17 September 2020
EMA/522604/2020 Corr.1
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Velphoro

Common name: sucroferric oxyhydroxide

Procedure No. EMEA/H/C/002705/X/0020/G

Note

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

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List of abbreviations

Alb	albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	Area under the concentration-time curve
BW	body weight
Chol	cholesterol
CKD	Chronic kidney disease
Cmax	Peak plasma concentration
Crea	creatinine
CRF	Chronic renal failure
CYP	Cytochrome P450
DDI	Drug-drug interaction
DPD	Deoxypyrodinoline
EMA	European Medicines Agency (previously EMEA)
ESRD	End stage renal disease
Epi	epithelium
FDA	Food and Drug Administration
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GRAS	Generally regarded as safe
Hb	haemoglobin
Hct	haematocrit
hERG	Human ether-a-go-go related gene
ICH	International Conference on Harmonisation
LN	lymph node
Macroph	macrophage
MCH	mean cell haemoglobin
MCHC	mean cell haemoglobin concentration
MCV	mean cell volume
Mesen	mesenteric
m/m	Mass per mass
NOEL	No observed effect level
NOAEL	No observed adverse effect level
PDE	Permitted daily exposure
Ph. Eur.	European Pharmacopoeia
Phos	phosphate
PT	prothrombin time
PTH	Parathyroid hormone
RBC	red blood cell
Retic	reticulocyte
RES	Reticulo-endothelial system
SCFA	Short-chain fatty acids
SG	specific gravity

TG	triglyceride
TIBC	total iron binding capacity
TIM TNO	gastrointestinal model of stomach and small intestine (TIM-1) and large intestine (TIM-2)
US	United States
USP	United States Pharmacopoeia
Vol	Volume

1. Background information on the procedure

1.1. Submission of the dossier

Vifor Fresenius Medical Care Renal Pharma France submitted on 20 August 2019 a group of variation(s) consisting of extensions of the marketing authorisation and the following variation:

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH applied for an addition of a new pharmaceutical form with a new strength -powder for oral suspension 125 mg.

In addition, the MAH proposed an extension of indication to add an indication to use Velphoro for the control of serum phosphorus levels in paediatric patients 2 years of age and older with CKD stages 4-5 (defined by a glomerular filtration rate <30 mL/min/1.73 m2) or with CKD on dialysis, based on the results from an open-label, randomised, active-controlled, parallel group, multicentre, phase 3 study investigating the safety and efficacy of Velphoro and calcium acetate in paediatric and adolescent CKD patients with hyperphosphataemia (Study PA-CL-PED-01). As a consequence, sections 4.1, 4.2, 4.8, and 5.1 of the SmPC are updated. The RMP version 7.0 has also been submitted. The Package Leaflet and Labelling are updated in accordance.

Furthermore, the list of local representatives was updated, and the PI is brought in line with the latest QRD template version 10.1

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) points (c) and (d) - Extensions of marketing authorisations

And Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Information on Paediatric requirements

Pursuant to Regulation (EC) No 1901/2006, the application included an EMA Decision(s) **P/0196/2018** on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP **P/0196/2018** was completed.

The PDCO issued an opinion on compliance for the PIP **P/0196/2018.**

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Additional Marketing protection

The MAH requested consideration of one year marketing protection in regards of its application for a new indication in accordance with Article 10(1) of Directive 2001/83/EC / Article 14(11) of Regulation (EC) No 726/2004.

Scientific advice

No scientific advice with regard to the proposed paediatric indication had been requested.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Simona Stankeviciute

The application was received by the EMA on	20 August 2019
The procedure started on	3 October 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	20 December 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	20 December 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	27 December 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 January 2020
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	30 January 2020
The MAH submitted the responses to the CHMP consolidated List of Questions on	24 April 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	27 May 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 June 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	25 June 2020
The MAH submitted the responses to the CHMP List of Outstanding Issues on	18 August 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	02 September 2020
The outstanding issues were addressed by the MAH during an oral	n/a

explanation before the CHMP during the meeting on	
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Velphoro on	17 September 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Within this procedure, the MAH proposes the following new additional therapeutic indication:

"Velphoro is indicated for the control of serum phosphorus levels in paediatric patients 2 years of age and older with CKD stages 4-5 (defined by a glomerular filtration rate <30 mL/min/1.73 m^2) or with CKD on dialysis."

2.1.2. Epidemiology and risk factors, screening tools/prevention

Hyperphosphataemia in chronic kidney disease (CKD)

Hyperphosphataemia is a common and serious complication in patients with CKD, particularly those with end-stage renal disease (ESRD) requiring dialysis, and it occurs in over 70% of ESRD patients.

2.1.3. Biologic features

Hyperphosphatemia plays an important role in the pathophysiology of major CKD complications, such as secondary hyperparathyroidism, mineral and bone disorder (MBD) and cardiovascular disease. Complications most relevant to the paediatric population are renal bone disease, cardiovascular disease and growth failure. High serum phosphorus levels are considered a risk factor for mortality, morbidity and hospitalisation in patients with ESRD.

2.1.4. Clinical presentation

See chapter above.

2.1.5. Management

Transplantation is the preferred treatment for ESRD in the paediatric population, and dialysis is used for the relatively limited period while awaiting a transplant, or in patients not qualifying for renal transplantation. However, the waiting period before transplantation is variable. Kovalski et al., 2007 reported that more than 75% of children require chronic dialysis while awaiting transplantation, with waiting periods varying between a few months and several years. Hyperphosphatemia cannot be satisfactorily controlled by dietary restriction alone in these patients. Protein restriction is not effective in slowing the progression of CKD in children and is generally not recommended due to the possibility

of adverse effects on growth and development. In addition, dialysis is not particularly effective in removing phosphate, as phosphates are mainly stored intracellularly after gastrointestinal (GI) absorption; hence, it is necessary to employ therapeutic means of binding phosphate to reduce dietary uptake.

For adults, several phosphate binders are currently available for treating hyperphosphatemia with CKD and on dialysis (haemodialysis (HD), peritoneal dialysis (PD)). Calcium salts are widely used, but their use is limited by the development of hypercalcaemia, which has been reported to occur in over 50% of CKD patients on HD. Furthermore, calcium salts exacerbate hypercalcaemia caused by resorption of calcium from the bones, particularly in patients receiving active Vitamin D metabolites (which increase intestinal calcium absorption) or when bone turnover is low. Together with raised phosphorus levels, this may contribute to vascular calcification and arterial and coronary sclerosis. For this reason, it has been suggested that calcium-based phosphate binders should be avoided in many, if not most, adult patients undergoing dialysis. Use of calcium salts may also result in over-suppression of parathyroid hormone. Aluminium salts are rarely used today and are associated with toxicity related to aluminium absorption which may lead to Vitamin D-resistant osteomalacia and neurological problems such as encephalopathy and dementia. Newer phosphate binder products include sevelamer hydrochloride, sevelamer carbonate and lanthanum carbonate. Sevelamer is a non-absorbable, cationic polymer capable of reversibly binding anions such as phosphate. It is effective in reducing phosphorus levels, but has a relatively high pill burden, requires swallowing of large tablets without chewing. Lanthanum carbonate appears to be well tolerated and has a reduced pill burden compared to sevelamer.

In children, the use of phosphate binders for treatment of hyperphosphatemia with advanced CKD is widespread, but not all of these substances are approved in this population. To date, only sevelamer powder for oral suspension is approved for children >6 years of age. The National Kidney Foundation (NKF) (Kidney Disease Improving Global Outcomes (KDIGO) CKD-MBD Guidelines and Kidney Disease Outcomes Quality Initiative (KDOQI) Guidelines) and the UK National Institute for Health and Clinical Excellence recommend the use of phosphate binders in children. Calcium-based phosphate binders are recommended by these guidelines as the first choice, in addition to dietary management. Hence, although used off-label, with these medicinal products, is most experience in children in clinical practice. Their use is, however, associated with the risk of hypercalcaemia.

About the product

Velphoro contains sucroferric oxyhydroxide, also known as, PA21 or a mixture of polynuclear iron (III)-oxyhydroxide (pn-FeOOH), sucrose and starches. It is an iron-based phosphate binder for oral administration. Phosphate binding takes place by ligand exchange between hydroxyl groups and/or water and the phosphate ions throughout the physiological pH range of the gastrointestinal tract. Serum phosphorus levels are reduced as a consequence of the reduced dietary phosphate absorption.

Velphoro is currently approved as 500 mg chewable tablets for use in adults only. The MAH, Vifor Fresenius Medical Care Renal Pharma France (VFMCRP), submitted a grouped extension/ type II variation application for authorisation of a new pharmaceutical form of a powder for oral suspension with a new strength 125 mg for a separate indication in the paediatric population from 2 years of age with CKD with hyperphosphatemia.

Therefore, the MAH provided results of a quality-related study for the development of the powder for oral suspension and results of study PA-CL-PED-01, which is an open-label, randomised, multicentre, active-controlled parallel group trial to evaluate efficacy and safety of PA21 in children from birth to less than 18 years of age with hyperphosphatemia in chronic kidney disease, with a 24-week open-label extension to evaluate safety.

Based on these study data, the MAH applies/requests for the authorization of:

- a new pharmaceutical form of an oral powder suspension associated with a new strength 125 mg, for a separate indication in paediatric CKD patients aged 2 years and older with hyperphosphataemia,
- an update of the SmPC for the existing 500 mg chewable tablets with the paediatric indication,
- consequential changes to SmPC sections 4.1, 4.2, 4.8 and 5.1 and patient leaflet and an updated version of the RMP 7.0, and
- an extended marketing protection period for a new indication of significant clinical benefit in comparison to existing therapies.

The current therapeutic indication is:

"Velphoro is indicated for the control of serum phosphorus levels in adult chronic kidney disease (CKD) patients on haemodialysis (HD) or peritoneal dialysis (PD). Velphoro should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxy vitamin D3 or one of its analogues, or calcimimetics to control the development of renal bone disease."

Velphoro is currently only indicated in adult patients. The safety and efficacy of Velphoro in children and adolescents below the age of 18 years has not yet been established. No data were available.

Within this procedure, the MAH proposes the following new additional therapeutic indication:

"Velphoro is indicated for the control of serum phosphorus levels in paediatric patients 2 years of age and older with CKD stages 4-5 (defined by a glomerular filtration rate <30 mL/min/1.73 m2) or with CKD on dialysis."

Type of Application and aspects on development

Scientific advice

No scientific advice with regard to the proposed paediatric indication has been requested.

Paediatric Investigation Plan (PIP)

Within this application, the MAH submits final results for an agreed Paediatric Investigation Plan (PIP) for Velphoro® (PA21), EMA PIP number EMEA-001061-PIP01-10-M03, as approved on 17 July 2018 (EMA decision P/0196/2018) and requests verification of compliance with the agreed PIP as a part of the validation of this line extension application.

2.2. Quality aspects

2.2.1. Introduction

The present application concerns a line-extension of the already authorised product Velphoro 500 mg, chewable tablets using the same active substance. The MAH applied for the addition of a new pharmaceutical form with a new strength -oral powder in sachet 125 mg for paediatric patients.

The finished product is presented as an oral powder in sachet containing 125 mg iron (as sucroferric oxyhydroxide also known as a mixture of polynuclear iron (III)-oxyhydroxide, sucrose, and starches (potato starch and pregelatinized maize starch)) as active substance.

Other ingredients are: maltodextrin, microcrystalline cellulose, xanthan gum, colloidal anhydrous silica and magnesium stearate.

The product is available in child-resistant twin single-dose polyethylene terephthalate / aluminium / polyethylene laminate sachets.

2.2.2. Active Substance

The active substance (PA21) is a mixture of iron (III)-oxyhydroxide, sucrose and starches (polynuclear iron (III)-oxyhydroxide stabilised with sucrose and starches). A mixture of pregelatinised starch and potato starch is used. The active substance part of the dossier remains the same as for the authorised Velphoro 500 mg chewable tablets, except for minor changes and corrections of typing errors to the specification of the raw material and minor textual change in section 3.2.S.3.2 that are part of the variation application. These changes are acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Velphoro oral powder in sachet consists of a reddish-brownish granulated powder which may contain white speckles in single dose sachets. The powder is suitable for suspension in water or mixing with food. The commercial product contains 125 mg iron per sachet. Velphoro oral powder is contained in child-resistant twin sachets with aluminium as water vapour barrier as the primary packaging material.

The oral powder in sachet has been developed in addition to the chewable tablets which are not considered appropriate for children less than 6 years of age by the MAH due to the tablet size and the risk of accidental choking. The quality target product profile (QTPP), an evaluation of the active substance properties and intended finished product properties has been the starting point in the development of meaningful in vitro performance tests, both for the tablet and the powder formulation. The choice of the pharmaceutical form and strength adequately addressed the clinical need. No further elements of QbD have been used.

Velphoro acts by adsorbing dietary phosphate in the GI tract, preventing its uptake into the blood, thereby reducing the serum phosphorus levels. The tablets and the granulated powder contain polynuclear iron (III)-oxyhydroxide and work by disintegrating in the upper GI tract and binding dietary phosphate on its surface, which is then eliminated via faeces. Thus, the site of action for this drug lies in the GI tract. The iron (III)-oxyhydroxide in PA21 is practically insoluble.

Characteristics of the active substance (AS) that potentially affect the finished product performance have been adequately discussed. Particle size of the active substance was not identified as critical but is controlled by laser diffraction as part of the active substance specification. The manufacturing process of the AS is well controlled and consistently produces the amorphous form which does not change upon storage.

The excipients in the formulation are well known, are widely used in oral pharmaceutical products. Compatibility studies were performed with binary mixtures of active substance with several standard excipients. The excipients colloidal silicon dioxide, woodberry flavour, magnesium stearate and neohesperidin dihydrochalcone, which are ingredients of the chewable tablet were also tested in binary mixtures. Appearance, phosphate adsorption, iron release and moisture content were evaluated showing no significant impact with the finished components. The choice of the excipients has been described and justified. The selected excipients have been shown not to impact the phosphate binding

capacity of the finished product, which is considered a relevant in vitro performance parameter. There are no direct safety issues foreseen with regards to the excipients and their quantities for use in children from 2 years of age and are considered acceptable for use in children as indicated. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Overall, the formulation development has in general been described in sufficient detail. The QTPP of the product seems logical in view of the aim to develop a suitable formulation for use in younger children where the chewable tablet formulation is less suitable. The formulation seems suitable to be used for children from the age of 2 years. The excipients are suitable, the strength of 125 mg provides sufficient dosing flexibility and the product seems to have been well accepted in the clinical studies.

During the clinical study more dose formulations (125 mg, 250 mg, 500 mg powder for oral suspension, and 250 mg, 500 mg chewable tablets) were available. The proposed strength and dose recommendations have been justified.

Velphoro 125 mg oral powder in sachet should be mixed with a small amount of soft food (such as apple sauce) or beverage and taken with meals according to the recommendation in the SmPC and taken within 30 minutes after being prepared. Results of a compatibility study of the finished product with apple sauce and tap water were provided. The compatibility was confirmed for 120 minutes at room temperature (i.e. 20-25°C). No impact on potency (iron content) and efficacy (phosphate adsorption) was seen. These results confirm the suitability of the SmPC recommendations. Although, acceptability/palatability of the finished product mixed with soft foods and beverages was not specifically investigated as part of the clinical studies, overall clinical study results were positive with regards to acceptability. This is considered sufficient. Furthermore, the feasibility of administration of the product through an enteral feeding tube (as claimed in the SmPC) has been investigated and relevant information has been included in the product information in accordance with the quality Q&A on Administration of oral immediate release medicinal products through enteral feeding tubes.

The batches of the powder formulation used in the clinical phase 3 paediatric efficacy and safety study are representative for the finished product. It has been sufficiently justified from a quality point of view that the different formulations (chewable tablet or powder) will not impact the finished product performance and no further bridging is needed.

The manufacturing process development has been adequately described. Wet granulation was selected to produce a good granulated powder for the sachet filling. Critical process parameters have been identified by a risk evaluation. Laboratory scale trials permitted the selection of the best formulation and process for scale-up. The scale-up trial confirmed the high-shear wet granulation as able to produce a good granulated powder for the sachet filling. Further optimisation trials were done with the wet granulation process by optimisation of the granulation (end point detection of the granulation) part. Optimisation of the tooling on the filling line and of the operational parameters was done and allowed the process to run with tight in-process control limits especially for the mass variation as described.

The finished product is packed in child-resistant twin single-dose polyethylene terephthalate/aluminium/ polyethylene laminate sachet. The container closure system provides suitable protection against moisture and light. The suitability of the container closure system was confirmed in the stability studies and seal integrity was demonstrated by dye-ingress testing.

During investigation it was observed that sachets cut along the drawing (diagonally at the lower right corner) could not be emptied completely and this resulted in out of specifications (OOS) for the iron content and uniformity of dosage units during the stability study. To improve the emptying of the sachet and prevent related OOS issues, the positioning of the cutting line was changed to allow for removal of the full amount of powder. The choice of the packaging has been justified. The sachet foil

composition was stated and a certificate of analysis of the sachet foil was provided. The packaging complies with EN 14375 (Version 2003). The resins of the inner layer made of PE are intended to be in contact with the product, comply with the compositional requirements of the Ph. Eur. (3.1.3 Polyolefines) and with the European Regulation No. 10/2011.

Manufacture of the product and process controls

The manufacturing process is a standard manufacturing process for solid dosage forms with wet granulation, fluid bed drying, sieving and subsequent filling into sachets. No process intermediates are isolated during the manufacturing process.

A risk assessment has been carried out with regard to the target product profile of the product, whereby the critical steps in the manufacture of the finished product have been identified and are controlled by acceptable in-process controls. Overall, the process is well under control and several batches have been manufactured with consistent quality.

The manufacture of the bulk powder has been evaluated on 20 batches at full production scale at the current manufacturing site. The sachet filling process has been evaluated on three full production scale batches. The process was shown to be adequately under control leading to finished product with consistent quality. For the current manufacturing site, the manufacturing process has been adequately validated.

The MAH submitted a change management protocol with the scope to switch to a new site for the commercial supply of the product together with some related changes in the wet granulation step by means of a post-approval variation. The protocol for this change has been provided in the dossier and is acceptable.

For the post-approval change of the manufacturing site, an adequate process validation scheme for the first three commercial batches of the 125 mg product has been provided.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for appearance (visual), suspendability (visual), identification of iron (colour reaction/precipitation-Ph. Eur.), uniformity of dosage units (Ph. Eur.), microbiological quality (Ph. Eur.), assay (complexometric titration), loss on drying (halogen moisture analyser), *in vitro* phosphate adsorption (UV), and iron release (UV).

The potential impurities of PA21 had been discussed in detail in the already approved active substance part. The active substance consists of polynuclear iron (III)-oxyhydroxide containing β-FeOOH, stabilised with sucrose, starch and pregelatinised starch. No impurities are present in the finished product which are not already present in the active substance. The effect of degradation of the components of the finished product on its pharmacological performance has been considered and found to be negligible.

A risk assessment for elemental impurities in accordance with ICH Q3D is described in the dossier. Active substance, excipients, manufacturing process and container closure system were evaluated as potential sources of elemental impurities. The starting material is identified as the main contributor of elemental impurities in the active substance. The assessment concludes that the risk of elemental impurity contribution from other sources than the active substance is negligible and the proposed control strategy for the finished product is sufficient to meet the requirements of ICH Q3D.

Risk assessment, in line with the "Questions and answers on Information on nitrosamines for marketing authorisation holders" and the "Information on nitrosamines for marketing authorisation holders" published on the EMA website, have been presented for both the finished product manufacturing process and the active substance with respect to potential formation of nitrosamine impurities. The outcome of the risk assessment confirms that there is no risk for nitrosamine impurities formation and no risk for cross-contamination with other products.

The analytical methods used have been adequately described and validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis data for nine production scale batches was provided and results complied with the specification and therefore indicate consistent manufacture of the finished product. In addition, supportive batch analysis of 14 batches of the 250 and 500 mg strengths (used in clinical studies) were also presented; all complied with the specifications.

Stability of the product

The stability studies were carried out on three commercial scale batches of Velphoro 125 mg oral powder in sachet manufactured at the proposed manufacturing site stored at long term conditions (25 °C ± 2 °C / 60 % ± 5 % RH and 30 °C ± 2 °C / 75 % ± 5 % RH) for 36 months and at accelerated conditions (40 °C ± 2 °C / 75 % ± 5 % RH) for 6 months according to the ICH guidelines.

Additional supportive stability data were presented for three batches of 500 mg oral powder in sachet (strength not intended for marketing) under the same storage conditions as supportive information.

The following parameters were investigated in the stability studies: appearance, microbiological quality, assay (iron), loss on drying, iron release, *in vitro* phosphate adsorption and uniformity of dosage units. The analytical methods used for testing the stability samples are the same as those used for release testing. The reported results complied with the specification under long term and accelerated conditions.

No clear trends were seen in any of the tested parameters at all three storage conditions. Incidental out-of-specification results (OOS) for assay and uniformity of dosage units have been observed in one of the three stability batches at a couple of time points stored under long term conditions. The observations and corrective action and preventive action (CAPA) were described in detail in the stability report. The root causes were identified, and subsequent batches were manufactured after the appropriate CAPA took place. The CAPA concerned adjustment of the sachet filling weight based on the actual iron content of the bulk and amended sachet opening instructions which allows the sachet to be completely emptied. The accelerated storage stability data indicated good chemical and physical stability. No chemical or physical changes have been observed. No OOS results have been reported.

The bulk powder was stated to be slightly hygroscopic. Although no formal photostability study for the powder formulation has been provided in the dossier, it is known from the chewable tablet formulation that both the active substance and chewable tablets were not sensitive to light exposure. It is considered justified to extrapolate these results to the powder formulation. Moreover, the finished product is packed in sachets that provide moisture as well as light protection and it is unlikely that the product will be stored outside its primary packaging. Therefore, it is not considered necessary that the need for moisture or light protection is further investigated or that a corresponding precautionary statement is included in the labelling.

Forced degradation studies were conducted on the active substance being subjected to aqueous, acidic, basic and photo stress conditions. The results of these studies which have been assessed during

the initial authorisation can be extrapolated to the finished product Velphoro 125 mg oral powder in sachet considering the nature of the active substance the formulation of the finished product and the excipient compatibility study results.

Based on the overall stability data the proposed shelf-life of 3 years without special storage conditions as per sections 6.3 and 6.4 can be accepted.

Adventitious agents

No excipients of human or animal origin are used in the manufacture of the finished product. The excipient magnesium stearate is of vegetable origin.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The manufacturing process for the finished product is non-standard and the required validation data has been provided. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that from a quality perspective the product should have a satisfactory and uniform clinical performance.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable and consistent. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

No new non-clinical studies have been submitted within this application which is considered acceptable by the CHMP.

2.3.2. Pharmacology

Non-clinical studies have shown that very little iron is released from PA21 in simulated GI) conditions representative of the fed state. Maximum release of iron (approximately 6%) has been shown to occur at pH <2, and in humans, pH levels <2 in the GI tract are normally observed in an empty stomach, i.e., in a fasting state. Since PA21 is to be administered with food, a pH <2 in the stomach will not be encountered in the normal clinical use of PA21. Moreover, only a fraction of the iron released from PA21 is expected to be absorbed. Iron absorption is a highly regulated process with physiological limits; in patients with CKD, levels of hepcidin are increased, resulting in reduced absorption of iron from the intestinal tract. Together with the low release of iron from PA21, systemic absorption of iron

from PA21 is expected to be low. As such, a conventional programme of clinical pharmacology studies has not been performed for PA21. No new Non-clinical Pharmacology studies have been submitted in this application which is considered acceptable by the CHMP.

2.3.3. Pharmacokinetics

Velphoro remains and acts locally in the GI tract. Therefore, systemic interactions are not considered likely, although they might occur in the GI tract. The approach taken was to study adsorption to PA21 and/or degradation of concomitant drugs in the presence of PA21 in vitro under physiologically relevant conditions. The low potential for PA21 to bind to or interact with an extensive number of commonly co-administered drugs and dietary components (including vitamins) has been demonstrated, and selected drugs were identified for a clinical study in vivo. No new Non-clinical Pharmacokinetic studies have been submitted in this application which is considered acceptable by the CHMP.

2.3.4. Toxicology

No new toxicology studies were submitted by the applicant. This was considered acceptable by the CHMP.

2.3.5. Ecotoxicity/environmental risk assessment

Carbohydrates like sucrose and starches are exempted because they are unlikely to result in significant risk to the environment (EMEA/CHMP/SWP/4447/00 corr 2, 2006). Therefore, only the polynuclear iron (III)-oxyhydroxide (pn-FeOOH) needs further consideration. Since Fe is an (essential) metal, the PBT assessment is not required. The default PECsw in the influent of the sewage treatment plants (STP) is estimated at 0.024 mg/L. Against a background concentration of phosphate (P) of 7 mg/L in STP influent in the Netherlands (CBS 2019), an environmental risk assessment is deemed not necessary, given the nature of the active ingredient that is bound to phosphate. It is also considered that in STP where chemical phosphate binding is required, iron salts are added to the influent water in a Fe/P ratio of 3:2. At 7 mg P/L iron would be added at a concentration of approximately 19 mg/L. Sucroferric oxyhydroxide is already used in existing marketed products and no significant increase in environmental exposure is anticipated based on above justification. Therefore, the increased use of Velphoro due to the newly added paediatric indication is not expected to pose a risk to the environment and no new ERA studies are warranted.

2.3.6. Discussion on non-clinical aspects

No new non-clinical data was submitted, and no issues are raised regarding the non-clinical aspects. Overall, the primary pharmacodynamic studies already provided with previous applications provided adequate evidence that Velphoro is efficacious for the proposed indication. The increase to the environment of velphoro due to the newly added paediatric indication does not warrant new ERA studies.

2.3.7. Conclusion on the non-clinical aspects

This application for a line extension / extension of indication is approvable from a non-clinical viewpoint.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Overview of clinical studies

One study was performed:

Study PA-CL-PED-01 was a Phase 3, multicentre, randomised, prospective, open-label, parallel-group, active-controlled study to investigate the efficacy and safety of PA21 (Velphoro®; sucroferric oxyhydroxide) for reducing serum phosphorus levels in paediatric and adolescent subjects with CKD in comparison with Phoslyra liquid solution, a calcium acetate phosphate binder, approved in the US without age restriction.

The PDCO had suggested the possibility of an additional comparison with an external control (e.g. sevelamer). The applicant made an effort for this additional comparison with an external control from paediatric Study SVCARB07609, a published Phase 2 study conducted with sevelamer carbonate (SC) in CKD patients with hyperphosphataemia (from Fathallah-Shaykh et al, 2018, and ClinicalTrials.gov NCT01574326).

2.4.2. Pharmacokinetics

The MAH did not perform new PK studies which was considered acceptable by the CHMP. This submission pertains to the agreed PIP, which were to include only single safety and efficacy study, thus no additional report was submitted on human PK. The PA21 drug substance is presented as a chewable tablet with a content of approximately 2.5 g PA21, containing 500 mg iron. Two slightly different PA21 drug formulations have been used to manufacture the PA21 chewable tablets used in the clinical studies. Comparability of the 2 drug substance formulations was demonstrated by comparison of iron release, structure, oxidation state, hydration state, particle size, batch analysis, and stability data.

In addition, a limited programme of non-clinical "bridging" studies showed that PA21-2 behaved in a similar manner to PA21-1 in terms of toxicity profile, genotoxic potential, and iron uptake/absorption.

Velphoro is almost not absorbed from the gastrointestinal tract.

PA21-2 drug substance was used to manufacture the chewable tablets used in the Phase 3 studies (PA-CL-05A/05B and PA-CL-PED-01) and in *in vivo* DDI studies. PA21-2 drug substance was also used for the powder for oral suspension used in the paediatric study PA-CL-PED-01, subject to this application.

In the Phase 3 paediatric study PA-CL-PED-01, 2 PA21 dosage forms were used: a powder for oral suspension, provided at dosage strengths of 125 mg, 250 mg and 500 mg and iron, and chewable tablets, provided at dosage strengths of 250 mg and 500 mg iron. The doses used in the paediatric study started at 125 to 1,250 mg iron depending on subject age and were up titrated to maximum doses of 1,000 to 3,000 mg iron.

The 500 mg chewable tablets used in the paediatric study PA-CL-PED-01 are similar to the registered

500 mg chewable tablets, while the 250 mg tablet is dose-proportional to the 500 mg tablet. The new powder for oral suspension was used to obtain the 500, 250 and 125 mg doses. The same drug substance as used in the registered chewable tablets, i.e. PA21-2, is used for the powder for the oral suspension. Considering the composition of the formulations, no difference in binding properties is expected.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were submitted. This was considered acceptable by the CHMP.

2.4.4. Discussion on clinical pharmacology

No new PK or PD data has been presented with this application which is considered acceptable by the CHMP. The 500 mg chewable tablets used in the paediatric study PA-CL-PED-01 are similar to the registered 500 mg chewable tablets, while the 250 mg tablet is dose proportional to the 500 mg tablet. The new powder for oral suspension was used to obtain the 500, 250 and 125 mg doses. The same drug substance as used in the registered chewable tablets, i.e. PA21-2, is used for the powder for the oral suspension. Considering the composition of the formulations, no difference in binding properties is expected.

2.4.5. Conclusions on clinical pharmacology

The application is considered approvable from a pharmacological viewpoint.

2.5. Clinical efficacy

2.5.1. Dose response studies

The MAH did not perform dedicated dose-response studies, this was considered acceptable by the CHMP.

2.5.2. Main study

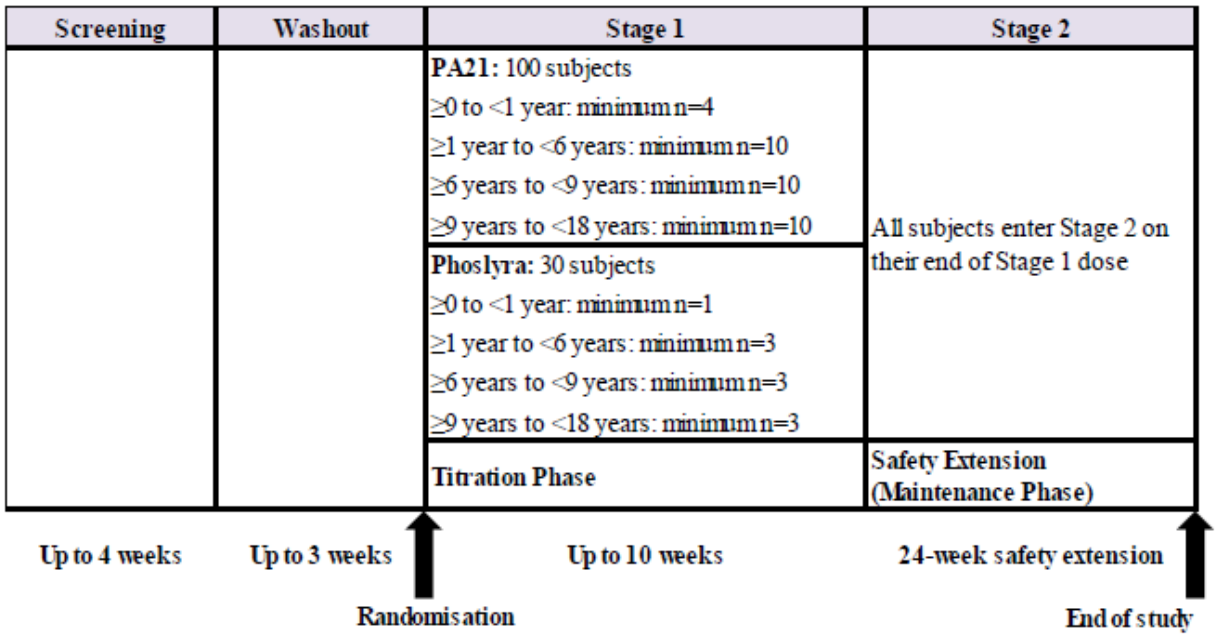
Study PA-CL-PED-01

Study PA-CL-PED-01 was a Phase 3, multicentre, randomised, prospective, open-label, parallel-group, active-controlled study to investigate the efficacy and safety of PA21 (Velphoro®; sucroferric oxyhydroxide) for reducing serum phosphorus levels in paediatric and adolescent subjects with CKD in comparison with Phoslyra liquid solution, a calcium acetate phosphate binder, approved in the US without age restriction.

Methods

A schematic diagram of the study design is presented below in Figure 1:

Figure 1 *Study design*



The study consisted of:

- a screening period of up to 4 weeks,
- a washout (pre-randomisation) period of up to 3 weeks for subjects previously taking PBs whose serum phosphorus levels were below age-specific targets,
- a dose titration period of up to 10 weeks (Stage 1),
- and a 24-week safety extension (Stage 2); subjects were followed for 14 days after their last study visit.

Thus, the expected duration of subject participation was a maximum of 43 weeks.

Study Participants

Subjects whose serum phosphorus levels were above age-specific pre-randomisation targets (see Figure 1 above) were eligible for the study.

Inclusion criteria

The study planned to enrol subjects 0 to <18 years old at the time of consent who had CKD and hyperphosphatemia according to age-specific criteria.

Subjects ≥1-year-old were to have:

- Stage 4-5 CKD defined by a glomerular filtration rate <30 ml/min/1.73 m2 or
- Stage 5 CKD with at least 2 months of adequate maintenance HD or PD before screening.
- Home HD subjects could be included; no nocturnal HD (overnight stay at the site) was allowed. Subjects < 1-year-old were to have CKD.

Subjects were to be either phosphate binder-naïve or receiving a stable regimen of a phosphate binder(s) for at least 1 month prior to screening. Subjects who were receiving phosphate binders whose serum phosphorus levels were below age-specific target ranges were to undergo a mandatory washout before randomisation.

Subjects or their parents/legal guardians were to provide written informed consent (and, where appropriate/required, assent) before any study-specific procedures were performed, including screening procedures.

Exclusion criteria

Key exclusion criteria were as follows: hypercalcaemia (per age-specific definition) or hypocalcaemia (serum total corrected calcium <1.9 mmol/l (7.6 mg/dl)) at screening; iPTH levels >700 pg/ml at screening; parathyroidectomy planned or expected within the next 12 months; body weight <5 kg (phosphate binder -naïve) or <6 kg (receiving stable phosphate binder regimens) at screening; a history of major GI surgery or significant GI disorders; estimated life expectancy of <12 months; (for subjects on PD) history of peritonitis in the last 3 months or ≥3 episodes in the last 12 months; and use of more than two phosphate binders concomitantly before screening.

Other exclusion criteria were: known sero-positivity to human immunodeficiency virus; a history of haemochromatosis or other iron accumulation disorders; alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal at screening; use of any prohibited medications; hypersensitivity or intolerance to any of the active substances or excipients to be administered; previous randomisation in this study; current participation in or recent completion of any other investigational drug or device study (within 30 days before screening), or use of any other investigational agent; pregnancy, breast-feeding, or unwillingness to use highly effective contraception during the study and up to 1 month after the last dose of study drug; a history of substance abuse within 2 years before screening; and any other significant medical condition or anticipated need for major surgery that could result in increased risk to the subject or interfere with study assessments or outcomes.

Treatments

Washout (pre-randomisation) period

Subjects who were phosphate binder -naïve or previously taking phosphate binders and whose serum phosphorus levels were as indicated in Table 2 could be randomised when results from the screening visit were available for assessment of study eligibility.

Subjects previously taking phosphate binders whose serum phosphorus levels were below pre-randomisation targets (Table 2) underwent a washout period of up to 3 weeks before randomisation.

Serum phosphorus levels were to be monitored weekly for up to 3 weeks of washout. As soon as their serum phosphorus levels increased to those specified in Table 2, they could be randomised and begin the treatment period. If serum phosphorus remained below the levels specified in Table 2 after 3 weeks of washout, the subject was not to be randomised.

Table 1 ***Study PA-CL-PED-01- Age-related serum phosphorus targets pre- and post-randomisation***

Age	Pre-Randomisation (For Washout Period)		Post-Randomisation	
	mmol/l	mg/dl	mmol/l	mg/dl
0 to <6 months	>2.62	>8.1	-	-
≥6 months to <1 year	>2.29	>7.1	-	-
0 to <1 year	-	-	1.62-2.52	5.0-7.8
≥1 year to <6 years	>2.02	>6.3	1.45-2.10	4.5-6.5
≥6 years to <13 years	>1.77	>5.5	1.16-1.87	3.6-5.8
≥13 years to <18 years	>1.36	>4.2	0.74-1.45	2.3-4.5

Stage 1

Stage 1 was an open-label, randomised, active-controlled, dose-titration period during which subjects received PA21 or Phoslyra for up to 10 weeks.

Doses of PA21 or Phoslyra were increased or decreased as required to achieve age-specific target serum phosphorus levels, provided a subject had received a stable dose for a minimum of 2 weeks (see Table 1 above), or for safety or tolerability reasons at any time.

Serum phosphorus levels were measured weekly during the screening and washout period and two-weekly during Stage 1 and Stage 2. Dose modifications could, therefore, be done two-weekly during Stage 1 and Stage 2.

Subjects randomised to PA21 received PA21 at a starting dose based on their age (see Table 2 and Table 3 below for dose modifications and maximum doses of Velphoro).

Subjects randomised to Phoslyra (calcium acetate) received either Phoslyra at the starting dose of 0.45 ml/kg/day *or an equivalent dose of their previous phosphate binder (calcium-based or sevelamer)* if the Investigator considered this more appropriate (see Table 4 and Table 5 below for dose modifications and maximum doses of Phoslyra).

Table 2 ***Stage 1 starting dose of PA21 - Total Daily Dose***

Age	PA21 (mg Iron/Day)
0 to <1 year	125
≥1 year to <6 years	500
≥6 years to <9 years	750
≥9 years to <18 years	1,250

Table 3 *PA21 dosing regimens*

Age	PA21 (mg Iron/Day)	
	Dose Increases or Decreases	Maximum Dose
0 to <1 year	125 or 250	1,000
≥1 year to <6 years	125 or 250	1,250
≥6 years to <9 years	125, 250 or 375	2,500
≥9 years to <18 years	250 or 500	3,000

Table 4 *Stage 1 starting dose and dosing regimen of Phoslyra (all age groups)*

Initial Dose	Dose Increase or Decrease	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

Table 5 *Maximum daily dose of Phoslyra*

Body Weight (kg)	Phoslyra Maximum Dose (ml/day)	Propylene Glycol (mg/kg/day)[1]	Elemental Ca (mg/day)[2]
5	6.0[1]	24	202.6
10	12.5[1]	25	422
15	18.5[1]	25	624.6
20	25[1]	25	845
25	31.0[1]	25	1,046.6
30	37.5[1]	25	1,267
35	43.5[1]	25	1,468.6
40	44[2]	22	1,487.2
45	44[2]	19.6	1,487.2
50	44[2]	17.6	1,487.2
60	44[2]	14.7	1,487.2
70	44[2]	12.6	1,487.2

Beginning at Week 4, once a subject achieved the age-specific target serum phosphorus level (see above - Table 2 for age-related serum phosphorus targets), he or she moved to Stage 2.

Stage 2

Stage 2 was an open-label, long-term safety extension lasting 24 weeks. All subjects were to enter this safety extension stage. During Stage 2, subjects continued the dose they were receiving at the end of Stage 1, unless a dose change was required; dose modifications followed the same guidelines used in Stage 1.

Numbers of participants to be included

It was planned to enrol approximately 130 subjects, of whom

- 100 would be randomised to receive PA21 and
- 30 would be randomised to receive the active comparator Phoslyra (calcium acetate).

The study also aimed to randomise minimum numbers of subjects in particular age groups.

Dosing of study medication

Subjects in this study were randomised to receive either the test medication PA21 (Velphoro) (100 subjects) or the active comparator Phoslyra (calcium actetate) (30 subjects).

- Subjects randomised to PA21 were to receive PA21 at a starting dose based on their age.

  Subjects randomised to PA21 were to be provided with the formulation most appropriate for their age group:

  - powder for oral suspension for subjects <6 years old or
  - chewable tablets for subjects ≥6 years old.
  - However, due to the possibility of increments of 125 mg/day for dose changes in subjects 6 to 9 years old, subjects in this age group would ideally receive powder for oral suspension.
  - Subjects could change formulations if necessary but were to continue the same dose.
- Subjects randomised to Phoslyra received either Phoslyra at the starting dose of 0.45 ml/kg/day or an equivalent dose of their previous phosphate binder (calcium-based or sevelamer) if the Investigator considered this more appropriate.

Doses of PA21 or Phoslyra were to be increased or decreased as required to achieve age-specific target serum phosphorus levels, or for safety or tolerability reasons (at any time). Serum phosphorus levels were measured weekly during the screening and washout period and two-weekly during Stage 1 and Stage 2. Dose modifications could, therefore, be done two-weekly during Stage 1 and Stage 2.

Study medications

- PA21 (Velphoro), at an age-dependent starting dose of 125, 500, 750 or 1,250 mg iron/day, to be titrated in increments of 125 to 500 mg iron/day according to efficacy and safety criteria (age-dependent maximum doses ranged from 1,000 to 3,000 mg iron/day). Two formulations of PA21 were used in this study: a red-brown powder for oral suspension, provided at dosage strengths of 125 mg, 250 mg and 500 mg, and a red-brown chewable tablet, provided at dosage strengths of 250 mg and 500 mg. Dose increments of 125 and 250 mg; 125, 250 and 375 mg; and 500 mg were possible for age groups 2-6 years, 6-9 years, and > 9 years, respectively.
- Calcium acetate (Phoslyra; Lyne Laboratories Inc., Brockton, MA 02301, US), at a starting dose of 0.45 ml/kg/day, to be titrated in increments of 0.1 to 0.2 ml/kg/day according to efficacy and safety criteria (body weight-dependent maximum doses ranged from 6.0 to 44 ml/day). Phoslyra was provided as an oral solution containing 667 mg of calcium acetate per 5 ml, equivalent to 169 mg (8.45 mEq) calcium.

Duration of study treatment

Duration of treatment was as follows:

- Stage 1: Up to 10 weeks.

  Beginning at Week 4, subjects who achieved the target levels or who completed 10 weeks of treatment could move on to Stage 2.

- Stage 2: 24 weeks.

  A long-term safety extension in which they continued on the same dose they were receiving at the end of Stage 1, unless dose change was required.

Objectives

Primary Objective

1. To evaluate the efficacy of PA21 in reducing serum phosphorus levels in paediatric and adolescent subjects with CKD at the end of Stage 1.

Secondary Objectives

2. To evaluate the efficacy of PA21 in maintaining the serum phosphorus lowering effects in paediatric and adolescent subjects with CKD at the end of Stage 2.
3. To evaluate the safety of PA21 in paediatric and adolescent subjects with CKD.
4. To evaluate the efficacy of Phoslyra in reducing and maintaining serum phosphorus levels in paediatric and adolescent subjects with CKD at the end of Stages 1 and 2.
5. To evaluate the safety of Phoslyra in paediatric and adolescent subjects with CKD.

Outcomes/endpoints

Primary efficacy endpoint

- Change in serum phosphorus levels from baseline to the end of Stage 1 in the PA21 group.

Secondary efficacy endpoints

- Change in serum phosphorus levels from baseline to the end of Stage 1 in the Phoslyra group
- Change in serum phosphorus levels from baseline to the end of Stage 2 in the PA21 and Phoslyra groups group
- Serum phosphorus values at each visit during Stage 1 and 2
- Percentage of subjects with serum phosphorus levels within the age-dependent target range (see above, Table 2) at each visit
- Percentage of subjects with serum phosphorus within the age-dependent normal range (see below table 19) at each visit

Secondary safety endpoints

- Adverse event (AE) profile (primary safety endpoint)
- Percentage of withdrawals due to AEs (primary safety endpoint)
- Serum total corrected calcium at each time point and change from baseline
- Percentage of subjects with at least 1 episode of sustained hypercalcaemia during study participation (confirmed by repeat sample 1 week later)
- Serum total corrected calcium-phosphorus product at each time point and change from baseline
- Serum iPTH levels at each time point and change from baseline

- Routine clinical laboratory tests

Other endpoints

- Patient-reported palatability and acceptability

Sample size

In the PA21 treatment group, assuming a mean change in serum phosphorus levels from baseline to end of Stage 1 of 1.2 mg/dl and a standard deviation for the change of 2.0, and further allowing for an estimated drop-out rate of 30%, 100 randomised subjects would provide more than 90% power. One hundred (100) subjects were also considered sufficient to provide robust safety and dosing information for PA21 in paediatric and adolescent subjects with CKD.

Randomisation

Eligible subjects were randomised to treatment (PA21 or Phoslyra) via IRT at the baseline visit at the beginning of Stage 1 (following screening or washout where required), and were allocated a randomisation number in accordance with the randomisation schedule generated by the Biostatistics department of ALMAC Clinical Technologies and reviewed by the Sponsor biostatistician.

Randomisation was stratified by age group, and also aimed to randomise minimum numbers of subjects per age group. Subjects retained their randomisation numbers for the duration of their participation; randomised subjects who withdrew from the study for any reason, regardless of whether they received treatment, also retained their randomisation numbers

Blinding (masking)

This study was conducted in an open-label manner. However, the Sponsor was not to receive any data or data summarised by treatment group during the conduct of the study in order to preserve the integrity of the trial. In particular, the Sponsor was not to attend closed sessions of DSMB meetings where data summarised by treatment group could be disclosed.

Statistical methods

Population used for the primary analysis

The following subject populations were used for presentation and analysis of the data:

- FAS population: all subjects randomised to treatment at Stage 1 who received at least 1 dose of randomised treatment and who had at least 1 post-BL assessment of the efficacy endpoint (serum phosphorus level), analysed according to treatment randomised.
- PPS population: all subjects in the FAS population who had no major protocol violations, analysed according to treatment randomised.
- Safety population: all subjects who received at least 1 dose of study medication, analysed according to treatment received.
- Stage 2 safety population: all subjects who received at least 1 dose of study medication during Stage 2, analysed according to treatment received.

The FAS population was the primary population for the analysis of efficacy parameters. It was also used for analyses of protocol deviations, demographic and BL characteristics and medical history. A subset of BL characteristics and efficacy parameters was evaluated for the PPS population. The safety population was the primary population for the analysis of safety endpoints.

General Methods

Tabulations were to be produced for appropriate demographic, baseline, efficacy and safety parameters. For categorical variables, summary tabulations would present the total number of observations and the number of missing observations as well as the number and percentage within each category of the parameter; for continuous variables, summary tabulations would present the total number of observations and the number of missing observations, mean, median, standard deviation (SD), first quartile (Q1), third quartile (Q3), minimum, and maximum values. Formal statistical hypothesis testing was to be performed on the primary endpoint only, at a 2-sided 0.05 significance level.

Summary statistics were to be presented, as well as confidence intervals for selected parameters, as described below. Other statistical testing within each group could be performed for the secondary efficacy endpoints depending on observed clinical differences.

Efficacy Analyses

The primary efficacy endpoint was change in serum phosphorus levels from baseline to the end of Stage 1 (i.e., considering the last available value from Stage 1) in the PA21 group. It was to be based on central laboratory data; in case of missing data, the change from baseline was to be computed using pre- and post-treatment values from the local laboratory.

The change from baseline was to be analysed using a linear mixed model with treatment, baseline serum phosphorus, age (in categories) at randomisation, region and gender as fixed effects. Summary statistics with the estimate of the adjusted mean change from baseline and its 95% confidence interval (95% CI) as well as the corresponding p-value from the t-test were also to be provided. Sensitivity analyses were to include a repeat of the main analysis based on observed data from the central laboratory only (with no imputation using local laboratory data).

Homogeneity of the results of the primary endpoint was to be investigated through analysis of change from baseline in subgroups defined by age at randomisation, region, gender, prescribed formulation, serum phosphorus at baseline according to the age-related normal range and the combination of age at randomisation and serum phosphorus at baseline according to the age-related normal range using the same linear mixed model as above.

For the secondary efficacy endpoints related to change from baseline in serum phosphorus level, summary statistics with 95% CIs for the mean change were to be provided by treatment group using the same linear mixed model as for the primary efficacy endpoint. Box plots were to be generated for the change in serum phosphorus levels from baseline for each treatment arm to the end of Stage 1 and to the end of Stage 2 for the FAS and PPS Populations. Serum phosphorus values over time based on central and local laboratory measurements were to be summarised separately by treatment group using descriptive statistics.

In addition, plots were to be provided with one curve for each treatment arm representing the mean change (±standard error of the mean (SEM)) from baseline in serum phosphorus levels at each time point to the end of Stage 1 and to the end of Stage 2 for the FAS and PPS Populations using central laboratory data. For the percentages of subjects with serum phosphorus values within specified ranges, number and percentage calculated using the number of subjects with non-missing serum phosphorus level as denominators with corresponding exact 95% CIs were to be provided by treatment group.

Safety Analyses

Summaries were to be presented for all TEAEs, for TEAEs by causality, by intensity (as assessed by the Investigator) and by age at randomisation (0-<2 years, 2-<6 years, 6-<12 years and 12-≤18 years), TEAEs of special interest (those potentially related to diarrhoea, potential iron overload, potential masking of GI bleeding, and deficiencies in growth and skeletal development or abnormalities of bone markers), treatment-related TEAEs, serious TEAEs, serious treatment-related TEAEs, serious TEAEs leading to death, non-serious TEAEs, TEAEs leading to study drug discontinuation, and TEAEs by time of onset.

Percentage of subjects who developed at least 1 episode of sustained hypercalcaemia after start of treatment was to be provided by treatment group. For clinical laboratory parameters including serum iPTH levels, actual values and changes from baseline were to be summarised at each time point by treatment group based on central laboratory measurements. For serum phosphorus, total calcium and albumin, both central and local laboratory summary tables were to be provided. Shift tables from baseline to each post-baseline visit were to be produced using the low/normal/high classification based on laboratory reference ranges (if available for the paediatric population).

For vital signs, actual values and changes from baseline at each time point were to be summarised by treatment group, also by categories of age at randomisation within treatment groups.

Other Analyses

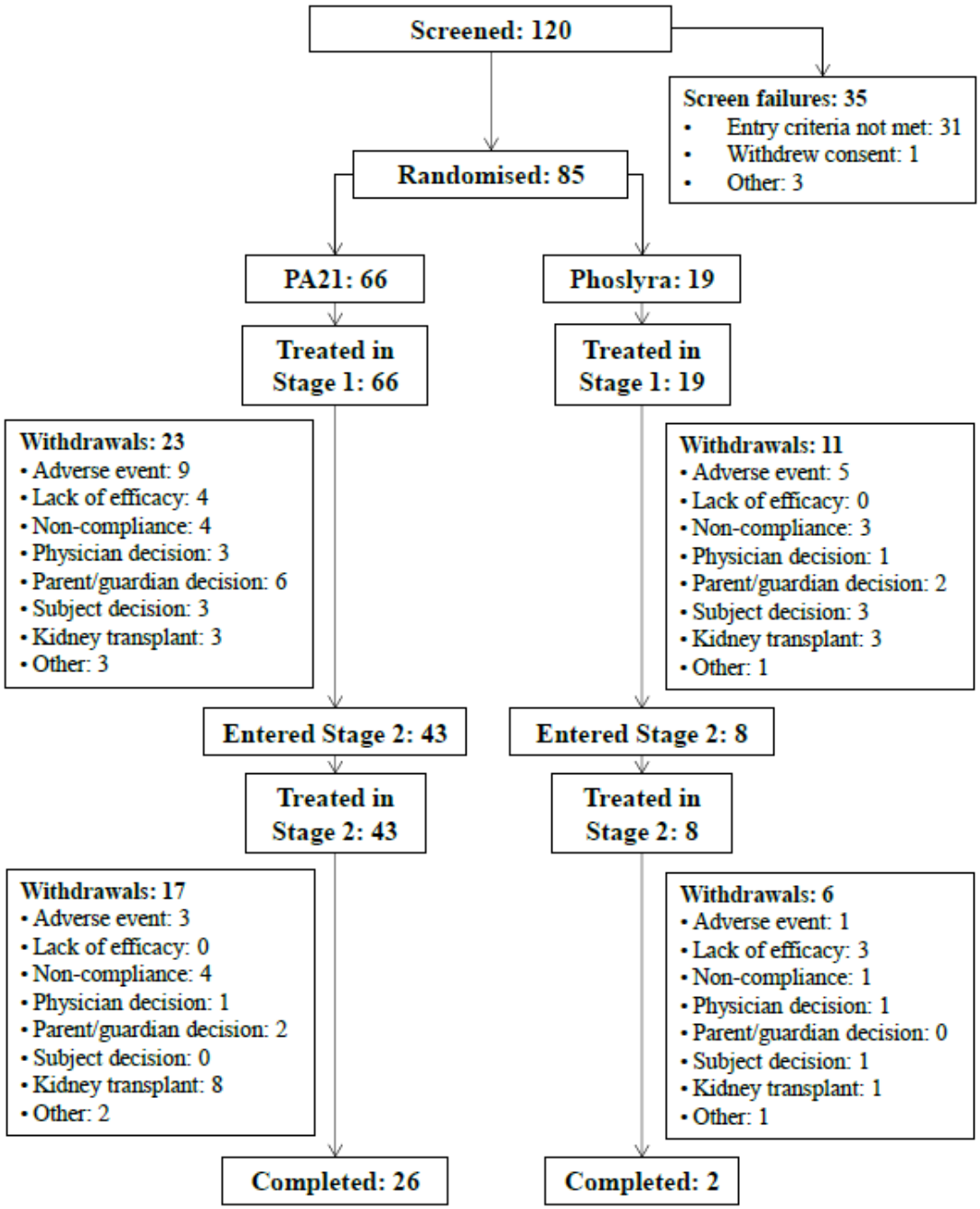
Patient-reported palatability and acceptability assessments were to be summarised by treatment group. Subject-reported palatability and acceptability were measured using a 5-point facial hedonic scale combined with a 10-cm VAS. The ends were defined as the extreme limits of the parameter to be measured, oriented from the left (better; lower scores) to the right (worse; higher scores).

Results

The MAH provided the following flow diagram of Figure 2. Of the 120 subjects screened, 85 subjects were randomised (66 subjects were randomised to PA21 and 19 were randomised to Phoslyra). All of these subjects received at least 1 dose of their randomised study treatment.

Participant flow

Figure 2 ***Disposition of study subjects (all enrolled subjects)***



Recruitment

Date of First Subject First Visit: 26 May 2016

Date of Last Subject Last Visit: 21 February 2019

Conduct of the study

Protocol amendments

- The clinical study protocol version 1.0 was finalised on 26 March 2015. An amendment to the protocol was issued during the phase of regulatory submission. The protocol version 2.0 was finalised on 22 September 2015 and was used for global study conduct.
- Two (2) country-specific substantial amendments were made to the protocol upon requests from local regulatory agencies: Protocol version 3.0 (France only), dated 23 June 2016, and Protocol version 4.0 (Russia only), dated 6 September 2016.
- On 17 July 2018, the EMA agreed to reduce the required minimum numbers of recruited subjects to at least 60 subjects to be randomised into the PA21 group, as mentioned earlier in this AR.

Following the agreements with the EMA and FDA, the Sponsor ended the study on 11 March 2019.

Protocol deviations

Major protocol deviations were identified in a total of 33 (41.3%) subjects, 23 (35.4%) subjects in the FAS PA21 group and 10 (66.7%) subjects in the FAS Phoslyra group. Most of the major deviations in the PA21 group and all of those in the Phoslyra group concerned non-compliance with study drug. Three subjects were included in the FAS and Safety Populations despite major deviations from study eligibility criteria (one took anti-convulsive medication; one started on growth hormone and one has exclusionary intact parathyroid hormone level). Major protocol deviations are summarized in table below (Table 6):

Table 6 ***Major protocol deviations (FAS population)***

Parameter	PA21 (N=65) n (%)	Phoslyra (N=15) n (%)	Total (N=80) n (%)
Subjects with at least 1 Major Deviation	23 (35.4%)	10 (66.7%)	33 (41.3%)
Prohibited medication	1 (1.5%)	0	1 (1.3%)
Exclusion criteria	3 (4.6%)	0	3 (3.8%)
Non-compliance with study drug	18 (27.7%)	10 (66.7%)	28 (35.0%)
Non-compliance with procedure	1 (1.5%)	0	1 (1.3%)

Note: N=total number of subjects; n=number of observations.

Treatment compliance

In the PA21 group, mean (SD) compliance was 87 (26.9) % during Stage 1, 75 (25.8) % during Stage 2 and 79 (23.6) % during the overall study.

In the Phoslyra group, mean (SD) compliance was 72 (56.0) % during Stage 1, 55 (35.8) % during Stage 2 and 62 (37.9) % during the overall study.

Results in each age group showed the same general pattern seen in the full Safety Population. Compliance during Stage 1 was generally comparable across age groups. During Stage 2 and during the overall study, compliance was lower among subjects ≥12 to ≤18 years old at randomisation than in the younger age groups.

Compliance was slightly higher among female subjects than among male subjects during Stage 1, slightly higher among male subjects during Stage 2 and comparable between genders during the overall study; standard deviations were large in both subgroups.

Compliance was slightly higher among non-US subjects than among US subjects; however, standard deviations were large in both subgroups.

During Stage 1 and during the overall study, compliance was slightly higher among subjects prescribed sachets only or both tablets and sachets than among those prescribed tablets only. However, the smaller numbers of subjects prescribed sachets only and both tablets and sachets should be considered. Standard deviations were also large in all 3 subgroups.

Baseline data

Demographic data

In the FAS population, subject age at randomisation ranged from 2 to 18 years. At baseline, 54 (67.5%) subjects in the FAS Population were on haemodialysis and 10 (12.5%) subjects were on peritoneal dialysis; no subjects were on both haemodialysis and peritoneal dialysis, and 16 (20.0%) subjects were not on dialysis. See Table 8 below for demographic data:

Table 7 *Demographic characteristics (FAS population)*

Parameter	Statistics	PA21 (N = 65)	Phoslyra (N = 15)	Total (N = 80)
Age at Randomisation (years)	n (missing)	65 (0)	15 (0)	80 (0)
	Mean (SD)	12.1 (4.10)	12.3 (3.96)	12.2 (4.05)
	Median	13.0	14.0	13.5
	Q1, Q3	9.0, 15.0	10.0, 15.0	9.0, 15.0
	Min, Max	2, 18	4, 17	2, 18
Age at Randomisation (years) - n (%)	0 - <2	0	0	0
	0 - <1	0	0	0
	1 - <2	0	0	0
	2 - <6	6 (9.2%)	1 (6.7%)	7 (8.8%)
	6 - <12	17 (26.2%)	4 (26.7%)	21 (26.3%)
	12 - ≤18	42 (64.6%)	10 (66.7%)	52 (65.0%)
Age at Randomisation - n (%)	Newborns (0-27 days)	0	0	0
	Infants (28 days-23 months)	0	0	0
	Children (2-11 years)	23 (35.4%)	5 (33.3%)	28 (35.0%)
	Adolescents (12-17 years)	41 (63.1%)	10 (66.7%)	51 (63.8%)
	Adults (18-64 years)	1 (1.5%)	0	1 (1.3%)
Sex - n (%)	n (missing)	65 (0)	15 (0)	80 (0)
	Male	31 (47.7%)	5 (33.3%)	36 (45.0%)
	Female	34 (52.3%)	10 (66.7%)	44 (55.0%)
Race - n (%)	n (missing)	60 (5)	15 (0)	75 (5)
	White	43 (71.7%)	11 (73.3%)	54 (72.0%)
	Black or African American	9 (15.0%)	2 (13.3%)	11 (14.7%)
	Other	6 (10.0%)	1 (6.7%)	7 (9.3%)
	Native Hawaiian or Other Pacific Islander	1 (1.7%)	1 (6.7%)	2 (2.7%)
	American Indian or Alaska Native	1 (1.7%)	0	1 (1.3%)
	Asian	0	0	0
Ethnicity - n (%)	n (missing)	65 (0)	15 (0)	80 (0)
	Not Hispanic or Latino	46 (70.8%)	12 (80.0%)	58 (72.5%)
	Hispanic or Latino	19 (29.2%)	3 (20.0%)	22 (27.5%)
	Not reported	0	0	0
	Unknown	0	0	0
Region - n (%)	n (missing)	65 (0)	15 (0)	80 (0)
	US	38 (58.5%)	11 (73.3%)	49 (61.3%)
	NON-US	27 (41.5%)	4 (26.7%)	31 (38.8%)
Baseline Height (cm)				
Age 2 to <6 years	n (missing)	6 (0)	1 (0)	7 (0)
	Mean (SD)	93.7 (11.33)	92.8	93.6 (10.35)
	Median	95.2	92.8	92.8
	Q1, Q3	82.0, 102.3	92.8, 92.8	82.0, 102.3
	Min, Max	81, 107	93, 93	81, 107
Baseline Height (cm) (cont'd)				
Age 6 to <12 years	n (missing)	17 (0)	4 (0)	21 (0)
	Mean (SD)	125.2 (15.20)	114.6 (12.59)	123.2 (15.06)
	Median	120.0	118.8	120.0
	Q1, Q3	116.0, 132.0	105.7, 123.5	114.5, 129.5
	Min, Max	105, 154	97, 124	97, 154
Age 12 to ≤18 years	n (missing)	42 (0)	10 (0)	52 (0)
	Mean (SD)	156.2 (12.22)	152.9 (17.29)	155.6 (13.21)
	Median	153.9	158.0	154.0
	Q1, Q3	148.0, 165.0	151.0, 167.0	148.5, 165.8
	Min, Max	131, 184	121, 169	121, 184
Baseline Weight (kg)				
Age 2 to <6 years	n (missing)	6 (0)	1 (0)	7 (0)
	Mean (SD)	13.92 (3.112)	15.40	14.13 (2.896)
	Median	14.50	15.40	15.40
	Q1, Q3	11.60, 16.70	15.40, 15.40	11.60, 16.70
	Min, Max	9.2, 17.0	15.4, 15.4	9.2, 17.0
Age 6 to <12 years	n (missing)	17 (0)	4 (0)	21 (0)
	Mean (SD)	29.22 (15.208)	20.08 (3.746)	27.48 (14.166)
	Median	24.10	21.60	22.60
	Q1, Q3	20.40, 35.80	18.05, 22.10	20.40, 27.00
	Min, Max	17.8, 81.5	14.5, 22.6	14.5, 81.5

Baseline weight (kg) (cont'd)				
Age 12 to ≤18 years	n (missing)	42 (0)	10 (0)	52 (0)
	Mean (SD)	51.26 (12.263)	46.47 (17.093)	50.34 (13.270)
	Median	50.85	43.35	49.40
	Q1, Q3	43.80, 58.90	33.90, 51.70	43.10, 58.35
	Min, Max	26.5, 95.0	26.1, 78.7	26.1, 95.0
Baseline Body Mass Index (kg/m^2)				
Age 2 to <6 years	n (missing)	6 (0)	1 (0)	7 (0)
	Mean (SD)	15.750 (1.5347)	17.880	16.054 (1.6159)
	Median	15.770	17.880	16.240
	Q1, Q3	14.590, 16.790	17.880, 17.880	14.590, 17.880
	Min, Max	13.68, 17.90	17.88, 17.88	13.68, 17.90
Age 6 to <12 years	n (missing)	17 (0)	4 (0)	21 (0)
	Mean (SD)	17.831 (4.8155)	15.235 (1.0160)	17.336 (4.4494)
	Median	16.300	15.205	16.130
	Q1, Q3	15.550, 18.340	14.495, 15.975	15.470, 17.020
	Min, Max	14.03, 34.23	14.05, 16.48	14.03, 34.23
Baseline Body Mass Index (kg/m^2) (cont'd)				
Age 12 to ≤18 years	n (missing)	42 (0)	10 (0)	52 (0)
	Mean (SD)	20.978 (4.3357)	19.636 (5.4902)	20.720 (4.5516)
	Median	20.485	17.720	20.330
	Q1, Q3	17.890, 23.410	16.350, 22.150	17.585, 23.285
	Min, Max	12.78, 33.59	12.46, 30.06	12.46, 33.59

Demographic characteristics in the PPS population were similar to those in the FAS population. Assessment of the baseline (BL) comparability of treatment groups is difficult in this population due to the small number of subjects in the PPS Phoslyra group (N=5).

Disease characteristics

Table 8 ***Baseline disease characteristics (FAS population)***

Parameter	Statistics	PA21 (N = 65)	Phoslyra (N = 15)	Total (N = 80)
Reason or Cause of CKD - n(%)	n (missing)	65 (0)	15 (0)	80 (0)
	Congenital anomalies of the kidney and urinary tract	19 (29.2%)	3 (20.0%)	22 (27.5%)
	Glomerulonephritis	10 (15.4%)	4 (26.7%)	14 (17.5%)
	Hypodysplasia and reflux	2 (3.1%)	2 (13.3%)	4 (5.0%)
	Obstructive uropathy	8 (12.3%)	1 (6.7%)	9 (11.3%)
	Polycystic kidney disease	3 (4.6%)	0	3 (3.8%)
	Haemolytic uraemic syndrome	0	0	0
	Other	23 (35.4%)	5 (33.3%)	28 (35.0%)
CKD Stage - n(%)	n (missing)	65 (0)	15 (0)	80 (0)
	Stage 1	0	0	0
	Stage 2	0	0	0
	Stage 3	0	0	0
	Stage 4	13 (20.0%)	1 (6.7%)	14 (17.5%)
	Stage 5	52 (80.0%)	14 (93.3%)	66 (82.5%)
Time since Onset of CKD (years)[1]	n (missing)	65 (0)	14 (1)	79 (1)
	Mean (SD)	6.49 (5.333)	4.81 (3.615)	6.19 (5.092)
	Median	5.42	3.50	5.07
	Q1, Q3	1.47, 11.59	1.73, 6.69	1.68, 11.44
	Min, Max	0.1, 17.5	0.8, 12.0	0.1, 17.5
Type of Dialysis - n(%)	n (missing)	65 (0)	15 (0)	80 (0)
	Haemodialysis	45 (69.2%)	9 (60.0%)	54 (67.5%)
	Peritoneal dialysis	5 (7.7%)	5 (33.3%)	10 (12.5%)
	Peritoneal dialysis and Haemodialysis	0	0	0
	None	15 (23.1%)	1 (6.7%)	16 (20.0%)
PB-Naïve - n(%)	n (missing)	65 (0)	15 (0)	80 (0)
	Yes	18 (27.7%)	3 (20.0%)	21 (26.3%)
	No	47 (72.3%)	12 (80.0%)	59 (73.8%)
Washout Period Needed - n(%)	n (missing)	47 (18)	12 (3)	59 (21)
	Yes	7 (14.9%)	4 (33.3%)	11 (18.6%)
	No	40 (85.1%)	8 (66.7%)	48 (81.4%)

Baseline Serum Phosphorus (mmol/l)[2]	n (missing)	65 (0)	15 (0)	80 (0)
	Mean (SD)	2.07 (0.522)	2.15 (0.669)	2.09 (0.549)
	Median	2.03	2.05	2.04
	Q1, Q3	1.68, 2.36	1.86, 2.42	1.69, 2.39
	Min, Max	1.0, 3.3	0.9, 3.8	0.9, 3.8
Baseline Serum Phosphorus (mg/dl)[2]	n (missing)	65 (0)	15 (0)	80 (0)
	Mean (SD)	6.41 (1.615)	6.67 (2.072)	6.46 (1.698)
	Median	6.28	6.35	6.32
	Q1, Q3	5.20, 7.31	5.76, 7.49	5.22, 7.40
	Min, Max	3.1, 10.3	2.7, 11.9	2.7, 11.9

1 Time is calculated until date of informed consent.
2 Data are from central laboratory.
Note: FAS=Full Analysis Set; N=total number of subjects; n=number of observations; CKD=chronic kidney disease; SD=standard deviation; Q1=first quartile; Q3=third quartile; Min=minimum; Max=maximum; PB=phosphate binder.

Baseline (BL) disease characteristics in the PPS and safety population were similar to those in the FAS population.

Dose

Forty-six (46) of the 66 subjects in the PA21 group were prescribed tablets only; 10 subjects were prescribed sachets only, and 10 subjects were prescribed both formulations. The average daily dosage and an average number of sachets/tablets for each subgroup are displayed below. Similar data are displayed according to age group.

During the overall study, the maximum prescribed daily dosage in the PA21 group ranged from 500 to 3000 mg iron, with a mean (SD) of 1856.1 (744.61) mg iron. The maximum prescribed daily dosage in the Phoslyra group ranged from 7 to 44 ml, with a mean (SD) of 25.3 (13.18) ml.

During Stage 1, the actual average daily number of tablets/sachets taken ranged from 0.7 to 6.9, with a mean (SD) of 3.18 (1.111) and a median of 3.14. During the overall study, the actual average daily number of tablets/sachets taken ranged from 0.5 to 7.5, with a mean (SD) of 3.24 (1.262) and a median of 3.26.

Table 9 *Dosing*

Parameter	Statistics	PA21		
		Only Sachets (N=10)	Only Tablets (N=46)	Sachets and Tablets (N=10)
	Min, Max	[illegible]	[illegible]	[illegible]
Prescribed average daily dosage (mg iron) during Stage 1	n	10	46	10
	Mean (SD)	762.38 (313.709)	1572.55 (363.354)	1201.51 (327.768)
	Median	709.91	1532.96	1182.69
	Q1, Q3	500.00, 914.29	1250.00, 1798.39	895.83, 1353.57
	Min, Max	500.0, 1465.8	750.0, 2360.5	750.0, 1739.4
Prescribed average daily dosage (mg iron), overall study	n	10	46	10
	Mean (SD)	843.92 (425.404)	1785.52 (523.983)	1405.83 (293.899)
	Median	709.91	1667.04	1468.62
	Q1, Q3	500.00, 1040.61	1422.22, 2053.57	1250.00, 1525.13
	Min, Max	500.0, 1822.7	750.0, 2859.7	750.0, 1834.8
Actual average daily number of tablets/sachets taken during Stage 1	n	9	46	10
	Mean (SD)	3.18 (0.870)	3.13 (1.133)	3.44 (1.266)
	Median	3.51	3.03	3.41
	Q1, Q3	2.89, 3.62	2.48, 3.64	2.96, 3.72
	Min, Max	1.3, 4.2	0.7, 6.9	1.2, 5.9
Actual average daily number of tablets/sachets taken, overall study	n	9	46	10
	Mean (SD)	3.33 (1.244)	3.21 (1.285)	3.29 (1.298)
	Median	3.38	3.03	3.43
	Q1, Q3	2.89, 4.04	2.44, 3.74	2.33, 3.74
	Min, Max	1.3, 5.0	0.5, 7.5	1.2, 5.9

Parameter	Statistics	PA21		
		≥2 to <6 Years (N=6)	≥6 to <12 Years (N=17)	≥12 to ≤18 Years (N=43)
Actual average daily dosage (mg iron for PA21; ml for Phoslyra) during Stage 1	n	5	17	43
	Mean (SD)	528.50 (240.591)	1030.58 (324.205)	1369.54 (531.433)
	Median	625.00	893.75	1344.83
	Q1, Q3	406.25, 697.37	740.00, 1304.55	1034.48, 1674.42
	Min, Max	166.7, 747.2	607.1, 1623.2	308.3, 2688.2
Actual average daily dosage (mg iron for PA21; ml for Phoslyra), overall study	n	5	17	43
	Mean (SD)	579.89 (382.878)	1208.65 (488.247)	1391.79 (626.405)
	Median	625.00	1190.76	1250.00
	Q1, Q3	276.04, 697.37	733.33, 1533.49	1046.88, 1728.57
	Min, Max	166.7, 1134.4	607.1, 2361.3	237.1, 3243.3

Actual average daily number of tablets/ sachets taken during Stage 1	n	5	17	43
	Mean (SD)	2.87 (1.017)	3.17 (0.492)	3.23 (1.295)
	Median	3.38	3.10	3.18
	Q1, Q3	2.36, 3.51	2.89, 3.51	2.44, 3.79
	Min, Max	1.3, 3.8	2.3, 4.2	0.7, 6.9
Actual average daily number of tablets/ sachets taken, overall study	n	5	17	43
	Mean (SD)	2.95 (1.438)	3.45 (0.843)	3.19 (1.389)
	Median	3.38	3.67	3.00
	Q1, Q3	1.58, 3.79	2.73, 3.92	2.24, 3.74
	Min, Max	1.3, 4.7	2.3, 5.0	0.5, 7.5

Numbers analysed

Numbers of subjects in the various analysis populations (defined in the statistical methods section of this synopsis) are presented in the table below in Table 10:

Table 10 ***Numbers of subjects included in populations for analysis (safety population)***

	PA21 (N = 66) n (%)	Phoslyra (N = 19) n (%)	Total (N = 85) n (%)
Safety Population	66 (100.0%)	19 (100.0%)	85 (100.0%)
Stage 2 Safety Population	43 (65.2%)	8 (42.1%)	51 (60.0%)
Full Analysis Set (FAS)	65 (98.5%)	15 (78.9%)	80 (94.1%)
Per Protocol Set (PPS)	42 (63.6%)	5 (26.3%)	47 (55.3%)

Note: N=total number of subjects; n=number of observations.

Only 51 subjects were included in the Stage 2 safety population, and only 47 subjects were included in the PPS; numbers were particularly small in the Phoslyra group (8 subjects and 5 subjects respectively).

Outcomes and estimation

Primary efficacy endpoint

The overall change in serum phosphorus levels from baseline to the end of Stage 1 in the ***PA21*** *group*

As shown in Table 12 below, change in serum phosphorus level from BL to the end of Stage 1 was not statistically significant in the FAS PA21 group (p=0.1456), with an LS mean (standard error (SE)) of -*0.120 (0.081) mmol/l (95% CI: -0.282, 0.043).*

Table 11 ***Change in serum phosphorus level from baseline to end of stage 1 in PA21 group (FAS population)***

Time Point	Unit	Statistics	PA21 (N=65)
Baseline	mmol/l	n	65
		Mean (SD)	2.08 (0.548)
		Median	2.03
		Q1, Q3	1.68, 2.36
		Min, max	1.0, 3.7
End of Stage 1	mmol/l	n	65
		Mean (SD)	1.91 (0.643)
		Median	1.79
		Q1, Q3	1.47, 2.23
		Min, max	1.0, 4.8
Change from baseline to end of Stage 1	mmol/l	n	65
		Mean (SD)	-0.17 (0.487)
		Median	-0.16
		Q1, Q3	-0.45, 0.12
		Min, max	-1.2, 1.6
		LS Mean (SE)[(1)]	-0.120 (0.081)
		95% CI	(-0.282, 0.043)
		P-value[(2)]	0.1456

Results of a sensitivity analysis without imputation of missing central laboratory values in the FAS population and results in the PPS population (N=42 for PA21) were similar.

*Change **per age group** in serum phosphorus levels from baseline to the end of Stage 1 in the **PA21** group*

Table 12 ***Change in serum phosphorus level from baseline to end of stage 1 in PA21 group, by age at randomization (FAS population)***

Time Point	Unit	Statistics	PA21 (N=65)		
			≥2 to <6 Years (N=6)	≥6 to <12 Years (N=17)	≥12 to ≤18 Years (N=42)
Change from Baseline to End of Stage 1	mmol/l	n	6	17	42
		Mean (SD)	-0.08 (0.253)	-0.23 (0.690)	-0.17 (0.417)
		Median	-0.08	-0.24	-0.16
		Q1, Q3	-0.21, 0.18	-0.76, 0.13	-0.42, 0.08
		Min, Max	-0.5, 0.2	-1.2, 1.6	-1.2, 1.1
		LS Mean (SE)[1]	-0.078 (0.123)	-0.200 (0.158)	-0.149 (0.062)
		95% CI	(-0.468, 0.312)	(-0.541, 0.141)	(-0.274, -0.023)
		P-value[2]	0.5682	0.2271	0.0220
	mg/dl	n	6	17	42
		Mean (SD)	-0.24 (0.783)	-0.72 (2.136)	-0.51 (1.291)
		Median	-0.23	-0.74	-0.48
		Q1, Q3	-0.65, 0.56	-2.35, 0.40	-1.30, 0.25
		Min, Max	-1.5, 0.6	-3.6, 4.9	-3.6, 3.4
		LS Mean (SE)[1]	-0.243 (0.380)	-0.620 (0.489)	-0.460 (0.192)
		95% CI	(-1.450, 0.965)	(-1.675, 0.436)	(-0.850, -0.070)
		P-value[2]	0.5682	0.2271	0.0220

As expected, baseline serum phosphorus levels were higher in the younger age groups.

Change in serum phosphorus level from baseline to the end of Stage 1 in the PA21 group was not statistically significant in the full FAS Population. Reductions in serum phosphorus level were observed with PA21 in all age groups; however, a statistically significant reduction in serum phosphorus was achieved only in the subgroup of subjects ≥12 to ≤18 years old at randomisation.

- Among subjects ≥2 to <6 years old at randomisation (N=6), the LS mean (SE) for change from baseline was -0.078 (0.123) mmol/l (95% CI: -0.468, 0.312) or -0.243 (0.380) mg/dl (95% CI: -1.450, 0.965).
- Among subjects ≥6 to <12 years old at randomisation (N=17), the LS mean (SE) for change from baseline was -0.200 (0.158) mmol/l (95% CI: -0.541, 0.141) or -0.620 (0.489) mg/dl (95% CI: -1.675, 0.436).
- Among subjects ≥12 to ≤18 years old at randomisation (N=42), the LS mean (SE) for change from baseline was -0.149 (0.062) mmol/l (95% CI -0.274, -0.023) or -0.460 (0.192) mg/dl (95% CI: -0.850, -0.070). The change from baseline in this age group was statistically significant (p=0.0220).

Secondary efficacy endpoints

Change in serum phosphorus levels from baseline to the end of Stage 1 in the **Phoslyra group**

The actual mean serum phosphorus levels for Phoslyra were 2.15 mmol/L at baseline and 2.14 mmol/L at stage 1 (reduction by 0.01 mmol/L). The LS mean (SE) for change between baseline and stage 1 was -0.615 (0.320) mmol/l (95% CI: -1.339, 0.110) based on the mixed model calculations (i.e. results are obtained from a linear mixed model which includes change in serum phosphorus levels from baseline to the end of Stage 1 as dependent variable and treatment, baseline serum phosphorus, age (in categories) at randomization, region (Non-US/US) and gender as fixed effects). Also, here the difference was not statistically significant.

In the PPS population, the LS mean (SE) for change in serum phosphorus level from BL to the end of Stage 1 in the Phoslyra group was -0.502 (0.000) mmol/l; the associated 95% CIs could not be computed due to the small number of subjects in this group (N=5) (see below Table 13).

Table 13 ***Change in serum phosphorus level from baseline to end of stage 1 in Phoslyra group (FAS population)***

Time Point	Unit	Statistics	Phoslyra (N = 15)
Baseline	mmol/l	n	15
		Mean (SD)	2.15 (0.669)
		Median	2.05
		Q1, Q3	1.86, 2.42
		Min, Max	0.9, 3.8
End of Stage 1	mmol/l	n	15
		Mean (SD)	2.14 (0.804)
		Median	1.90
		Q1, Q3	1.66, 2.97
		Min, Max	0.6, 3.7
Change from Baseline to End of Stage 1	mmol/l	n	15
		Mean (SD)	-0.02 (0.848)
		Median	-0.15
		Q1, Q3	-0.26, 0.06
		Min, Max	-1.4, 2.3
		LS Mean (SE)[1]	-0.615 (0.320)
		95% CI	(-1.339, 0.110)
		P-value[2]	0.0872

Change in serum phosphorus levels from baseline to the end of Stage 2 in the PA21 and Phoslyra groups

In the FAS population, the LS mean (SE) for change in serum phosphorus level from BL to the end of Stage 2 was 0.099 (0.198) mmol/l (95% CI: -0.306, 0.504) in the PA21 group and -0.393 (0.218)

mmol/l (95% CI: -3.167, 2.380) in the Phoslyra group. However, it should be noted that the corresponding 95% CIs did not exclude zero; therefore, no true underlying difference between treatments was demonstrated. It should be noted that results for the end of Stage 2 were available for only 36 subjects in the PA21 group and 6 subjects in the Phoslyra group. Serum phosphorus levels at BL were generally comparable between treatment groups (see below Table 15).

In the PPS population, results for the PA21 group were similar to those in the FAS population: the LS mean (SE) for change in serum phosphorus from BL to the end of Stage 2 in this group was 0.149 (0.198) mmol/l (95% CI: -0.266, 0.564) for the PA21 group. Data from the end of Stage 2 were available for only 3 subjects in the Phoslyra group; as a result, LS means (SEs) and corresponding 95% CIs for change from BL could not be calculated for this group.

Table 14 *Change in serum phosphorus level from baseline to end of stage 2 (FAS population; updated)*

Timepoint	Unit	Statistics	PA21 (N = 65)	Phoslyra (N = 15)	Total (N = 80)
Baseline	mmol/L	N	36	6	42
		Mean (SD)	1.85 (0.407)	2.01 (0.189)	1.88 (0.386)
		Median	1.81	2.00	1.85
		Q1 ; Q3	1.57 ; 2.10	1.86 ; 2.13	1.65 ; 2.13
		Min ; Max	1.0 ; 2.7	1.8 ; 2.3	1.0 ; 2.7
	mg/dL	N	36	6	42
		Mean (SD)	5.74 (1.260)	6.21 (0.586)	5.81 (1.194)
		Median	5.60	6.18	5.71
		Q1 ; Q3	4.85 ; 6.50	5.76 ; 6.59	5.11 ; 6.59
		Min ; Max	3.1 ; 8.2	5.5 ; 7.1	3.1 ; 8.2
End of Stage 2	mmol/L	N	36	6	42
		Mean (SD)	1.76 (0.505)	2.11 (0.702)	1.81 (0.541)
		Median	1.65	1.91	1.66
		Q1 ; Q3	1.39 ; 2.15	1.52 ; 2.81	1.39 ; 2.20
		Min ; Max	0.7 ; 2.6	1.4 ; 3.1	0.7 ; 3.1
	mg/dL	N	36	6	42
		Mean (SD)	5.44 (1.563)	6.52 (2.174)	5.60 (1.675)
		Median	5.09	5.91	5.14
		Q1 ; Q3	4.30 ; 6.64	4.71 ; 8.70	4.30 ; 6.81
		Min ; Max	2.3 ; 8.1	4.3 ; 9.6	2.3 ; 9.6

Timepoint	Unit	Statistics	PA21 (N = 65)	Phoslyra (N = 15)	Total (N = 80)
Change from Baseline to End of Stage 2	mmol/L	N	36	6	42
		Mean (SD)	-0.10 (0.550)	0.10 (0.584)	-0.07 (0.552)
		Median	-0.06	0.00	-0.06
		Q1 ; Q3	-0.42 ; 0.28	-0.42 ; 0.52	-0.42 ; 0.29
		Min ; Max	-1.9 ; 0.7	-0.5 ; 1.0	-1.9 ; 1.0
		LS Mean (SE)[1]	0.099 (0.198)	-0.393 (0.218)	
		95% CI	(-0.306, 0.504)	(-3.167, 2.380)	
		P-value[2]	0.6207	0.3226	
	mg/dL	N	36	6	42
		Mean (SD)	-0.29 (1.704)	0.30 (1.808)	-0.21 (1.710)
		Median	-0.17	0.00	-0.17
		Q1 ; Q3	-1.28 ; 0.85	-1.30 ; 1.61	-1.30 ; 0.90
		Min ; Max	-5.9 ; 2.3	-1.5 ; 3.0	-5.9 ; 3.0
		LS Mean (SE)[1]	0.307 (0.614)	-1.218 (0.676)	
		95% CI	(-0.947, 1.560)	(-9.804, 7.369)	
		P-value[2]	0.6207	0.3226	

Percentage of subjects with serum phosphorus levels within the age-dependent target range at each visit

The age-dependent target range for serum phosphorus levels in the study is as follows (Table 15):

Table 15*: age-related serum phosphorus targets post-randomization*

Age	mmol/l	
0 to <1 year	1.62-2.52	
≥1 year to <6 years	1.45-2.10	
≥6 years to <13 years	1.16-1.87	
≥13 years to <18 years	0.74-1.45	

Source: National Kidney Foundation Kidney Disease Outcomes Quality Initiative Nutrition Guidelines, 2008 [62] (prc

At BL, 2 (3.08%) subjects in the FAS PA21 group had a serum phosphorus level below the age-related target range as assessed by the central laboratory, 11 (16.92%) subjects had levels within target ranges, and 52 (80.00%) subjects had levels above target ranges.

In the Phoslyra group, 1 (6.67%) subject had a level below, 1 (6.67%) subject had a level within, and 13 (86.67%) subjects had levels above target ranges. At the end of Stage 1, 39.06% of PA21 subjects and 13.33% of Phoslyra subjects with central laboratory data had serum phosphorus levels within target ranges; the corresponding figures at the end of Stage 2 were 35.00% for PA21 and 25.00% for Phoslyra.

At BL, 1 (2.38%) subject in the PPS PA21 group had a serum phosphorus level below age-related target ranges as assessed by the central laboratory, 9 (21.43%) subjects had levels within target ranges, and 32 (76.19%) subjects had levels above target ranges. In the PPS Phoslyra group, all 5 subjects had BL levels above target ranges. At the end of Stage 1, 45.24% of PPS PA21 subjects and 40.00% of PPS Phoslyra subjects with central laboratory data had serum phosphorus levels within target ranges; the corresponding figures at the end of Stage 2 were 39.29% for PA21 and 50.00% for Phoslyra.

Table 16 ***serum phosphorus level over time according to the age-related target range – central lab measurement (FAS population)***

Timepoint	Category	PA21 (N = 65) n (%) [95% CI]	Phoslyra (N = 15) n (%) [95% CI]	Total (N = 80) n (%) [95% CI]
Baseline	N	65	15	80
	Below	2 (3.08%) [0.37%, 10.68%]	1 (6.67%) [0.17%, 31.95%]	3 (3.75%) [0.78%, 10.57%]
	Within	11 (16.92%) [8.76%, 28.27%]	1 (6.67%) [0.17%, 31.95%]	12 (15.00%) [8.00%, 24.74%]
	Above	52 (80.00%) [68.23%, 88.90%]	13 (86.67%) [59.54%, 98.34%]	65 (81.25%) [70.97%, 89.11%]
End of Stage 1	N	64	15	79
	Below	2 (3.13%) [0.38%, 10.84%]	1 (6.67%) [0.17%, 31.95%]	3 (3.80%) [0.79%, 10.70%]
	Within	25 (39.06%) [27.10%, 52.07%]	2 (13.33%) [1.66%, 40.46%]	27 (34.18%) [23.87%, 45.71%]
	Above	37 (57.81%) [44.82%, 70.06%]	12 (80.00%) [51.91%, 95.67%]	49 (62.03%) [50.41%, 72.72%]
End of Stage 2	N	40	8	48
	Below	1 (2.50%) [0.06%, 13.16%]	0	1 (2.08%) [0.05%, 11.07%]
	Within	14 (35.00%) [20.63%, 51.68%]	2 (25.00%) [3.19%, 65.09%]	16 (33.33%) [20.40%, 48.41%]
	Above	25 (62.50%) [45.80%, 77.27%]	6 (75.00%) [34.91%, 96.81%]	31 (64.58%) [49.46%, 77.84%]

Note: Exact 95% CIs are provided. Target ranges are from National Kidney Foundation Kidney Disease Outcomes Quality Initiative Nutrition Guidelines, 2008 [62].
N=total number of subjects; n=number of observations; CI=Confidence Interval; FAS=Full Analysis Set.

Percentage of subjects with serum phosphorus within the age-dependent normal range at each visit

The normal ranges for age-dependent serum phosphorus levels are as follows (see Table 17 below):

Table 17 *Age-related normal ranges for serum phosphorus*

Age	mmol/l	
	Lower Limit	Upper Limit
0 to <1 year	1.36	2.62
≥1 year to <6 years	1.03	1.97
≥6 years to <9 years	1.03	1.97
≥9 years to <10 years	1.03	1.97
≥10 years to <15 years	1.00	1.94
≥15 years to ≤18 years	0.71	1.65

At BL, 1 (1.54%) subject in the FAS PA21 group had a serum phosphorus level below the age-related normal range as assessed by the central laboratory, 24 (36.92%) subjects had levels within normal ranges, and 40 (61.54%) subjects had levels above normal ranges.

In the Phoslyra group, 1 (6.67%) subject had a level below, 5 (33.33%) subjects had levels within, and 9 (60.00%) subjects had levels above normal ranges.

At the end of Stage 1, 60.94% of PA21 subjects and 40.00% of Phoslyra subjects with central laboratory data had serum phosphorus levels within normal ranges; the corresponding figures at the end of Stage 2 were 57.50% for PA21 and 25.00% for Phoslyra.

Table 18 *Serum phosphorus level over time according to the age-related normal range – central lab measurement (FAS population)*

Timepoint	Category	PA21 (N = 65) n (%) [95% CI]	Phoslyra (N = 15) n (%) [95% CI]	Total (N = 80) n (%) [95% CI]
Baseline	N	65	15	80
	Below	1 (1.54%) [0.04%, 8.28%]	1 (6.67%) [0.17%, 31.95%]	2 (2.50%) [0.30%, 8.74%]
	Within	24 (36.92%) [25.28%, 49.80%]	5 (33.33%) [11.82%, 61.62%]	29 (36.25%) [25.79%, 47.76%]
	Above	40 (61.54%) [48.64%, 73.35%]	9 (60.00%) [32.29%, 83.66%]	49 (61.25%) [49.70%, 71.94%]
End of Stage 1	N	64	15	79
	Below	1 (1.56%) [0.04%, 8.40%]	1 (6.67%) [0.17%, 31.95%]	2 (2.53%) [0.31%, 8.85%]
	Within	39 (60.94%) [47.93%, 72.90%]	6 (40.00%) [16.34%, 67.71%]	45 (56.96%) [45.33%, 68.06%]
	Above	24 (37.50%) [25.70%, 50.49%]	8 (53.33%) [26.59%, 78.73%]	32 (40.51%) [29.60%, 52.15%]
End of Stage 2	N	40	8	48
	Below	1 (2.50%) [0.06%, 13.16%]	0	1 (2.08%) [0.05%, 11.07%]
	Within	23 (57.50%) [40.89%, 72.96%]	2 (25.00%) [3.19%, 65.09%]	25 (52.08%) [37.19%, 66.71%]
	Above	16 (40.00%) [24.86%, 56.67%]	6 (75.00%) [34.91%, 96.81%]	22 (45.83%) [31.37%, 60.83%]

Note: Exact 95% CIs are provided. Normal ranges are according to Covance central laboratory.
N=total number of subjects: n=number of observations: CI=Confidence Interval: FAS=Full Analysis Set.

At BL, 1 (2.38%) subject in the PPS PA21 group had a serum phosphorus level below the age-related normal range as assessed by the central laboratory; 16 (38.10%) subjects had levels within normal ranges and 25 (59.52%) subjects had levels above normal ranges.

In the PPS Phoslyra group, 3 (60.00%) of the 5 subjects had levels within normal ranges and 2 (40.00%) had levels above normal ranges. At the end of Stage 1, 71.43% of PPS PA21 subjects and 80.00% of PPS Phoslyra subjects with central laboratory data had serum phosphorus values within normal ranges; the corresponding figures at the end of Stage 2 were 57.14% for PA21 and 50.00% for Phoslyra.

At BL, only 2 subjects in the PPS PA21 group had local laboratory assessment of serum phosphorus; 1 (50.00%) subject had a level within the age-related normal range and 1 (50.00%) subject had a level above the normal range. No subjects in the Phoslyra group had local laboratory data at BL. At the end of Stage 1, 50.00% of PPS PA21 subjects and 33.33% of PPS Phoslyra subjects with local laboratory data had serum phosphorus values within normal ranges; the corresponding figures at the end of Stage 2 were 60.00% for PA21 and 0% for Phoslyra (it should be noted that results for end of Stage 2 were available for only 15 PPS PA21 subjects and 2 PPS Phoslyra subjects).

In summary, reductions in serum phosphorus level were observed with PA21 in all age groups; however, a statistically significant reduction in serum phosphorus was achieved only in the subgroup of subjects ≥12 to ≤18 years old at randomisation. Important and statistically significant reduction in

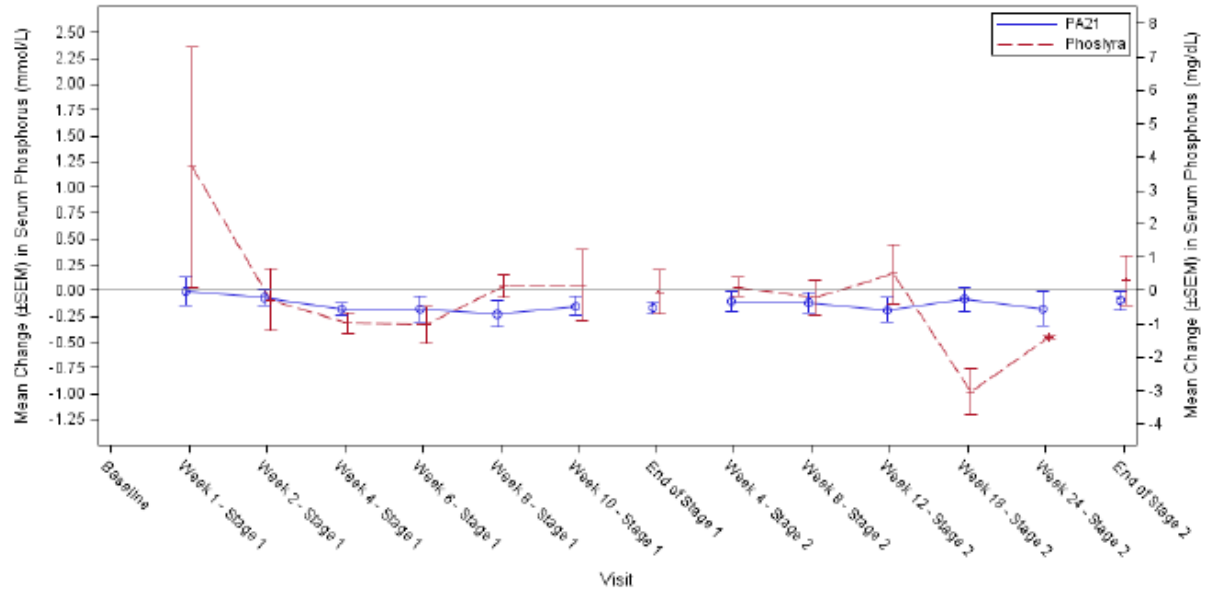
serum phosphorus was achieved in subjects with serum phosphorus levels above the age-related normal range at BL.

Serum phosphorus values at each visit during Stage 1 and 2

In the FAS population, serum phosphorus levels assessed by the central laboratory showed consistent slight decreases from BL in the PA21 group, while fluctuation relative to BL was observed in the Phoslyra group: the small numbers of subjects in the Phoslyra group (total N=15) should be noted (see Figure 3).

In the PPS population, serum phosphorus levels assessed by the central laboratory showed slight decreases from BL at nearly all time points in the PA21 group. In this population, the Phoslyra group also showed small decreases from BL at most time points; it should be noted that only 5 Phoslyra subjects were included in the PPS population.

Figure 3 Mean change (±SEM) from baseline in serum phosphorus levels to end of stage 2 (FAS population)



Notes: Data are from central laboratory.
SEM=standard error of the mean; FAS=Full Analysis Set.

Patient-reported palatability and acceptability

Subject-reported palatability and acceptability were measured using a 5-point facial hedonic scale combined with a 10-cm VAS. The ends were defined as the extreme limits of the parameter to be measured, oriented from the left (better; lower scores) to the right (worse; higher scores).

At time points where data were available for more than a few subjects, scores were generally low (indicating good palatability/acceptability) for both treatments. At the end of Stage 2, mean scores were lower (more favourable) for PA21 than for Phoslyra. Time points at week 4, end of Stage 1 and 2 were scored by 49, 60 and 39 subjects, respectively.

- Overall like/dislike: mean (SD) scores at the end of Stage 1 were 3.58 (2.445) cm in the PA21 group, and 3.39 (2.905) cm in the Phoslyra group; corresponding figures at the end of Stage 2 were 2.43 (2.862) cm in the PA21 group and 5.47 (4.161) cm in the Phoslyra group.

- Adherence – compliance with the study drug compared with other PBs (if relevant): mean (SD) scores at the end of Stage 1 were 3.36 (2.467) cm in the PA21 group, and 3.67 (3.197) cm in the Phoslyra group; corresponding figures at the end of Stage 2 were 2.63 (2.819) cm in the PA21 group and 4.66 (3.323) cm in the Phoslyra group.
- Ease of taking study drug: mean (SD) scores at the end of Stage 1 were 3.28 (2.941) cm in the PA21 group, and 4.11 (3.270) cm in the Phoslyra group; corresponding figures at the end of Stage 2 were 2.39 (2.734) cm in the PA21 group and 2.61 (2.271) cm in the Phoslyra group.
- Palatability/acceptability of the study drug compared with other medications the subject has to take: mean (SD) scores at the end of Stage 1 were 4.13 (3.006) cm in the PA21 group and 3.95 (3.603) cm in the Phoslyra group; corresponding figures at the end of Stage 2 were 4.47 (3.729) cm in the PA21 group and 5.10 (3.607) cm in the Phoslyra group.

The items "how easy to give to your child" and "your child found acceptable" were assessed by the parent or carer for subjects ≤2 years old using a 10-cm VAS. The ends were defined as the extreme limits of the parameter to be measured, oriented from the left (better; lower scores) to the right (worse; higher scores). Results for these items were available for only 1 PA21 subject for most time points, and no data were available for Phoslyra.

- How easy to give to your child: scores in the PA21 group ranged from 0.30 to 7.90 cm; the mean score at the end of Stage 1 was 4.10 cm.
- Your child found acceptable: scores in the PA21 group ranged from 0.50 to 8.00 cm; the mean score at the end of Stage 1 was 3.90 cm.

In conclusion, results for subject-reported palatability and acceptability were available for very few subjects at most time points. At time points where data were available for more than a few subjects, scores were generally low (indicating good palatability/acceptability) for both treatments. At the end of Stage 2, mean scores were lower (more favourable) for PA21 than for Phoslyra.

Ancillary analyses

Primary efficacy endpoint according to age-related normal ranges at baseline

Among subjects whose serum phosphorus was above age-related normal ranges at baseline (N=40), serum phosphorus levels showed statistically significant decrease from baseline to the end of Stage 1 (LS mean (SE): -0.282 (0.096) mmol/l (95% CI: -0.476, -0.087) p=0.0058), while no significant change was observed among subjects whose baseline phosphorus was within or below normal ranges (N=25; LS mean (SE): 0.082 (0.146) mmol/l (95% CI: -0.224, 0.388).

Greater reduction was seen in all age groups among subjects with high baseline phosphorus. Among subjects ≥12 to ≤18 years old at randomisation, the decrease seen among subjects with high baseline phosphorus (N=23) was statistically significant (LS mean (SE): -0.312 (0.081) mmol/l (95% CI: -0.482, -0.141) p=0.0011).

Table 19: *Change in serum phosphorus level from baseline to end of stage 1 in PA21 groups (FAS population)*

Time Point	Unit	Statistics	PA21					
			Full FAS PA21 Group (N=65)	By Age at Randomisation			By Baseline Serum Phosphorus	
				≥2 to <6 Years (N=6)	≥6 to <12 Years (N=17)	≥12 to ≤18 Years (N=42)	Above Age-Related Normal Range (N=40)	Below or Within Age-Related Normal Range (N=25)
Baseline	mmol/l	n	65	6	17	42	40	25
		Mean (SD)	2.08 (0.548)	2.37 (0.644)	2.24 (0.608)	1.98 (0.491)	2.40 (0.441)	1.58 (0.234)
		Median	2.03	2.43	2.20	1.92	2.28	1.61
		Min/Max	1.0/3.7	1.4/3.0	1.0/3.7	1.2/3.3	1.7/3.7	1.0/2.0
End of Stage 1	mmol/l	n	65	6	17	42	40	25
		Mean (SD)	1.91 (0.643)	2.29 (0.621)	2.01 (0.882)	1.81 (0.510)	2.07 (0.724)	1.64 (0.367)
		Median	1.79	2.46	1.87	1.78	1.97	1.55
		Min/Max	1.0/4.8	1.5/3.0	1.1/4.8	1.0/3.5	1.0/4.8	1.1/2.4
Change from baseline to end of Stage 1	mmol/l	n	65	6	17	42	40	25
		Mean (SD)	-0.17 (0.487)	-0.08 (0.253)	-0.23 (0.690)	-0.17 (0.417)	-0.33 (0.503)	0.07 (0.350)
		Median	-0.16	-0.08	-0.24	-0.16	-0.39	0.03
		Min/max	-1.2/1.6	-0.5/0.2	-1.2/1.6	-1.2/1.1	-1.2/1.6	-0.4/1.1
		LS mean (SE)[1]	-0.120 (0.081)	-0.078 (0.123)	-0.200 (0.158)	-0.149 (0.062)	-0.282 (0.096)	0.082 (0.146)
		95% CI	(-0.282, 0.043)	(-0.468, 0.312)	(-0.541, 0.141)	(-0.274, -0.023)	(-0.476, -0.087)	(-0.224, 0.388)
		P-value[2]	0.1456	0.5682	0.2271	0.0220	0.0058	0.5801

Primary efficacy endpoint according to other subgroups

Patients not on dialysis

Additional analyses have been performed to investigate the characteristics of the group of paediatric patients not on dialysis at baseline as well as the treatment effect, safety profile and the dosing in order to address the benefit/risk in this group.

- Demographics

Regarding the demographic characteristics, it was shown that from the total of 66 subjects on Velphoro in the SAF population, 15 (23%) were not on dialysis and 51 (77%) were on dialysis. Distribution of subjects not on dialysis and on dialysis (and their demographic characteristics) was reasonably balanced across age groups: 12-≤18 years (60% in not on dialysis group; 66.7% in group on dialysis), 6-<12 years (26.7% and 25.5%) and 2-<6 years (13.3% and 7.8%).

- Treatment effect

A smaller change in serum phosphorus level from baseline to end of stage 1 was observed in the group not on dialysis (LS mean (SE) of -0.042 (0.080) mmol/L vs -1.174 (-0.083) on dialysis), which can likely be explained by the lower, close to normal range, serum phosphorus level at baseline in this group not on dialysis (i.e. 1.84 mmol/L) than in the group on dialysis (i.e. 2.15 mmol/L) and percentage already at normal range at baseline (60% vs 32%), and thus on average a lower need for change to reach normal serum phosphorus levels.

Also, the proportion of patients reaching normal range levels was slightly higher in the subjects not on dialysis at stage 1 (20% vs 25%) and stage 2 (13% vs 23%), however, the total proportion of patients in the normal range was greater in the patients not on dialysis than for the dialysis patients both at Stage 1 (57% vs 80%) and during the maintenance phase Stage 2 (55% vs 73%).

- Dosing

The average daily dose was only slightly lower in the not on dialysis group (1742 mg vs 1890 mg), and the actual number of tablets/sachets taken were comparable (n=3.1 vs n=3.3). The number of subjects with at least one dose change was generally comparable between groups not on dialysis (n=10 (67%)) and on dialysis (n=37 (72.5%)). Findings were largely similar across age groups. These

data suggest that comparable dosing has been applied to patients not on dialysis, and dose recommendations should therefore not be different for these group of patients.

Gender

Subgroup analysis of the primary endpoint by gender showed greater decreases in serum phosphorus in females than in males. However, the 95% CIs for the respective subgroups overlapped considerably. LS means (SEs) for change from baseline were -0.177 (0.096) mmol/l (95% CI: -0.373, 0.018) for females and -0.026 (0.130) mmol/l (95% CI: -0.294, 0.242) for males.

Region

Subgroup analysis of the primary endpoint by region (US/non-US) showed greater decreases in serum phosphorus in US subjects than in non-US subjects; the decrease observed among the US subjects was statistically significant. However, the 95% CIs for the respective subgroups overlapped considerably. LS means (SEs) for change from baseline were -0.214 (0.103) mmol/l (95% CI: -0.424, -0.005) for US subjects (p=0.0450) and -0.060 (0.139) mmol/l (95% CI: -0.348, 0.228) for non-US subjects.

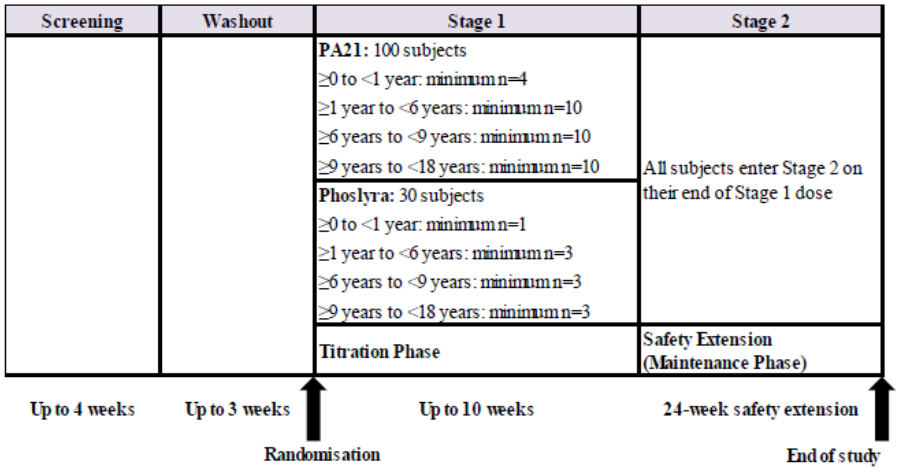
Formulation

Subgroup analysis of the primary endpoint by formulation - Greater decreases in serum phosphorus from baseline to the end of Stage 1 were observed among PA21 subjects who were prescribed sachets only or both formulations than among those prescribed tablets only; however, the 95% CIs for the respective subgroups overlapped considerably. Among subjects who were prescribed tablets only (N=46), the LS mean (SE) for change from baseline was -0.032 (0.094) mmol/l (95% CI: -0.222, 0.159). Among subjects who were prescribed sachets only (N=10), the LS mean (SE) for change from baseline was -0.232 (0.140) mmol/l (95% CI: -0.621, 0.157). Among subjects who were prescribed both formulations (N=9), the LS mean (SE) for change from baseline was -0.166 (0.166) mmol/l (95% CI: -0.626, 0.293). However, the smaller numbers of subjects prescribed sachets only and both tablets and sachets should be considered.

Summary of main study

The following tables summarise the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 20 ***Summary of Efficacy for trial PA-CL-PED-01***

Title: An Open-label, Randomised, 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	
Study identifier	PA-CL-PED-01
Design	Study PA-CL-PED-01 was a Phase 3, multicentre, randomised, prospective, open-label, parallel-group, active-controlled study. Stage 1 was an open-label, randomised, active-controlled, dose titration period during which subjects received PA21 or Phoslyra. Stage 2 was an open-label, long-term safety extension lasting 24 weeks. All subjects were to enter this safety extension stage. During Stage 2, subjects continued the dose they were receiving at the end of Stage 1, unless a dose change was required. Serum phosphorus levels were measured weekly during the screening and washout period and two-weekly during Stage 1 and Stage 2. Dose modifications could therefore be done two-weekly during Stage 1 and Stage 2. To evaluate the efficacy of PA21 in reducing serum phosphorus levels in paediatric and adolescent subjects with CKD at the end of Stage 1. Primary objective to evaluate the efficacy of PA21 in reducing serum phosphorus levels in paediatric and adolescent subjects with CKD at the end of Stage 1. **Figure 1 Study Design**  Source: Protocol Figure 1.
Duration of main phase:	Maximum of 43 weeks
Screening	Up of 4 weeks
Washout	Up to 3 weeks

	Stage 1 (titration phase)		Up to 10 weeks
	Stage 2 (extension/ maintenance phase)		24 weeks safety extension; subjects were followed for 14 days after their last study visit.
Hypothesis	The primary hypothesis is a reduction in serum phosphorus levels from baseline to the end of Stage 1 in the PA21 group.		
Treatments groups	PA21 (Velphoro; sucroferric oxyhydroxide)		100 subjects to receive PA21 at a starting dose based on their age. In Stage 1 dose will be increased or decreased as required to achieve age-specific target serum phosphorus levels (see Tables 5 and 6 above for dose modifications and maximum doses of PA21).
	Phoslyra (calcium acetate)		30 subjects to receive Phoslyra received either Phoslyra at the starting dose of 0.45 ml/kg/day (see Tables 7 and 8 above for dose modifications and maximum doses of Phoslyra) or an equivalent dose of their previous PB number randomized.
Endpoints and definitions	Primary endpoint	sP level change from BL to Stage 1	Change in serum phosphorus levels from baseline to the end of Stage 1 in the PA21
	Secondary efficacy endpoints	sP level change from BL to Stage 1	Change in serum phosphorus levels from baseline to the end of Stage 1 in the Phoslyra group
		sP level change from BL to Stage 2	Change in serum phosphorus levels from baseline to the end of Stage 2 in the PA21 and Phoslyra groups group
		sP levels at each visit	Serum phosphorus values at each visit during Stage 1 and 2
		% within sP target range	Percentage of subjects with serum phosphorus levels within the age-dependent target range at each visit
		% within sP normal range	Percentage of subjects with serum phosphorus within the age-dependent normal range at each visit
Database lock	-		

Results and Analysis				
Analysis description	**Primary Analysis - Efficacy**			
Analysis population and time point description	Full Analysis Set (FAS) Population: all subjects randomised to treatment at Stage 1 who received at least 1 dose of randomised treatment and who had at least 1 post-baseline assessment of the efficacy endpoint (serum phosphorus level), analysed according to randomised treatment.			
Descriptive statistics and estimate variability	Treatment group	PA21 (prim endpoint)	Phoslyra (sec eff endpoint)	-
	Number of subjects	N=66	N=19	-
	sP level change from BL to Stage 1, LS mean (mmol/L)	-0.120 (0.081)	-0.615 (0.320)	-
	95% CI	-0.282, 0.043	-1.339, 0.110	-
	sP level change from BL to Stage 1, ⩾2 to <6 years old (n=6), LS mean (mmol/L)	-0.078 (0.123)	-	-
	95% CI	-0.468, 0.312	-	-
	sP level change from BL to Stage 1, ⩾6 to <12 years old (n=17), LS mean (mmol/L)	-0.200 (0.158	-	-
	95% CI	-0.541, 0.141	-	-
	sP level change from BL to Stage 1, ⩾12 to ⩽18 years old (n=42), LS mean (mmol/L)	-0.149 (0.062)	-	-
	95% CI	-0.274, -0.023)	-	-

	sP level change from BL to Stage 2 (sec eff endpoint), LS mean (mmol/L)	0.099 (0.198)	-0.393 (0.218)	-
	95% CI	-0.306, 0.504	-3.167, 2.380	-
	sP levels at each visit (sec eff endpoint)	consistent slight decreases from baseline	fluctuation relative to baseline	-
	% within sP target range (sec eff endpoint)	39% (stage 1) 35% (stage 2)	13% (stage 1) 25% (stage 2)	-
	% within sP normal range (sec eff endpoint)	61% (stage 1) 58% (stage 2)	40% (stage 1) 25% (stage 2)	-

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

No clinical studies in special population were submitted this was considered acceptable by the CHMP

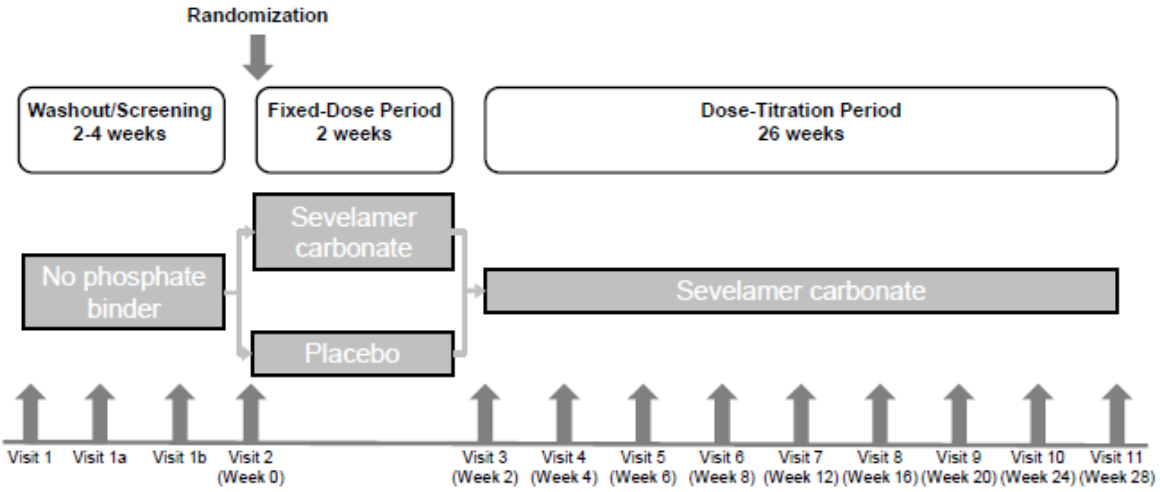
Supportive study

Descriptive comparison with Sevelamer

Following EMA Paediatric Committee advice from the Modification Summary Report Day 30 (EMA/170421/2018), the Sponsor decided to include additional comparison with an external control from paediatric Study SVCARB07609 (EudraCT No. 2011-002329- 23), a Phase 2 study conducted with sevelamer carbonate (SC) in CKD patients with hyperphosphataemia (Fathallah-Shaykh et al, 2018) where appropriate.

The Sponsor selected this external control from available studies in hyperphosphataemic paediatric patients with CKD due to the large sample size and the fact that results of this study supported the extension of the indication for SC to paediatric patients in the EU (EMA/271022/2016 and EMA/352101/2017). However, due to differences in the design of the studies, there are limitations to this comparison.

Figure 3 Design of sevelamer study SVCARB07609



Most notably, the age-related pre-randomisation target levels for sP were slightly higher in Study SVCARB07609 and a long term 26 weeks titration period after 2 weeks of fixed dose period was applied for the sevelamer study, while a titration period of 10 weeks followed by 24 weeks stable dosing was applied for Velphoro.

Baseline sP levels were higher in Study SVCARB07609 (means (SDs): 7.22 (2.07) mg/dl for the SC group and 7.15 (1.92) mg/dl for the placebo group) than in Study PA-CL-PED-01 (means (SDs): 6.41 (1.615) mg/dl for the FAS Velphoro group used in the efficacy analyses; 6.38 (1.625) mg/dl for the safety population), and higher percentages of subjects in Study SVCARB07609 had elevated sP at baseline.

In both studies, compliance with study treatment was generally good; mean compliance rates were ≥68% in all treatment groups and study periods. Compliance rates for Velphoro treatment were higher than those for SC or its matching placebo.

Although decreases in sP levels were observed with Velphoro treatment both at the end of the DTP (Stage 1; primary efficacy endpoint) and at the end of the maintenance period (Stage 2; secondary endpoint), these changes were not statistically significant.

In contrast to Velphoro, with sevelamer the change from baseline in sP levels was statistically significantly greater with SC than with placebo at the end of the 2-week fixed dose phase; little change was observed in the placebo group. At the end of the DTP (titration phase), changes from baseline in sP level were statistically significant in both treatment groups (subjects originally randomised to SC and subjects who crossed over from placebo to SC during the DTP), as well as in the 2 groups combined ($p<0.0001$). Mean changes from baseline in sP level in the SC treatment groups were numerically greater than those observed with Velphoro; however, the differences in the designs of the 2 studies limit the interpretability of this difference.

- In Study PA-CL-PED-01 (Velphoro), the LS mean (standard error (SE)) change from baseline in sP levels at the end of Stage 1 (DTP) was -0.371 (0.251) mg/dl in the FAS Velphoro group ($p=0.1456$); the LS (SE) for change from baseline to the end of the maintenance period (Stage 2) was 0.307 (0.614) mg/dl ($p=0.6207$).
- In Study SVCARB07609 (sevelamer), the LS mean (SE) difference between the SC and placebo groups in sP levels at the end of the FDP (SC minus placebo) was -0.90 (0.270) mg/dl ($p=0.001$);

mean (SD) changes from baseline at this time point were -0.86 (1.649) mg/dl for SC and 0.04 (1.478) mg/dl for placebo. At the end of the DTP, mean (SD) changes from baseline in sP levels were -1.23 (2.206) mg/dl among subjects originally randomised to SC (p=0.001) and -1.13 (2.061) mg/dl among subjects who crossed over from placebo to SC (p=0.0001); among subjects who completed the study, corresponding figures were -0.94 (2.116) mg/dl among subjects originally randomised to SC (p=0.0010) and -1.12 (1.840) mg/dl among subjects who crossed over from placebo to SC (p=0.0001).

Subgroup analysis sevelamer study

In Study PA-CL-PED-01, statistically significant decrease in sP levels from baseline to the end of Stage 1 (DTP) was also seen amongst subjects ≥12 to ≤18 years old at randomisation (N=42; LS mean (SE): -0.460 (0.192) mg/dl; p=0.0220; PA-CL-PED-01 CSR); changes from baseline to the end of Stage 1 were not statistically significant for subjects <12 years old at randomisation (LS means (SEs): -0.243 (0.380) mg/dl (p=0.5682) for subjects ≥2 to <6 years old and -0.620 (0.489) mg/dl (p=0.2271) for subjects ≥6 to <12 years old; PA-CL-PED-01 CSR). Subgroup analysis by both age group and baseline sP level showed a statistically significant decrease in sP levels from baseline to the end of Stage 1 (DTP) amongst subjects ≥12 to ≤18 years old at randomisation whose baseline phosphorus was above age-related normal ranges (N=23; LS mean (SE): -0.965 (0.252) mg/dl; p=0.0011), but not amongst subjects in this age group whose baseline phosphorus was below or within age-related normal ranges (LS mean (SE): 0.146 (0.287); p=0.6198).

Results for Study SVCARB07609 were not reported by age in the publication by Fathallah-Shaykh et al, 2018. However, the FDA Office of Clinical Pharmacology Integrated Review Report observed that the difference between treatments in LS mean change from baseline (SD) amongst subjects 6 to <13 years old was 0.05 (0.55) mg/dl (95% CI: -1.04, 1.15) versus -1.40 (0.34) mg/dl (95% CI: -2.07, -0.72) for subjects 13 to 18 years old (N=35 for SC; N=36 for placebo), though the small number of subjects in the younger group (N=13) was noted. Moreover, the US Prescribing Information for Renvela (SC) notes that the subgroup with sP levels <7.0 mg/dl (who showed little difference between treatment groups) included many subjects who were 6 to <13 years old and/or not on dialysis.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study PA-CL-PED-01 was a Phase 3, multicentre, randomised, prospective, open-label, parallel-group, active-controlled study to investigate the efficacy and safety of PA21 (Velphoro®; sucroferric oxyhydroxide) for reducing serum phosphorus levels in paediatric and adolescent subjects with CKD, both on dialysis as not on dialysis aged 2 years and above, in comparison with Phoslyra liquid solution, a calcium acetate phosphate binder, approved in the US without age restriction. The study also aimed to introduce a new paediatric formulation of 125 mg powder for oral suspension to the already available 500 mg chewable tablets. The study consists of a dose-titration period of up to 10 weeks (Stage 1), and a 24-week safety extension (Stage 2). The protocol of Study PA-CL-PED-01 has been agreed upon in the PIP for PA21 (PIP decision: EMEA-001061-PIP01-10-M03), however amendments have been made to the number of patients included (see results).

The inclusion criteria are generally acceptable to identify a paediatric population with CKD and hyperphosphatemia. It should be noted that the inclusion criteria and the newly claimed paediatric indication are wider than the current adult indication, as paediatric patients not on dialysis and

classified as CKD Stage 4-5 could also be included. Exclusion criteria are generally acceptable, especially to yield possible optimal patient inclusion during the entire study period.

The dosing and duration of treatment, objectives, the primary efficacy endpoint and secondary efficacy endpoints, as well as the safety endpoints, the proposed sample size, the randomization, the blinding and methodology are in general in line with the assessment of the protocol as agreed in the PIP (PIP-decision EMEA-001061-PIP01-10-M03), and therefore acceptable.

However, it should be noted that only single measurements were used for baseline and primary and relevant secondary endpoints, which can limit interpretation of the data.

Furthermore, the primary analysis was performed using a linear mixed model including baseline value, age, region and gender as covariates, while in the PIP-decision a paired t-test was proposed. But additional analyses (paired t-test and the 2 post-hoc sensitivity) show similar and consistent results with those displayed in the CSR of the PA-CL-PED-01 study concerning the primary efficacy endpoint.

Efficacy data and additional analyses

Patient flow

Eighty-five children were randomized in the study (Velphoro: n=66 and Phoslyra: n=19). This was lower as the initially planned sample size due to recruitment problems, but the number of the patients randomized in the study is in line with what has been agreed by PDCO/EMA on 17 July 2018, to reduce the required minimum numbers of recruited subjects to at least 60 subjects to be randomized into the Velphoro group. However, due to these limited number of patients the study was not adequately powered to make an adequate comparison with Phoslyra (calcium acetate) to provide clear findings to evaluate the effect for reducing serum phosphorus levels. Also, indirect comparison with sevelamer (as requested by PDCO) should be handled with caution due to study differences and small study numbers.

There were 35 screening failures, 31 of who did not meet the inclusion criteria.

Furthermore, the number of patients who completed the study was low, with 28 out of 85 (33%) randomized patients. However, safety or lack of efficacy was not the main reason for decision of discontinuation. Further, although numbers are small and thus data should be interpreted carefully, subjects with high serum phosphorus, CKD Stage 4 and those not on dialysis at baseline were at higher risk for discontinuations, which can be expected, since the stage of disease might play an important role in discontinuations.The majority of the patients are recruited from the US, with the rest of the population recruited in EU, which may somewhat limit interpretation for the EU setting.

Major protocol deviations mainly included non-compliance. Compliance was generally higher in the PA21 group (87%) versus the Phoslyra group (72%), but numbers were too small to conclude that this may impact the interpretation of the data.

Demographics and disease characteristics

The baseline characteristics were generally sufficiently well distributed across the two treatment groups, although the number of patients in the Phoslyra group was small. The study population can be considered representative of paediatric and adolescent patients with Stage 4-5 CKD. The mean baseline phosphorus level was just above the target level (2.08 mmol/L; see Table 4 for age-related target levels) likely due to immediate inclusion of patients just after a higher level than target level was observed based on a single measurement.

Dose

Considerations with regards to the dose recommendations during the study, the dose recommendation currently proposed in the SmPC, and dosing results in the study have been sufficiently justified and are appropriately reflected in the product information.

Primary and secondary endpoints

The primary endpoint showed a limited non-statistically significant LS mean (SE) difference from baseline to end of stage 1 (titration phase) in serum phosphorus levels of -0.120 (0.081) mmol/l (95% CI: -0.282, 0.043) in the PA21 treatment group (n=65) based on the mixed model calculations with actual data showing a mean of 2.08 mmol/L at baseline and 1.91 mmol/L at stage 1 (reduction by 0.17 mmol/L).

A limited effect was maintained during the 24 weeks follow-up (stage 2), although some fluctuations in mean effect over time were noticed with an effect of 0.099 (0.198) mmol/L (95% CI -0.306, 0.504) observed at the end of the 24 weeks period (stage 2).

The observed decrease in serum phosphorus levels resulted in 39% of the patients being within the target range at stage 1 and 35% at the end of 24-week stage 2, with 17% being within the target range at baseline. It should however be noted that the number of patients above the target range still consisted of the largest group of patients, with 80% at baseline to 58% at Stage 1 and 63% at the end of Stage 2.

A statistically non-significant and substantially less than initially envisaged treatment effect in these children was observed, that can be explained by the difficulties in treating these patient groups and based on several factors in design and conduct of the study, including large proportion at normal serum phosphorus levels. Despite these limitations, the long-term maintenance of serum phosphorus levels in the patients within the normal range is considered of main clinical relevance to reduce morbidity and mortality in this paediatric population.

Efficacy for comparator Phoslyra (calcium acetate)

The limited number of patients (n=15) treated with Phoslyra (calcium actetate) showed comparable efficacy with Velphoro although no formal statistical testing was performed. Phoslyra showed an effect from baseline to the end of stage 1 of -0.615 (0.320) mmol/l (95% CI: -1.339, 0.110) with actual data showing a decrease of 0.01 mmol/L from a baseline level of 2.15 mmol/L to 2.14 mmol/L at the end of stage 1 (titration phase).

The effect (LS mean (SE) difference) was -0.393 (0.218) mmol/L (95%CI -3.167, 2.380) at end of the 24 weeks period (stage 2), and 13% and 25% of the children were within the target range at stage 1 and 2, respectively, while 7% of the children were within target range at baseline. Also, here, the majority of pediatric patients remained with a serum phosphorus level above the target range (87%, 80%, 75% at baseline, stage 1 and stage 2, respectively).

Subgroup analyses

For the approximately 20% of the children who were not on dialysis, a clinically relevant treatment effect in patients not on dialysis comparable to dialysis patients has been observed. A smaller change in serum phosphorus level from baseline to end of stage 1 was observed in the group not on dialysis (LS mean (SE) of -0.042 (0.080) mmol/L vs -1.174 (-0.083) on dialysis), which can likely be explained by the lower, close to normal range, serum phosphorus level at baseline in this group not on dialysis (i.e. 1.84 mmol/L) than in the group on dialysis (i.e. 2.15 mmol/L) and percentage already at normal range at baseline (60% vs 32%), and thus on average a lower need for change to reach normal serum phosphorus levels. Also, the proportion of patients reaching normal range levels was slightly higher in

the subjects not on dialysis at stage 1 (20% vs 25%) and stage 2 (13% vs 23%), however, the total proportion of patients in the normal range was still greater in the patients not on dialysis than for the dialysis patients both at Stage 1 (80% vs 57%) and during the maintenance phase Stage 2 (73% vs 55%). Overall, such findings are considered of clinical relevance for both the dialysis and the non-dialysis patients.

Also, the average daily dose was only slightly lower in the not on dialysis group (1742 mg vs 1890 mg), and the actual number of tablets/sachets taken were comparable (n=3.1 vs n=3.3). The number of subjects with at least one dose change was generally comparable between groups not on dialysis (n=10 (67%)) and on dialysis (n=37 (72.5%)). Dosing applied appears therefore not to deviate substantially from the dialysis group and thus dose recommendations could be similar.

The effect for the primary endpoint (change of serum phosphorus levels from baseline to stage 1) appears not to be consistent across several subgroups.

Especially, the youngest age group of 2 to 6 years showed a lower effect (LS mean (SE) of -0.078 (0.123) mmol/L (95% CI: -0.468, 0312) than older pediatric patients (LS mean (SE) of -0.200 (0.158) mmol/L (95% CI: -0.541, 0,141) for 6 to 12 years of age and -0.149 (0.062) mmol/L (95% CI: -0.274, -0.023), p=0.020 in 12 to 18 years of age), despite the highest baseline serum phosphorus levels in the youngest age group (mean (SD) of 2.37 (0.644) mmol/L compared to 2.24 mmol/L in the ≥6 to <12 years old children and 1.98 mmol/L in the oldest group of children). Thus, reductions in serum phosphorus level were observed with PA21 in all age groups. However, statistically significant reduction in serum phosphorus was achieved only in the subgroup of subjects ≥12 to ≤18 years of age.

Furthermore, subjects whose serum phosphorus levels were higher or above age-related normal ranges at baseline serum phosphorus levels showed greater reduction from baseline to the end of Stage 1. Among subjects whose serum phosphorus was above age-related normal ranges at baseline (N=40), serum phosphorus levels showed statistically significant decrease from baseline to the end of Stage 1 (LS mean (SE): -0.282 (0.096) mmol/l (95% CI: -0.476, -0.087) p=0.0058), while no significant change was observed among subjects whose baseline phosphorus was within or below normal ranges (N=25; LS mean (SE): 0.082 (0.146) mmol/l (95% CI: -0.224, 0.388). This could be a result of a large proportion of patients with normal range at baseline (36%) included in the study, which was due to a large overlap of the different target ranges at screening and at baseline and patient intra-variability.

Also, a difference in gender with a higher reduction in females compared to males (LS means (SEs) for change from baseline to stage 1 were -0.177 (0.096) mmol/l (95% CI: -0.373, 0.018) for females and -0.026 (0.130) mmol/l (95% CI: -0.294, 0.242) for males) was observed.

Moreover, US patients have shown greater decreases in serum phosphorus levels compared to non-US patients (LS means (SEs) for change from baseline to stage 1 were -0.214 (0.103) mmol/l (95% CI: -0.424, -0.005) for US subjects (p=0.0450) and -0.060 (0.139) mmol/l (95% CI: -0.348, 0.228) for non-US subjects).

Also, greater decreases in serum phosphorus from baseline to the end of Stage 1 were observed among PA21 subjects who were prescribed sachets only or both formulations than among those prescribed tablets only. Among subjects who were prescribed tablets only (N=46), the LS mean (SE) for change from baseline to stage 1 was -0.032 (0.094) mmol/l (95% CI: -0.222, 0.159), for subjects on sachets only (N=10) this was -0.232 (0.140) mmol/l (95% CI: -0.621, 0.157), and for subjects on both formulations (N=10), this was -0.166 (0.166) mmol/l (95% CI: -0.626, 0.293).

Comparison to adult data

In general, the effect observed in this study is substantially lower than observed in adults. Adult data as stated in section 5.1 of the SmPC for Velphoro are: "*Mean serum phosphorus levels were 2.5 mmol/L at baseline and 1.8 mmol/L at week 12 for Velphoro (reduction by 0.7 mmol/L).*"

However, the response rates of children in the current study showed generally similar rates within the target range compared to adult data (45.3% at week 12 and 51.9% at week 52).

Comparison to the adult studies may be difficult due to several reasons including difference in population and study conduct such as mean baseline phosphorus level only marginally higher than target level with a substantial proportion of patients being already within the normal ranges of serum phosphorus levels at baseline, compliance issues, uncertainty on baseline and endpoint values due to single measurements among other possible reasons. Also, the findings in Phoslyra hampers the same issues when any comparison to adult effects are being made.

Comparison to sevelamer study data

As requested by PDCO an indirect comparison was made between the Velphoro study and the sevelamer study. However, differences in study design and inclusion criteria, amongst other possible differences limit the interpretation of this comparison. Most notable differences are the higher baseline levels of phosphorus in the sevelamer study population, inclusion of patients > 6 years only in the sevelamer study and the difference in titration phase (26 weeks) for sevelamer versus stable dosing phase (24 weeks; stage 2) subsequent to the 10-week titration phase (stage 1) for Velphoro.

Considering all these limitations, the best available comparison would be to compare data for patients >6 years only at the end of the study periods for both studies. For PA21 the effect from baseline to the end of stage 1 (as stage 2 data are not available) is LS mean (SE) of -0.620 (0.489) mg/dl (95% CI: -1.675, 0.436) among subjects ≥6 to <12 years old (n=17), while for sevelamer the effect was from baseline (SD) to the end of the study amongst subjects 6 to <13 years old: LS mean change 0.05 (0.55) mg/dl (95% CI: -1.04, 1.15). But the groups were small.

Among subjects in the PA21 group ≥12 to ≤18 years old at randomization (N=42), the LS mean (SE) of PA21 for change from baseline was -0.460 (0.192) mg/dl (95% CI: -0.850, -0.070). The change from baseline in this age group was statistically significant (p=0.0220). For sevelamer the effect was -1.40 (0.34) mg/dl (95% CI: -2.07, -0.72) for subjects 13 to 18 years old (N=35).

These data fluctuated values and do not show large differences between both medicinal products, although this comparison should be handled with caution due to study differences.

Palatability and acceptability

Palatability and acceptability of the formulations used in the study were generally scored as good for PA21 and similar to better than Phoslyra.

Starting dose and dose increments

Based on the study protocol, the starting dose in the age group 2-6 years was 500mg and the recommended increments were 125 mg and 250 mg. The Applicant explained their initial proposal of

250mg dose increments with that actual dose increments used during the study have shown to be 250 mg in 4 out of 6 patients. None of the children in this age group needed a dose increment of 125 mg. However, to align with the study protocol, the Applicant has amended the dose increments in the SmPC from 250mg to both 125 and 250 mg in children from 2-6 years. This is agreed.

Regarding the starting dose in the group 6-9 years – The Applicant presented study data that for one of the seven patients the 750 mg was effective. Based on this information, it can be agreed that 750 mg as a starting dose can be acceptable, and that 875 mg would be too high and would likely lead to more intolerability, as for the two patients on 750 mg they discontinued due to gastrointestinal events. The justification currently provided by the Applicant of a starting dose of 750 mg is supported.

Regarding the dose increments - Based on the study protocol, the recommended increments in the group of 6-9 years were 125, 250 and 375 mg. The actual dose increments used during the study have shown to be 2 by increment of 125 mg, 10 by increment of 250 mg and 6 by increment of 375 mg. The Applicant proposed to only have dose increment of 250 mg in this age group for convenience for a simple administration scheme. However, this was not considered appropriate as it is conflicting with the proposal in the younger age group - two dose increments of 125 and 250 – being in line with the study protocol. Therefore, for consistency with the study protocol and the study data, the dose increment in the age group 6-9 years was amended in the SmPC into 125, 250 and 375 mg.

The dose recommendation for the group of 9-<12 years of age was 1000 mg and was based on the median daily prescribed dose of 1,293 mg and clinical practice of dose steps of 250 and 500 mg in this age group, which is also in line with the recommendations in the study protocol. The dose recommendation in the SmPC for this age group of 9-<12 years can therefore be acceptable.

2.5.4. Conclusions on the clinical efficacy

An overall limited reduction of serum phosphorus levels was observed in paediatric patients from 2 to 18 years of age during 24 weeks of treatment of PA21, but this was not statistically significant. The limited treatment effect (which is also smaller than hypothesized) may be due to a mean phosphorus baseline level only marginally higher than the target level with even a substantial proportion already at normal level (and thus no inherent need for substantial phosphorus lowering), as a result of the study design and conduct. Compliance issues, intra-patient variability and perhaps suboptimal titration may have been other reason, among other unidentified reasons. Despite the marginal effect, a large proportion of patients was within the age-adjusted normal phosphorus range after treatment, comparable to that observed for adults, which thus can be considered clinically relevant. Moreover, based on the local mechanism of action, any differences in effect to adults is not to be expected.

The effect appears not to be consistent across several subgroups. However, data are too limited to draw any appropriate conclusions.

This effect was generally comparable to what has been found with the use of calcium acetate and sevelamer, although no formal statistics were performed for comparisons. The overall effect on the decrease of serum phosphorus levels with Velphoro was lower than in adults, but the responder rates of children in the current study showed generally similar rates compared to adult data. A more limited effect than for adults may likely have been driven by several issues in study conduct. The overall decrease in serum phosphorus levels observed in the paediatric population was small but clinically relevant mainly in terms of responder rates.

2.6. Clinical safety

Patient exposure

In total, 66 subjects received Velphoro and 19 received Phoslyra (calcium acetate).

Study drug exposure to PA21 and Phoslyra in Study PA-CL-PED-01 is summarised overall and by age group at randomisation in the table below (Table 21):

Table 21 *Study PA-CL-PED-01 Extent of Exposure by Age Group – Stage 1 (up to 10 weeks) and Overall Study (Safety Population)*

Parameter	Statistics	Velphoro				Phoslyra			
		All	⩾2 to <6 Y	⩾6 to <12 Y	⩾12 to ⩽18 Y	**All**	⩾2 to <6	⩾6 to <12	⩾12 to ⩽18
Duration of exposure (days) for Stage 1	n	**66**	6	17	43	**19**	1	5	13
	Mean (SD)	**45.7 (23.23)**	27.2 (18.51)	42.6 (23.48)	49.5 (22.74)	**37.8 (28.38)**	4.0	24.4 (19.32)	45.5 (29.13)
	Median	**43.0**	23.5	43.0	48.0	**36.0**	4.0	32.0	57.0
	Min/max	**3, 85**	9/53	7/78	3/85	**1, 74**	4/4	3/46	1/74
Overall duration of exposure (days)	n	**66**	6	17	43	**19**	1	5	13
	Mean (SD)	**126.5 (83.92)**	78.5 (89.39)	135.2 (95.18)	129.7 (78.26)	**73.9 (73.57)**	4.0	65.2 (79.77)	82.7 (74.00)
	Median	**128.0**	36.0	189.0	131.0	**49.0**	4.0	36.0	63.0
	Min/max	**3, 245**	9/213	7/245	3/240	**1, 239**	4/4	3/194	1/239
Actual average daily dosage (mg iron for PA21; ml for Phoslyra) during Stage 1	n	**65**	5	17	43	**18**	1	5	12
	Mean (SD)	**1216.19 (526.433)**	528.50 (240.591)	1,030.58 (324.205)	1,369.54 (531.433)	**12.41 (8.071)**	4.17	9.99 (7.464)	14.11 (8.271)
	Median	**1206.90**	625.00	893.75	1,344.83	**13.36**	4.17	9.63	14.39
	Min/max	**166.7, 2688.2**	166.7/747.2	607.1/1,623.2	308.3/2,688.2	**0.9, 29.2**	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	**65**	5	17	43	**18**	1	5	12
	Mean (SD)	**1281.44 (611.800)**	579.89 (382.878)	1,208.65 (488.247)	1,391.79 (626.405)	**12.26 (8.782)**	4.17	10.22 (8.633)	13.79 (9.039)
	Median	**1198.98**	625.00	1,190.76	1,250.00	**12.69**	4.17	7.64	13.23
	Min/max	**166.7, 3243.3**	166.7/1,134.4	607.1/2,361.3	237.1/3,243.3	**0.9, 31.1**	4.2/4.2	0.9/22.8	2.7/31.1

The highest daily doses that were prescribed in this paediatric trial were:

- 1250 mg iron per day in subjects 2 to 6 years old at randomisation
- 2250 mg iron per day in subjects 6 to 9 years old and
- 3000 mg iron per day in subjects 9 to 18 years old

The mean (SD) actual average daily dosage in the PA21 group was 1216.19 (526.433) mg iron during Stage 1, and 1281.44 (611.800) mg iron for the overall study; the mean (SD) actual average daily dosage in the Phoslyra group was 12.41 (8.071) ml during Stage 1 and 12.26 (8.782) ml for the overall study.

In the PA21 group, duration of exposure was slightly longer for female subjects (N=34; means (SDs) 48.2 (23.21) days during Stage 1 and 131.2 (80.99) days during the overall study) than for male

subjects (N=32; means (SDs) 43.0 (23.32) days during Stage 1 and 121.4 (87.94) days during the overall study); actual average daily dosages and maximum prescribed daily dosages were comparable between genders.

In the PA21 group, duration of exposure during Stage 1 was slightly longer among non-US subjects (N=27; mean (SD) 49.1 (22.94) days) than among US subjects (N=39; mean (SD) 43.3 (23.43) days); duration of exposure considering the overall study, actual average daily dosages and maximum prescribed daily dosages were comparable between regions.

Sachets or tablets

- 46 of the 66 subjects in the PA21 group were prescribed tablets only;
- 10 subjects were prescribed sachets only and
- 10 subjects were prescribed both formulations.

Duration of exposure, prescribed average daily dosages, maximum prescribed daily dosages and actual average daily dosages were higher among subjects who were prescribed tablets only than among those who were prescribed sachets only; maximum prescribed daily dosages and actual average daily dosages were higher among subjects who were prescribed tablets only than among those who were prescribed both formulations. Total numbers of tablets/sachets taken (during Stage 1 and overall) were higher for subjects who were prescribed tablets than for those who were prescribed sachets only, and were highest for those who were prescribed both formulations. As in the full Safety Population, prescribed dosages (and to a lesser extent actual dosages) were higher when considering the overall study than when considering Stage 1 only.

Table 22 *Exposure to PA21 Drug, by prescribed formulation - Stage 1 and Overall Study-Safety Population*

	Mean (SD)		
Parameter	**Powders**	**Tablets**	**Both**
	N=10	**N=46**	**N=10**
n	9	46	10
Total number of tablets/powders taken during Stage 1	130.2 (99.84)	151.2 (107.41)	178.0 (100.08)
Total number of tablets/powders taken overall study	409.8 (374.89)	435.6 (350.52)	454.3 (328.15)
Actual average daily number of tablets/powders taken during Stage 1	3.18 (0.870)	3.13 (1.133)	3.44 (1.266)
Actual average daily number of tablets/powders taken overall study	3.33 (1.244)	3.21 (1.285)	3.29 (1.298)
Actual average daily dosage (mg iron) during Stage 1	709.17 (329.073)	1334.16 (503.672)	1129.89 (519.188)
Actual average daily dosage (mg iron) overall study	760.85 (393.828)	1407.28 (620.344)	1171.10 (483.943)
Prescribed Average Daily Dosage (mg iron) during Stage 1	762.38 (313.709)	1572.55 (363.354)	1201.51 (327.768)
Prescribed Average Daily Dosage (mg iron) overall study	843.92 (425.404)	1785.52 (523.983)	1405.83 (293.899)
Duration of Exposure (days) for Stage 1	34.4 (24.63)	47.3 (22.60)	49.6 (23.79)
Overall Duration of Exposure (days)	102.2 (91.53)	130.2 (82.02)	133.5 (89.82)
Compliance1 (%) for Stage 1	89.25 (27.863)	85.42 (26.155)	93.69 (31.169)
Overall Compliance1 (%)	85.67 (29.950)	78.26 (22.309)	82.10 (25.343)
Maximum prescribed daily dose (mg iron) during Stage 1	862.5 (418.54)	1918.5 (610.22)	1400.0 (485.20)
Maximum prescribed daily dose (mg iron) overall study	987.5 (693.35)	2076.1 (655.89)	1712.5 (513.87)

The compliance is defined as 100 * the total number of mg of iron received (calculated from the number of tablets/powders dispensed - unused tablets/powders returned - unused tablets/powders reported as lost) divided by the total prescribed dose in mg iron. Actual exposure data and compliance are set to missing in case all dispensed drug was reported as lost and without returned date collected.

Adverse events

The adverse event profile was one of the study's primary safety endpoints.

Overall summary of adverse events

Overall summaries of the TEAEs reported in PA-CL-PED-01 are presented in the table below (Table 23):

Table 23 *Overview of TEAEs in Study PA-CL-PED-01 - Safety Population*

	Stage 1 -Dose titration period ≤10 weeks		Stage 2 -Maintenance period ≤34 weeks (cumulative)	
	Velphoro (N=66)	**Phoslyra (N=19)**	**Velphoro (N=66)**	**Phoslyra (N=19)**
	n (%) E	n (%) E	n (%) E	n (%) E
Any TEAE	42 (63.6) 123	13 (68.4) 46	50 (75.8) 204	14 (73.7) 63
Any treatment-related TEAE	**24 (36.4) 43**	**7 (36.8) 13**	**26 (39.4) 50**	**7 (36.8) 13**
Any serious TEAE	13 (19.7) 19	3 (15.8) 7	18 (27.3) 43	3 (15.8) 9
Any treatment-related serious TEAE	**2 (3.0) 2**	**0**	**3 (4.5)**	**0**
Any severe TEAE	8 (12.1) 14	2 (10.5) 2	13 (19.7) 30	3 (15.8) 4
Any TEAE Leading to Death	0	0	0	0
Any TEAE Leading to Study Drug Withdrawal	11 (16.7) 17	6 (31.6) 8	12 (18.2) 19	6 (31.6) 8

Notes: Treatment-emergent adverse events with onset dates occurring after the first treatment day and before or on the last visit in Stage 1 or 2. E=Total number of events; n=Number of subjects, each subject counts only once for each adverse event. N=total number of subjects; TEAE=Treatment-emergent adverse event.

Most common adverse events

Percentages of subjects experiencing at least 1 TEAE were slightly higher in the Phoslyra group during Stage 1 (PA21: 42 (63.6%) subjects; Phoslyra: 13 (68.4%) subjects) and comparable between treatment groups during the overall study (PA21: 50 (75.8%) subjects; Phoslyra: 14 (73.7%) subjects).

TEAEs reported in more than 1 subject in either treatment group up to the end of Stage 2) are summarised in the following table (Table 24):

Table 24 *TEAEs with Incidence >1 Subject in Either Treatment Group in PA-CL-PED-01 - Until End of Stage 2 (Safety Population)*

	PA21	Phoslyra
System Organ Class	(N=66)	(N=19)
Preferred Term	n (%) E	n (%) E
Any treatment-emergent adverse events	50 (75.8) 204	14 (73.7) 63
Gastrointestinal Disorders	31 (47.0) 51	7 (36.8) 10
Diarrhoea	12 (18.2) 14	0 (0.0) 0
Nausea	8 (12.1) 10	2 (10.5) 2
Vomiting	6 (9.1) 6	3 (15.8) 4
Constipation	4 (6.1) 4	1 (5.3) 1
Abdominal pain	3 (4.5) 3	1 (5.3) 1
Abdominal pain upper	2 (3.0) 2	1 (5.3) 1

	PA21	Phoslyra
System Organ Class	(N=66)	(N=19)
Faeces discoloured	2 (3.0) 2	0 (0.0) 0
Gastritis	2 (3.0) 2	0 (0.0) 0
Infections and Infestations	16 (24.2) 31	9 (47.4) 14
Urinary tract infection	3 (4.5) 5	2 (10.5) 3
Nasopharyngitis	2 (3.0) 2	0 (0.0) 0
Upper respiratory tract infection	2 (3.0) 2	1 (5.3) 2
Metabolism and Nutrition Disorders	15 (22.7) 23	9 (47.4) 13
Hypercalcaemia	4 (6.1) 4	4 (21.1) 4
Hyperphosphataemia	3 (4.5) 3	3 (15.8) 3
Decreased appetite	2 (3.0) 3	0 (0.0) 0
Fluid overload	2 (3.0) 2	0 (0.0) 0
Hyperkalaemia	2 (3.0) 3	1 (5.3) 1
General Disorders and Administration Site Conditions	10 (15.2) 16	3 (15.8) 3
Pyrexia	3 (4.5) 3	2 (10.5) 2
Vascular Disorders	9 (13.6) 16	1 (5.3) 1
Hypertension	6 (9.1) 9	0 (0.0) 0
Haematoma	2 (3.0) 2	0 (0.0) 0
Hypotension	2 (3.0) 3	0 (0.0) 0
Investigations	8 (12.1) 13	3 (15.8) 4
Blood potassium increased	2 (3.0) 2	0 (0.0) 0
Weight increased	2 (3.0) 2	0 (0.0) 0
Renal and Urinary Disorders	6 (9.1) 10	2 (10.5) 2
Chronic kidney disease	2 (3.0) 3	0 (0.0) 0
Hydronephrosis	2 (3.0) 2	0 (0.0) 0
Blood and Lymphatic System Disorders	5 (7.6) 6	0 (0.0) 0
Anaemia	3 (4.5) 3	0 (0.0) 0
Nephrogenic anaemia	2 (3.0) 2	0 (0.0) 0
Respiratory, Thoracic and Mediastinal Disorders	5 (7.6) 5	2 (10.5) 4
Cough	1 (1.5) 1	2 (10.5) 2
Nervous System Disorders	4 (6.1) 5	2 (10.5) 2
Headache	2 (3.0) 2	1 (5.3) 1
Endocrine Disorders	3 (4.5) 5	2 (10.5) 2
Hyperparathyroidism	2 (3.0) 3	1 (5.3) 1
Product Issues	3 (4.5) 4	1 (5.3) 2
Device malfunction	2 (3.0) 3	0 (0.0) 0

Notes: Adverse events are coded using version 19.1 of the MedDRA terminology. SOCs are sorted in descending frequency as reported in the PA21 column; PTs are sorted in descending frequency within SOC. If a subject experienced more than 1 event in a given SOC, that subject is counted once for the SOC. If a subject experienced more than 1 event with a given PT, that subject is counted only once for that PT.
E=Total number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=Total number of subjects; n=Number of subjects; PT=Preferred term; SOC=System organ class; EAE=Treatment-emergent adverse event.

Treatment-related TEAEs

Approximately 25% of the TEAEs reported up to the end of Stage 2 were considered related to study treatment. Percentages of subjects experiencing at least 1 treatment related TEAE up to the end of

Stage 2 were generally comparable between treatment groups (PA21: 26 (39.4%) subjects; Phoslyra: 7 (36.8%) subjects). Treatment-related TEAEs were reported most frequently in the SOCs of gastrointestinal disorders and metabolism and nutrition disorders.

The following events were considered treatment-related by the investigator:

Table 25 *Treatment-related TEAEs in Either Treatment Group - Until End of Stage 2 (Safety Population)*

	PA21	Phoslyra
System Organ Class	(N=66)	(N=19)
Preferred Term	n (%) E	n (%) E
Any Treatment-Emergent Adverse Events	**26 (39.4) 50**	**7 (36.8) 13**
Gastrointestinal disorders	**22 (33.3) 35**	**4 (21.1) 6**
Diarrhoea	11 (16.7) 13	0 (0.0) 0
Nausea	4 (6.1) 4	2 (10.5) 2
Vomiting	4 (6.1) 4	1 (5.3) 1
Constipation	3 (4.5) 3	1 (5.3) 1
Abdominal pain	3 (4.5) 3	1 (5.3) 1
Abdominal pain upper	1 (1.5) 1	1 (5.3) 1
Faeces discoloured	2 (3.0) 2	0 (0.0) 0
Gastritis	2 (3.0) 2	0 (0.0) 0
Faeces soft	1 (1.5) 1	0 (0.0) 0
Ileus	1 (1.5) 1	0 (0.0) 0
Lip swelling	1 (1.5) 1	0 (0.0) 0
Metabolism and nutrition disorders	**5 (7.6) 5**	**5 (26.3) 5**
Hypercalcaemia	1 (1.5) 1	4 (21.1) 4
Decreased appetite	1 (1.5) 1	0 (0.0) 0
Hyperphosphataemia	2 (3.0) 2	1 (5.3) 1
Dehydration	1 (1.5) 1	0 (0.0) 0
Investigations	**3 (4.5) 4**	**1 (5.3) 1**
Blood creatine phosphokinase increased	1 (1.5) 1	0 (0.0) 0
Blood phosphorus decreased	1 (1.5) 1	0 (0.0) 0
Blood pressure increased	1 (1.5) 1	0 (0.0) 0
Weight decreased	1 (1.5) 1	0 (0.0) 0
Blood phosphorus increased	0 (0.0) 0	1 (5.3) 1
Vascular disorders	**1 (1.5) 3**	**0 (0.0) 0**
Hypertension	1 (1.5) 2	0 (0.0) 0
Vena cava thrombosis	1 (1.5) 1	0 (0.0) 0
Respiratory, thoracic and mediastinal disorders	**1 (1.5) 1**	**0 (0.0) 0**
Hyperactive pharyngeal reflex	1 (1.5) 1	0 (0.0) 0
Endocrine disorders	**1 (1.5) 2**	**0 (0.0) 0**
Hyperparathyroidism	1 (1.5) 2	0 (0.0) 0
Skin and subcutaneous tissue disorders	**0 (0.0) 0**	**1 (5.3) 1**
Rash	0 (0.0) 0	1 (5.3) 1

If a subject experienced more than 1 event in a given SOC, that subject is counted once for the SOC. If a subject experienced more than 1 event with a given PT, that subject is counted only once for that PT.
E = Total number of adverse events; n = Number of subjects
Related events include events with certain or probable/likely or possible as causality assessed by the investigator.
Unrelated events include events with unlikely or unrelated as causality assessed by the investigator.

Adverse events over time

An overview of TEAEs (all TEAEs, GI system SOC, and diarrhoea PT) reported up to the end of Stage 2 by time of onset is presented in Table 26:

Table 26 *TEAEs Reported in PA-CL-PED-01 up to End of Stage 2 by Time of Onset (Safety Population)*

System Organ Class Preferred Term	PA21 N=66						
	<4 Weeks						
	<1 Week	1-<2 Weeks	2-<4 Weeks	Total	4-<12 Weeks	12-<24	≥24 Weeks
	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E
Any treatment-emergent adverse events	19 (28.8) 32	11 (16.7) 14	23 (34.8) 37	41 (62.1) 83	20 (30.3) 63	17 (25.8) 39	11 (16.7) 19
Gastrointestinal Disorders	13 (19.7) 19	2 (3.0) 2	12 (18.2) 14	25 (37.9) 35	8 (12.1) 12	2 (3.0) 2	2 (3.0) 2
Diarrhoea	7 (10.6) 7	0 (0.0) 0	4 (6.1) 4	11 (16.7) 11	2 (3.0) 3	0 (0.0) 0	0 (0.0) 0
	Phoslyra N=19						
Any treatment-emergent adverse events	6 (31.6) 14	4 (21.1) 4	8 (42.1) 14	10 (52.6) 32	8 (42.1) 19	4 (21.1) 11	1 (5.3) 1
Gastrointestinal Disorders	4 (21.1) 6	0 (0.0) 0	1 (5.3) 1	5 (26.3) 7	2 (10.5) 2	1 (5.3) 1	0 (0.0) 0
Diarrhoea	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0

Notes: E=Total number of events; N=Total number of subjects; n=Number of subjects.

Overall and in both treatment groups, the incidence of TEAEs was higher during the first 4 weeks of treatment than during the subsequent (and mostly longer) periods considered (4 to <12 weeks, 12 to <24 weeks, and ≥24 weeks after treatment start). In the SOC of GI Disorders, there was a notable decrease in incidence after the first week of treatment in both the PA21 and the Phoslyra groups (28). In particular, 7 of the 14 reported TEAEs of diarrhoea (all in the PA21 group) occurred during the first week of treatment; 11 of them occurred during the first 4 weeks. In the Phoslyra group as well, 6 of the 10 TEAEs reported in the GI Disorders SOC (PTs nausea, vomiting, constipation and abdominal pain upper) occurred during the first week of treatment.

Adverse events by age group

An overall summary of TEAEs reported up to the end of Stage 2 by age group at randomisation is presented in the table below:

Table 27 *Overview of TEAEs in PA-CL-PED-01 by Age - Until End of Stage 2 (Safety Population)*

	PA21			Phoslyra		
	Age (Years) ⩾2-<6 (N=6)	Age (Years) ⩾6-<12 (N=17)	Age (Years) ⩾12-⩽18 (N=43)	Age (Years) ⩾2-<6 (N=1)	Age (Years) ⩾6-<12 (N=5)	Age (Years) ⩾12-⩽18 (N=13)
	n (%) E	**n (%) E**	**n (%) E**	**n (%) E**	**n (%) E**	**n (%) E**
Any TEAE	4 (66.7) 13	14 (82.4) 54	32 (74.4) 137	1 (100) 1	4 (80.0) 24	9 (69.2) 38
Any treatment-related TEAE	2 (33.3) 5	7 (41.2) 15	17 (39.5) 30	0 (0.0) 0	3 (60.0) 4	4 (30.8) 9
Any serious TEAE	0 (0.0) 0	6 (35.3) 11	12 (27.9) 32	0 (0.0) 0	2 (40.0) 4	1 (7.7) 5
Any severe TEAE	1 (16.7) 1	6 (35.3) 10	6 (14.0) 19	0 (0.0) 0	2 (40.0) 3	1 (7.7) 1
Any TEAE Leading to Death	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	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	0 (0.0) 0	3 (60.0) 4	3 (23.1) 4

Notes: Age (years) at randomisation is displayed. No subjects were 0-<2 years old.
E=Total number of events; n=Number of subjects, each subject counts only once for each adverse event; N=Total number of subjects; TEAE=Treatment-emergent adverse event.

Overall, TEAEs were reported in 5 (71.4%) subjects ≥2 to <6 years old at randomisation, 18 (81.8%) subjects ≥6 to <12 years old and 41 (73.2%) subjects ≥12 to ≤18 years old; the majority of TEAEs in all age groups were reported during Stage 1. The small number of subjects ≥2 to <6 years old at randomisation (N=7 overall) limits the conclusions that can be drawn concerning this group. No serious TEAEs were reported in this age group.

TEAEs reported in each age group were qualitatively similar to those reported in the full Safety Population, with events reported most frequently in the SOCs of gastrointestinal disorders, infections and infestations, and metabolism and nutrition disorders. The greater variety of PTs reported in the older groups most likely results from the higher numbers of subjects in these groups.

Adverse events by Maximum Dose Prescribed

An overview of TEAEs reported up to the end of Stage 2 in the PA21 group by maximum dose prescribed is presented in the following table:

Table 28 *Overview of TEAE by Maximum Dose Prescribed - PA21*

	≤2.5 g/day (N=4)	>2.5-≤5.0 g/day (N=4)	>5.0-≤7.5 g/day (N=18)	>7.5-≤10.0 g/day (N=15)	>10.0-≤12.5 g/day (N=13)	>12.5-≤15.0 g/day (N=12)
	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E
Any TEAE	2 (50.0) 4	4 (100) 15	16 (88.9) 60	12 (80.0) 39	9 (69.2) 57	7 (58.3) 29
Any treatment-related TEAE	1 (25.0) 1	4 (100) 11	5 (27.8) 8	8 (53.3) 15	4 (30.8) 8	4 (33.3) 7
Any serious TEAE	0	0	5 (27.8) 8	5 (33.3) 10	6 (46.2) 18	2 (16.7) 7
Any treatment-related serious TEAE	0	0	0	1 (6.7) 3	1 (7.7) 1	1 (8.3) 1
Any severe TEAE	0	1 (25.0) 2	3 (16.7) 3	3 (20.0) 7	5 (38.5) 15	1 (8.3) 3
Any TEAE Leading to Death	0	0	0	0	0	0
Any TEAE Leading to Study Drug Withdrawal	1 (25.0) 2	4 (100) 7	3 (16.7) 5	3 (20.0) 3	1 (7.7) 2	0

Note: TEAE: Treatment-Emergent Adverse Events
E = Total number of adverse events; n = Number of subjects, each subject counts only once for each adverse event..
Source: Table 14.3.1.5.1

Table 29 *Overview of TEAE by Maximum Dose Prescribed - Phoslyra*

	Phoslyra <15 (N = 5)	Phoslyra [15 – 25] (N = 7)	Phoslyra [25 – 35] (N = 1)	Phoslyra [35 – 44] (N = 4)	Phoslyra =44 (N = 2)
	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E
Any TEAE	4 (80.0) 19	5 (71.4) 19	1 (100) 9	2 (50.0) 3	2 (100) 13
Any treatment-related TEAE	2 (40.0) 5	3 (42.9) 6	1 (100) 1	0	1 (50.0) 1
Any serious TEAE	0	2 (28.6) 6	1 (100) 3	0	0
Any treatment-related serious TEAE	0	0	0	0	0
Any severe TEAE	0	1 (14.3) 1	1 (100) 2	0	1 (50.0) 1
Any TEAE Leading to Death	0	0	0	0	0
Any TEAE Leading to Study Drug Withdrawal	1 (20.0) 1	4 (57.1) 6	1 (100) 1	0	0

Note: TEAE: Treatment-Emergent Adverse Events
E = Total number of adverse events; n = Number of subjects, each subject counts only once for each adverse event..

Although numbers of subjects in each maximum dose prescribed category were small, there did not appear to be a relationship between maximum dose prescribed and incidence of TEAEs in the categories examined. It should be noted that many subjects required dose adjustments during the study, and that TEAEs may have occurred at a dose level lower than the subject's maximum.

Percentages of subjects experiencing TEAEs graded as severe up to the end of Stage 2 were generally comparable between treatment groups (PA21: 13 (19.7%) subjects; Phoslyra: 3 (15.8%) subjects), while percentages experiencing TEAEs graded as moderate were higher in the Phoslyra group (PA21: 26 (39.4%) subjects; Phoslyra: 9 (47.4%) subjects).

Patients not on dialysis

From the total of 66 subjects on PA21 in the SAF population, 51 (77%) were on dialysis and 15 (23%) were not on dialysis.

Overall, no trend could have been identified from the AEs reported in the patients on dialysis (65% Stage 1 and 75% Stage 2) as compared to patients not on dialysis (60% Stage 1 and 80% Stage 2)). The differences were small.

Also, no substantial differences according to AE categories suggest for a different safety profile of the non-dialysis patients. The percentage of subjects experiencing a TEAE in the SOC of Gastrointestinal Disorders was higher in the dialysis group (26 subjects (51.0%)) as compared to 5 subjects (33.3%) in the not on dialysis group, but diarrhoea and nausea was more present in the not on dialysis group (diarrhoea: 33% not on dialysis vs 14% on dialyses and nausea: 13% not on dialysis vs 8% on dialysis).

Regarding the treatment-related AEs occurring in more than 1 subject (PA21, not on dialysis at baseline group) until end of Stages 1 and 2 included PT diarrhoea was higher (5 subjects, 33%) in comparison to subjects on dialysis at baseline (6 subjects (12%)). However, the percentage of subjects experiencing a TEAE in the SOC of Gastrointestinal Disorders was comparable between the PA21 groups on dialysis (33%) and not on dialysis (33%) in both stages of the study treatment and does also not suggest for a difference in safety profile.

The numbers of serious AEs and treatment-related serious AEs were too low to draw any appropriate conclusions. Regarding serious AEs 2 subjects (13%) were not on dialysis and 11 subjects (22%) at Stage 1. At the end of Stage 2, the percentage of subjects experiencing any serious TEAE was 13% (2 subjects) in the non-dialysis group an 31% (16 subjects) in the on dialysis group. None of the two serious AEs in the not on dialysis group were reported as treatment-related or were the SOC Gastrointestinal Disorders.

The percentage of subjects experiencing any TEAE leading to drug withdrawal was higher in the on dialysis group (20%) in comparison to the not on dialysis group (7%). Also, the intensity was more reported as mild in the not on dialysis group (73%; n=11) compared to the dialysis group (49%; n=25).

Serious adverse event/deaths/other significant events

Serious Adverse Events

Table 30 *Serious Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term - Until End of Stage 2 (Safety Population)*

	PA21	Phoslyra
System Organ Class	(N=66)	(N=19)
Preferred Term	n (%) E	n (%) E
Any Serious Treatment-Emergent Adverse Events	18 (27.3) 43	3 (15.8) 9
Any serious treatment-related TEAEs	**3 (4.5) 5**	**0 (0.0) 0**
Gastrointestinal disorders	2 (3.0) 2	0 (0.0) 0
Gastritis	1 (1.5) 1	0 (0.0) 0
Ileus	1 (1.5) 1	0 (0.0) 0
Investigations	1 (1.5) 1	0 (0.0) 0
Blood pressure increased	1 (1.5) 1	0 (0.0) 0
Vascular disorders	1 (1.5) 2	0 (0.0) 0
Hypertension	1 (1.5) 1	0 (0.0) 0
Vena cava thrombosis	1 (1.5) 1	0 (0.0) 0

Note: TEAE: Treatment-Emergent Adverse Events
E = Total number of adverse events; n = Number of subjects, each subject counts only once for each adverse event..

Percentages of subjects with serious TEAEs were generally comparable between treatment groups during Stage 1 (13 (19.7%) vs 3 (15.8%)) and were higher for PA21 than for Phoslyra during the overall study (18 (27.3%) vs 3 (15.8%)). PTs reported as serious in more than 1 subject in the PA21 group were hypertension (5 subjects), device malfunction (2 subjects), fluid overload (2 subjects) and weight increased (2 subjects); no PT was reported as serious in more than 1 Phoslyra subject.

Serious GI TEAEs were reported in 5 subjects: gastritis, ileus, and small intestinal obstruction in the PA21 group and small intestinal perforation and vomiting in the Phoslyra group. Five serious TEAEs in 3 subjects were considered related to study treatment by the investigator, all in the PA21 group: blood pressure increased, gastritis, hypertension, ileus and vena cava thrombosis, reported in 1 subject each; the blood pressure increased, hypertension and vena cava thrombosis were reported in the same subject.

Deaths

No TEAEs leading to death were reported in either treatment group.

Other Significant AEs

AEs of special interest were defined in the SAP based on the known safety profile of PA21, and included events potentially related to diarrhoea, potential iron overload, potential masking of GI bleeding, and deficiencies in growth and skeletal development or abnormalities of bone markers.

Table 31 *Treatment-Emergent Adverse Events of Special Interest (Safety Population)*

	End of stage 1		End of stage 2	
	PA21	Phoslyra	PA21	Phoslyra
System Organ Class	(N=66)	(N=19)	(N=66)	(N=19)
Preferred Term	n (%) E	n (%) E	n (%) E	n (%) E
Any Treatment-Emergent Adverse Events	17 (25.8) 21	4 (21.1) 4	17 (25.8) 22	4 (21.1) 4
Gastrointestinal disorders	13 (19.7) 17	0 (0.0) 0	13 (19.7) 17	0 (0.0) 0
Diarrhoea	12 (18.2) 14	0 (0.0) 0	12 (18.2) 14	0 (0.0) 0
Faeces discoloured	2 (3.0) 2	0 (0.0) 0	2 (3.0) 2	0 (0.0) 0
Haematochezia	1 (1.5) 1	0 (0.0) 0	1 (1.5) 1	0 (0.0) 0
Metabolism and nutrition disorders	4 (6.1) 4	4 (21.1) 4	5 (7.6) 5	4 (21.1) 4
Hypercalcaemia	3 (4.5) 3	4 (21.1) 4	4 (6.1) 4	4 (21.1) 4
Hypocalcaemia	1 (1.5) 1	0 (0.0) 0	1 (1.5) 1	0 (0.0) 0

Note: TEAE: Treatment-Emergent Adverse Events
E = Total number of adverse events; n = Number of subjects, each subject counts only once for each adverse event..

Most TEAEs of special interest in the PA21 group were GI (mainly diarrhoea), while all TEAEs of special interest reported in the Phoslyra group consisted of hypercalcaemia. There were no reports of TEAEs that would suggest either potential iron accumulation or masking of GI bleeding by PA21-associated discolouration of faeces. One TEAE of haematochezia (considered unrelated to study treatment) was reported in the PA21 group; no TEAE of faeces discoloured was reported for the subject concerned.

Only 1 TEAE of special interest was graded as severe (an event of diarrhoea in the PA21 group); there were no serious TEAEs of special interest in either group. Percentages of subjects with TEAEs of special interest that led to study drug withdrawal were comparable between treatment groups (PA21: 8 (12.1%) subjects; Phoslyra: 3 (15.8%) subjects).

Laboratory findings

In Study PA-CL-PED-01, safety endpoints included serum total corrected calcium, phosphorus, Ca × P, and iPTH levels, percentage of subjects with at least 1 episode of sustained hypercalcaemia (confirmed by repeat sample 1 week later), and routine clinical laboratory tests (including blood iron parameters, vitamin parameters and bone markers); eGFR, vital signs and physical examination findings were also monitored. As in the studies in adults, the only consistent and clinically significant effect of treatment with PA21 for up to 34 weeks was reduction in serum phosphorus levels, the intended clinical effect.

Changes from baseline in serum total corrected calcium were minimal in both treatment groups.

- As expected, the incidence of sustained hypercalcaemia was higher in the Phoslyra group than in the PA21 group: 4 (21.1%) subjects in the Phoslyra group and 6 (9.1%) subjects in the PA21 group experienced at least 1 episode of sustained hypercalcaemia during the study.
- In the PA21 group, mean values for serum total corrected calciumphosphorus product (based on central laboratory assessment) were at or below the KDOQI target level of 4.4 mmol2/l2 from Week 8 Stage 1 until the end of Stage 2; in the Phoslyra group, mean values were generally above this target level (however, the small numbers of subjects with available results should be noted).
- Mean (SD) baseline values for serum iPTH were 30.36 (26.393) pmol/l or 0.286 (0.2490) ng/ml in the PA21 group and 37.12 (19.527) pmol/l or 0.350 (0.1842) ng/ml in the Phoslyra group. No clinically meaningful changes were observed during the study.

- Mean (SD) baseline values for eGFR were 29.89 (17.864) ml/min/1.73 m2 in the PA21 group and 20.36 (3.229) ml/min/1.73 m2 in the Phoslyra group; this difference is probably related to the higher percentage of Phoslyra subjects with Stage 5 CKD (17 (89.5%) subjects vs 52 (78.8%) subjects for PA21 in the Safety Population). No clinically meaningful changes were observed during the study.
- Although some changes from baseline and individual shifts relative to normal ranges were observed for clinical laboratory parameters including routine haematology and chemistry, liver enzymes, iron status parameters, vitamins and bone markers, they showed no trends or clinically relevant changes.
- For haematocrit and haemoglobin, shifts from normal to low were observed in both treatment groups, but showed no trends. The majority of subjects had low baseline values for these parameters: of the subjects with data for End of Stage 1 (N=59 for PA21 and N=13 for Phoslyra), 72.9% of PA21 subjects and 61.5% of Phoslyra subjects had low baseline haematocrit; 66.1% of PA21 subjects and 61.5% of Phoslyra subjects had low baseline haemoglobin. Medical histories of anaemia were frequent (anaemia was reported in 42.4% of subjects overall in the Safety Population, nephrogenic anaemia in 32.9% and iron deficiency anaemia in 5.9%), and most subjects in both treatment groups were receiving antianaemic medications including growth factors, iron preparations, folic acid and Vitamin B12 (PA21: 53 (80.3%) subjects; Phoslyra: 18 (94.7%) subjects); approximately half were receiving iron supplementation.
- There were no clinically meaningful effects on vital signs or physical examination findings, and no relevant differences between treatment groups were observed.

Changes from BL in serum total corrected calcium were minimal in both treatment groups. Mean values for Ca × P in the PA21 group were at or below the KDOQI target level of 4.4 mmol2/l2 beginning at Week 8 Stage 1. As expected, the incidence of sustained hypercalcaemia was higher with Phoslyra than with PA21 (4 (21.1%) versus 6 (9.1%) subjects). No clinically meaningful changes in serum iPTH levels or in eGFR were observed during the study.

Although some changes from BL and individual shifts relative to normal ranges were observed for clinical laboratory parameters including routine haematology and chemistry, liver enzymes, iron status parameters, vitamins and bone markers, they showed no trends or clinically relevant changes.

Safety related to drug-drug interactions and other interactions

No new drug-drug interaction studies were submitted. This was considered acceptable by the CHMP.

Discontinuation due to adverse events

The percentage of subjects experiencing TEAEs that led to study drug withdrawal was lower for PA21 than for Phoslyra both during Stage 1 (PA21: 11 (16.7%) subjects; Phoslyra: 6 (31.6%) subjects) and during the overall study (PA21: 12 (18.2%) subjects; Phoslyra: 6 (31.6%) subjects).

Considering all events reported up to the end of Stage 2, TEAEs leading to study drug withdrawal were reported most frequently in the SOCs of gastrointestinal disorders, metabolism and nutrition disorders and infections and infestations. Preferred terms that led to study drug withdrawal in more than one subject in the PA21 group were diarrhoea (6 subjects), nausea (2 subjects) and vomiting (2 subjects); those in the Phoslyra group were hypercalcaemia (3 subjects) and hyperphosphatemia (2 subjects).

Table 32 *Treatment-Emergent- Adverse Events that Lead to Study Drug Withdrawal by MedDRA System Organ Class and Preferred Term - - Safety Population*

	Until End of Stage 1			Until End of Stage 2		
System Organ Class Preferred Term	PA21 (N=66)	Phoslyra (N=19)	Total (N=85)	PA21 (N=66)	Phoslyra (N=19)	Total (N=85)
	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E
Any Treatment-Emergent Adverse Events	11 (16.7) 17	6 (31.6) 8	17 (20.0) 25	12 (18.2) 19	6 (31.6) 8	18 (21.2) 27
Gastrointestinal disorders	8 (12.1) 12	1 (5.3) 2	9 (10.6) 14	8 (12.1) 12	1 (5.3) 2	9 (10.6) 14
Diarrhoea	6 (9.1) 6	0 (0.0) 0	6 (7.1) 6	6 (9.1) 6	0 (0.0) 0	6 (7.1) 6
Nausea	2 (3.0) 2	1 (5.3) 1	3 (3.5) 3	2 (3.0) 2	1 (5.3) 1	3 (3.5) 3
Vomiting	2 (3.0) 2	1 (5.3) 1	3 (3.5) 3	2 (3.0) 2	1 (5.3) 1	3 (3.5) 3
Abdominal pain	1 (1.5) 1	0 (0.0) 0	1 (1.2) 1	1 (1.5) 1	0 (0.0) 0	1 (1.2) 1
Faeces discoloured	1 (1.5) 1	0 (0.0) 0	1 (1.2) 1	1 (1.5) 1	0 (0.0) 0	1 (1.2) 1
Metabolism and nutrition disorders	3 (4.5) 3	4 (21.1) 5	7 (8.2) 8	3 (4.5) 3	4 (21.1) 5	7 (8.2) 8
Dehydration	1 (1.5) 1	0 (0.0) 0	1 (1.2) 1	1 (1.5) 1	0 (0.0) 0	1 (1.2) 1
Hypercalcaemia	1 (1.5) 1	3 (15.8) 3	4 (4.7) 4	1 (1.5) 1	3 (15.8) 3	4 (4.7) 4
Hypocalcaemia	1 (1.5) 1	0 (0.0) 0	1 (1.2) 1	1 (1.5) 1	0 (0.0) 0	1 (1.2) 1
Hyperphosphataemia	0 (0.0) 0	2 (10.5) 2	2 (2.4) 2	0 (0.0) 0	2 (10.5) 2	2 (2.4) 2
General disorders and administration site conditions	1 (1.5) 1	0 (0.0) 0	1 (1.2) 1	1 (1.5) 1	0 (0.0) 0	1 (1.2) 1
Pyrexia	1 (1.5) 1	0 (0.0) 0	1 (1.2) 1	1 (1.5) 1	0 (0.0) 0	1 (1.2) 1
Infections and infestations	1 (1.5) 1	1 (5.3) 1	2 (2.4) 2	1 (1.5) 1	0 (0.0) 0	1 (1.2) 1
Device related sepsis	1 (1.5) 1	0 (0.0) 0	1 (1.2) 1	1 (1.5) 1	0 (0.0) 0	1 (1.2) 1
Gastroenteritis	0 (0.0) 0	1 (5.3) 1	1 (1.2) 1	1 (1.5) 1	1 (5.3) 1	2 (2.4) 2
Nervous system disorders				1 (1.5) 1	0 (0.0) 0	1 (1.2) 1
Benign intracranial hypertension				0 (0.0) 0	1 (5.3) 1	1 (1.2) 1

Note: TEAE: Treatment-Emergent Adverse Events
E = Total number of adverse events; n = Number of subjects, each subject counts only once for each adverse event..

Supportive study

The PDCO had suggested the possibility of an additional comparison with an external control (e.g. sevelamer). The applicant made an effort for this additional comparison with an external control from paediatric Study SVCARB07609, a published Phase 2 study conducted with sevelamer carbonate (SC) in CKD patients with hyperphosphataemia (from Fathallah-Shaykh et al, 2018, and ClinicalTrials.gov NCT01574326).

This external control was selected due to the large sample size and the fact that results of this study supported the extension of the indication for SC to paediatric patients in the EU (EMA/271022/2016 and EMA/352101/2017). However, there were several limitations to this comparison due to differences in study design: there was the unequal durations of the study periods and the different methods of summarising the reported events.

An overview of the TEAEs during both studies is given below:

Table 33 *Incidence of TEAEs in studies PA-CL-PED-01 and SVCARB07609*

PA-CL-PED-01	Dose titration period (stage 1) ≤10 weeks		Maintenance period stage 2) ≤34 weeks (cumulative)	
	PA21 (N=66)	Phoslyra (N=19)	PA21 (N=66)	Phoslyra (N=19)
	n (%) E	n (%) E	n (%) E	n (%) E
Any TEAE	42 (63.6) 123	13 (68.4) 46	50 (75.8) 204	14 (73.7) 63
Any treatment-related TEAE	**24 (36.4) 43**	**7 (36.8) 13**	**26 (39.4) 50**	**7 (36.8) 13**
Any serious TEAE	13 (19.7) 19	3 (15.8) 7	18 (27.3) 43	3 (15.8) 9
Any treatment-related serious TEAE	**2 (3.0) 2**	**0**	**3 (4.5)**	**0**
Any severe TEAE	8 (12.1) 14	2 (10.5) 2	13 (19.7) 30	3 (15.8) 4
Any TEAE Leading to Death	0	0	0	0
Any TEAE Leading to Study Drug Withdrawal	**11 (16.7) 17**	**6 (31.6) 8**	**12 (18.2) 19**	**6 (31.6) 8**
SVCARB07609	**Fixed dose period (FDP) 2 weeks**		**Dose Titration Period (DTP) 26 weeks (not cumulative)**	
	Sevelamer (N=49)	**Placebo (N=51)**	**Continuous Sevelamer (N=49)**	**Placebo Crossover to Sevelamer (N=51)**
	n (%)	n (%)	n (%)	n (%)
Any TEAE	19 (38.8)	20 (39.2)	35 (71.4)	42 (82.4)
Any treatment-related TEAE	**2 (4.1)**	**3 (5.9)**	**4 (8.2)**	**9 (17.6)**
Any serious TEAE	4 (8.2)	1 (2.0)	17 (34.7)	14 (27.5)
Any treatment-related serious TEAE	**0**	**0**	**2 (4.1)**	**2 (3.9)**
Any severe TEAE	1 (2.0)	1 (2.0)	10 (20.4)	10 (19.6)
Any TEAE Leading to Death	0	0	0	0
Any TEAE Leading to Study Drug Withdrawal	**1 (2.0)**	**1 (2.0)**	**3 (6.1)**	**0**

Note: TEAE: Treatment-Emergent Adverse Events
n = Number of subjects, each subject counts only once for each adverse event.

Description of AEs in Study SVCARB07609:

Note: The documentation does not report frequencies of TEAEs other than hypertension and vomiting; serious and non-serious events are summarised separately (so no overall frequencies are presented for events reported as both serious and non-serious) and provides frequencies by preferred term only; for non-serious events, a cut-off of 5% of subjects is used, apparently based on frequencies during the DTP (overall rather than by original randomised treatment). Thus, it is not possible to provide detail for all of the statements made in the Fathallah-Shaykh paper. In particular, no information is available concerning the frequency of constipation.

The following information on TEAEs is available:

The **most frequent TEAEs** during the FDP were hypertension in the sevelamer group (reported in 2 (4.1%) subjects) and vomiting in the placebo group (reported in 3 (5.9%) subjects). Other common TEAEs in the placebo group included nausea, constipation and upper abdominal pain; non-serious events of nausea and upper abdominal pain were each reported in 2 (3.4%) subjects in this group. The most frequent TEAEs during the DTP were GI disorders, including constipation, vomiting and upper abdominal pain. Non-serious TEAEs of vomiting were reported in 19 (19%) subjects overall, nausea was reported in 15 (15%) subjects, abdominal pain in 13 (13%) subjects, upper abdominal pain in 9 (9%) subjects and diarrhoea in 8 (8%) subjects.

Most **SAEs** consisted of viral or bacterial infections; others included GI disorders, metabolism and nutrition disorders and vascular disorders. The most frequent SAEs in the SC group were abdominal pain, dialysis catheter malfunction and/or occlusion and pyrexia; the most frequent SAE in the placebo group was renal impairment. SAEs reported in the SC group during the FDP were hypertension in 2 (4.1%) subjects and device occlusion, hyperkalaemia and peritonitis in 1 (2.0%) subject each; the single SAE in the placebo group was viral gastroenteritis. During the DTP, SAEs reported in >1 subject overall were abdominal pain and pyrexia in 3 (3.0%) subjects each and anaemia, bacteraemia, constipation, device malfunction, hyperkalaemia, hypocalcaemia, hypotension, peritonitis, upper respiratory tract infection and urinary tract infection in 2 (2.0%) subjects each.

Two subjects, 1 in each treatment group, experienced TEAEs leading to **discontinuation** of study drug during the FDP; these consisted of mild hyperphosphataemia in both cases. During the DTP, 3 subjects in the continuous SC group experienced TEAEs leading to discontinuation of study drug.

Summary

In summary, the applicant considered that the frequencies of TEAEs overall and of SAEs were roughly comparable between the Velphoro and SC groups, given the limitations resulting from the unequal durations of the study periods considered and the different methods of summarising the reported events (cumulative versus separate for each period). In both groups of subjects, GI disorders and events related to the underlying disease were prominent; hypertension was also noted in both groups. Diarrhoea, the most frequent TEAE reported in the Velphoro group, is known to be associated with orally administered iron compounds. Diarrhoea was not mentioned in the Fathallah-Shaykh 2018 publication; according to the clinicaltrials.gov posting for Study SVCARB07609, non-serious events of diarrhoea were reported in 1 (2.0%) subject in the SC group during the FDP (versus none in the placebo group) and in 8 (8.0%) subjects overall during the DTP, and there was 1 SAE of diarrhoea during the DTP. Reported SAEs in both the Velphoro and the SC treatment groups were characteristic of the studied population; few SAEs in either treatment group were considered treatment-related. Treatment-related TEAEs were more frequent among subjects receiving Velphoro than among those receiving SC; in the Velphoro group, treatment-related events consisted predominantly of GI symptoms that occurred early in treatment. TEAEs leading to study drug withdrawal were more frequent in Study PA-CL-PED-01 (in both treatment groups) than in Study SVCARB07609 (in either treatment group). In the Velphoro treatment group, the most frequent TEAEs leading to study drug withdrawal were GI symptoms, most of which occurred early in treatment, while in Study SVCARB07609, TEAEs leading to study drug withdrawal were related to the underlying condition of hyperphosphataemia.

Overall, the AE profile of Velphoro in Study PA-CL-PED-01 was similar to that reported for SC in Study SVCARB07609, the main difference being the occurrence of GI symptoms known to be associated with orally administered iron compounds (notably diarrhoea and discolouration of faeces). These events resulted in higher frequencies of TEAEs considered related to study treatment and of TEAEs leading to withdrawal of the study drug in Study PA-CL-PED-01. It should be noted that most of these GI events (and particularly diarrhoea) tended to occur early in the study, with a notable decrease in incidence after the first week of treatment.

No trends or clinically relevant changes were observed for clinical laboratory values or vital signs in either study.

Post marketing experience

No data with regard to post marketing experience have been submitted.

2.6.1. Discussion on clinical safety

Known safety profile of Velphoro in adults

The safety profile of Velphoro is characterised by gastrointestinal adverse events of mild nature, which reflects its local action and limited absorption. Most common events are diarrhoea and discoloured faeces. Potential concerns include events potentially related to diarrhoea, potential iron overload, potential masking of GI bleeding, and deficiencies in growth and skeletal development or abnormalities of bone markers. There were no new concerns or signals with regard to the TEAEs of special interest for Velphoro used in the paediatric population

Pediatric study

The applicant has submitted a clinical study (Study PA-CL-PED-01) to extend the indication to the pediatric population (see efficacy section for the specific design). The primary safety endpoints of this study were defined as the AE profile and the percentage of withdrawals due to AEs.

The safety population was smaller than originally planned, due to enrolment difficulties. The study enrolled 66 subjects on Velphoro and 19 on Phoslyra, aged 0 to <18 years old. Six children in the age group ≥2 to <6 years were included in the Velphoro arm and 1 in the Phoslyra arm, which somewhat limits the interpretation of the safety data. The small number of patients in each age group for Phoslyra also suffers similar limitations.

The overall duration of exposure was longer on Velphoro, compared to Phoslyra. During Stage 1, mean (SD) duration of exposure was 45.7 (23.23) days for Velphoro vs 37.8 (28.38) days for Phoslyra; for the overall study, this was 126.5 (83.92) days and 73.9 (73.57) days respectively. This may be affected to the fact that approximately 58% of subjects in the Phoslyra group withdrew from the study during Stage 1 compared to 35% for Velphoro.

A high proportion of subjects experiencing at least 1 TEAE for both Velphoro and Phoslyra during the overall study (Velphoro: 50 (75.8%) subjects; Phoslyra: 14 (73.7%) subjects), but this could likely be of the underlying disease. Diarrhoea (18.2%), nausea (12.1%), and vomiting (9.1%) were mostly reported in the Velphoro group and mostly occurred at initiation and dose titration of therapy in line with adult observations. However, dose titration limitations due to AEs (i.e. 2 out of the 26 diarrhoea, nausea or vomiting reports) were rarely observed. Diarrhoea and discoloured faeces were only seen on Velphoro. This appears approximately in line with study data in adults, which showed 42% GI events with, 18.1% diarrhea, 14.9% faeces discoloured, 6.3% nausea, 4.1% vomiting. Overall, approximately 25% of the TEAEs were considered related to study treatment. Treatment-related TEAEs were reported most frequently in the SOCs of GI Disorders for PA21 and Metabolism and Nutrition Disorders for Phoslyra. Incidence of treatment-related TEAEs of diarrhoea was most frequently observed for Velphoro (16.7%), while incidence of treatment-related hypercalcaemia (21.1%), was the most frequently observed treatment-related adverse event in the Phoslyra group. The adverse event profile for patients with CKD, but not on dialysis (15 patients, 60% Stage 1 and 80% Stage 2) does not suggest for any substantial differences in safety compared to patients on dialysis (65% Stage 1 and 75% Stage 2).-

Although serious TEAEs were frequently reported and higher in the Velphoro group than with Phoslyra (18 (27.3%) vs 3 (15.8%)), only five serious GI TEAEs were considered treatment related; 3 subjects in the Velphoro group: one subject with ileus and one subject with gastritis during stage 1 and one

subject with blood pressure increased/hypertension/vena cava thrombosis during stage 2; and 2 subjects in the Phoslyra group: small intestinal perforation and vomiting. For the Velphoro serious adverse events, all events resolved during the study. In other cases, Velphoro was only temporarily interrupted in one case and treatment was maintained in the other case, which is sufficiently reassuring. Any case of gastro-intestinal perforation has not been observed with Velphoro, which is reassuring, but data are limited to detect such rare cases. No adverse events leading to death were reported in either treatment group, which is reassuring.

Discontinuations due to TEAEs were lower in the Velphoro group (12 (18.2%) subjects) than in the Phoslyra group (6 (31.6%) subjects). Reasons for discontinuations appears to be slightly different, with GI symptoms being the most prominent reason for discontinuation in Velphoro patients (diarrhoea (6 subjects), nausea (2 subjects) and vomiting (2 subjects)), and metabolism disorders (hypercalcaemia (3 subjects) and hyperphosphatemia (2 subjects)) in the Phoslyra group, although data were limited.

There were no new concerns or signals with regard to the TEAEs of special interest for Velphoro used in the paediatric population: diarrhoea (as expected), potential iron overload (none), potential masking of GI bleeding (none), and deficiencies in growth and skeletal development or abnormalities of bone markers (e.g., fractures: none), or Phoslyra: hypercalcemia (as expected).

No dose-relationship between dose and incidence of adverse events could be observed. However, this would be difficult to establish, as dose-adjustments and titration were done frequently based on efficacy, therefore making it difficult to know the exact dose at which the adverse events occurred. Also, subjects on higher doses should be expected to tolerate the drug better.

Some changes from baseline and individual shifts relative to normal ranges were observed for clinical laboratory parameters including routine haematology and chemistry, liver enzymes, iron status parameters, vitamins and bone markers, but showed no trends or clinically relevant changes. Hypercalcemia is mainly observed in calcium-based phosphate binders; accordingly, as expected, incidence of sustained hypercalcaemia was higher in the Phoslyra group than in the Velphoro group. As in the studies in adults, results for serum phosphorus showed decreases from baseline for up to 34 weeks in the Velphoro group (the intended clinical effect) while fluctuation relative to baseline was observed in the Phoslyra group. No trends or clinically relevant changes were observed for other clinical laboratory values or vital signs in both treatment groups.

Supportive study (external control)

As a request of the PDCO, an additional comparison was made with an external control from paediatric Study SVCARB07609, a Phase 2 study conducted with sevelamer carbonate (SC) in CKD patients with hyperphosphataemia. Sevelamer is approved for use in children >6 years. There were several limitations to this comparison due to differences in study design, like the age of the population, unequal durations of the study periods and the different methods of summarising the reported events.

Frequencies of TEAEs overall and of SAEs could be considered roughly comparable between the Velphoro and sevelamer; however, besides the limitations in design, also detailed safety data are not available.

TEAEs leading to study discontinuation were more frequent for Velphoro and Phoslyra than for sevelamer (or comparator group). The most frequent TEAEs on leading to study discontinuation were related to the known safety profile: for Velphoro GI symptoms and for Phoslyra metabolism disorders. For sevelamer, TEAEs leading to study drug withdrawal were related to the underlying condition of hyperphosphatemia.

From the safety database all the adverse reactions reported in the clinical trial are included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The safety profile of Velphoro in paediatric and adolescent subjects with CKD was generally comparable to that previously observed in adult ESRD subjects, particularly with respect to gastrointestinal AEs, including diarrhoea. No new or unexpected safety signals were identified during the conduct of this study in the paediatric and adolescent population compared to the adult population.

2.7. Risk Management Plan

Safety concerns

There are no safety concerns remaining for this product. During parallel procedures X/10 and II/21, the company provided sufficient justification to remove all safety concerns. In line with GVP V rev2, the original missing information does not have an impact on the benefit risk of the product and can therefore be removed. The original important and potential risks were removed from the safety specification after the submission of the results from the study VERIFIE suggested that their frequency, severity and transient occurrence were similar to those seen in clinical trials. Further characterisation as part of additional pharmacovigilance activities is unlikely, therefore, these risks are considered to be sufficiently characterised and can be removed from the risk management plan.

Conclusion

The CHMP and PRAC considered that the risk management plan version 9.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Velphoro 500 mg chewable tablets. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Velphoro is an iron-based phosphate binder for the treatment of hyperphosphatemia in adult patients with (severe) chronic kidney disease (CKD).

The following additional indication is claimed for Velphoro:

"*Velphoro is indicated for the control of serum phosphorus levels in paediatric patients 2 years of age and older with CKD stages 4-5 (defined by a glomerular filtration rate <30 mL/min/1.73 m2) or with CKD on dialysis.*"

Hyperphosphatemia is common in patients with (severe) CKD due to the inability to excrete dietary phosphorus, particularly those with end-stage renal disease (ESRD) requiring dialysis. Dietary phosphate restriction is generally not sufficient to compensate for hyperphosphatemia and particularly challenging in children, also considering the general need for nutrients for growth and development. Besides, intensification of dialysis may also be too demanding for young children. Hyperphosphatemia plays an important role in the pathophysiology of major CKD complications, such as secondary hyperparathyroidism, mineral and bone disorder (MBD) and cardiovascular disease and is considered a risk factor for mortality, morbidity and hospitalisation in patients with ESRD. Complications most relevant to the paediatric population are renal bone disease, cardiovascular disease and growth failure.

3.1.2. Available therapies and unmet medical need

In adults with CKD and on dialysis, several phosphate binders are currently available for treating hyperphosphatemia. Calcium salts are widely used. Newer PB products include sevelamer HCl, sevelamer carbonate and lanthanum carbonate.

Phosphate binding takes place by ligand exchange between hydroxyl groups and/or water and the phosphate ions throughout the physiological pH range of the gastrointestinal tract. Serum phosphorus levels are reduced as a consequence of the reduced dietary phosphate absorption.

In children with advanced CKD, the use of phosphate binders for treatment of hyperphosphatemia is widespread, but not all of these substances are approved in this population. To date, calcium-carbonate and calcium-acetate are both approved for hyperphosphatemia in CKD patients without age restriction. Sevelamer powder for oral suspension is approved for children >6 years of age.

KDIGO and KDOQI guidelines recommend the use of phosphate binders in children with calcium-based phosphate binders as the first choice, in addition to dietary management. Hence, with these medicinal products is the most experience in children in clinical practice.

3.1.3. Main clinical studies

In line with PDCO requirements, as stated in the approved PIP, one clinical multicentre, randomised, prospective, open-label, parallel-group, active-controlled study with Velphoro (n=66) (in comparison to Phoslyra calcium acetate (n=19)) was submitted to (1) evaluate the effect for reducing serum phosphorus levels in paediatric and adolescent subjects with CKD stage 4-5 with or without dialysis and age-specific hyperphosphatemia and, (2) to introduce a new paediatric formulation of 125 mg

powder for oral suspension. The study consisted of a dose-titration period of up to 10 weeks (Stage 1), and a 24-week safety extension (Stage 2).

3.2. Favourable effects

The primary endpoint showed a limited non-statistically significant LS mean (SE) difference from baseline to end of stage 1 (titration phase) in serum phosphorus levels of -0.120 (0.081) mmol/l (95% CI: -0.282, 0.043) in the PA21 treatment group (n=65) based on the mixed model calculations with actual data showing a mean of 2.08 mmol/L at baseline and 1.91 mmol/L at the end of stage 1 (reduction by 0.17 mmol/L). The effect was maintained during the follow-up period (stage 2), although some fluctuations in mean effect over time were noticed (0.099 (0.198) mmol/L (95% CI -0.306, 0.504). The observed decrease in serum phosphorus levels resulted in an increase from 17% of the patients being within the normal range at baseline to 61% at the end of stage 1 and was maintained at 58% at the end of stage 2. Also, patients did not exceed the maximum age-specific daily dosing scheme as mentioned in the study protocol.

For the approximately 20% of the children who were not on dialysis, a clinical relevant treatment effect in patients not on dialysis comparable to dialysis patients has been observed (i.e. the total proportion of patients in the normal range was greater in the patients not on dialysis than for the dialysis patients both at Stage 1 (80% vs 57%) and during the maintenance phase Stage 2 (73% vs 55%)). Also, dosing applied appears not to deviate substantially from the dialysis group and thus dose recommendations can be similar (the average daily dose was 1742mg the not on dialysis group vs 1890 mg in the dialysis group).

When Velphoro pediatric data are compared to pediatric data of Phoslyra, comparable efficacy was shown. Based on the indirect comparison with pediatric data of a historical sevelamer study, data were variable across age-groups and did not show large differences between both medicinal products. Furthermore, the use of the new formulation of 125 mg powder for oral suspension can be acceptable and meets, in general, the quality requirements and facilitates dose recommendations according to study and labeling recommendations, especially for the youngest children.

Palatability and acceptability of the formulations used in the study were generally scored as good for Velphoro and similar to better than Phoslyra.

3.3. Uncertainties and limitations about favourable effects

The two-arm controlled study was not adequately powered to make an adequate comparison with Phoslyra (calcium actetate) and numbers of patients included were limited to provide clear findings to evaluate the effect for reducing serum phosphorus levels in paediatric and adolescent subjects with CKD stage 4-5 with or without dialysis and age-specific hyperphosphatemia. The number of the patients randomized in the study, however, is in line with what has been agreed by PDCO/EMA, to reduce the required minimum numbers of recruited subjects to at least 60 subjects to be randomized into the Velphoro group. Also, indirect comparison with sevelamer (as requested by PDCO) should be handled with caution due to study differences and small study numbers.

In general, the effect observed in this pediatric study is substantially lower than observed in adults, in whom levels were reduced by 0.7 mmol/L (section 5.1 SmPC Velphoro). The response rates of children in the current study showed, however, generally similar rates within the target range compared to adult data (58% end of the study in normal range paediatrics; adult at the normal range is 45.3% at week 12 and 51.9% at week 52).

The effect for the primary endpoint (change of serum phosphorus levels from baseline to stage 1)

appears not to be consistent across several subgroups, but data are limited. With regards to age subgroups, although the youngest age group of ≥2-<6 years was small (n=6), they showed an effect change (LS mean) of -0.078 mmol/L (95% CI: -0.468, 0312). This effect was lower compared to older pediatric patients (-0.200 mmol/L (95% CI: -0.541, 0,141) in children ≥6 to <12 years and -0.149 mmol/L (95% CI: -0.274, -0.023), p=0.020 in children ≥12 to <18 years), despite the relatively high baseline serum phosphorus levels mean of 2.37 mmol/L in the youngest age group compared to 2.24 mmol/L in the ≥6 to <12 years old children and 1.98 mmol/L in the oldest group of children of ≥12 to <18 years of age.

An inconsistent reduction was also observed in females compared to males (-0.177 mmol/l vs -0.026 mmol/l), in US patients compared to non-US patients (-0.214 mmol/l vs -0.060 mmol/l), and in subjects who were prescribed sachets only (n=10, -0.232 mmol/l) or both formulations (n=10, -0.166 mmol/l) compared to those prescribed tablets only (n=46, -0.032 mmol/l). However, data are too limited to draw any appropriate conclusions. Furthermore, as expected, subjects whose serum phosphorus levels were above age-related normal ranges at baseline serum phosphorus levels showed a statistically significant reduction (n=40, -0.282 mmol/l p=0.0058), while no significant change was observed among subjects whose baseline phosphorus level was within or below normal ranges (n=25; 0.082 mmol/l).

3.4. Unfavourable effects

In line with the currently known safety profile as included in the product information for adults, most commonly reported treatment-related adverse events were gastrointestinal disorders (33% treatment-related) including diarrhoea (16.7%), vomiting (6.1%), gastritis (3.0%) and discoloured faeces (3.0%). Diarrhoea was mostly mild and occurred mostly during the first weeks of treatment initiation.

Serious TEAEs were generally observed with a high-frequency n=13 (19.7%) during Stage 1 and during the overall study (18 (27.3%) vs 3 (15.8%)). However, only 5 serious TEAEs (in 3 subjects) were considered related to study treatment (gastritis, ileus, blood pressure increased hypertension, and vena cava thrombosis (last 3 in one subject)) and did not result in study discontinuation, with only one case of temporary treatment interruption. No fatal events were reported during the study.

The adverse event profile for patients with CKD, but not on dialysis (approximately 20%) does not suggest for any substantial differences in safety, compared to patients on dialysis.

Like in previous studies in adults, discontinuation rates were high (16.7%), with GI symptoms as most prominent reason for discontinuation in Velphoro patients (diarrhoea (6 subjects), nausea (2 subjects) and vomiting (2 subjects)).

Hypercalcemia was only reported in 9.1% subjects, while no trends or clinically relevant changes were observed for the other clinical laboratory parameters.

Despite the small number of patients, comparison with Phoslyra (calcium acetate) showed some differences in the type of AEs reported due to the nature of the two compounds (iron-containing and calcium-containing). Differences mainly included more common GI adverse events for Velphoro and more hypercalcemia for Phoslyra.

3.5. Uncertainties and limitations about unfavourable effects

Percentages of total TEAEs and serious TEAEs were slightly higher in subjects ≥6 to <12 years compared to the other age groups. TEAEs leading to study drug discontinuation were highest in the

youngest age group (n=2), but no serious TEAEs were reported, although the number of patients in the youngest age group (≥2-<6 years of age) was very limited (N=6).

No dose effect was observed on the safety data but the interpretation is difficult as most patients started treatment at different doses, dose-adjustments were made during the study (up and down titration), and the dose was based on age and weight. Some patients were below the age appropriate starting dose at the end of the study. However, dose titration limitations due to AEs were rarely observed.

3.6. Effects Table

Table 34: *Effects Table for Velphoro (sucroferric oxyhydroxide) for for use in paediatric chronic kidney disease (CKD) patients with hyperphosphataemia (data cut-off: 16 July 2019)*

Effect	Short description	Unit	Velphoro N=66	Phoslyra N=19	Uncertainties / Strength of evidence	References
Favourable Effects						
sP level	Primary endpoint: Change in serum phosphorus levels from baseline to the end of Stage 1	LS mean (mmol/L) (95% CI)	-0.12 (-0.28, 0.04)	-0.62 (-1.34, 0.11)	Similar effect in data with sevelamer. Lower effect compared to adults. Inconsistent effect across age, gender, region, high vs within target range.	PA-CL-PED-01 and SVCARB07609 and SmPC Velphoro
% within sP normal range	Secondary endpoint: Percentage of subjects with serum phosphorus within the age-dependent normal range at each visit	%	61% (stage 1) 58% (stage 2)	40% (stage 1) 25% (stage 2)	Response rates generally similar compared to adult data (45.3% at week 12 and 51.9% at week 52)	PA-CL-PED-01 and SmPC Velphoro
Unfavourable Effects						
Diarrhoea	Most frequent adverse event	n (%) [related]	12 (18.2) [11 (16.7)]	0	Expected event, inherent to mechanism of action, 'very common' in PI	PA-CL-PED-01
Hypercalcemia	Events that could lead to deficiencies in growth and skeletal development or abnormalities of bone markers (SOC: Metabolism and nutrition	n (%) [related]	4 (6.1) [1 (1.5)]	4 (21.1) [4 (21.1)]	Hypercalcaemia as expected more frequent on Phoslyra (calcium cabonate)	PA-CL-PED-01

	disorders)					
Hyperphosphatemia	Events that could lead to deficiencies in growth and skeletal development or abnormalities of bone markers (SOC: Metabolism and nutrition disorders)	n (%) [related]	3 (4.5) [2 (3.0)]	3 (15.8) [1 (5.3)]	Lack of efficacy	PA-CL-PED-01

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Maintaining patients within a serum phosphorus level within the normal ranges of phosphorus is considered of clinical relevance to potentially reduce morbidity and mortality, as best demonstrated for adults. During the possible several years of treatment, it is at least considered important that children do no become markedly dysregulated until their transplantation. In the current study, a limited effect of Velphoro on the decrease in serum phosphorus levels has been observed in the paediatric population and a new paediatric formulation of 125 mg powder for oral suspension was introduced. The limited treatment effect (which is also smaller than hypothesized) may be due to a mean phosphorus baseline level only marginally higher than the target level with even a substantial proportion already at normal level (and thus no inherent need for substantial phosphorus lowering), as a result of the study design and conduct. Compliance issues, intra-patient variability and perhaps suboptimal titration may have been other reason, among other unidentified reasons. Despite the marginal effect, a large proportion of patients was within the age-adjusted normal phosphorus range after treatment, comparable to that observed for adults, which thus can be considered clinically relevant. Moreover, based on the local mechanism of action, any differences in effect to adults is not to be expected. Further, the treatment effect of Velphoro in children is approximately comparable with the treatment effect seen in children on other phosphate binders (Phoslyra and in historical control data of sevelamer), although such comparisons are subject to limitations.

The safety profile of Velphoro in paediatric and adolescent subjects with CKD, including those not on dialysis, was generally comparable to that previously observed in adult subjects. It is mainly characterised by gastrointestinal adverse events, including diarrhoea, starting at the initiation of therapy and potentially compromising long term treatment and treatment compliance. Frequencies of serious adverse events were limited and did not importantly compromise treatment continuation. Intestinal perforation or any suggestion for GI bleeding was not observed; however, the database was far too limited to detect such rate events. Further, hypercalcemia was infrequent with Velphoro, which may be an advantage when the risk for hypercalcemia can be expected and thus guideline-recommended calcium-based phosphate binders for younger patients may be less appropriate. Overall, no new or unexpected safety signals were identified during the conduct of this study in the paediatric and adolescent population compared to the adult population.

3.7.2. Balance of benefits and risks

The overall decrease in serum phosphorus levels observed in the paediatric population was small but clinically relevant mainly in terms of responder rates. The safety profile of Velphoro in children is acceptable. The use of the new formulation of 125 mg powder for oral suspension can also be acceptable for both paediatric and adult patients and meets the quality requirements. The choice of the new formulation will depend on patient's age, preference, characteristics and compliance.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Velphoro in the indication *"control of serum phosphorus levels in paediatric patients 2 years of age and older with CKD stages 4-5 (defined by a glomerular filtration rate <30 mL/min/1.73 m2) or with CKD on dialysis*" and for the paediatric formulation of the 125 mg powder for oral suspension is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Velphoro 125 mg powder for oral suspension is favourable in the following indications:

Velphoro is indicated for the control of serum phosphorus levels in adult chronic kidney disease (CKD) patients on haemodialysis (HD) or peritoneal dialysis (PD).

Velphoro is indicated for the control of serum phosphorus levels in paediatric patients 2 years of age and older with CKD stages 4-5 (defined by a glomerular filtration rate <30 mL/min/1.73 m²) or with CKD on dialysis.

Velphoro should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxy vitamin D_3 or one of its analogues, or calcimimetics to control the development of renal bone disease.

The CHMP therefore recommends the extension of the marketing authorisation for Velphoro subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional Data exclusivity/Marketing protection

Furthermore, the CHMP reviewed the data submitted by the Vifor Fresenius Medical Care Renal Pharma France, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0196/2018 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In addition, CHMP recommends the variations to the terms of the marketing authorisation, concerning the following changes:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of indication to add indication to use Velphoro for the control of serum phosphorus levels in paediatric patients 2 years of age and older with CKD stages 4-5 (defined by a glomerular filtration

rate <30 mL/min/1.73 m2) or with CKD on dialysis, based on the results from an open-label, randomised, active-controlled, parallel group, multicentre, phase 3 study investigating the safety and efficacy of Velphoro and calcium acetate in paediatric and adolescent CKD patients with hyperphosphataemia (Study PA-CL-PED-01). As a consequence, sections 4.1, 4.2, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. The RMP version 9.0 is also agreed. Furthermore, the PI is brought in line with the latest QRD template version 10.1.