorus was modest. The least squares (LS) mean (SE) reduction in serum phosphorus levels from baseline to the end of the dose titration period in the Velphoro group (N=65) was -0.4 (0.3) mg/dL (95% CI: -0.9, 0.1). The magnitude of the effect, as assessed via the point estimate, appeared to vary among the subgroups, although the confidence intervals were wide and overlapping. At the doses studied, Velphoro appeared to have the largest effect in patients 6 to 18 years of age with baseline serum phosphorus levels above normal for age; however, it is challenging to draw reliable inferences from the data given the small sample sizes. Among patients with baseline serum phosphorus levels above the normal range for age, the LS mean reduction was 0.5 mg/dL in patients 2 to <6 years of age, 1.2 mg/dL in patients 6 to <12 years of age, and 1.0 mg/dL in patients 12 to 18 years of age, but confidence intervals were wide. Given what appeared to be a smaller mean effect in patients 2 to <6 years of age and the small size of the age group, patient level data were reviewed. Review of these data showed significant variability in response, with only one patient demonstrating what might be considered to be a clinically relevant reduction in serum phosphorus levels.

Safety

In the clinical trials conducted to support the approval of Velphoro in adults, the most common adverse reactions were gastrointestinal adverse reactions. In the pediatric study, the safety profile of Velphoro was generally similar to that observed in adult patients. Adverse reactions occurring in more than 5% of patients in the Velphoro group included diarrhea (18%), nausea (12%), vomiting (9%), and constipation (6%). The most common adverse reaction leading to withdrawal was diarrhea (9%).

Conclusion

(b) (4)

(b) (4)

## 1.2 Benefit-Risk Assessment

Table 1. Benefit-Risk Framework

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Analysis of Condition** | Hyperphosphatemia is common in patients with kidney failure treated with dialysis and has been associated with secondary hyperparathyroidism, vascular, valvular, and other soft tissue calcification, cardiovascular disease, and death. In pediatric patients with CKD, hyperphosphatemia and secondary hyperparathyroidism is also associated with poor growth, skeletal maturation delay, and skeletal deformities. | Epidemiologic data and biologic plausibility suggest that treating hyperphosphatemia should improve patient outcomes; however, to date, there are no data from outcome studies demonstrating that a treatment's effect on serum phosphorus predicts its effect on clinical outcomes associated with CKD. |
| **Current Treatment Options** | Hyperphosphatemia is usually managed by restricting dietary phosphate and taking phosphate binders to restrict intestinal absorption of phosphate. Several phosphate binders are approved for use in hyperphosphatemic adult patients with CKD on dialysis; however, only one (sevelamer carbonate) is approved for use in pediatric patients (down to 6 years of age). | There is an unmet medical need for additional treatments to manage hyperphosphatemia in pediatric patients with CKD. |
| **Benefit/Data to Support Dosing** | The least squares (LS) mean (SE) reduction in serum phosphorus levels from baseline to the end of the dose titration period in the Velphoro group (N=65) was -0.4 (0.3) mg/dL (95% CI: -0.9, 0.1). The point estimate of the mean reduction varied among subgroups, though confidence intervals were wide and overlapping. | (b) (4) |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | Among patients with baseline serum phosphorus levels above the normal range for age, the LS mean reduction was 0.5 mg/dL in patients 2 to <6 years of age, 1.2 mg/dL in patients 6 to <12 years of age, and 1.0 mg/dL in patients 12 to 18 years of age, but confidence intervals were wide. | (b) (4) |
| **Risk and Management** | In the pediatric study, the safety profile of Velphoro was generally similar to that observed in adults. The most common adverse reactions were diarrhea (18%), vomiting (9%), and constipation (6%). | Diarrhea, vomiting, and constipation were the most common adverse reactions in pediatric patients treated with Velphoro. (b) (4) . |

# 2. Introduction and Regulatory Background

## 2.1 Background

On November 27, 2013, the Agency approved Velphoro chewable tablets for the control of serum phosphorus levels in adult patients with CKD on dialysis. At the time of approval, the Agency issued a post-marketing requirement (PMR) for a deferred efficacy and safety study under the Pediatric Research and Equity Act for pediatric patients 1 month to 17 years of age with advanced CKD; this PMR was subsequently changed to a safety, tolerability, and pharmacodynamic study in patients 2 to 17 years of age. To address these requirements, the Applicant conducted an open-label, randomized, controlled, multicenter study in pediatric patients birth to 17 years of age with hyperphosphatemia and stage 4 or 5 CKD (estimated glomerular filtration rate <30 mL/min/1.73 $m^2$) or stage 5D CKD receiving maintenance hemodialysis or peritoneal dialysis. (b) (4)

Hyperphosphatemia is common in patients with kidney failure treated with 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 addition, in pediatric patients with CKD, hyperphosphatemia and secondary hyperparathyroidism have been associated with poor growth, skeletal maturation delay, and skeletal deformities.

To date, the Agency has approved four major classes of phosphate binders for the control of serum phosphorus in adult patients with CKD on dialysis: calcium-based binders, sevelamer-based products, lanthanum carbonate and iron-based binding agents. All these agents were approved for use in adults based on reductions in serum phosphorus.[1] Sevelamer carbonate (Renvela) is currently the only phosphate binder approved for use in pediatric patients down to 6 years of age.

## 2.2 Ferric Oxyhydroxide Product Information

Velphoro (ferric oxyhydroxide, PA21) is an iron-based phosphate binder. Velphoro lowers serum phosphorus levels by binding dietary phosphate in the gastrointestinal tract, which is then eliminated with the feces. The active moiety of Velphoro is practically insoluble and clinical studies do not indicate significant absorption of iron from the product.

Velphoro is currently marketed as a 500-mg strength chewable tablet. (b) (4) .

[1] There are no data from outcome studies demonstrating that a treatment's effect on serum phosphorus levels predicts its effect on clinical outcomes associated with elevated serum phosphorus levels. Nevertheless, the Division of Cardiology and Nephology, following the precedent set by the former Division of Metabolism and Endocrinology Products, treats serum phosphorus reduction as a valid surrogate in patients with CKD on dialysis.

## 2.3 Regulatory History Related to Submission

At the time of approval of Velphoro chewable tablets, the Agency waived pediatric studies in patients birth to <1 month of age because studies would be impossible or impracticable because of the low number of eligible patients, and issued a post-marketing requirement (PMR) for a deferred study under the Pediatric Research and Equity Act (PREA):

2103-1 Conduct a safety and efficacy trial in pediatrics aged 1 month to 17 years.
Primary objective(s):

- To evaluate the efficacy of PA21 in maintaining the serum phosphorus lowering effect in pediatric patients with CKD in Stages 4-5 (defined by a glomerular filtration rate <30 mL/min/1.73 $m^2$) or with CKD Stage 5D receiving adequate maintenance HD or PD for at least 3 months prior to screening (versus placebo).

Secondary Objective(s):

- To evaluate the safety of PA21 in pediatric patients with CKD.
- To evaluate the safety of Phoslyra™ in pediatric patients with CKD.

Final report submission: February 28, 2019.

After the PMR was issued, the Agency determined that full extrapolation of efficacy was appropriate and released PMR 2103-1 and issued a new PMR for a dosing and safety study.

On April 27, 2015, the Agency also issued a Written Request (WR) for a pediatric study in patients 0 to 17 years of age. The WR was subsequently amended and reissued as discussed in the table below.

Over the years, there were a number of interactions with the Agency regarding the design of the pediatric study, the PMR and WR. For a summary of key regulatory milestones, agreements and advice related to this protocol, see Table 2. The Division of Pediatrics and Maternal Health (DPMH) was consulted and participated in these discussions.

Table 2. Summary of Key Regulatory Milestones, Agreements, and Advice

| Source | Advice from Agency |
|---|---|
| October 4, 2010 | The Division received a synopsis of protocol PA-CL-PED-01 for a randomized active-controlled, parallel-group, open-label, phase 3 safety and tolerability study in pediatric patients 1 to <18 years of age. |
| November 22, 2010 Meeting Preliminary Comments | The Division did not agree that a safety and tolerability study was sufficient. To assess effectiveness and provide data to support dosing in pediatric patients, the Division recommended a placebo controlled randomized-withdrawal design that would not require an active comparator. |
| July 30, 2014 Type C Meeting (minutes dated August 14, 2014) | The Division concluded that it was appropriate to extrapolate efficacy from adults to pediatric patients and that the pediatric study should be designed to obtain data on safety and to inform dosing. Because of the mechanism of action of Velphoro as a phosphate binder acting locally in the gastrointestinal tract, its effect in lowering serum phosphorus levels was expected to be similar in adult and pediatric patients. As such, a randomized withdrawal phase would not be needed. |
| November 5, 2014 Advice Letter | The Division agreed that a food diary was not necessary (the Applicant had indicated that it was too burdensome for patients and families). |

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|---|---|
| November 26, 2014<br>Advice Letter | The Division denied the Applicant's request (b) (4) |
| January 29, 2015<br>Advice Letter | The Division requested the study include active monitoring for gastrointestinal adverse events, including diarrhea, nausea, constipation, vomiting and dyspepsia. |
| April 27, 2015<br>Written Request | The Agency issued a WR for an open-label, randomized, controlled, parallel group, multicenter, phase 3 study in pediatric patients 0 to 17 years of age with hyperphosphatemia and stage 4 or 5 CKD (eGFR <30 mL/min/1.73 $m^2$) or stage 5D CKD receiving adequate maintenance hemodialysis or peritoneal dialysis. The study was to have a washout phase for patients already on phosphate binders, a controlled dose titration phase to achieve an age-appropriate target serum phosphorus level, and a 24 week or longer controlled safety extension phase. A minimum of 60 patients were to be treated with Velphoro in the safety extension phase including a minimum of 10 patients in each of the age categories 0 to <2 years, 2 to 6 years, 6 to 9 years, and 9 to 17 years. The objective was to provide safety and dosing data to guide the use of Velphoro in pediatric patients with CKD and hyperphosphatemia. |
| (b) (4) | |
| March 9, 2018<br>Type C Meeting<br>(minutes dated March 23, 2018) | Because of enrollment challenges (65 patients were randomized as of January 8, 2018), the Division agreed with the Applicant's proposal to:<br>– stop recruitment in patients 12 to <18 years of age noting that the 23 patients who had reached Stage 2 of the study should be adequate to assess safety and dosing in this age group<br>– stop recruitment in the active comparator (Phoslyra) arm<br>– a new age stratification for the study population by combining patients 6 to <12 years of age because the information on use of the product was likely generalizable from 12 years down to 6 years of age based on the mechanism of action, method of elimination, and known safety risks of the product<br>The Division maintained its expectation that the Applicant enroll 10 patients in each new age cohort. |
| August 20, 2018<br>Type C Meeting<br>(minutes dated September 19, 2018)<br>November 13, 2018<br>E-mail to Applicant | The Division did not agree with (b) (4) The Division noted that a partial waiver in patients <2 years of age could be justified on the basis that necessary studies were impossible or highly impracticable and recommended that the Applicant submit a formal request to amend the PREA PMR and WR and provide supportive rationale for the proposed changes in their request. |

| | |
|---|---|
| March 6, 2019<br>Written Request Amendment #1 | The Agency revised the WR to:<br>– remove the required minimum number of patients <2 years of age<br>– reduce the minimum number of patients treated with Velphoro from 60 to 30 patients in the safety extension phase and remove the minimum number requirements by age group |
| (b) (4) | (b) (4) |
| March 13, 2020 | The Division (b) (4) issued PMR 3824-1 changing the lower age for study from 1 month to 2 years of age. Final Report Submission: January 31, 2021. |
| January 5, 2021<br>New Written Request | The WR expired on February 28, 2020. A new WR was issued changing the timeframe for reporting the studies from February 28, 2020 to January 31, 2021. |
| January 7, 2021 | The Applicant submitted the pediatric study reports to NDA 205109 supplement 009 (b) (4) |

# 3. Interdisciplinary Collaborative Review

## 3.1 Approach to the Review

This was a joint clinical pharmacology and clinical review.

## 3.2 Trial Design

**Title**

"An open-label, randomized, active-controlled, parallel group, multicentre, phase 3 study to investigate the safety and efficacy of PA21 (Velphoro®) and calcium acetate (Phoslyra®) in paediatric and adolescent CKD patients with hyperphosphataemia."

**Objective**

The stated primary objective of the protocol was "to evaluate the efficacy of Velphoro in reducing serum phosphorus levels in pediatric and adolescent patients with CKD at the end of Stage 1."

*Reviewer's comment: As stated in the WR, from the Agency's perspective, the objective of the study was to provide safety and dosing data to guide the use of Velphoro in pediatric patients with CKD and hyperphosphatemia.*

**Study Design**

The study was a multicenter, randomized, active-controlled study in pediatric patients 2 years of age and older with CKD. The study consisted of a screening period of up to 4 weeks, a washout period of up to 3 weeks for patients previously taking phosphate binders, a dose titration period of up to 10 weeks (Stage 1), and a 24-week safety extension (Stage 2). Patients were followed up 14 days after their last Stage 2 study visit.

Stage 1 was an open-label, randomized, active-controlled, dose titration period during which patients received Velphoro or Phoslyra for up to 10 weeks. The starting dose of Velphoro was based on age

(Table 3); Phoslyra was started at a fixed weight-based dose (Table 4) or an equivalent dose of the patient's previous phosphate binders (calcium-based or sevelamer) if the investigator considered this more appropriate. Subsequently, dose titration was allowed to achieve age-specific target serum phosphorus levels if a patient had been receiving a stable dose of study drug for a minimum of 2 weeks, or for safety or tolerability reasons at any time. Beginning at Week 4, patients that achieved the age-specific target serum phosphorus levels moved to Stage 2. During Stage 2, patients continued the dose they were receiving at the end of Stage 1. If a dose change was required, dose modifications followed the same guidelines as Stage 1.

Table 3. Velphoro Dosing Regimen

| **Age (years)** | **Starting Dose (mg Iron/Day)** | **Dose Increases or Decreases (mg Iron/Day)** | **Maximum Dose (mg Iron/Day)** |
|---|---|---|---|
| 0 to <1 | 125 | 125 or 250 | 1000 |
| 1 to <6 | 500 | 125 or 250 | 1250 |
| 6 to <9 | 750 | 125, 250, or 375 | 2500 |
| 9 to <18 | 1250 | 250 or 500 | 3000 |

Source: Applicant's PA-CL-PED-01 Clinical Study Report (Tables 5 and 6, page 61)

Table 4. Phoslyra Dosing Regimen

| **Initial dose** | **Dose Increases or Decreases** | **Maximum Dose (up to 35 kg)** | **Maximum Dose (above 35 kg)** |
|---|---|---|---|
| 0.45 mL/kg/day | 0.1 to 0.2 mL/kg/day | 1.25 mL/kg/day | 44 mL/day |

Source: Applicant's PA-CL-PED-01 Clinical Study Report (Table 7, page 62)

The age-related serum phosphorus targets and safety limits (applied as dose titration criteria) are shown in Table 5.

Table 5. The Age-related Serum Phosphorus Targets and Safety Limits.

| Age | Serum phosphorus target | Upper safety limit | Lower safety limit |
|---|---|---|---|
| 0 to <1 year | 5.0-7.8 mg/dL | 9.0 | 5.0 |
| ≥1 year to <6 years | 4.5-6.5 mg/dL | 7.5 | 4.5 |
| ≥6 years to <13 years | 3.6-5.8 mg/dL | 7.0 | 3.5 |
| ≥13 years to <18 years | 2.3-4.5 mg/dL | 7.0 | 2.5 |

Source: Applicant's PA-CL-PED-01 Clinical Study Report (Tables 1 and 4, pages 49 and 60).

**Treatment Drug**

The dosage forms of Velphoro and Phoslyra used in the study are shown in Table 6.

Table 6. Summary of Dosage Forms

| Age | PA21 | | Phoslyra Oral Solution (mL) |
|---|---|---|---|
| | Powder for Oral Suspension (mg Iron) | Chewable Tablet (mg Iron) | |
| 0 to <1 year | 125, 250, 500 | – | Multiple-dose [redacted] bottles 473 mL with a [redacted] |
| ≥1 year to <6 years | 125, 250, 500 | – | |
| ≥6 years to <9 years | 125, 250, 500 | 250, 500 | |
| ≥9 years to <18 years | 250, 500 | 250, 500 | |

Source: Applicant's Velphoro Protocol PA-CL-PED-01 Version 2.0 (Table B, page 4)
Abbreviations: PET = Polyethylene terephthalate.

**Pharmacodynamic Analyses**

As agreed upon in the WR and revised PMR, the objective of the study was to evaluate safety and to confirm dosing with only descriptive statistics of the pharmacodynamic effects on serum phosphorus. The baseline serum phosphorus was the last value before the first dose of study drug. For hemodialysis patients, laboratory assessments were obtained before the dialysis treatment.

**Eligibility Criteria**

Key inclusion criteria

- Age at consent 0 to <18 years with an eGFR <30 mL/min/1.73 $m^2$ including patients on stable hemodialysis or peritoneal dialysis for ≥2 months before screening and hyperphosphatemia according to age-specific criteria
- Naïve to phosphate binders or on a stable regimen of ≤2 phosphate binders for ≥1 month before screening
- Patients on phosphate binders were required to undergo a mandatory washout before randomization unless serum phosphorus levels were above age-related targets

Key exclusion criteria:

- Hypercalcemia (per age-related definition) or hypocalcemia (serum total corrected calcium <7.6 mg/dL) at screening
- Intact parathyroid hormone (iPTH) levels >700 pg/mL at screening
- Parathyroidectomy planned or expected within 12 months
- Body weight <5 kg (phosphate binder-naïve) or <6 kg (receiving stable phosphate binder regimens) at screening
- History of major gastrointestinal surgery or significant gastrointestinal disorders
- History of haemochromatosis or other iron accumulation disorders
- History of peritonitis in the last 3 months or ≥3 episodes in the last 12 months (for patients on peritoneal dialysis)
- Use of >2 phosphate binders concomitantly before screening

**Protocol Amendments**

The original protocol (version 1.0) was submitted on October 31, 2014 and amended once (version 2.0) on December 23, 2015. The amendment made minor edits to the inclusion criteria, and clarified that the final laboratory assessments at the end of Stage 1 should be sent to the central laboratory, the visits

when standard validated local laboratory assessments were acceptable, and that primary efficacy analyses will be based on central laboratory assessments.

## 3.3 Analyses and Pharmacodynamic Results

**Patient Disposition**

A total of 120 patients were screened. Of those, 31 patients did not meet entry criteria, 3 discontinued for "other" reasons and one chose not to participate. A total of 85 patients were randomized: 66 to Velphoro and 19 to Phoslyra. All randomized patients received at least one dose of study drug. In the Velphoro group, 43 patients (65%) completed the dose titration period (Stage 1) and entered the long-term extension Stage 2, and 26 (39%) completed the study. See Table 7 for additional information.

Table 7. Disposition of Enrolled Patients

| Parameter | PA21 n (%) | Phoslyra n (%) | Total n (%) |
|---|---|---|---|
| Subjects Screened | - | - | 120 |
| Screen Failures | - | - | 35 |
| Reason for Screen Failure | | | |
| Entry Criteria Not Met | - | - | 31 |
| Withdrew Consent | - | - | 1 |
| Other | - | - | 3 |
| Randomised | 66 | 19 | 85 |
| Treated (Safety Population) | 66 | 19 | 85 |
| Treated in Stage 1 | 66 (100.0%) | 19 (100.0%) | 85 (100.0%) |
| Entered Stage 2 | 43 (65.2%) | 8 (42.1%) | 51 (60.0%) |
| Completed | 26 (39.4%) | 2 (10.5%) | 28 (32.9%) |
| Terminated Prematurely | 40 (60.6%) | 17 (89.5%) | 57 (67.1%) |

Source: Applicant's PA-CL-PED-01 Clinical Study Report V1.0 (Table 17, page 101).
Notes: Includes all patients with a signed informed consent. Percentages are based on the number of treated patients, i.e. on the Safety Population. n=number of observations.

Overall, 40 patients (61%) in the Velphoro group discontinued treatment prematurely, 23 (35%) during Stage 1 (Table 8). During Stage 1, the most common reasons for early discontinuations in the Velphoro group were AEs (9 patients) and withdrawal by the parent/guardian (6 patients). In Stage 2, the most common reason was kidney transplant (8 patients). For further discussion of early discontinuations for AEs, see Section 3.4 Safety Results.

Table 8. Reasons for Early Termination, Safety Population

| Treatment Arm | Parameter | During Stage 1 n (%) | During Stage 2 n (%) | Any Time during the Study n (%) |
|---|---|---|---|---|
| PA21 (N=66) | Subjects who terminated prematurely | 23 (34.8%) | 17 (25.8%) | 40 (60.6%) |
| | Reason for Early Termination[1] | | | |
| | Adverse Event | 9 (13.6%) | 3 (4.5%) | 12 (18.2%) |
| | Lack of efficacy | 4 (6.1%) | 0 | 4 (6.1%) |
| | Non-compliance with study drug | 4 (6.1%) | 4 (6.1%) | 8 (12.1%) |
| | Physician decision | 3 (4.5%) | 1 (1.5%) | 4 (6.1%) |
| | Withdrawal by parent/legal guardian | 6 (9.1%) | 2 (3.0%) | 8 (12.1%) |
| | Withdrawal by subject | 3 (4.5%) | 0 | 3 (4.5%) |
| | Kidney transplant | 3 (4.5%) | 8 (12.1%) | 11 (16.7%) |
| | Other | 3 (4.5%) | 2 (3.0%) | 5 (7.6%) |
| Phoslyra (N=19) | Subjects who terminated prematurely | 11 (57.9%) | 6 (31.6%) | 17 (89.5%) |
| | Reason for Early Termination[1] | | | |
| | Adverse Event | 5 (26.3%) | 1 (5.3%) | 6 (31.6%) |
| | Lack of efficacy | 0 | 3 (15.8%) | 3 (15.8%) |
| | Non-compliance with study drug | 3 (15.8%) | 1 (5.3%) | 4 (21.1%) |
| | Physician decision | 1 (5.3%) | 1 (5.3%) | 2 (10.5%) |
| | Withdrawal by parent/legal guardian | 2 (10.5%) | 0 | 2 (10.5%) |
| | Withdrawal by subject | 3 (15.8%) | 1 (5.3%) | 4 (21.1%) |
| | Kidney transplant | 3 (15.8%) | 1 (5.3%) | 4 (21.1%) |
| | Other | 1 (5.3%) | 1 (5.3%) | 2 (10.5%) |

Source: Applicant's PA-CL-PED-01 Clinical Study Report V1.0 (Table 18, page 102).
Notes: N=total number of patients; n=number of observations.

**Baseline Characteristics**

Baseline demographics are shown in Table 9. Patients 12 to 18 years of age accounted for 65% of enrollment in the Velphoro arm; only six patients in the Velphoro arm (9%) were 2 to <6 years of age. Of those enrolled in the Velphoro arm, 52% were female, 72% were white, 15% black, and 59% were enrolled in the United States.

Table 9. Baseline Demographic Characteristics, Full Analysis Set

| **Parameter** | **Statistics** | **Velphoro (N=65)** | **Phoslyra (N = 15)** |
|---|---|---|---|
| Age at Randomization (years) - n (%) | Birth to <2 | 0 | 0 |
| | 2 to <6 | 6 (9) | 1 (7) |
| | 6 to <12 | 17 (26) | 4 (27) |
| | 12 to 18 | 42 (65) | 10 (67) |
| Sex - n (%) | n (missing) | 65 (0) | 15 (0) |
| | Male | 31 (48) | 5 (33) |
| | Female | 34 (52) | 10 (67) |
| Race - n (%) | n (missing) | 60 (5) | 15 (0) |
| | White | 43 (72) | 11 (73) |
| | Black or African American | 9 (15) | 2 (13) |
| | Other | 6 (10) | 1 (7) |
| | Native Hawaiian or Other Pacific Islander | 1 (2) | 1 (7) |
| | American Indian or Alaska Native | 1 (2) | 0 |
| Ethnicity – n (%) | n (missing) | 65 (0) | 15 (0) |
| | Not Hispanic or Latino | 46 (71) | 12 (80) |
| | Hispanic or Latino | 19 (29) | 3 (20) |
| | Asian | 0 | 0 |
| | Not reported | 0 | 0 |
| | Unknown | 0 | 0 |
| Region - n (%) | n (missing) | 65 (0) | 15 (0) |
| | US | 38 (59) | 11 (73) |
| | NON-US | 27 (42) | 4 (27) |
| Baseline Body Mass Index ($kg/m^2$) | | | |
| Age 2 to <6 years | n (missing) | 6 (0) | 1 (0) |
| | Mean (SD) | 15.8 (1.5) | 17.9 |
| | Median | 15.8 | 17.9 |
| | Q1, Q3 | 14.6, 16.8 | 17.9, 17.9 |
| | Min, Max | 13.7, 17.9 | 17.9, 17.9 |
| Age 6 to <12 years | n (missing) | 17 (0) | 4 (0) |
| | Mean (SD) | 17.8 (4.8) | 15.2 (1.0) |
| | Median | 16.3 | 15.2 |
| | Q1, Q3 | 15.6, 18.3 | 14.4, 16.0 |
| | Min, Max | 14.0, 34.2 | 14.1, 16.5 |
| Age 12 to ≤18 years | n (missing) | 42 (0) | 10 (0) |
| | Mean (SD) | 21.0 (4.3) | 19.6 (5.5) |
| | Median | 20.5 | 17.7 |
| | Q1, Q3 | 17.9, 23.4 | 16.3, 22.1 |
| | Min, Max | 12.8, 33.6 | 125, 30.1 |

Source: Applicant's PA-CL-PED-01 Clinical Study Report V1.0 (Table 21, pages 106-110).

Notes: FAS=Full Analysis Set; N=total number of patients; n=number of observations; SD=standard deviation; Q1=first quartile; Q3=third quartile; Min=minimum; Max=maximum; US=United States.

As shown in Table 10, the most common cause of CKD in the Velphoro arm was congenital anomalies of the kidney and urinary tract (CAKUT), which is a common cause of CKD in pediatric patients in the U.S. The majority of patients were on dialysis; of those on dialysis, most were on hemodialysis. Most patients were on phosphorus binders at the time of enrollment, and, among those who were on a phosphorus binder at the time of enrollment, the majority did not require a washout period.

Table 10. Baseline Disease Characteristics, Full Analysis Set

| Parameter | Statistics | Velphoro (N=65) | Phoslyra (N = 15) |
|---|---|---|---|
| Reason or Cause of CKD - n(%) | n (missing) | 65 (0) | 15 (0) |
| | Congenital anomalies of the kidney and urinary tract | 19 (29) | 3 (20) |
| | Glomerulonephritis | 10 (15) | 4 (27) |
| | Hypodysplasia and reflux | 2 (3) | 2 (13) |
| | Obstructive uropathy | 8 (12) | 1 (7) |
| | Polycystic kidney disease | 3 (5) | 0 |
| | Hemolytic uremic syndrome | 0 | 0 |
| | Other | 23 (35) | 5 (33) |
| CKD Stage - n(%) | n (missing) | 65 (0) | 15 (0) |
| | Stage 1 | 0 | 0 |
| | Stage 2 | 0 | 0 |
| | Stage 3 | 0 | 0 |
| | Stage 4 | 13 (20) | 1 (6.7) |
| | Stage 5 | 52 (80) | 14 (93.3) |
| Time since Onset of CKD (years)[1] | n (missing) | 65 (0) | 14 (1) |
| | Mean (SD) | 6.5 (5.3) | 4.8 (3.6) |
| | Median | 5.4 | 3.5 |
| | Q1, Q3 | 1.5, 11.6 | 1.7, 6.7 |
| | Min, Max | 0.1, 17.5 | 0.8, 12.0 |
| Type of Dialysis - n(%) | n (missing) | 65 (0) | 15 (0) |
| | Hemodialysis | 45 (69) | 9 (60) |
| | Peritoneal dialysis | 5 (8) | 5 (33) |
| | Peritoneal dialysis and Hemodialysis | 0 | 0 |
| | None | 15 (23) | 1 (7) |
| Phosphate Binder-Naïve - n(%) | n (missing) | 65 (0) | 15 (0) |
| | Yes | 18 (28) | 3 (20) |
| | No | 47 (72) | 12 (80) |
| Washout Period Needed - n(%) | n (missing) | 47 (18) | 12 (3) |
| | Yes | 7 (15) | 4 (33) |
| | No | 40 (85) | 8 (67) |
| Baseline Serum Phosphorus (mg/dL)[2] | n (missing) | 65 (0) | 15 (0) |
| | Mean (SD) | 6.4 (1.6) | 6. 7 (2.1) |
| | Median | 6.1 | 6.4 |
| | Q1, Q3 | 5.2, 7.3 | 5.8, 7.5 |
| | Min, Max | 3.1, 10.3 | 2.7, 11.9 |

[1.] Time is calculated until date of informed consent.

[2.] Data are from central laboratory.

Source: Applicant's PA-CL-PED-01 Clinical Study Report V1.0 (Table 22, pages 113-114).

Notes: FAS=Full Analysis Set; N=total number of patients; n=number of observations; SD=standard deviation; Q1=first quartile; Q3=third quartile; Min=minimum; Max=maximum; US=United States. Time since Onset of CKD was calculated until date of informed consent.

**Protocol Deviations**

Major protocol deviations that resulted in exclusion from the PPS Population in the Velphoro arm occurred in 23 patients (35%); most of these deviations reflected non-compliance with study drug (Table 11). Three patients in the Velphoro group were included in the FAS and Safety Populations despite major deviations from study eligibility criteria:

- (b) (6): This patient took anti-convulsive medication during the study.
- : This patient initiated growth hormone treatment 17 days before randomization. The protocol required patients receiving growth hormone to have been on a stable dose for 2 months before study entry; although this was not the case for this patient, there were no changes to her growth hormone dosage during the study.
- (b) (6): This patient was enrolled despite an exclusionary intact parathyroid hormone level, as the test result was not received on time at the site. The patient was permitted to continue in the study.

Table 11. Major Protocol Deviations

| Parameter | Velphoro (N=65) n (%) | Phoslyra (N=15) n (%) |
|---|---|---|
| Patients with at least 1 Major Deviation | 23 (35) | 10 (67) |
| Prohibited medication | 1 (2) | 0 |
| Exclusion criteria | 3 (5) | 0 |
| Non-compliance with study drug | 18 (28) | 10 (67) |
| Non-compliance with procedure | 1 (2) | 0 |

Source: Applicant's PA-CL-PED-01 Clinical Study Report V1.0 (Table 19, pages 104).
Notes: N=total number of patients; n=number of observations.

**Pharmacodynamic Effects of Velphoro**

As previously noted, the Agency agreed to the concept of extrapolation of efficacy from adult to pediatric patients. As such, the objective of the study was to evaluate safety and to confirm dosing with only descriptive statistics of the pharmacodynamic effect on serum phosphorus. Notable findings in the Velphoro treatment arm were as follows:

- (b) (4)
-
-

(b) (4)

(b) (4)

Table 12. Change from Baseline to End of Stage 1 in Serum Phosphorus, Patients 2 to <6 Years of Age

| Patient | Age at Consent | Baseline Serum Phosphorus (mg/dL) | Change from Baseline (mg/dL) |
|---|---|---|---|
| (b) (6) | 4 years | | (b) (4) |
| | 23 months | | |
| | 3 years | | |
| | 5 years | | |
| | 24 months | | |
| | 5 years | | |

Clinical pharmacology reviewer analyses.

Compliance was similar among the age groups, and there were no differences in baseline iPTH, calcium, vitamin D levels or serum bicarbonate between the age groups. An information request was sent to the Applicant regarding factors that might explain the findings in this age group. According to the Applicant, the small sample size and premature discontinuation of treatment in some patients contributed to the findings. Information on dietary phosphate intake was not collected.

## 3.4 Safety Results

**Important Safety Issues with Velphoro and Related Drugs**

To date, four major classes of phosphate binders have been approved in the United States for the control of serum phosphorus in adult patients with CKD on dialysis: calcium-based binders, sevelamer-based products, lanthanum carbonate and iron-based binding agents. One, sevelamer carbonate, has been approved for use in pediatric patients. Common adverse reactions of phosphate binders include gastrointestinal side effects including vomiting, nausea, diarrhea, dyspepsia, abdominal pain, flatulence, and constipation. In the clinical trials conducted to support the approval of Velphoro in adults, the most common adverse reactions were diarrhea, discolored feces, and nausea. Most diarrhea events were mild and transient, occurring soon after initiation of treatment, and resolving with continued treatment.

**Safety Analysis Set and Overall Exposure**

Safety analyses focused on the "safety population," which included 85 enrolled patients, 66 randomized to Velphoro, and 19 to Phoslyra, who received at least one dose of study drug. Safety evaluations included vital signs, physical examinations, and laboratory tests, which were performed at regular intervals.

As shown in Table 13, the mean (SD) duration of exposure was 127 (84) days for Velphoro and 74 (74) days for Phoslyra.

Table 13. Exposure to Study Drug - Stage 1 and Overall Study, Safety Population

| Parameter | Statistics | Velphoro N=66 | Phoslyra N=19 |
|---|---|---|---|
| Duration of exposure (days) for Stage 1 | n | 66 | 19 |
| | Mean (SD) | 46 (23) | 368 (28) |
| | Median | 43 | 36 |
| | Q1, Q3 | 29, 71 | 4, 71 |
| | Min, Max | 3, 85 | 1, 74 |
| Overall duration of exposure (days) | n | 66 | 19 |
| | Mean (SD) | 127 (84) | 74 (74) |
| | Median | 128 | 49 |
| | Q1, Q3 | 40, 197 | 4, 125 |
| | Min, Max | 3, 425 | 1, 239 |
| Actual average daily dosage (mg for Velphoro; mL for Phoslyra) during Stage 1 | n | 65 | 18 |
| | Mean (SD) | 1216 (526) | 12 (8) |
| | Median | 1207 | 13 |
| | Q1, Q3 | 864, 1598 | 4, 19 |
| | Min, Max | 167, 26887 | 1, 29 |
| Actual average daily dosage (mg for Velphoro; mL for Phoslyra) overall study | n | 65 | 18 |
| | Mean (SD) | 1281 (612) | 12 (9) |
| | Median | 1199 | 13 |
| | Q1, Q3 | 885, 1653 | 43, 15 |
| | Min, Max | 167, 3243 | 1, 31 |

Source: Applicant's Table 36, PA-CL-PED-01 Clinical Study Report V1.0.
Abbreviations: N = number of patients in treatment arm; n = number of observations; SD = standard deviation; Q1 = first quartile; Q3 = third quartile; Min = minimum; Max = maximum.

As shown in Table 14, the duration of exposure was greater in patients ≥6 years of age than in those 2 to <6 years of age.

Table 14. Exposure to Study Drug by Age Group – Stage 1 and Overall Study, Safety Population

| Parameter | Statistics | PA21 | | | Phoslyra | | |
|---|---|---|---|---|---|---|---|
| | | ≥2 to <6 Years (N=6) | ≥6 to <12 Years (N=17) | ≥12 to ≤18 Years (N=43) | ≥2 to <6 Years (N=1) | ≥6 to <12 Years (N=5) | ≥12 to ≤18 Years (N=13) |
| Duration of exposure (days) for Stage 1 | n | 6 | 17 | 43 | 1 | 5 | 13 |
| | Mean (SD) | 27.2 (18.51) | 42.6 (23.48) | 49.5 (22.74) | 4.0 | 24.4 (19.32) | 45.5 (29.13) |
| | Median | 23.5 | 43.0 | 48.0 | 4.0 | 32.0 | 57.0 |
| | Q1, Q3 | 9.0, 45.0 | 28.0, 60.0 | 29.0, 71.0 | 4.0, 4.0 | 5.0, 36.0 | 24.0, 71.0 |
| | Min, Max | 9, 53 | 7, 78 | 3, 85 | 4, 4 | 3, 46 | 1, 74 |
| Overall duration of exposure (days) | n | 6 | 17 | 43 | 1 | 5 | 13 |
| | Mean (SD) | 78.5 (89.39) | 135.2 (95.18) | 129.7 (78.26) | 4.0 | 65.2 (79.77) | 82.7 (74.00) |
| | Median | 36.0 | 189.0 | 131.0 | 4.0 | 36.0 | 63.0 |
| | Q1, Q3 | 9.0, 168.0 | 28.0, 211.0 | 62.0, 196.0 | 4.0, 4.0 | 5.0, 88.0 | 24.0, 125.0 |
| | Min, Max | 9, 213 | 7, 245 | 3, 240 | 4, 4 | 3, 194 | 1, 239 |
| Actual average daily dosage (mg iron for PA21; ml for Phoslyra) during Stage 1 | n | 5 | 17 | 43 | 1 | 5 | 12 |
| | Mean (SD) | 528.50 (240.591) | 1030.58 (324.205) | 1369.54 (531.433) | 4.17 | 9.99 (7.464) | 14.11 (8.271) |
| | Median | 625.00 | 893.75 | 1344.83 | 4.17 | 9.63 | 14.39 |
| | Q1, Q3 | 406.25, 697.37 | 740.00, 1304.55 | 1034.48, 1674.42 | 4.17, 4.17 | 5.00, 14.76 | 6.63, 20.32 |
| | Min, Max | 166.7, 747.2 | 607.1, 1623.2 | 308.3, 2688.2 | 4.2, 4.2 | 0.9, 19.6 | 2.8, 29.2 |
| Actual average daily dosage (mg iron for PA21; ml for Phoslyra), overall study | n | 5 | 17 | 43 | 1 | 5 | 12 |
| | Mean (SD) | 579.89 (382.878) | 1208.65 (488.247) | 1391.79 (626.405) | 4.17 | 10.22 (8.633) | 13.79 (9.039) |
| | Median | 625.00 | 1190.76 | 1250.00 | 4.17 | 7.64 | 13.23 |
| | Q1, Q3 | 276.04, 697.37 | 733.33, 1533.49 | 1046.88, 1728.57 | 4.17, 4.17 | 5.00, 14.76 | 7.88, 15.35 |
| | Min, Max | 166.7, 1134.4 | 607.1, 2361.3 | 237.1, 3243.3 | 4.2, 4.2 | 0.9, 22.8 | 2.7, 31.1 |

Source: Applicant's Table 37, PA-CL-PED-01 Clinical Study Report V1.0.
Abbreviations: N = number of patients in treatment arm; n = number of observations; SD = standard deviation; Q1 = first quartile; Q3 = third quartile; Min = minimum; Max = maximum.

In the Velphoro group, 46 patients (70%) received tablets only, 10 (15%) received oral powder, and 10 (15%) received a combination of the two formulations.

**Categorization of Adverse Events**

The Applicant categorized adverse events (AEs) and serious AEs (SAEs) by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1. A treatment-emergent adverse event (TEAE) was defined as an AE that occurred or worsened on or after the first dose of study drug. AEs were collected from the time of informed consent until the last study follow-up visit. AEs of special interest (AESI) included diarrhea, potential of iron accumulation, masking of gastrointestinal bleeding due to discolored stool, events that could be linked to deficiencies in growth and skeletal development, and review of bone markers.

**Overall Adverse Event Summary**

Overall, 267 TEAEs were reported in 64 patients (75%) including 204 TEAEs in 50 patients (76%) in the Velphoro group (Table 15). Most reported AEs were mild or moderate in severity. SAEs occurred in 18 patients (27%) in the Velphoro group. Twelve patients (18%) in the Velphoro group and six (32%) in Phoslyra discontinued study drug because of AEs. The most common TEAEs (incidence ≥5%) in the Velphoro group were diarrhea in 12 patients (18%), nausea in eight (12%), vomiting in six (9%), constipation in four (6%), hypercalcemia in four (6%), and hypertension in six (9%).

Table 15. Overview of Treatment-Emergent Adverse Events Until End of Stage 2, Safety Population

| | PA21 (N = 66) | | Phoslyra (N = 19) | |
|---|---|---|---|---|
| | n (%) | E | n (%) | E |
| Any TEAE | 50 (75.8) | 204 | 14 (73.7) | 63 |
| Any treatment-related TEAE | 26 (39.4) | 50 | 7 (36.8) | 13 |
| Any serious TEAE | 18 (27.3) | 43 | 3 (15.8) | 9 |
| Any severe TEAE | 13 (19.7) | 30 | 3 (15.8) | 4 |
| Any TEAE Leading to Death | 0 | 0 | 0 | 0 |
| Any TEAE Leading to Study Drug Withdrawal | 12 (18.2) | 19 | 6 (31.6) | 8 |

Source: Applicant's Table 37, PA-CL-PED-01 Clinical Study Report V1.0.
Abbreviations: TEAE = treatment-emergent adverse event; N = total number of patients in treatment arm; E = total number of events; n = number of patients, each patient counts only once for each adverse event.

Review of TEAEs by age group did not reveal any obvious patterns; however, sample sizes were limited (Table 16).

Table 16. Overview of Treatment-emergent Adverse Events by Age at Randomization Until the End of Stage 2, Velphoro Group, Safety Population

| | PA21 | | |
|---|---|---|---|
| | Age (years) ≥2-<6 (N = 6) | Age (years) ≥6-<12 (N = 17) | Age (years) ≥12-≤18 (N = 43) |
| | n (%) E | n (%) E | n (%) E |
| Any TEAE | 4 (66.7) 13 | 14 (82.4) 54 | 32 (74.4) 137 |
| Any treatment-related TEAE | 2 (33.3) 5 | 7 (41.2) 15 | 17 (39.5) 30 |
| Any serious TEAE | 0 (0.0) 0 | 6 (35.3) 11 | 12 (27.9) 32 |
| Any severe TEAE | 1 (16.7) 1 | 6 (35.3) 10 | 6 (14.0) 19 |
| Any TEAE Leading to Death | 0 (0.0) 0 | 0 (0.0) 0 | 0 (0.0) 0 |
| Any TEAE Leading to Study Drug Withdrawal | 2 (33.3) 3 | 5 (29.4) 8 | 5 (11.6) 8 |

Source: Applicant's Table 45, PA-CL-PED-01 Clinical Study Report V1.0.
Abbreviations: TEAE = treatment-emergent adverse event; N = total number of patients in treatment arm; E = total number of events; n = number of patients, each patient counts only once for each adverse event.

**Deaths**
There were no deaths in the study.

**Non-Fatal Serious Adverse Events**
SAEs occurred in 18 patients (27%) in the Velphoro group and three (16%) in Phoslyra (Table 17). The most common SAEs that occurred in more than one patient in the Velphoro group were hypertension (5 patients [8%]), device malfunction (2 patients [3%]), and weight increased (2 patients [3%]); no SAEs occurred in more than one patient in the Phoslyra group. These are not unexpected events in a population such as this.

Table 17. Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term Until End of Stage 2, Safety Population

| System Organ Class<br>Preferred Term | PA21<br>(N=66)<br>n (%) E | Phoslyra<br>(N=19)<br>n (%) E |
|---|---|---|
| Any serious TEAEs | 18 (27.3) 43 | 3 (15.8) 9 |
| Investigations | 5 (7.6) 5 | 1 (5.3) 1 |
| Weight increased | 2 (3.0) 2 | 0 (0.0) 0 |
| Blood creatinine increased | 1 (1.5) 1 | 0 (0.0) 0 |
| Blood pressure increased | 1 (1.5) 1 | 0 (0.0) 0 |
| Glomerular filtration rate decreased | 1 (1.5) 1 | 0 (0.0) 0 |
| Weight decreased | 0 (0.0) 0 | 1 (5.3) 1 |
| Vascular disorders | 5 (7.6) 9 | 1 (5.3) 1 |
| Hypertension | 5 (7.6) 6 | 0 (0.0) 0 |
| Hypotension | 1 (1.5) 1 | 0 (0.0) 0 |
| Vena cava thrombosis | 1 (1.5) 1 | 0 (0.0) 0 |
| Venous thrombosis | 1 (1.5) 1 | 0 (0.0) 0 |
| Malignant hypertension | 0 (0.0) 0 | 1 (5.3) 1 |
| Gastrointestinal disorders | 3 (4.5) 3 | 2 (10.5) 2 |
| Gastritis | 1 (1.5) 1 | 0 (0.0) 0 |
| Ileus | 1 (1.5) 1 | 0 (0.0) 0 |
| Small intestinal obstruction | 1 (1.5) 1 | 0 (0.0) 0 |
| Small intestinal perforation | 0 (0.0) 0 | 1 (5.3) 1 |
| Vomiting | 0 (0.0) 0 | 1 (5.3) 1 |
| General disorders and administration site conditions | 3 (4.5) 3 | 1 (5.3) 1 |
| Catheter site haematoma | 1 (1.5) 1 | 0 (0.0) 0 |
| Oedema peripheral | 1 (1.5) 1 | 0 (0.0) 0 |
| Puncture site reaction | 1 (1.5) 1 | 0 (0.0) 0 |
| Pyrexia | 0 (0.0) 0 | 1 (5.3) 1 |
| Infections and infestations | 3 (4.5) 5 | 0 (0.0) 0 |
| Device related sepsis | 1 (1.5) 1 | 0 (0.0) 0 |
| Sepsis | 1 (1.5) 2 | 0 (0.0) 0 |
| Superinfection | 1 (1.5) 1 | 0 (0.0) 0 |
| Tonsillitis streptococcal | 1 (1.5) 1 | 0 (0.0) 0 |
| Injury, poisoning and procedural complications | 3 (4.5) 3 | 0 (0.0) 0 |
| Arteriovenous fistula site complication | 1 (1.5) 1 | 0 (0.0) 0 |
| Arteriovenous fistula site haematoma | 1 (1.5) 1 | 0 (0.0) 0 |
| Arteriovenous fistula thrombosis | 1 (1.5) 1 | 0 (0.0) 0 |

| System Organ Class<br>Preferred Term | PA21<br>(N=66)<br>n (%) E | Phoslyra<br>(N=19)<br>n (%) E |
|---|---|---|
| Product issues | 3 (4.5) 4 | 1 (5.3) 2 |
| Device malfunction | 2 (3.0) 3 | 0 (0.0) 0 |
| Device extrusion | 1 (1.5) 1 | 0 (0.0) 0 |
| Device occlusion | 0 (0.0) 0 | 1 (5.3) 2 |
| Cardiac disorders | 2 (3.0) 2 | 0 (0.0) 0 |
| Bradycardia | 1 (1.5) 1 | 0 (0.0) 0 |
| Cardiac tamponade | 1 (1.5) 1 | 0 (0.0) 0 |
| Metabolism and nutrition disorders | 2 (3.0) 3 | 1 (5.3) 2 |
| Fluid overload | 2 (3.0) 2 | 0 (0.0) 0 |
| Decreased appetite | 1 (1.5) 1 | 0 (0.0) 0 |
| Dehydration | 0 (0.0) 0 | 1 (5.3) 1 |
| Electrolyte imbalance | 0 (0.0) 0 | 1 (5.3) 1 |
| Renal and urinary disorders | 2 (3.0) 3 | 0 (0.0) 0 |
| Azotaemia | 1 (1.5) 1 | 0 (0.0) 0 |
| End stage renal disease | 1 (1.5) 1 | 0 (0.0) 0 |
| Hydronephrosis | 1 (1.5) 1 | 0 (0.0) 0 |
| Eye disorders | 1 (1.5) 1 | 0 (0.0) 0 |
| Papilloedema | 1 (1.5) 1 | 0 (0.0) 0 |
| Nervous system disorders | 1 (1.5) 1 | 0 (0.0) 0 |
| Benign intracranial hypertension | 1 (1.5) 1 | 0 (0.0) 0 |
| Respiratory, thoracic and mediastinal disorders | 1 (1.5) 1 | 0 (0.0) 0 |
| Lung disorder | 1 (1.5) 1 | 0 (0.0) 0 |

Source: Applicant's Table 50, PA-CL-PED-01 Clinical Study Report V1.0.
Abbreviations: TEAE = treatment-emergent adverse event; N = total number of patients in treatment arm; E = total number of events; n = number of patients.
Notes: System organ classes (SOCs) are sorted in descending frequency as reported in PA21 column; Preferred terms (PTs) are sorted in descending frequency within system organ class. If a patient experienced more than 1 event in a given SOC, that patient is counted once for the SOC. If a patient experienced more than 1 event with a given PT, that patient is counted only once for that PT.

Three gastrointestinal SAEs (gastritis, ileus, and small intestinal obstruction) occurred in three patients ((b) (6)). No patient discontinued Velphoro because of these SAEs and review of these events did not reveal an obvious association with study drug (see Appendix).

**Dropouts or Discontinuations Due to Adverse Events**

Overall, 18 patients (21%) discontinued study drug because of AEs, 12 (18%) in the Velphoro group and six (32%) in Phoslyra. All but one patient (Velphoro group) discontinued study drug during the dose titration phase. The most common AEs leading to study drug discontinuation in the Velphoro group were diarrhea (9%), nausea (3%), and vomiting (3%). In contrast, in the Phoslyra group, the most common were hypercalcemia (16%) and hyperphosphatemia (11%). Among patients 2 to <6, 6 to <12, and 12 to 18 years of age, 2 (33%), 5 (29%) and 4 (9%) patients, respectively, in the Velphoro group, and 0, 3 (60%) and 3 (23%) patients, respectively, in the Phoslyra group discontinued study drug because of

an AE. Review of all the study drug discontinuations due to an AE did not identify any new risks or raise concern for a previously unidentified risk.

**Adverse Events of Special Interest**

The Applicant also conducted analyses of Adverse Events of Special Interest (AESI); these events as well as the terms used to identify these events are shown in Table 18.

Table 18. Adverse Events of Special Interest

| Events of Special Interest | MedDRA |
|---|---|
| Diarrhoea | MedDRA PT:<br>• Diarrhoea |
| Potential of iron accumulation | MedDRA PT:<br>• Cardiac iron overload<br>• Haemochromatosis<br>• Haemosiderosis<br>• Hereditary haemochromatosis<br>• Hepatic siderosis<br>• Iron overload<br>• Pulmonary haemosiderosis<br>• Superficial siderosis of central nervous system |
| Masking of GI bleeding due to discoloured stool | MedDRA PT:<br>• Faeces discoloured<br>MedDRA SMQs:<br>• SMQ GI haemorrhage |
| Events that could be linked to (deficiencies in) growth and skeletal development and review of bone markers | SOC: Musculoskeletal and connective tissue disorders<br>• HLT: Bone disorders NEC (from HLGT Bone disorders (excl congenital and fractures))<br>• HLT: Metabolic bone disorders NEC (from HLGT Bone disorders (excl congenital and fractures))<br>• HLGT: Fractures<br><br>SOC: Metabolism and nutrition disorders<br>• HLT: Bone metabolism disorders (HLGT: Bone, calcium, magnesium and phosphorus metabolism disorders)<br>• HLT: Calcium metabolism disorders (HLGT: Bone, calcium, magnesium and phosphorus metabolism disorders) |

Source: Applicant's Table 15, PA-CL-PED-01 Clinical Study Report V1.0.
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred term; GI = Gastrointestinal; SMQ = Standard MedDRA query; SOC = System organ class; HLT = High-level term; NEC = Not elsewhere classified; HLGT = High-level group term.

AESI were reported in 21 patients (25%) including 17 patients (26%) in the Velphoro group and four (21%) in Phoslyra (Table 19). In the Velphoro group, AESIs that were reported in >5% of patients were diarrhea (18%) and hypercalcemia (6%). Less common AESIs included feces discolored (3%), hematochezia (2%), and hypocalcemia (2%). There were no AESI that mapped to the Preferred Terms for

iron accumulation, SMQ GI hemorrhage, or SOC musculoskeletal and connective tissue disorders. One event of diarrhea in the Velphoro group was severe; all other events were mild or moderate in severity.

Table 19. Adverse Events of Special Interest by System Organ Class and Preferred Term Until End of Stage 2, Safety Population

| System Organ Class<br>Preferred Term | PA21<br>(N=66)<br>n (%) E | Phoslyra<br>(N=19)<br>n (%) E |
|---|---|---|
| Any Treatment-Emergent Adverse Events | 17 ( 25.8) 22 | 4 ( 21.1) 4 |
| Gastrointestinal disorders | 13 ( 19.7) 17 | 0 ( 0.0) 0 |
| Diarrhoea | 12 ( 18.2) 14 | 0 ( 0.0) 0 |
| Faeces discoloured | 2 ( 3.0) 2 | 0 ( 0.0) 0 |
| Haematochezia | 1 ( 1.5) 1 | 0 ( 0.0) 0 |
| Metabolism and nutrition disorders | 5 ( 7.6) 5 | 4 ( 21.1) 4 |
| Hypercalcaemia | 4 ( 6.1) 4 | 4 ( 21.1) 4 |
| Hypocalcaemia | 1 ( 1.5) 1 | 0 ( 0.0) 0 |

Source: Applicant's Table 14.3.1.21, PA-CL-PED-01 Primary Analysis Report V1.0.
Abbreviations: E = Total number of adverse events; N = Total number of patients in treatment arm; n = number of patients with adverse event.

**Safety Summary and Conclusion**

Previously identified safety concerns/side effects of Velphoro in adult patients with CKD on dialysis include discolored feces, diarrhea, and nausea. In the pediatric study, the most common AE leading to withdrawal of study drug was diarrhea. The safety profile of Velphoro in pediatric patients was generally similar to that observed in adult patients.

(b) (4)

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(b) (4)

## 5. Additional Information

### 5.1 Review Team

| Role | Name |
|---|---|
| Regulatory Project Manager | Sabry Soukehal * |
| Nonclinical Reviewer | Baichun Yang* |
| Nonclinical Team Leader | Xuan Chi* |
| Clinical Pharmacology Reviewer | Li Wang |
| Clinical Pharmacology Team Leader | Sudharshan Hariharan* |
| Clinical Pharmacology Deputy Division Director | Doanh Tran |
| Clinical Reviewer | Kirtida Mistry |
| Statistical Reviewer | Ling-Wan Chan* |
| Statistical Team Leader | Jialu Zhang* |
| Secondary Clinical Reviewer and Signatory | Aliza Thompson |

*Participated in relevant discussions during the review but did not author the review.

## 5.2 Appendix

Table 25. Change in Serum Phosphorus Level (mg/dL) from Baseline to End of Stage 1 in the Velphoro Group, by Age at Randomization and Serum Phosphorus at Baseline According to Age-related Normal Range, FAS Population

| Statistics | Velphoro (N=65) ≥2 to <6 Years BL-P above normal range (n=5) | ≥2 to <6 Years BL-P below/within normal range (n=1) | ≥6 to <12 Years BL-P above normal range (n=12) | ≥6 to <12 Years BL-P below/within normal range (n=5) | ≥12 to ≤18 Years BL-P above normal range (n=23) | ≥12 to ≤18 Years BL-P below/within normal range (n=19) |
|---|---|---|---|---|---|---|
| Mean (SD) | (b) (4) | | | | | |
| Median | | | | | | |
| Q1, Q3 | | | | | | |
| Min, Max | | | | | | |
| Mean (SD) | | | | | | |
| Median | | | | | | |
| Q1, Q3 | | | | | | |
| Min, Max | | | | | | |
| Mean (SD) | | | | | | |
| Median | | | | | | |
| Q1, Q3 | | | | | | |
| Min, Max | | | | | | |
| LS Mean (SE) | | | | | | |
| 95% CI | | | | | | |

Source: Applicant's PA-CL-PED-01 Clinical Study Report V1.0 (Table 28, page 132).
Abbreviations: FAS=Full Analysis Set; N=total number of patients; n=number of observations; SD=standard deviation; Q1=first quartile; Q3=third quartile; Min=minimum; Max=maximum; LS=least squares; SE=standard error.

### Narratives for Patients 2 to <6 Years of Age

- (b) (6): 4-year-old patient with baseline serum phosphorus 9.4 mg/dL. The patient was on a phosphorus binder before this study, and received Velphoro for 19 days during Stage 1, then discontinued treatment because the family moved out of the city. No dose adjustment was performed in this patient.

- (b) (6) 23-month-old male with history of CAKUT, phosphate-binder naïve at enrollment, on hemodialysis. The patient received Velphoro powder 500 mg/day from Day 1 to 9. On Day 9 he developed moderate non-serious vomiting and pyrexia. He received the last dose of Velphoro on Day 9 (treatment withdrawn because of AEs). The AEs recovered on Day 10. The patient was withdrawn from the study on Day 54 due to kidney transplant.

- (b) (6) 3-year-old patient with baseline serum phosphorus 6.2 mg/dL, phosphate-binder naïve at enrollment. The patient was treated for 28 days during Stage 1 (168 days in total) and completed the study as per protocol. No dose adjustment was performed. Compliance during Stage 1 was 81%. The change in serum phosphorus from baseline to the end of Stage 1 was -1.5 mg/dL.

- (b) (6) 5-year-old patient with baseline serum phosphorus 8.2 mg/dL, was on a binder before enrollment. The patient was treated for 45 days in Stage 1 (213 days in total) and completed the

study as per protocol. Dose adjustments for efficacy were performed three times. Compliance during Stage 1 was 97%. The change in serum phosphorus from baseline to the end of Stage 1 was (b) (4) mg/dL. The serum phosphorus value used to assess the change at end of Stage 1 was the value at Visit 8 (b) (4) mg/dL) based on the rule described in the Statistical Analysis Plan for defining the time window of the analysis visits. The Applicant notes that serum phosphorus decreased at subsequent visits (b) (4) mg/dL at Unscheduled Visit 8 with a change from baseline of (b) (4) mg/dL).

- (b) (6) 24-month-old female with CAKUT, was on a calcium-based binder, not on dialysis. On Day 1 she started Velphoro 500 mg/d. On Day 3 she had mild soft stools but continued the same dose of Velphoro. On Day 18 the Velphoro was increased to 750 mg/day. She had mild diarrhea on Day 25. Velphoro was continued and on Day 36 the diarrhea resolved. On Day 40, she had mild diarrhea, which recovered on Day 43. Velphoro was continued. On Day 53 mild diarrhea recurred and Velphoro was discontinued because of the AE of diarrhea (last day Velphoro was Day 53). Diarrhea resolved on Day 55. The patient was withdrawn from the study on Day 74 because of moderate AE diarrhea. Compliance during Stage 1 was 93%. The change in serum phosphorus from baseline to the end of Stage 1 was (b) (4) mg/dL. According to the Applicant serum phosphorus assessment at the end of Stage 1 was performed few days after last dose of Velphoro.

- (b) (6) 5-year-old patient with baseline serum phosphorus 9.2 mg/dL, phosphate binder naïve at enrollment. The patient was treated for 9 days in Stage 1 (9 days in total) and was discontinued due to withdrawal by parent/guardian. No dose adjustment was performed in this patient. Serum phosphorus assessment at the end of Stage 1 was performed one day after last dose of PA21.

**Narratives for SAEs of Interest**

- (b) (6) 15-year-old female with a history of CKD secondary to focal and segmental glomerulosclerosis (FSGS) on hemodialysis, facial edema, hypocalcemia, vitamin D deficiency, anemia, hyperthyroidism, nephrotic syndrome, hypertension, and left radial arteriovenous fistula (AVF). The patient was on concomitant ascorbic acid, cholecalciferol, cyanocobalamin, folic acid, levocarnitine, vitamin-B complex, sodium bicarbonate, morphine, esomeprazole, enoxaparin, sodium polystyrene sulfonate, and alfacalcidol. She was not on a phosphate binder before enrollment. On Day 1, Velphoro chewable tablets 1250 mg/day were started and increased to 1750 and 2000 mg/day on Days 8 and 13, respectively. On Day 14, she was hospitalized for management of an AVF thrombosis and Velphoro dosing was interrupted. On Day 17, the patient developed SAEs of ileus and “pneumopathy.” She was treated with enoxaparin sodium, oxygen, nasogastric tube, darbepoetin alfa, and creation of an AVF (Day 34). Velphoro was restarted on Day 23 at 2000 mg/day. The ileus and lung disorder were reported as recovered on Day 27 and AVF thrombosis recovered on Day 34. On Days 41 and 48, the Velphoro dose was increased for efficacy to 2750 and 3000 mg/day, respectively. The patient received the last dose of Velphoro on Day 70 and was withdrawn from the study on Day 87 for lack of efficacy.

- (b) (6) 16-year-old female with a history of CKD secondary to nephronophthisis on hemodialysis, diabetes mellitus, and pulmonary embolism. Concomitant medications included vitamin B-complex, levocarnitine, cyanocobalamin, ascorbic acid, darbepoetin alfa, saccharated

iron oxide, amlodipine besylate, acebutolol hydrochloride, enoxaparin sodium, sodium bicarbonate, and alfacalcidol. The patient was not on phosphate binders prior to enrollment. On Day 1, Velphoro chewable tablets 1250 mg/day were started and on Day 10 the formulation was changed to oral powder (same dose). The patient was hospitalized on Day 10 for gastritis (mild severity) and treated with omeprazole. The gastritis was reported as recovered on Day 12. There was no change in the dose of Velphoro due to the SAE of gastritis. On Days 20 and 27, Velphoro dose was increased to 1750, and 2250 mg/day, respectively. On Day 29, the patient developed an AE of hyperglycemia. The patient received the last dose of Velphoro on Day 40 and the investigator withdrew the patient from the study on Day 59 because of non-compliance with the study drug.

- (b) (6): 13-year-old male with a history of CKD secondary to obstructive uropathy on hemodialysis, metabolic acidosis, CKD mineral and bone disorder, anemia, hyperparathyroidism, immunodeficiency due to past transplantation, secondary hypertension, pericardial effusion, orthopnea, bronchial hyperreactivity, and seizures on concomitant diazepam. Hyperphosphatemia was previously treated with calcium carbonate. The patient's serum phosphorus was (b) (4) mg/dL during washout and (b) (4) mg/dL at baseline. He was randomized to Velphoro and started chewable tablets 1250 mg/day on Day 1. On Day 16, the patient underwent a diagnostic laparoscopy and was diagnosed with small bowel obstruction secondary to adhesions, which was assessed as severe and serious due to need for hospitalization for surgical intervention. The Velphoro dose was temporarily interrupted from Day 17 to Day 22. On Day 19, the outcome of the small bowel obstruction was reported as recovered. On Day 23, Velphoro chewable tablets 1250 mg/day were restarted. On Days 46, 127, 156, and 197 the dose was increased for efficacy to 1500, 1750, 2000, and 2250 mg/day, respectively. The patient received the last dose of Velphoro on Day 239 and completed the study on Day 258. He did not experience any other AEs. The investigator considered the small bowel obstruction to be unlikely related to the study drug.

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