Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Sucroferric oxyhydroxide

Proprietary Product Name: Velphoro

Sponsor: Vifor Pharma Pty Ltd

February 2015

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
AE	Adverse event
AUC	Area under the concentration time curve
BAP	Bone-specific alkaline phosphatase
Ca × P	Calcium-phosphorus product
CER	Clinical evaluation report
CI	Confidence interval
CKD	Chronic kidney disease
Cmax	Maximum plasma drug concentration
CMI	Consumer Medicine Information
CSR	Clinical Study Report
CVD	Cardiovascular disease
DDI	Drug-drug interaction
DOPPS	International Dialysis Outcomes and Practice Patterns Study
ECG	Electrocardiogram
EMA	European Medicines Agency
ESRD	End stage renal disease
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
Fe	Iron
GFR	Glomerular filtration rate
GI	Gastrointestinal
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A

Abbreviation	Meaning
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
iPTH	Intact parathyroid hormone
IV	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
Kt/V	K = Dialyser clearance of urea; t = dialysis time; V = subject's total body water
L	Litre
PD	Pharmacodynamic/s
PK	Pharmacokinetic/s
PPS	Per protocol set
PTH	Parathyroid hormone
SAE	Serious adverse event
SD	Standard deviation
SI	International System (of Units) (Systèm International d'Unités)
SOC	System organ class
SS	Safety set
t½	Terminal half-life
TEAE	Treatment emergent adverse event
Tmax	Time to reach maximum plasma drug concentration
TSAT	Transferrin saturation
US	United States

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	18 November 2014
Active ingredient:	Sucroferric oxyhydroxide
Product name:	Velphoro
Sponsor's name and address:	Vifor Pharma Pty Ltd Level 8, 80 Dorcas Street South Bank, Melbourne, VIC, 3006
Dose form:	Chewable tablet
Strength:	2500 mg (equivalent to 500 mg iron)
Containers:	Blister, bottle
Pack sizes:	30, 90 (blister or bottle)]
Approved therapeutic use:	*Velphoro is indicated for the control of serum phosphorus levels in adult patients with chronic kidney disease (CKD) on dialysis.*
Route of administration:	Oral
Dosage (abbreviated):	The recommended starting dose of Velphoro is 1,500 mg iron per day (3 tablets). Velphoro is for oral administration only and must be taken with meals. [See approved Product Information for full *Dosage and Administration*]
ARTG number:	216701, 216702

Product background

Declining kidney function is associated with a progressive deterioration of mineral homeostasis, including that of phosphorus and calcium (Kidney Disease Outcomes Quality Initiative (KDOQI), 2003[1]). Hyperphosphataemia is very common in patients with chronic kidney disease (CKD), particularly those requiring dialysis, occurring in over 70% of patients.

[1] Kidney Disease Outcomes Quality Initiative. KDOQI Clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*. 2003;42(Suppl 3):S10-201.

In large epidemiological studies, hyperphosphataemia has consistently been shown to be associated with increased morbidity, hospitalisation, and mortality in ESRD patients (Tentori, 2008[2]; Kestenbaum, 2005[3]; Block, 2004[4]).

Several drug products are currently available that reduce the amount of phosphorus taken up from food. The currently approved phosphate binders include calcium salts (carbonate, citrate, acetate), aluminium salts (mostly hydroxides), a lanthanum salt (lanthanum carbonate) and a cationic polymer (sevelamer HCl).

The proposed phosphate binder sucroferric oxyhydroxide is a mixture of polynuclear iron(III)-oxyhydroxide (the active moiety of Velphoro), sucrose and starches. In vivo, 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. The iron and phosphate are then excreted. Serum phosphorus levels are reduced as a consequence of the reduced dietary phosphate absorption.

This AusPAR describes the application by Vifor Pharma Pty Ltd (the sponsor) to register chewable tablets, containing 2500 mg sucroferric oxyhydroxide (equivalent to 500 mg iron) for the following indication:

> *Velphoro is indicated for the control of serum phosphorus levels in patients with end stage renal disease (ESRD).*

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 27 November 2014.

At the time the TGA considered this application, a similar application had been approved in the European Union (EU, August 2014) and the USA (November 2013) and was under evaluation in Switzerland and Singapore.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

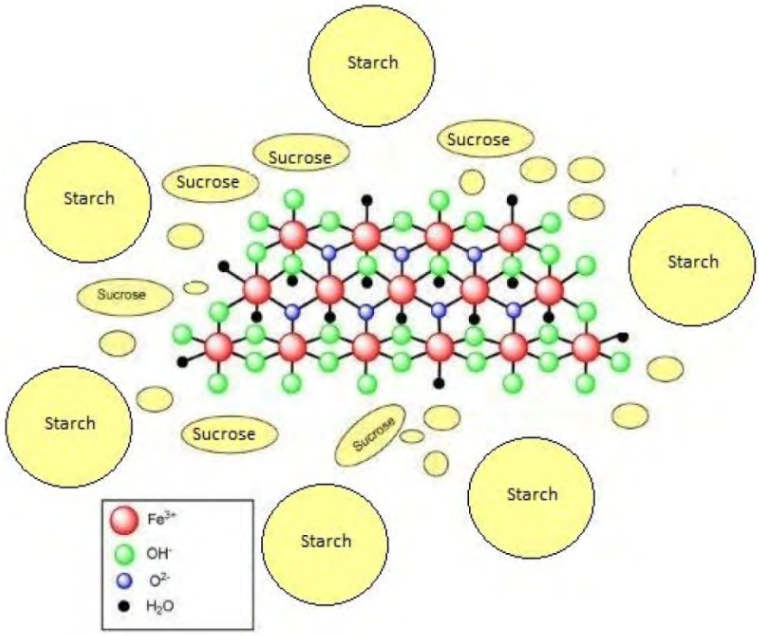
II. Quality findings

Introduction

Sucroferric oxyhydroxide (company code: PA21) is not a well-defined species. It contains small polynuclear iron(III)-oxyhydroxide, that is, 'rust' cores, sucrose, and starches. The drug substance contains about 33% polynuclear iron(III)-oxyhydroxide, 30% sucrose, 28% starches, and up to 10% water on a weight basis. The sponsor's model of the structure is shown in Figure 1:

[2] Tentori F, et al. Mortality risk for dialysis patients with different levels of serum phosphorus, and PTH. The Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis*. 2008;52(3):519-530.
[3] Kestenbaum B, et al. Serum phosphate levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol.* 2005;16(2):520-528.
[4] Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol*. 2004;15(8):2208-2218.

Figure 1: Model of structure of sucroferric oxyhydroxide



In vivo, the insoluble iron particles, partly "wrapped" by the carbohydrates, adsorb phosphate ions. Phosphate is bound to the surface of the iron oxide particles, not interstitially. The iron and phosphate are then excreted. If the iron oxide dissolves it does not absorb phosphate and the iron itself can be absorbed.

Labelling

There is no formal 'International Nonproprietary Name' for the active ingredient yet. The non-proprietary name 'sucroferric oxyhydroxide' has been adopted for PA21 by the United States Adopted Names (USAN) council and is the name now being used in European and American markets.

The finished product is intended to act as a phosphate adsorber, so any release of free iron from the tablets in vivo is undesirable. Phosphate adsorption is correlated to particle area rather than iron content per se. Nevertheless, Vifor proposes labelling the tablets only in terms of their iron content: "Velphoro 500 mg" "each chewable tablet contains 500 mg iron as sucroferric oxyhydroxide"

The best labelling (2.5 g versus 500 mg) is debatable, however, given that both European and American labelling will apparently be in terms of iron, this approach is now perhaps least confusing.

Drug substance (active ingredient)

Sucroferric oxyhydroxide is a brown, amorphous powder. The drug substance is relatively poorly defined, so that the manufacturing process is particularly important. Sucroferric oxyhydroxide is prepared by basifying a ferric chloride solution, giving a polynuclear iron(III)-oxyhydroxide suspension which is mixed with potato and maize starches and sucrose.

Vifor states that the sucrose stabilises the iron core and thus maintain the high phosphate adsorption capacity while the starches function as processing aids, but they are added simultaneously and the drug substance is probably a complex mixture of species.

The solubility of the active moiety, polynuclear iron oxyhydroxide, is evidently low in the gastrointestinal (GI) tract so that iron absorption is low. Aqueous solubility at different pH has been very poorly quantified. Vifor states that the "sucrose part is soluble in water, iron(III)-oxyhydroxide/starch mixture is practically insoluble in water."

While the iron oxide particle size is important in determining the phosphate binding, it is relatively difficult to directly measure. The sucrose/starch "wrapped" drug substance particle size is established and the process is controlled, but it does not correlate well with phosphate adsorption.

Sucroferric oxyhydroxide cannot be controlled in the manner of a well-defined molecular drug and some variability between batches is likely. The drug substance specification includes a phosphate adsorption test.

Vifor has tested the adsorption of a range of other in vivo chemical species to sucroferric oxyhydroxide and not identified any likely to be strongly bound, or affect phosphate binding, except for oxalate. Some drugs, however, do interact, for example alendronate is strongly absorbed (and the PI warnings in that context should be generalised to all bisphosphonates, not just identify the single drug in class studied).

Drug product

The proposed uncoated, unscored chewable tablets contain 2.5 g sucroferric oxyhydroxide (equivalent to 500 mg iron). The tablets are red-brown, round, flat-faced and embossed with "PA 500". Tablet dimensions are relatively large (6.5 x 20 mm).

Both bottle and blister packs of 30 and 90 chewable tablets are proposed. The bottles contain desiccant and are equipped with a tamper evident induction seal, child resistant closure and a cotton plug to cushion the tablets against physical damage.

The tablets are almost entirely comprised of the active ingredient (about 97% of tablet mass), with a complex flavouring agent, magnesium stearate, colloidal silica and a rare sweetener (neohesperidin dihydrochalcone). Sucrose exposure is 2.25–4.5 g per day. The starch will be degraded to glucose and maltose. The formulation is intended to disintegrate even if the tablets are not properly chewed.

The chewable tablets are made by direct compression. The target mass is adjusted based on the particular iron content of the drug substance batch.

The active moiety of the drug substance, polynuclear iron(III)-oxyhydroxide, is insoluble and not intended to be absorbed in vivo. Thus a dissolution test is not appropriate. A disintegration test is used to test for batch consistency, although, for chewed tablets, disintegration is not clinically relevant.

The specification includes a phosphate adsorption test.

Tablets are tested to limit undesirable iron release (solubilisation) at pH 3.0 in vitro. Gastric acid/base (pH) can, of course, be lower than that. Vifor claims that iron release is significantly reduced in the presence of phosphate, citing their own recent literature[5]. There is also some direct clinical trial data on absorption (see Biopharmaceutics below).

Both aluminium (Al/Al) blisters and high dentistry polyethylene (HDPE) bottles are proposed. These are stored below 30°C. No significant changes have been detected on closed storage. Due to adsorption of water vapour [and to mimic patient use], a 45 day in-use shelf-life is recommended for the bottles.

[5] M. Wilhelm, S. Gaillard, V. Rakov, and F. Funk. The iron-based phosphate binder PA21 has potent phosphate binding capacity and minimal iron release across a physiological pH range in vitro. *Clinical Nephrology*, 2014:81(4); 251-258.

Clinical trial formulations

Half strength trial formulations (250 mg iron) were used in Phase I and II clinical trials. These differed from the proposed formulation with regards to manufacturing methods and excipients.

The proposed drug substance was used in 500 mg iron formulations for the Phase IIIA and Phase IIIB trials; the formulations were similar but not identical to the proposed commercial formulation.

Because of the inapplicability of conventional dissolution tests, it is not possible to be sure that the different formulations are equivalent in vivo. In vitro phosphate binding results are broadly similar.

Biopharmaceutics

As a product intended for local action in the GI tract, systemic exposure is undesirable. The active moiety in Velphoro, polynuclear iron oxyhydroxide, is apparently not absorbed, so conventional pharmacokinetics (PK) are not relevant. Enzymatic hydrolysis and degradation of the starch and sucrose components is likely.

Nevertheless some iron can be dissolved from the active moiety (particularly under very acid conditions) and may be absorbed.

Study Q-24120 was a test of radiolabelled (^{59}Fe) 10 g sucroferric oxyhydroxide (2 g iron) doses in patients with chronic kidney disease (CKD and healthy volunteers with low iron stores. The study did not use tablets but a suspension of sucroferric oxyhydroxide in water. As manufacturing, especially mixing processes may well affect the particle size and perhaps carbohydrate binding, it remains unclear if this labelled sample is representative of the commercial tablets. Circulating radioactivity in blood reached, at most, 1.25% of the oral dose (higher in volunteers than patients); this was not compared to intravenous (IV) iron distributions. The study will not necessarily predict iron absorption after tablet dosing.

Vifor argues, however, that almost all patients undergoing dialysis are iron deficient and are receiving regular iron replacement treatment intravenously, so that any exposure to absorbable iron is not clinically important. Vifor refers to measurements of iron storage monitored during clinical studies.

Advisory committee considerations

This application was not referred for advice from the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM).

Quality summary and conclusions

Some labelling details were being finalised. Subject to satisfactory resolution of the labels, registration is recommended with respect to chemistry and quality control aspects.

III. Nonclinical findings

Introduction

The overall quality of the non-clinical dossier was good with all pivotal studies conducted according to Good Laboratory Practice (GLP) principles. Two formulations of sucroferric

oxyhydroxide were used in the preclinical studies, referred to as PA21 and PA21-2. The majority of the studies were conducted using PA21. The material manufactured for the Phase III clinical trials and which is intended for marketing uses a mixture of potato starch and pregelatinized corn starch. This material is referred to as PA21-2. The active moiety of PA21 is not absorbed in the GI tract and therefore standard PK studies could not be conducted.

Pharmacology

Primary pharmacology

PA21 is a mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches which functions as an iron-based phosphate binder. It has been developed as an agent to control serum phosphate levels in patients with end stage renal disease. In PA21, the iron(III)-oxyhydroxide is practically insoluble and releases very little iron under normal GI tract conditions. This minimises the risk of excessive iron uptake with consequent iron overload. In vitro primary pharmacology studies established the efficacy of PA21 (and PA21-2, the material that will be marketed prepared with the potato/corn starch mixture) in binding phosphate under a range of pH conditions. Comparison with other available phosphate binders (RenaGel, Fosrenol, PhosLo, calcium carbonate) indicated the phosphate binding performance of PA21 was higher than the calcium based agents at pH 3.0 (typical of the stomach after food) but lower at higher pH values [except calcium carbonate at pH 8]. Binding at these higher pH values was, however, still robust up to slightly alkaline conditions (pH 8.1). In vitro studies also demonstrated negligible iron release except at pH 1.6 (corresponding to a fasting state in the stomach) where release was 6.3%. PA21 and PA21-2 showed minor bile-acid sequestering properties in a simulated upper GI system.

In vivo actions were examined in an animal model of adenine diet induced chronic renal failure (CRF) in rats. PA21 in the diet of these animals reduced serum phosphorus and parathyroid hormone (PTH) levels and reduced the occurrence of vascular calcification. PA21 performed satisfactorily in comparisons with other phosphate binding agents in reducing elevated serum and urinary phosphorus levels. Administration of PA21 over 4 weeks in this rat model did not induce defective bone mineralisation. PA21 and lanthanum carbonate reduced elevated bone turnover in CRF rats and no iron deposits were noted in the bones of the animals treated with PA21.

Secondary pharmacodynamics and safety pharmacology

A standard battery of safety pharmacology studies covering cardiovascular, central nervous system and respiratory function in vivo was conducted. A study examining possible effects on human ether-a-go-go related gene (hERG) currents in vitro was not performed. The sponsor justified this omission on the basis that PA21 has a high molecular weight and has poor solubility. PA21 was negative in all the in vivo safety studies including assessment of QT intervals[6] in the cardiovascular safety study (exposure ratio (ER) based on mg/kg dose ($ER_{mg/kg}$) 5). The omission of the in vitro hERG study is not a cause for concern.

A study on the effects of PA21 on GI transit times was also conducted. PA21 could potentially affect these as the oral drug load could be as high as 15 g/day. Doses of 2500

[6] QT interval of the ECG. The QT interval is the portion of an electrocardiogram between the onset of the Q wave and the end of the T wave, representing the total time for ventricular depolarization and repolarization. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias such as torsade de pointes and sudden death.

and 5000 mg/kg increased the transit distance of a 5% weight/volume (w/v) suspension of medicinal charcoal in rats. Although the sponsor did not consider these results biologically significant they do suggest that the potential for some effect on GI transit times exists. Diarrhoea is listed as a very common adverse reaction in the sponsor's clinical overview.

Possible pharmacodynamic (PD) drug interactions were principally assessed by measuring adsorption of the test drug to PA21 in vitro. Studies were performed in the presence of α-amylase and at different pH values (3.0, 5.5, and 8.0). Extensive adsorption to PA21 was observed for furosemide, losartan, atorvastatin, doxycycline, alendronate, levothyroxine, paricalcitol, cephalexin and doxercalciferol. With the adsorbed drugs there was some variation in the extent of adsorption with pH. In vitro studies also found no evidence for adsorption or degradation of water soluble vitamins, amino acids or the anions fluoride, oxalate or sulphate.

Pharmacokinetics

Absorption:

The active moiety of PA21 is not absorbed in the GI tract and therefore conventional PK parameters such as plasma area under the concentration time curve (AUC) and maximum concentration (Cmax) could not be determined. Systemic absorption of PA21 associated radioactivity was determined via gamma counting in blood and plasma samples following oral dosing in mice, rats and dogs. Very small amounts of drug associated radioactivity were detected in whole blood of mice and rats but not in dogs.

Distribution

Plasma protein binding by PA21was not investigated. Tissue distribution in rats, pigmented rats and dogs after oral administration of radiolabelled iron (^{59}Fe)-PA21 (250 mg/kg) was very limited due to the very limited oral absorption of the drug. Drug-associated radioactivity was detected in small amounts in blood cells of mice, rats, and dogs accounting for less than 2% of dose administered. Tissue distribution of drug associated radioactivity in rats was limited to liver spleen and bone marrow at levels 0.18% or less of administered dose. No penetration was present in other tissues such as central nervous system or prostate. In humans drug associated iron was associated with blood cells at levels ranging from 0.02 -0.43% dose with the lowest values seen in haemodialysis patients as might be expected due to the disease condition of these individuals.

Metabolism

No formal metabolism studies on PA21were conducted since it is essentially not absorbed systemically from the GI tract. The likely metabolic pathway in the GI tract would involve degradation of the carbohydrate components and this was demonstrated in vitro. The sucrose component is likely to be hydrolysed by sucrase enzymes into glucose and fructose while the starch component is likely to be broken down by hydrolysis into glucose and maltose. The iron containing degradation product of iron (III)-oxyhydroxide is mononuclear iron (III)-hydroxide. The in vitro studies of iron release in simulated GI environments showed low iron release when phosphate was present but at low pH (1.2) in the absence of phosphate there was 66.9% of iron released.

Excretion

Excretion is via the faeces. No urinary excretion was evident in rats, or dogs. Biliary excretion was not demonstrated in bile duct cannulated rats.

Conclusion on pharmacokinetics

Due to the nature of PA21 with respect to insolubility and near complete lack of systemic absorption the PK profiles in animals and humans can be expected to be similar. In humans and nonclinical species there was evidence of drug associated iron binding to red blood cells at very low levels following oral doses of PA21. The proposed patient population are hyperphosphataemic and this is a critical difference between the animal species used and the results seen in pre-dialysis and haemodialysis patients. This is not considered a deficiency of the nonclinical program since the systemic absorption of drug associated iron in the target patient population is expected to be lower than in normo-phosphataemic animals and humans.

Pharmacokinetic drug interactions

An in vivo study in mice examined radiolabelled iron uptake in the presence of caffeine, ascorbic acid, calcium gluconate, magnesium aspartate, phytic acid, furosemide, enalapril and captopril. Animals given ^{59}Fe labelled PA21 with ascorbic acid showed a small increase in iron in the blood and liver but no effects were seen with the other compounds.

Treatment of rats with PA21 (2 weeks) did not result in any significant changes in cytochrome P450 (CYP) enzyme protein level or activity in liver and intestinal microsomes with respect to the CYP1A, CYP2B and CYP3A subfamilies. Therefore effects on the metabolism of other drugs co-administered with PA21 are unlikely.

Toxicology

Acute toxicity

One single dose toxicity study was conducted in rats. No toxicity was observed at the only dose tested (5000 mg/kg; $ER_{mg/kg}$ 25). Almost no deaths occurred in the repeat dose toxicity studies in mice, rats and dogs. PA21 has a very low order of acute oral toxicity.

Repeat dose toxicity

Repeat dose toxicity studies were conducted in two species: rat and dog. The majority of the studies were conducted using PA21, a material manufactured using potato starch. The material manufactured for the Phase III clinical trials and which is intended for marketing uses a mixture of potato starch and pregelatinized maize starch. This material is referred to as PA21-2. A bridging study was conducted in rats to compare the materials. No differences between the effects of the formulations were noted. PA21 was administered via the diet in rats and in capsules in the dog. The durations of the pivotal studies, the species used and the group sizes were consistent with relevant International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines. The maximum doses employed in the pivotal studies were 4000 mg/kg/day ($ER_{mg/kg}$, 20) in the rat and 2000 mg/kg/day ($ER_{mg/kg}$, 10) in the dog. The exposure margins are in general accordance with the ICH guidelines in both species. Studies of up to 26 weeks duration were conducted in rats and 39 weeks duration in dogs. The no observed adverse effect level (NOAEL) in the 26-week toxicity study in rats was 200 mg/kg/day ($ER_{mg/kg}$=1). In the 39 week study in dogs the NOAEL was 2000 mg/kg/day ($ER_{mg/kg}$=10).

Relative exposure

Plasma PK parameters for sucroferric oxyhydroxide could not be obtained in humans due to the insolubility and degradation characteristics of the drug. Therefore assessments of safety margins for PA21 have been performed on a dose comparison basis rather than using plasma disposition parameters of AUC and Cmax. Furthermore, comparisons on the basis of body surface area are also not considered appropriate since the drug is not absorbed systemically and therefore the parameters of mammalian biology specifically considered by BSA comparisons are not relevant.

The sponsor investigated differences in colon volume of the animals used in repeat dose studies. The volumes calculated were 1,885 cm^3 for humans, 6.62 cm^3 for rats, 0.53 cm^3 for mice and 318 cm^3 for dogs. These differences in volume suggested that the exposure of the GI tract (mg iron/cm^3) in humans may be lower than that in nonclinical species. The sponsor used different dosages to make these comparisons. When the same dose level (40 mg iron (Fe)/kg) is used for all species the calculated Fe exposure at the mucosal surface is: 2.6, 3.6, 1.3, and 1.6 mg Fe/cm^3 in mice, rats, dogs, and humans, respectively. Although mice and rats have slightly lower values for colon volume per body weight than humans the differences are not considered significant enough to warrant the use of this metric for exposure comparisons.

The sponsor has calculated exposure margins based on a 75 kg patient although the nonclinical overview and the Risk Management Plan (RMP) refer to a 70 kg patient. The difference in the exposure margins is not great but all margins are lower if they refer to a 70 kg individual. However, it should be noted that some clinical trial subjects had bodyweights as low as 50 kg and if this bodyweight is used then the exposure ratios in the table below will be one third lower.

The maximum recommended dose is 3,000 mg iron (6 x 2.5 g tablets, 500 mg iron/tablet) per day which equates to 200 mg/kg sucroferric oxyhydroxide based on a 75 kg individual. The table below presents exposure ratios for nonclinical species calculated on an animal: human dose basis using the maximum recommended human dose (200 mg/kg). Exposure ratios reached 25, 20, and 10 times the maximum human dose in mice, rats and dogs respectively. Exposure ratios at NOAEL levels (shown in bold font in Table 1) were low to moderate reaching a value of 10 in dog studies.

Table 1: Relative exposure (to total sucroferric oxyhydroxide) in repeat dose toxicity and carcinogenicity studies

Species	Study duration	Dose mg/kg/day	Exposure ratio mg/kg dose animal:human
Mouse (CD-1)	2 years [carcinogenicity]	1250	6.25
		2500	12.5
		5000	25
Rat (SD)	4 weeks	500	2.5
		1000	5
		2500	12.5
		4000	20

Species	Study duration	Dose mg/kg/day	Exposure ratio mg/kg dose animal:human
	13 weeks	300	1.5
		1000	5
		3000	15
	26 weeks	200	1
		750	3.75
		2500	12.5
	2 years [carcinogenicity]	200	1
		750	3.75
		2500	12.5
Dog (Beagle)	4 weeks	500	2.5
		1000	5
		2000	10
	13 weeks	500	2.5
		1000	5
		2000	10
	26 or 39 weeks	200	1
		600	3
		2000	10
Human	Recommended maximum daily dose	200	–

Major toxicities

A number of the changes seen in the repeat-dose studies were related to the expected pharmacological action of PA21 that is, reduction of the uptake of dietary phosphate. Elevated alkaline phosphatase (ALP), increased serum calcium and phosphorus, elevated urine calcium, decreased urine phosphorus, elevated serum osteocalcin and urinary deoxypyridinoline (DPD), and increased serum vitamin D metabolites can all be understood in the context of responses to PA21 in animals with normal phosphate levels at the outset of the studies. In response to the reduced phosphate levels, phosphate (and simultaneously calcium) is mobilised from bone in order to maintain adequate phosphate

levels. These changes were more pronounced in rats than in dogs, possibly as a result of the higher doses given to rats. These changes can all be interpreted as adaptive changes rather than toxic effects of PA21.

Increased tissue iron levels were observed in the liver, spleen and kidney and there was evidence of increased iron deposition in the liver (periportal hepatocytes and Kupffer cells), spleen (red pulp macrophages), mesenteric lymph node macrophages, epithelial cells or lamina propria macrophages in the small and large intestine, indicated by increased Perls' positive staining of the tissues. There was no evidence of pathological changes associated with the increased iron in any of the tissues. Small increases in haemoglobin and haematocrit were seen in males and females at 2500 mg/kg/day (PA21) in the 26 week rat study and in males after 4 weeks with PA21-2 (4000 mg/kg/day). No effects on haematological parameters were seen in dogs. Pharmacokinetic studies in rats with ^{59}Fe labelled PA21 found very low absorption (1-1.5%) with a single dose of 250 mg/kg. It seems unlikely that iron accumulation will present any risk at the anticipated clinical doses. Moderate haemosiderosis was seen in the spleen in the 26 week repeat dose study in rats but there was no evidence of haemochromatosis. Even the limited iron uptake seen in these animal studies exceeds what would be expected in hyperphosphataemic patients.

Hyperplasia was observed in the GI tract and urinary bladder of both mice and rats in repeat-dose studies. These results are discussed below under *Carcinogenicity*.

Genotoxicity

PA21 was negative in the standard Ames test. While both PA21 and PA21-2 showed increases in the frequency of structural aberrations in vitro in Chinese hamster lung cells at the highest concentration used of 5000 µg/mL, the results were not of concern as there was no dose response or clear replication of results, and the test article was precipitating at this concentration.

Due to the lack of absorption following oral administration, a conventional in vivo, rodent, bone marrow micronucleus test was not conducted, since it was not possible to achieve exposure of the target tissue by the oral route, and IV administration was not feasible due to the low solubility of PA21 in any vehicle suitable for IV administration. In view of concerns over the high oral iron load of PA21, lack of absorption of the material or its iron content, in vivo "site of contact" genetic toxicity studies were performed in rats (that is, Comet assays for deoxyribonucleic acid (DNA) damage in the stomach, duodenum and colon). PA21 was negative in this modified Comet assay. Assessment of peripheral blood reticulocytes for incidence of micronuclei after 4 or 24 weeks of treatment in a 26 week repeat dose toxicity study in rats also gave negative results.

Carcinogenicity

Two year carcinogenicity studies were conducted in mice and rats using daily oral dosing up to 5000 mg/kg/day PA21 ($ER_{mg/kg}$, 25; equivalent to 1000 mg Fe/kg/day) in mice and 2500 mg/kg/day PA21 ($ER_{mg/kg}$, 12.5; equivalent to 500 mg Fe/kg/day) in rats. Both studies employed administration via dietary admixture. Both maximum doses were the maximum tolerated doses (MTDs) based on repeat-dose studies. The lowest PA21 dose in the mouse study (1250 mg/kg/day) was 6.25 fold the maximum human dose and the lowest dose in the rat study (200 mg/kg/day) was similar to the maximum anticipated human dose of PA21. The sponsor indicated that protocol for the mouse study was reviewed by the Executive Carcinogenicity Advisory Committee at the US FDA, and termination strategy for both studies was also agreed in discussion with FDA.

In the mouse study, treatment related hyperplastic and neoplastic changes were observed in the caecum and colon, with higher incidence in males than females (tabulated; note dosing is in terms of mg Fe/day/kg):

Table 2: Treatment related hyperplastic and neoplastic changes in mice

Dose (mg Fe/kg/day)	Males				Females			
	Control	250	500	1,000	Control	250	500	1,000
Colon[1]								
Number examined	57	60	57	60	59	58	57	60
Adenocarcinoma	1	3++	5++	9++*	0	0	0	3+
Epithelial hyperplasia	5	16*	22**	25**	3	5	6	21**
Mucosal diverticulum/ cysts/hyperplasia	2	1	3	6	0	0	2	4
Caecum[1]								
Number examined	51	58	50	54	57	54	55	59
Adenocarcinoma	0	1	2	1	0	1	0	0
Adenoma	0	0	0	1	0	0	0	0
Epithelial hyperplasia	2	3	3	15**	0	0	0	8**
Mucosal diverticulum/ cysts/hyperplasia	0	3	4	12**	0	0	0	3

1 Data shown for decedent and terminal mice combined.
Notes: + = p<0.05; ++ = p<0.01 (trend test); * = p<0.05; ** = p<0.01 (pairwise vs. control group).

The sponsor initiated a reanalysis of the neoplastic data with a particular emphasis on the two categories of large intestinal lesions: cystic diverticular lesions and mucosal adenocarcinomas. A subset of the former was initially diagnosed by the study pathologist as adenocarcinoma based on the single criterion of physical herniation through the outer smooth muscle wall of the large intestine. Upon re-analysis, the diagnosis of these as adenocarcinoma was considered inappropriate as the morphological features did not differ from identical large intestine lesions without herniation through the outer gut muscular wall. The re-analysed data are presented below (note that the dosing is in terms of mg Fe/day/kg):

Table 3: Treatment related hyperplastic and neoplastic changes in mice: Re-analysis

Dose (mg Fe/kg/day)	Males				Females			
	Control	250	500	1,000	Control	250	500	1,000
Colon								
No. examined	57	60	57	60	59	58	57	60
Adenocarcinoma								
Original classification	1	3	5	9	0	0	0	3
Re-classification	0	0	3	1	0	0	0	0
Caecum								
No. examined	51	58	50	54	57	54	55	59
Adenocarcinoma								
Original classification	0	1	2	1	0	1	0	0
Re-classification	0	0	0	0	0	0	0	0
Adenoma[1]	0	0	0	1	0	0	0	0

1 Expert agreed with original diagnosis/classification.

Even after re-analysis the incidence of adenocarcinoma and/or adenoma was considered above historical background range (0% for adenoma, 0-1.7% for adenocarcinoma) for males at 500 and 1,000 mg Fe/kg/day (2500 and 5000 mg/kg/day PA21). Adenocarcinomas were evident at the middle dose with an exposure ratio of ≥ 12.5. A no effect level (NOEL) was established at an ER of 6.25.

The sponsor has reviewed the nonclinical section of the report (above) and provided a response. The response included a Pathology Working Group (PWG) report after the review of selected slides from mice containing proliferative changes involving the colon and cecum from the carcinogenicity Study by Dietary Administration to CD-1 Mice for 104 Weeks with PA21. The PWG classified each lesion and resolved any differences in

diagnoses that existed between the initial findings reported in the study report and those reported in the expert opinion report.

The results of the PWG review of adenocarcinomas and diverticula reported in the caecum and colon are summarised below. As a result of the PWG review, 2 of the adenocarcinomas previously reported in the colon were reclassified as diverticula and one as an adenoma. The single adenocarcinoma was considered unlikely to be test article-related by the PWG. The diverticula were observed in association with mucosal hyperplasia and the diverticula were often cystic in nature.

Table 4: Treatment related hyperplastic and neoplastic changes in mice: Review by the Pathology Working Group (PWG)

	Male				Female			
Dose (mg/kg/day)	**0**	**1,250**	**2,500**	**5,000**	**0**	**1,250**	**2,500**	**5,000**
No. Animals/Group	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**
Colon								
Adenocarcinoma (Study Pathologist)	1	3	5	9	0	0	0	3
Adenocarcinoma (Reviewing Pathologist)	0	0	3	1	0	0	0	0
Adenocarcinoma (PWG)	0	0	1	0	0	0	0	0
Adenoma[1] (PWG)	0	0	0	1	0	0	0	0
Diverticulum/Cysts/Epithelial Hyperplasia (Study Pathologist)	2	1	3	6	0	0	2	4
Diverticulum (Reviewing Pathologist)	3	4	5	14	0	0	2	7
Diverticulum (PWG)	2	4	7	13	0	0	2	7
Caecum								
Adenocarcinoma (Study Pathologist)	0	1	2	1	0	1	0	0
Adenocarcinoma (Reviewing Pathologist)	0	0	0	0	0	0	0	0
Adenocarcinoma (PWG)	0	0	0	0	0	0	0	0
Diverticulum/Cysts/Epithelial Hyperplasia (Study Pathologist)	0	3	4	12	0	0	0	3
Diverticulum (Reviewing Pathologist)	0	4	4	13	0	1	0	3
Diverticulum (PWG)	0	4	4	12	0	1	0	3

1 One adenoma reported in the caecum of 1 Group 4 male mouse, Animal # 236, by the Study Pathologist and confirmed by the Reviewing Pathologist, was considered by the PWG to be a protrusion of the adenoma in the colon into the lumen of the caecum and not a separate neoplasm. The morphology of the adenoma was clearly different from the diverticula with cysts. It consisted of a polypoid growth in the lumen of the colon. The adenoma was considered unlikely to be test article-related by the PWG.

Note: PWG = Pathology Working Group.

In the rat study neoplastic changes were seen with a statistically significant increase in thyroid c-cell adenomas in males at the highest dose of 2500 mg/kg/day PA21, with incidences higher than historical control means in all male treatment groups. No corresponding increases were observed in females. There was also a tendency to increased thyroid c-cell hyperplasia in both genders although incidences did not achieve statistical significance. The tendency towards increased hyperplasia in the thyroid (and decreased hyperplasia in the parathyroid) is likely to be related to PA21-induced phosphate depletion which triggers homeostatic alterations in 1, 25-dihydroxyvitamin D3, PTH and calcitonin secretion. Such effects represent exaggerated pharmacology and are not directly relevant to patients given PA21 at the proposed doses.

Hyperplastic changes were seen in the mouse at termination in the caecum and colon and in the non-glandular region of the stomach and the transitional epithelium of the urinary bladder (males only). Treatment related increases in the incidence of epithelial hyperplasia were observed in the duodenum, caecum, colon and rectum in both male (≥ 750 mg/kg/day PA21) and female rats (2500 mg/kg/day PA21). There was submucosal inflammation present in the caecum, colon and rectum but this was also present in control animals.

Mucosal hyperplasia was seen in various regions of the lower GI tract in the repeat dose studies in rats (summarised in the table below). The frequency was low but there were some instances in high dose males in all studies. Incidence in females was much lower.

Hyperplasia in the transitional epithelium of the urinary bladder was also observed in both rodent species (see table)

Table 5: Mucosal hyperplasia in the repeat dose studies in rats

Study	Organ	Dose PA21 (mg/kg/day)	Frequency	
			Male	Female
Mouse				
WLY0032	Stomach	100000 ppm	1/6	0/6
VFR0105	Colon	≥ 2500	8/36	9/36
	Rectum	≥ 5000	11/24	1/12
	Urinary bladder	10000	3/12	0/12
Rat				
VFR075	Rectum	4000	2/10	1/10
VFR0117	Caecum	4000 (PA21 & PA21-2)	5/20	0/20
	Rectum	4000 (PA21)	2/10	1/10
VFR0087	Caecum	3000	3/10	0/10
	Colon	3000	0/10	1/10
	Rectum	3000	2/10	0/10
	Urinary bladder	3000	1/10	0/10
VFR0096	Caecum	2500	3/15	0/15
	Colon	750	1/15	0/15
		2500	1/15;1/6 (recovery)	0/15
	Rectum	2500	1/15	0/15
	Urinary bladder	2500	3/15	0/15

At the high doses used in the rodent studies PA21 can cause thyroid c-cell adenomas, hyperplastic change in the GI tract, and hyperplastic changes in the urinary bladder. It seems most likely that these changes are secondary to the pharmacological actions of PA21. In the GI tract the heavy burden of the drug causes prolonged irritation and inflammation. In the urinary bladder altered electrolyte excretion patterns, particularly of

calcium, may cause irritation of the epithelium. Altered calcium and phosphate homeostasis may underlie the hyperplasia and malignancy in the thyroid gland. Despite the sporadic positive results of the chromosome aberration test, the evidence from the Ames test and the modified Comet assay using GI tract tissues indicated no direct mutagenic potential of PA21.

The weight of evidence suggests that PA21 is not directly carcinogenic but prolonged exposure to very high doses has the potential to induce hyperplastic change and increase the risk of neoplasms. Such effects are considered unlikely in humans at clinically relevant doses.

Reproductive toxicity

Reproductive toxicity was assessed in rats and rabbits in GLP compliant studies. The studies investigated potential effects on male and female fertility in rats, embryofetal toxicity (rats and rabbits) and pre-/postnatal development (rats). Adequate animal numbers were used in the pivotal studies and treatment periods were appropriate. Exposure levels for PA21 achieved were greater than the anticipated clinical exposure (see Table 6, below). PA21 did not affect male or female fertility at doses up to 4000 mg/kg/day.

In rats, PA21 caused a statistically significant ($p<0.05$) increase in post-implantation loss at the high dose of 4000 mg/kg. However, group mean results were skewed by an extreme outlier (one female with six resorptions and a post-implantation loss of 46.2%), the exclusion of which negated any significant differences from the controls. Given that the concurrent controls were at the lower limits of the normal ranges, that the mean number of live young and the sex ratios were similar to concurrent control values, and that all values were within normal background ranges, this finding was not considered treatment-related and the maternal and fetal NOAEL values were set at 4000 mg/kg/day.

PA21 did cause some reductions in fetal body weights in rabbits (1000 mg/kg/day) and there was a trend towards incomplete ossification at a maternotoxic dose of 1000 mg/kg/day. Decreased mean fetal weight and delayed ossification have also been noted in rabbit embryo-fetal development studies with other phosphate binders (lanthanum carbonate). The NOAEL for embryofetal development in the rabbit was 500 mg/kg ($ER_{mg/kg}$=2.5).

PA21 did not affect the postnatal development of rats including sexual maturation and reproductive function at up to 4000 mg/kg/day ($ER_{mg/kg}$=20).

Table 6: Relative exposure in reproductive toxicity studies

Species	Study	Dose mg/kg/day	Exposure ratio#
Rat (SD)	Fertility	500	2.5
		1400	7
		4000	20
	Embryofetal development	500	2.5
		1400	7
		4000	20

Species	Study	Dose mg/kg/day	Exposure ratio#
Rabbit (NZW)	Embryofetal development	250	1.25
		500	2.5
		1000	5
Human	Recommended maximum daily dose	200	Human

= animal:human dose (mg/kg)

Pregnancy classification

The sponsor has proposed Pregnancy Category B1[7] for use of Velphoro during pregnancy. Given the effects on fetal bodyweight and ossification in rabbits this should be changed to B3[8] and the *Use In Pregnancy* statements in the PI amended accordingly.

Paediatric use

Velphoro is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Nonclinical summary and conclusions

- The overall quality of the nonclinical dossier was good with all pivotal studies conducted according to GLP. Two formulations of sucroferric oxyhydroxide were used in the preclinical studies referred to as PA21 and PA21-2. The majority of the studies were conducted using PA21.
- In vitro primary pharmacology studies established the efficacy of PA21 and PA21-2, in binding phosphate under a range of pH conditions. Phosphate binding performance of PA21 was comparable to other available phosphate binding agents. In animal models of chronic renal failure PA21 performed satisfactorily in comparisons with other phosphate binding agents in reducing elevated serum and urinary phosphorus levels.
- PA21 was negative in a standard battery of safety pharmacology studies covering cardiovascular, central nervous system and respiratory function in vivo. Pharmacodynamic drug interactions were assessed by measuring adsorption of other drugs to PA21 in vitro. Extensive adsorption to PA21 was observed for furosemide, losartan, atorvastatin, doxycycline, alendronate, levothyroxine, paricalcitol, cephalexin and doxercalciferol.
- The active moiety of PA21 is not absorbed in the GI tract and therefore conventional PK parameters such as plasma AUC and Cmax could not be determined. Small amounts of drug derived iron were detected in red blood cells of nonclinical species and in

[7] The definition of Category B1 for use of medicines in pregnancy is: *Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.*
[8] Category B3 is defined as: *Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.*
Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

humans. The percentages of administered dose detected in blood cells were very low, < 2% in animals and < 0.5% in humans. The in vitro investigations of iron release from the PA21 drug product mostly indicated very low propensity for iron release in an acidic environment except in the absence of phosphate. The absorption of PA21 derived iron is expected to be lower in patients with hyperphosphataemia, such as those with CKD on dialysis.

- PA21 has a very low order of acute oral toxicity in mice and rats at doses up to 5000 mg/kg and dogs at doses up to 2000 mg/kg.
- The majority of the effects seen in the repeat dose toxicity studies were the result of administering a phosphate binder to normophosphataemic animals. These effects were elevated ALP, increased serum calcium and phosphorus, elevated urine calcium, decreased urine phosphorus, elevated serum osteocalcin and urinary DPD, and increased serum vitamin D metabolites. There were also small increases in the iron content of the kidney, liver and spleen, and evidence of iron deposition particularly in the reticuloendothelial system. Hyperplasia of various regions of the GI tract of both mice and rats occurred in repeat dose studies. This effect was more frequent in males. Hyperplasia of the urinary bladder was also observed in male animals.
- PA21 was negative in the Ames test and in a modified Comet assays assessing DNA damage in the stomach, duodenum and colon of rats. Results from tests for mutagenic potential in vitro in Chinese hamster lung cells were equivocal at 5000 mg/mL. The weight of evidence suggests that PA21 does not pose a genotoxic concern.
- At the high doses used in the rodent studies PA21 can cause thyroid c-cell adenomas, hyperplastic changes in the GI tract and hyperplastic changes in the urinary bladder. It seems most likely that these changes are secondary to the pharmacological actions of PA21. In the GI tract the heavy burden of the drug causes prolonged irritation and inflammation. In the urinary bladder altered electrolyte excretion patterns, particularly calcium may cause irritation of the epithelium. Altered calcium and phosphate homeostasis may underlie the hyperplasia and malignancy in the thyroid gland. PA21 does not appear to be mutagenic and the balance of evidence suggests that PA21 is not directly carcinogenic. However, prolonged exposure to very high doses has the potential to induce hyperplastic change which may progress to neoplastic change. Such effects are considered unlikely in humans at clinically relevant doses.
- PA21 had no effects on fertility, embryofetal or post-natal development in rats. However, PA21 did cause some reductions in fetal body weights in rabbits (at 1000 mg/kg/day; 5 times maximum clinical dose) and there was a trend towards incomplete ossification at this maternotoxic dose. The NOAEL for embryofetal development in the rabbit was 500 mg/kg ($ER_{mg/kg}$=2.5).

Conclusions and recommendation

- There are no major deficiencies in the nonclinical data set.
- Primary pharmacology studies in vitro confirmed that PA21 and PA21-2 bind phosphate under a range of conditions. In animal models of chronic renal failure PA21 reduced elevated serum and urinary phosphorus levels.
- No clinically relevant hazards were identified in safety studies. Secondary PD studies in vitro demonstrated extensive adsorption to PA21 of furosemide, losartan, atorvastatin, doxycycline, alendronate, levothyroxine, paricalcitol, cephalexin and doxercalciferol.

- The active moiety of PA21 is not absorbed in the GI tract and therefore standard PK studies were not carried out. Only very small amounts of iron were detected in nonclinical species and humans following oral PA21.
- Many of the effects seen in the repeat dose toxicity studies can be interpreted as adaptive changes in normophosphataemic animals rather than toxic effects of PA21 and are consequently not anticipated in hyperphosphataemic patients. Hyperplasia was observed in the GI tract and urinary bladder of both mice and rats in repeat-dose studies.
- The weight of evidence suggests that PA21 does not pose a genotoxic concern.
- PA21 is not directly carcinogenic but prolonged exposure to very high doses has the potential to induce hyperplastic change and increase the risk of neoplasms. Such effects are considered unlikely in humans at clinically relevant doses.
- The only reproductive toxicity shown by Velphoro was a reduction in fetal bodyweight and delayed ossification observed in a rabbit embryofetal development study at a maternotoxic dose (5 times the maximum clinical dose). A Pregnancy category of B3 is recommended based on this finding.

There are no nonclinical objections to registration.

Recommended revisions to nonclinical statements in the draft PI are beyond the scope of the AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Velphoro belongs to the pharmacotherapeutic group of drugs for treatment of hyperkalaemia and hyperphosphataemia. Velphoro contains a mixture of polynuclear iron(III)-oxyhydroxide, sucrose, and starches. Phosphate binding takes place by ligand exchange between hydroxyl groups and/or water and the phosphate ions throughout the physiological pH range of the GI tract. The proposed indication for Velphoro is:

> *Velphoro is indicated for the control of serum phosphorus levels in patients with end stage renal disease (ESRD).*

Clinical rationale

Chronic kidney disease is an international public health problem affecting 5% to 10% of the world population. Given the pathogenic progression of kidney disease, patients with CKD are at high risk for progression to end stage renal disease (ESRD), a condition requiring dialysis or kidney transplantation to maintain patients' long-term survival. Since the 1960s, the incidence and prevalence of patients with ESRD has increased dramatically. It was predicted that, by 2010, the number of ESRD patients worldwide would exceed 2 million (Lysaght, 2002[9]). Declining kidney function is also associated with a progressive deterioration of mineral homeostasis, including that of phosphorus and calcium [Kidney

[9] Lysaght MJ. Maintenance dialysis population dynamics: current trends and long-term implications. *J Am Soc Nephrol.* 2002;13:S37-S40.

Disease Outcomes Quality Initiative (KDOQI), 2003[10]]. Hyperphosphataemia is very common in patients with CKD (particularly those requiring dialysis), occurring in over 70% of patients.

In large epidemiological studies, hyperphosphataemia has consistently been shown to be associated with increased morbidity, hospitalisation, and mortality in ESRD patients (Tentori, 2008[11]; Kestenbaum, 2005[12]; Block, 2004[13]). Hyperphosphataemia contributes to cardiovascular disease (CVD) through the development of vascular calcification in the media of arterial walls. At high serum phosphorus concentrations, vascular smooth muscle cells undergo a phenotypic switch to exhibit features of bone-forming cells (Giachelli, 2001[14]; Jono, 2000[15]). In addition, at excessive serum phosphorus levels, complexes are formed with calcium, with a direct precipitation in the vasculature of calcium-phosphorus product (Ca × P) (Ossareh, 2011[16]). In this context, prolonged hyperphosphataemia is recognised as an independent risk factor for CVD in patients with renal failure.

A graded independent association was demonstrated between serum phosphorus levels and mortality (mainly cardiovascular events) and the progression of renal disease (that is, loss of glomerular filtration rate; GFR) (Kanbray M, 2009[17]). In patients with CKD, there was a consistent association between higher serum phosphorus levels and mortality. The risk of death increased 18% for every 0.32 mmol/L (1 mg/dL) increase in serum phosphorus (relative risk: 1.18; 95% confidence interval (CI): 1.12, 1.25) (Palmer, 2011[18]). The evidence suggests that the control of serum phosphorus levels is a critical issue in the care of patients with CKD.

The National Kidney Foundation KDOQI guidelines recommend that CKD patients consume a restricted phosphorus diet of approximately 900 mg phosphorus/day, and that serum phosphorus levels in dialysis patients should not exceed 1.78 mmol/L (5.5 mg/dL). The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (KDIGO, 2009[19]) suggest further lowering the serum phosphorus levels towards the normal range (0.81 to 1.45 mmol/L (2.5 to 4.5 mg/dL)). Effective control of serum phosphorus levels in these patients by dietary restriction alone has proven to be virtually impossible. The International Dialysis Outcomes and Practice Patterns study (DOPPS) found that in approximately 50% of dialysis patients, serum phosphorus levels remain higher than the guideline recommendations (Port, 2006[20]) and suggests that suboptimal use of phosphate binder therapy is at least partially responsible for this high rate of hyperphosphataemia.

[10] Kidney Disease Outcomes Quality Initiative. KDOQI Clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*. 2003;42(Suppl 3):S10-201.
[11] Tentori F, et al. Mortality risk for dialysis patients with different levels of serum phosphorus, and PTH. The Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis*. 2008;52(3):519-30.
[12] Kestenbaum B, et al. Serum phosphate levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol.* 2005;16(2):520-8.
[13] Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol*. 2004;15(8):2208-18.
[14] Giachelli CM, Jono S, Shioi A, Nishizawa Y, Mori K, Morii H. Vascular calcification and inorganic phosphate. *Am J Kidney Dis*. 2001;38(4 Suppl 1):S34-7.
[15] Jono S, et al. Phosphate regulation of vascular smooth muscle cell calcification. *Circ Res*. 2000;87(7):e10-7.
[16] Ossareh S. Vascular calcification in chronic kidney disease: mechanisms and clinical implications. *Iran J Kidney Dis*. 2011 Sep;5(5):285-99.
[17] Kanbay M, Goldsmith D, Akcay A, Covic A. Phosphate - the silent stealthy cardiorenal culprit in all stages of chronic kidney disease: a systematic review. *Blood Purif*. 2009;27:220-30.
[18] Palmer SC, et al. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease. *JAMA*. 2011 Mar 16;305(11):1119-27.
[19] Kidney Disease: Improving Global Outcomes. KDIGO Clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int*. 2009 Aug;76 Suppl 113:S22-99.
[20] Port FK, et al. Improving outcomes for dialysis patients in the international dialysis outcomes and practice patterns study. *Clin J Am Soc Nephrol*. 2006;1(2):246-55.

Several drug products are available that reduce the amount of phosphorus taken up from food, but most have considerable therapeutic drawbacks. Calcium salts (carbonate, citrate, acetate) and aluminium salts (mostly hydroxides) have been widely used for over 40 years; newer products include a cationic polymer (sevelamer hydrochloride (HCl)[21], sevelamer carbonate) and a lanthanum salt (lanthanum carbonate[22]).

The use of calcium salts is limited by calcium loading of the patients and the development of hypercalcaemia, which has been reported to occur in over 50% of CKD patients on haemodialysis receiving calcium-based phosphate binders (Meric, 1990[23]). In conjunction with raised phosphorus levels, this may contribute to cardiovascular calcification, with potentially fatal consequences (Block, 2001[24]). It has been suggested that calcium-based phosphate binders should be avoided in many, if not most patients who are undergoing dialysis (Moe, 2006[25]).

Aluminium salts are generally regarded as second-line therapy because of the toxicity of aluminium absorption, which may lead to Vitamin D resistant osteomalacia and various neurological problems, including encephalopathy and dementia (Wills, 1983[26]; Alfrey, 1976[27]).

Sevelamer (available as HCl and carbonate) is a non-absorbable, cationic polymer capable of reversibly binding anions such as phosphate (Chertow GM, 1997[28]; Burke, 1997[29]), and is currently widely regarded as the phosphate binder of choice. Gastrointestinal problems are the most frequently reported adverse events (see Renagel (sevelamer HCl) tablet product information, 2011; Renvala (sevelamer carbonate) product information, 2011). Severe constipation is a concern with sevelamer treatment and cases of bowel obstruction and perforation have been reported with sevelamer use. Sevelamer tablets must be swallowed without chewing, and cases of dysphagia and oesophageal tablet retention have been reported. Doses range from 2.4 to 14.4 g/day, which equate to 3 to 18 tablets/day, representing a relatively high pill burden for the patient.

Lanthanum carbonate appears to be well tolerated and has a reduced pill burden compared to sevelamer (Mohammed, 2008[30]). The most common adverse events are GI events such as nausea and vomiting. Low, but measurable absorption of lanthanum has been observed (Pennick, 2006[31]; Damment, 2008[32]), and further studies are needed to address the longer-term toxic effect on bone and other organs.

[21] Available as Renagel 400 and 800 mg tablets in Australia
[22] Available as Fosrenol 500, 750 and 1000 mg tablets in Australia
[23] Meric F, Yap P, Bia MJ. Etiology of hypercalcemia in hemodialysis patients on calcium carbonate therapy. *Am J Kidney Dis*. 1990 Nov;16(5):459-464.
[24] Block GA. Control of serum phosphorus: implications for coronary artery calcification and calcific uremic arteriolopathy (calciphylaxis). *Curr Opin Nephrol Hypertens*. 2001;10(6):741-747.
[25] Moe SM, Chertow GM. The case against calcium-based phosphate binders. *Clin J Am Soc Nephrol*. 2006;1(4):697-703.
[26] Wills MR, Savory J. Aluminium poisoning: dialysis encephalopathy, osteomalacia, and anaemia. *Lance*t. 1983 Jul 2:29-34.
[27] Alfrey AC, LeGendre GR, Kaehny WD. The dialysis encephalopathy syndrome. Possible aluminum intoxication. *N Engl J Med*. 1976 Jan 22;294(4):184-188.
[28] Chertow GM, et al. Poly[allylamine hydrochloride] (RenaGel): a noncalcemic phosphate binder for the treatment of hyperphosphatemia in chronic renal failure. *Am J Kidney Dis*. 1997 Jan;29(1):66-71.
[29] Burke SK, Slatopolsky EA, Goldberg DI. RenaGel, a novel calcium- and aluminium-free phosphate binder, inhibits phosphate absorption in normal volunteers. *Nephrol Dial Transplant*. 1997;12(8):1640-1644.
[30] Mohammed IA, Hutchison AJ. Phosphate binding therapy in dialysis patients: focus on lanthanum carbonate. *Ther Clin Risk Manag*. 2008;4(5):887-93.
[31] Pennick M, Dennis K, Damment SJP. Absolute bioavailability and disposition of lanthanum in healthy human subjects administered lanthanum carbonate*. J Clin Pharmacol.* 2006;46(7):738-46
[32] Damment SJP, Pennick M. Clinical pharmacokinetics of the phosphate binder lanthanum carbonate. *Clin Pharmacokinet*. 2008;47(9):553-63.

Vifor Pharma aimed to develop an efficacious, well tolerated, calcium and aluminium free phosphate binder with a reduced pill burden, compared to other available products. PA21 is a new iron-based phosphate binder for oral administration (Geisser, 2009[33]). It consists of a mixture of polynuclear iron(III)-oxyhydroxide (about 33% mass/mass (m/m)), stabilised by sucrose (about 30% m/m), and starches (about 38% m/m). The iron content of PA21 is about 21% (m/m). It is well known that iron compounds have phosphate adsorption properties; however, oxidic iron compounds like Fe_2O_3 have a rather low phosphate adsorption capacity, whereas soluble iron complexes have the disadvantage of being absorbed in the intestine. The iron(III)-oxyhydroxide of PA21 powder is practically insoluble and possesses a high phosphate adsorption capacity in combination with a low iron release.

Guidance

The overall clinical program was designed based on feedback from the US FDA and thorough discussion with some national authorities in the EU.

Contents of the clinical dossier

The submission contained the following clinical information:

- 7 clinical pharmacology studies (Q-24120, VIT-CI-01/2, PA-DDI-001, PA-DDI-002, PA-DDI-003, PA-DDI-004 and PA-DDI-005).
- Phase II dose ranging Study PA-CL-03A.
- Pivotal efficacy/safety Phase III Study PA-CL-05A.
- Long term safety extension Study PA-CL-05B.
- Other studies: Synopses of 2 additional studies (a Phase I Study PA1101 and a Phase II Study PA1201) conducted by Vifor Pharma's Japanese partner, Kissei Pharmaceutical Co., for registration purposes in Japan) are also included as supportive secondary data in the dossier. In these studies, 30 healthy male subjects and 146 adult CKD patients on dialysis received PA21 for up to 6 weeks. However, the complete study reports (CSR) of these Japanese studies were not available for review.
- Pooled and meta-analyses, Integrated Summary of Safety.
- Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety, and literature references.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

The PA21 development programme adhered to the principles outlined in the ICH Guideline for Good Clinical Practice.

[33] Geisser P, Philipp E. PA21: a novel phosphate binder for the treatment of hyperphosphatemia in chronic kidney disease. *Clin Nephrol*. 2010 Jul;74(1):4-11.

Pharmacokinetics

Studies providing pharmacokinetic data

Velphoro works by binding phosphate in the GI tract and thus the serum concentration is not relevant for its efficacy. Given the insolubility and degradation characteristics of PA21, and the minimal absorption of the active moiety, iron(III)-oxyhydroxide, no classical PK studies can be carried out, for example, determination of the distribution volume, area under the curve, or mean residence time. The Phase I clinical programme (summarised in Table 7), therefore, focussed on measures for phosphate-binding capacity, iron release and absorption, and drug interactions.

> **Evaluator's comments**: Given the characteristics of Velphoro and its mechanism of action, the lack of conventional PK studies in the submission is acceptable.

Table 7: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	General PK - Single dose	Q-24120
	- Multi-dose	VIT-CI-01/2
	Bioequivalence† - Single dose - Multi-dose	None
	Food effect	None
PK in special populations	Target population§	Study Q24120
	Hepatic impairment	None
	Renal impairment	Same as target population
	Neonates/infants/children/ adolescents	None
	Elderly	None
Genetic/ gender-related PK	Males versus females	None
PK interactions	DDI study with Losartan	PA-DDI-001
	DDI study with furosemide	PADDI-002
	DDI study with omeprazole	PA-DDI-003
	DDI study with digoxin	PA-DDI-004
	DDI study with warfarin	PA-DDI-005

PK topic	Subtopic	Study ID
Population PK analyses	Healthy subjects	None
	Target population	None
	Other	None

DDI: drug-drug interaction; † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

Evaluator's conclusions on pharmacokinetics

Velphoro works by binding phosphate in the GI tract and thus the serum concentration is not relevant for its efficacy. Given the insolubility and degradation characteristics of PA21, and the minimal absorption of the active moiety, iron(III)-oxyhydroxide, no classical PK studies can be carried out, for example, determination of the distribution volume, area under the curve, or mean residence time. No formal food interaction studies with PA21 were performed.

Nonclinical studies have shown that very little iron is released from PA21 in simulated GI conditions representative of the fed state and maximum release of iron (approximately 6%) has been shown to occur at pH < 2. In humans, pH levels < 2 in the GI tract are normally observed in an empty stomach, that is, in a fasting state, but PA21 has to be taken with food and the proposed PI and Consumer Medicine Information (CMI) has adequate instructions to ensure it is administered with food. Hence, the lack of conventional bioavailability, bioavailability versus oral solution, and food effect studies is justified.

Systemic absorption of iron was estimated based upon blood volume and the concentration of radioactivity in blood. Hence, the Phase I clinical programme, therefore, focussed on measures for phosphate-binding capacity, iron release and absorption, and drug-drug interactions (DDIs).

The iron uptake from radiolabelled Velphoro drug substance, 2,000 mg in 1 day, was investigated in 16 patients with CKD (8 pre-dialysis and 8 haemodialysis patients) and 8 healthy volunteers with low iron stores (serum ferritin < 100 µg/L) in the open-label Absorption, Distribution, Metabolism, Excretion (ADME) Study Q-24120. In healthy subjects, the median uptake of radiolabelled iron in the blood was 0.43% on Day 21. In CKD patients the median uptake was 0.04% on Day 21, which was approximately 10 times lower than in the healthy volunteers. Hence, subjects on haemodialysis had a maximum uptake of 0.04% of iron from PA21 which would equate to absorption of 1.2 mg iron/day (approximately 36 mg/month), following administration of the maximum proposed daily clinical dose of 3,000 mg. The potential amount of iron absorption from PA21 should be considered in the context that high levels of hepcidin in CKD patients (especially with ESRD) act to block iron uptake and almost all CKD patients undergoing dialysis are iron deficient and are receiving regular iron replacement treatment intravenously[34].

In the Phase III Studies PA-CL-05A/05B, iron storage parameters, liver function tests, and haematological laboratory parameters were routinely monitored over 52 weeks of treatment with PA21 or sevelamer, and analysed post-hoc according to concomitant IV iron use. Results from the Phase III studies provide support for the absorption of a small amount of iron from PA21, as seen in Study Q-24120. Thus, the risk that uptake of iron

[34] Among iron treated patients in the US between August 2010 and July 2011, the median prescribed dose of IV iron was approximately 190 mg/month with 13 to 18% of patients typically prescribed at least 500 mg IV iron/month. This equates to a daily systemic requirement of up to 6 mg iron.

from PA21 should lead to iron overload during long term treatment can be considered as low.

Results of human DDI studies have shown that despite the results of the in vitro studies, in vivo interactions in humans were not observed. The human DDI studies showed that PA21 did not affect the AUCs of losartan, furosemide, omeprazole, digoxin or warfarin when given concomitantly or 2 hours prior; the ratios of all AUCs fell within the pre-defined bioequivalence range (80 to 125%). Although the Cmax ratios fell outside the bioequivalence range for losartan, furosemide, and omeprazole when these drugs were co-administered with PA21 and food, the results were consistent with known food effects on the PK of these drugs. Furthermore, for losartan, the Cmax ratios of the active metabolite (EXP 3174) were well within the bioequivalence range. Although it is possible the reduction in Cmax may not be entirely explained by a food effect for furosemide and omeprazole, all AUC geometric mean ratios comparing the concomitant administration of PA21 with these drugs fell within the bioequivalence range. As the clinical effects of these drugs are more dependent on the overall extent of exposure (that is, as measured by AUCs), any potential reduction of the Cmax of these drugs by PA21 would not be clinically significant.

The clinical data from these studies support the proposed dosing regimen of PA21 being taken with food, which maximises the absorption of phosphate from the diet, and minimises iron release from PA21, thus reducing the potential for iron absorption and potential iron overload.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 8 shows the studies relating to each PD topic.

Table 8: Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID
Primary pharmacology	Effect on serum phosphorous levels & iron absorption	Q241240
	Effect on serum phosphorous levels	VIT-C1-01/2
	Japanese Phase 1 safety/ tolerability and PDs	PA1101
Secondary pharmacology	Effect on vitamins A,D,E and K	VIT-C1-01/2
Gender other genetic and age related differences in PD response		None
PD interactions	Post hoc analysis to evaluate effect of PA21 on lipid lowering drugs.	Post hoc analysis of data from PA-CL-05A/ 05B.

PD Topic	Subtopic	Study ID
Population PD and PK-PD analyses	Healthy subjects	None
	Target population	None

None of the PD studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacodynamics

Primary pharmacodynamic effects

Despite the short term treatment (7 days) with PA21 in Study Q-24120, a tendency for a reduction in serum phosphorus levels could be seen. Decreases in serum phosphorus were larger for CKD pre-dialysis patients (-0.34 mmol/L) and CKD patients on dialysis (-0.60 mmol/L) than for the healthy volunteers (-0.08 mmol/L). The percent changes from baseline in serum phosphorus were -24.3% and -21.1% in pre-dialysis and dialysis patients, respectively. In Study VIT-CI-01/2, which included 57 healthy volunteers, no remarkable or statistically significant differences in serum phosphorus concentrations were observed between active treatment groups and placebo groups after 8 days of PA21 treatment at dose levels ranging from 3.75 g/day to 12.5 g/day. Similarly, in Study PA1101 (Japanese study) which included 30 healthy Japanese male volunteers, there were no changes in serum phosphorus, The lack of clinically significant findings in Studies Q-24120 and PA1101 was not unexpected as they were performed in healthy volunteers whose normal homeostatic mechanisms would have been activated to prevent marked changes in serum or urinary phosphorus levels.

In Study Q24120, the reduction in serum phosphorous was observed within 1 week after start of dosing, with similar results observed in the Phase II and III studies (PA-CL-03A, PA-CL-05A).

Secondary Pharmacodynamic effects

In the Phase I Study VIT-CI-01/02 involving 57 healthy subjects, administration of ascending single and multiple doses of PA21 did not have any consistent or clinically relevant effects on serum vitamins (A, D, E and K), calcium metabolism, or iron parameters. However, interpretation was limited due to the short treatment period.

In the combined PA-CL-05A/05B Studies, decreases in mean low density lipoprotein cholesterol (LDL-C) and mean total cholesterol (Total-C) were observed in the sevelamer treatment group, consistent with the known lipid-lowering effect of sevelamer[35]. This PD effect was observed after 4 weeks of treatment and was maintained for the duration of Studies PA-CL-05A/05B. No similar PD effect on LDL-C and Total-C was observed in the PA21 treatment group. In the post-hoc analyses of lipid levels (LDL-C, Total-C, and triglycerides) in Studies PA-CL-05A/05B, no clinically relevant results in patients were observed when PA21 treated subjects were co-administered atorvastatin, simvastatin or other statins. Although adsorption/binding with PA21 was shown in the in vitro studies, these drugs can be co-administered with PA21 without any specific recommendations regarding the timing of administration or dose adjustments. However, when administering any medicinal product that is known to interact with iron, the medicinal product should be administered at least 1 hour before or 2 hours after PA21.

[35] Chertow GM, Burke SK, Dillon MA, Slatopolsky E; RenaGel Study Group. Long-term effects of sevelamer hydrochloride on the calcium x phosphate product and lipid profile of haemodialysis patients. *Nephrol Dial Transplant*. 1999;14:2907-2914.

The PD section of the proposed PI is an accurate representation of the data presented in this submission.

Dosage selection for the pivotal studies

Two studies were considered:

- **Phase II Study PA-CL-03A**

PA-CL-03A was a Phase II, parallel group, randomised, open label, active controlled, multicentre, dose ranging study. The primary objective was to investigate the ability of different doses of PA21 to lower serum phosphorus levels in patients with CKD on maintenance haemodialysis. This 9 week study compared 5 dosage regimens of PA21 with a single dosage regimen of sevelamer HCl. The doses of PA21 were as follows:

- Group 1: A daily dose of 1.25 g PA21 was taken with the largest meal of the day.
- Group 2: A daily dose of 5.0 g PA21 (of the 4 tablets, 2 tablets were taken with the largest meal of the day and 1 tablet each with the 2 smaller meals of the day).
- Group 3: A daily dose of 7.5 g PA21: Of the 6 tablets, 2 tablets were taken with each meal of the day.
- Group 4: A daily dose of 10.0 g PA21 was taken: Of the 8 tablets, 4 tablets were taken with the largest meal of the day and 2 tablets each with the 2 smaller meals of the day.
- Group 5: A daily dose of 12.5 g PA21 was taken: Of the 10 tablets, 4 tablets were taken with the largest meal of the day and 3 tablets each with the 2 smaller meals of the day.

> **Evaluator's comments**: There was an active control group receiving sevelamer HCl, but no formal statistical analyses were done to show non-inferiority or equivalence between PA21 and sevelamer in this Phase II dose finding study. The primary endpoint for the efficacy analysis of this study was the decrease in serum phosphorus levels, and for all PA21 groups except the lowest dose group there was a statistically significant decrease in this measure. The decrease was comparable to that observed with the active control sevelamer HCl. The decrease for PA21 was of rapid onset, appeared to be dose-dependent, and the relationship of the decrease to the administration of PA21 was clearly seen by the rapid reversal of the effect on stopping treatment. Control of serum phosphorus levels, to the levels defined by the KDQOI, was also good during treatment.

- **Phase II dose ranging Study PA1201**

PA1201 was a Japanese, Phase II, dose ranging study in 183 haemodialysis patients with hyperphosphataemia. The study was conducted at 14 centres in Japan. The main objective was to investigate dose-response efficacy and safety, when PA21 was orally administering at single doses of 1.25, 2.5, 3.75 or 5 g, 3 times daily immediately prior to meals for 6 weeks.

> **Comments**: The use of placebo control in this Japanese study was not appropriate considering the fact that unblinding would have taken place due to discolouration of stools observed in subjects taking PA21 (due to its iron content). However, this is not likely to affect efficacy results of this study as the endpoints are objective. Results from this study provide some supportive evidence for dose-dependent reduction in serum phosphorous in the dose range evaluated in this study (3.75 g/day to 15 g/day).

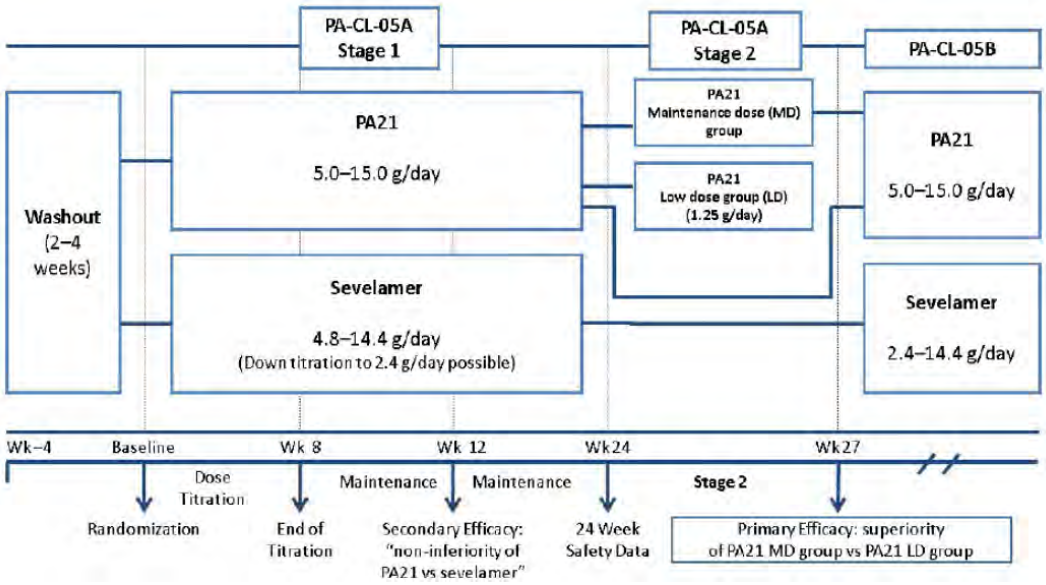
Efficacy

Studies providing efficacy data

- **Pivotal efficacy Study PA-CL-05A**

PA-CL-05A was an open-label, randomised, active-controlled, parallel group, multicentre, Phase III study to investigate the safety and efficacy of PA21 compared with sevelamer carbonate, followed by a randomised comparison of PA21 maintenance dose versus PA21 low dose in 1059 dialysis patients with hyperphosphataemia. The study design is summarised in Figure 2:

Figure 2: Pivotal study PA-CL-05A design



The study investigational treatments (summarised in Table 9) included PA21 chewable tablets containing 2.5 g PA21 (doses ranged from 5.0 to 15.0 g/day) and PA21 chewable tablets containing 1.25 g PA21 (dose was 1.25 g/day) and the active control treatment was sevelamer carbonate: Renvela tablets containing 800 mg of sevelamer carbonate (doses ranged from 2.4 to 14.4 g/day).

Table 9: Summary of study treatment doses administered

Treatment Period	Treatment Arm	Starting Dose	Minimum Dose	Maximum Dose
Stage 1	PA21-2	5.0 g/day	5.0 g/day	15.0 g/day
	Sevelamer	4.8 g/day	2.4 g/day	14.4 g/day
Stage 2	PA21-2 MD	Stage 1 ending dose	Fixed	Fixed
	PA21-1 LD	1.25 g/day	Fixed	Fixed

Notes: LD = Low dose; MD = Maintenance dose.

The primary efficacy objective was to establish the superiority of PA21 maintenance dose versus PA21 low dose control in maintaining the phosphorus lowering effect in patients undergoing haemodialysis, by comparing the change in serum phosphorus levels during a 3-week period (Stage 2) that follows 24 weeks of PA21 treatment. The secondary objectives were to establish the non-inferiority (with possible assessment of superiority) of PA21 versus sevelamer carbonate (sevelamer) in lowering serum phosphorus in patients on dialysis after 12 weeks of treatment; Assess quality of life; compare safety and tolerability of PA21 versus sevelamer.

- **Other efficacy Study PA-CL-05B**

PA-CL-05B was a Phase III, parallel group, randomised, open label, active controlled, multicentre, long term extension study evaluating PA21 in comparison with sevelamer. Subjects that completed treatment in PA-CL-05A (including those completing Stage 2 on maintenance dose[36]) and met all eligibility criteria were enrolled in this 28 week extension study. Enrolled subjects in PA-CL-05B continued to receive either PA21 or sevelamer according to their randomisation into PA-CL-05A. Subjects were treated for an additional 28 weeks in PA-CL-05B (for a total of 52 to 55 weeks of treatment).

The primary objective was to assess the long term safety and tolerability of PA21; the secondary objectives were to compare the long term serum phosphorus control (efficacy) and the safety/tolerability of PA21 versus sevelamer.

- **Pooled analyses performed across trials**

An integrated analysis of Studies PA-CL-05A and PA-CL-05B (pooled data) was provided.

Evaluator's conclusions on efficacy

Efficacy for the control of serum phosphorus levels in patients with end stage renal disease

The dosing recommendations for Velphoro are based on the active iron content of the tablet. The proposed Velphoro chewable tablet contains 500 mg iron (equivalent to 2,500 mg sucroferric oxyhydroxide). However, in some of the clinical studies a lower strength tablet containing 250 mg iron (equivalent to 1250 mg sucroferric oxyhydroxide) was used and hence the following Table has been provided to clarify the conversion between the component and parent for each strength of Velphoro tablets used in the clinical studies.

Table 10: Component and parent strengths for Velphoro tablets used in clinical studies

Velphoro tablet	Sucroferric oxyhydroxide (PA21) content	Iron content
1.25 g or 1250 mg tablet	1250 mg	250 mg
2.5 g or 2500 mg tablet	2500 mg	500 mg

The main evidence for efficacy of PA21 for reduction of serum phosphorous was provided by the Phase II Study PA-CL-03A (see section on *Dosage selection for the pivotal studies*, above) and the Phase III Studies PA-CL-05A and PA-CL-05B. These studies were conducted using parallel groups with central randomisation to avoid selection bias.

An open label design was used because of challenges in maintaining blinding[37] of study treatment and it did not bias the primary efficacy endpoint of serum phosphorus because this is an objective laboratory measurement which was analysed by a central laboratory. Studies 05A/05B included a sevelamer carbonate group to assess assay sensitivity and to provide an active control group for comparability of efficacy and tolerability. The patient

[36] Subjects randomised to the PA21 low dose group of the Stage 2 primary efficacy assessment of Protocol PA–CL-05A were excluded from this extension study.
[37] There were differences in the modes of administration of the 2 study treatments: PA21 tablets are chewed and then swallowed whereas sevelamer HCl tablets are swallowed whole. Discolouration of faeces occurs with PA21, as expected because of its iron content, but not with sevelamer HCl.

population in Studies PA-CL-03A and PA-CL-05A was representative of the target patient population for PA21 with the majority on haemodialysis (92%). Most of the exclusion criteria were reflected in the *Contraindications/Precautions* section of the proposed PI.

The primary efficacy endpoint (change from baseline in serum phosphorus at the end of treatment) was selected as the most accurate and objective measure to determine the direct effect of PA21. This endpoint is typically used in studies of phosphate binders and is accepted by regulatory agencies. Secondary endpoints were selected to provide a more comprehensive benefit-risk profile of PA21, based on studies of other phosphate binders, and the guidelines of the KDOQI. These included proportions of subjects achieving controlled serum phosphorus levels at various time points, as defined in the KDOQI guidelines, and the safety-specific measures of phosphorus, calcium and intact parathyroid hormone (iPTH) at various time points, as high or low levels of these parameters are critical risks for this patient population.

Results of the Phase II, dose ranging Study PA-CL-03 involving 154 CKD patients on haemodialysis showed that the 1.25 g/day dose was ineffective. All PA21 treatment groups > 5.0 g/day, and the sevelamer HCl 4.8 g/day group showed a statistically significant reduction in serum phosphorus levels from baseline to end of treatment in both the full analysis set (FAS) and per-protocol set (PPS) ($p < 0.016$).

The largest mean changes from baseline were seen in the PA21 10.0 g/day group [-0.64 mmol/L (-2.00 mg/dL)] and the PA21 12.5 g/day group [-0.55 mmol/L (-1.69 mg/dL)]; the change from baseline in the sevelamer HCl group (-0.341mmol/L) was similar to that observed with PA21 5.0 mg/day (-0.348 mmol/L). Control of serum phosphorus levels, to the levels defined by the KDQOI was good: observed in 21.1%, 41.2%, 35%, 42.9%, 60% and 42.1% in the PA21 1.25 g/day, 5.0 g/day, 7.5 g/day, 10 g/day, 12.5 g/day and sevelamer 4.5g/day groups, respectively.

Although this Phase II dose finding study had an active control group receiving sevelamer HCl, no formal statistical analyses were done to show non-inferiority or equivalence. The decrease for PA21 was of rapid onset, appeared to be dose dependent, and the relationship of the decrease to the administration of PA21 was clearly seen by the rapid reversal of the effect on stopping treatment.

The main evidence for efficacy of PA21 was provided by the pivotal, Phase III Study PA-CL-05A and its 28 week extension (PA-CL-05B) involving 1059 patients with CKD on dialysis (subjects enrolled in these studies were representative of the target patient population for PA21. PA21 and sevelamer treatment groups were generally well matched according to baseline demographics and disease characteristics for the PA-CL-05A analyses, the integrated PA-CL-05A/PA-CL-05B analyses, and the PA-CL-05B analyses.

The PA-CL-05A primary efficacy in Stage 2 demonstrated the superiority of PA21 maintenance dose over the low dose control ($p < 0.001$; Analysis of Covariance-Last Observation Carried Forward (ANCOVA-LOCF)). The PA-CL-05A key secondary analysis in Stage 1 established the non-inferiority of PA21 versus sevelamer in reducing serum phosphorus levels in subjects on haemodialysis and peritoneal dialysis after 12 weeks of treatment. Notwithstanding the lack of adequate placebo controlled data with sevelamer, there is a slight chance that the non-inferiority margin chosen will not be able to demonstrate that the effect of size seen with PA21 will be significantly greater than zero (or placebo); however, this may have been partly addressed by the demonstration of superiority of the PA21 maintenance dose group versus the non-effective low dose control group which essentially functions as a placebo control group. It is conventional, however, to state confidence intervals (CIs) with 95%, not 97.5% boundaries and the sponsors have not justified use of the 97.5% one-sided CI for defining the non-inferiority margin between PA21 and sevelamer. This is especially relevant considering the fact that at 12 Weeks, sevelamer was actually found to be superior to PA21 in terms of reduction in serum

phosphorous levels. This question has been raised in the section on *Clinical questions*, below.

The proposed starting dose of PA21 is 1,500 mg/day (3 tablets/day) with meals, but the starting dose evaluated in the pivotal Phase III study was 1000 mg/day (2 tablets/day). The selection of 1,500 mg/day as the starting dose is based on the clinical data from Studies PA-CL-03A and PA-CL-05A. In the Phase II dose ranging studies, 61 subjects received a starting dose of 1,500 mg/day, and were maintained at this dose for 6 weeks. In the Phase III trials, a total of 610 subjects (86.3%) were exposed to at least 1,500 mg/day for an average duration of 223.7 days. The number of exposures at the intended starting dose is in line with the ICH Guideline CHMP/ICH/375/95 (ICH Topic E 1. *Note for Guidance on Population Exposure: The Extent of Population Exposure to Assess Clinical Safety*) recommendation which considers 300-600 subjects as adequate for an assessment of common adverse events (AEs). In the dose-finding Study PA-CL-03A, PA21 doses of 1,000 mg/day and 1,500 mg/day were shown to be comparable in efficacy to an approved starting dose of sevelamer (4.8 g/day). Similarly, in PA-CL-05A, most subjects (82.8%) were up-titrated to 1,500 mg/day (or above) by Week 8, suggesting that the 1,000 mg/day starting dose is insufficient for the majority of subjects.

Very few dose dependent or dose limiting AEs were observed with PA21 in the 2 pivotal studies. In the fixed dose studies, Study PA-CL-03A and the supporting Study PA1201, the incidence of GI treatment emergent adverse events (TEAEs) at the proposed starting dose of 1,500 mg/day was similar to those at the lower doses. In Study PA1201, the frequency of GI TEAEs increased substantially at starting doses above 1,500 mg/day. It is therefore reasonable to recommend a starting dose of 1,500 mg/day, as more than 50% of subjects would be expected to be controlled, with no increase in the incidence of GI TEAEs when compared with lower doses. For PA21, a starting dose of 1,500 mg/day equates to 3 tablets per day instead of 2 tablets per day with a dose of 1,000 mg/day. Three tablets per day would allow more flexibility and better distribution of drug administration during the day, thus ensuring that PA21 tablet is consumed with meals.

As shown in both pivotal studies, 1,000 mg/day PA21 was also effective for some subjects. Therefore, the dose of PA21 may be decreased or increased by 500 mg (1 tablet) per day every 2 to 4 weeks, to a minimum of 1,000 mg/day and a maximum of 3,000 mg/day based on serum phosphorus level. As the serum phosphorus lowering effect of PA21 is rapid, it is also reasonable that dose titration can be started as early as 1-2 weeks after initiation of treatment or after any dose change.

The efficacy of PA21 was achieved with a lower pill burden compared with sevelamer. The mean pill burden was (PA21 versus sevelamer) 2.8 versus 7.6 tablets/day during the titration period (Week 0 to Week 12) and 3.6 versus 8.7 tablets/day during the maintenance period (Week 12 to Week 24). Serum phosphorus levels declined rapidly in both treatment groups during the first few weeks, but the reduction was significantly greater with sevelamer compared to PA21 for the first 12 weeks and became similar thereafter.

Results of the responder analyses based on the KDOQI and KDIGO target ranges supported the key secondary efficacy results. The median time for subjects to achieve control based on KDOQI was 23.0 days with PA21 and 18.6 days with sevelamer ($p \leq 0.005$) however, the difference of the few days was not clinically relevant. No significant difference between treatment groups and no change over time was observed for serum total calcium. Changes in serum calcium-phosphorus product are reflective of the changes in serum phosphorus. Serum iPTH decreased over time in both treatment groups, but there were no statistically significant differences between treatment groups. Scores for patient preference, patient satisfaction, and quality of life were similar for subjects treated with PA21 and sevelamer. There were no medically relevant changes observed in dietary habits or dialysis parameters and no differences were seen between treatment groups.

PA21 efficacy results were shown to be robust. PA21 was equally efficacious across all subgroups evaluated (dialysis status, region, sex, age, race, ethnicity, and prior sevelamer use) and no interactions were demonstrated with baseline demographic or disease characteristics (region, dialysis status, sex, age, race, ethnicity, reason for ESRD, time to first dialysis, number of previous phosphate binder, and prior use of sevelamer).

Long term efficacy

In PA-CL-05B, the efficacy of PA21 was maintained over an additional 28 weeks (52 to 55 weeks total), and was comparable to sevelamer. Throughout the PA-CL-05B extension study, serum phosphorus levels remained similar to levels achieved at the end of PA-CL-05A (PA21 versus sevelamer: 1.8 versus 1.7 mmol/L at both Week 24 and Week 27) and there were minimal changes in mean serum phosphorus levels, indicating good control over time by both treatments through the 52 weeks treatment. Control of serum phosphorus based on the KDOQI target was maintained during the additional 28 weeks of treatment as the proportion of subjects that were responders to PA21 and sevelamer did not change significantly over the duration of the study [PA21 versus sevelamer: 53.1% versus 53.6% at Week 24 and 51.9% versus 55.2% at Week 52 in the FAS]. For subjects who completed at least 52 weeks of continuous treatment (completers) the mean reduction in serum phosphorus levels throughout the studies was similar to that observed in the FAS. The proportion of responders among subjects who completed at least 52 weeks of treatment was very similar to the proportion of responders in the FAS. There was no difference between treatment groups and control was maintained in the same proportion of subjects from Week 24 through Week 52.

The long term control of serum phosphorus was achieved with a lower pill burden for PA21 compared with sevelamer; the (mean (median) number of tablets/day over the combined studies (52 weeks duration) was 3.3 (3.1) and 8.7 (8.1), respectively.

Changes in serum total calcium-phosphorus product mirrored changes in serum phosphorus during the PA-CL-05A and PA-CL-05B Studies and did not differ between treatment groups for subjects in the FAS. There was significant variability in serum iPTH levels among subjects in both treatment groups throughout treatment over 52 weeks, but there were no clinically relevant mean changes from baseline in iPTH at Week 52 and no difference between treatment groups in the FAS. Dietary habits and dialysis parameters generally remained unchanged in both treatment groups and no medically relevant difference between groups were observed. The efficacy of PA21 in lowering and maintaining serum phosphorus in PA-CL-05B was consistent across all subgroups and was not affected by regions, sex, age, race, and dialysis status.

Supportive evidence of efficacy of PA21 was provided by the Japanese Study PA1201 involving 146 adult CKD patients on dialysis who received PA21 for up to 6 weeks.

Safety

Studies providing evaluable safety data

The following studies provided evaluable safety data:

- 7 Phase I studies,
- a single pivotal Phase II dose ranging study (PA-CL-03A), and
- a pivotal Phase III efficacy and safety study with a long-term safety extension (PA-CL-05A and PA-CL-05B).

Two Japanese studies (Phase I Study PA1101 and Phase II Study PA1201) have been completed by Kissei Pharmaceutical Co. Ltd. as part of a strategic partnership; however,

only translations of the study synopsis were provided in the submitted dossier (CSRs not provided).

Pooled analysis of the Studies PA-CL-03A and PA-CL-05A/05B was not done because of the differences in their study designs: that is, fixed dose versus dose titration, 6 week versus 12 month treatment duration, and imbalance in study sizes and randomisation ratios. Furthermore, incidences of TEAEs were mostly lower in the short term PA-CL-03A Study and pooling the data would lead to a dilution of the true incidence of TEAEs which is best represented in the long-term PA-CL-5A/05B Studies.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 13.1 and summarised by system organ class (SOC) and preferred term (PT). Summary statistics were provided for the incidence and prevalence of the TEAE for the safety set (SS) and SS5B. Serious adverse events (SAE), SAEs that led to death, and TEAEs or SAEs that led to withdrawal were also summarised and listed. Changes in laboratory values, vital signs, physical examinations results, and electrocardiogram (ECG) parameters were also summarised for the SS by treatment group using descriptive statistics and/or shift tables. Changes in laboratory values for iron parameters were also summarised for completers. The proportions of subjects with new or re-occurring incidents of hypo/hyperphosphataemia, hypo/hypercalcaemia, and hyperparathyroidism were summarised.

Patient exposure

The number of subjects who received at least 1 dose of study medication in the Vifor Pharma clinical program is summarised in Table 11.

Table 11: Number of subjects in the Vifor Pharma PA21 Clinical program

Study Number	Placebo n	PA21 n	Sevelamer n	Other[1] n
Completed Phase 1 (Clinical Pharmacology)				
VIT-CI-01/2	14	43	0	0
Q-24120	0	24	0	0
PA-DDI-001[2]	0	41	0	41
PA-DDI-002[2]	0	41	0	41
PA-DDI-003[2]	0	43	0	43
PA-DDI-004[2]	0	42	0	42
PA-DDI-005[2]	0	43	0	43
Completed Phase 2 and 3				
PA-CL-03A	0	128	26[3]	0
PA-CL-05A	0	707	348[4]	0
PA-CL-05B[5]	0	391[5]	267[5]	0
Overall Total[5]	14	1,112	374	210

1 Other includes digoxin, furosemide, losartan, omeprazole, warfarin.
2 Cross-over studies in which subjects received PA21 in more than 1 period of the study – each subject is counted only once.
3 Subjects received sevelamer hydrochloride (Renagel®).
4 Subjects received sevelamer carbonate (Renvela®).
5 Subjects in Study PA-CL-05B are not unique patients, as all were previously included in Study PA-CL-05A.
Notes: Subjects received PA21 outside the Vifor Pharma clinical programme: In Study PA1101, 24 subjects received PA21; in Study PA1201, 146 subjects (safety set) received PA21 and are not included in this table.

Safety issues with the potential for major regulatory impact

Liver toxicity

The liver is seen as a potential target organ for toxicity for many drugs, particularly those that may affect iron metabolism, in view of its sensitivity to iron toxicity. Alkaline phosphatase showed modest but sustained rises during treatment, more so with sevelamer than with PA21. In the absence of any changes in the other liver enzyme parameters, these clinically marginal changes are more likely to be due to increases in BAP, and are not an indication of changes in hepatic function.

Haematological toxicity

No clinically relevant changes were observed in haematological parameters.

Serious skin reactions

None.

Cardiovascular safety

Serious cardiac ischaemic events are not unexpected in patients with CKD undergoing dialysis, as many have significant comorbidities as risk factors. Although the clinical study protocols for pivotal studies stated that subjects with unstable angina, unstable hypertension (in the investigator's opinion in PA-CL-05A/05B Studies) or moderate to severe arrhythmic disorders (in PA-CL-03A Study) were to be excluded, many subjects with a medical history of cardiac or cardiovascular disorders were included in those clinical trials. In the Phase II Study PA-CL-03A, approximately 44% of subjects (PA21: 45.3%; sevelamer 38.5%) had a prior history of cardiac disorders. These included a variety of cardiac conditions such as coronary artery disease including previous myocardial infarctions, cardiac failure, cardiomyopathies, and various valvular and arrhythmic disorders. Furthermore, 75.8% of the PA21 treated subjects and 69.2% of the sevelamer treated subjects had pre-existing hypertension, a common CVD causing ESRD.

In the PA-CL-05A/05B Studies, 53.3% of subjects (PA21: 54.9%; sevelamer: 50.0%) had prior history of cardiac disorders. As seen in the PA-CL-03A Study, similar significant cardiac diseases were included, such as coronary artery disease, myocardial infarction, cardiomyopathies, and valvular and arrhythmic disorders. Pre-existing hypertension existed in 86.7% of PA-CL-05A/05B Study subjects (PA21: 86.6%; sevelamer: 87.1%).

Based on the number of subjects who had been treated with PA21 in the pivotal trials, there is adequate information available for adult CKD patients on haemodialysis or peritoneal dialysis with cardiac impairment as a representative number of randomised patients had documented a medical history of cardiac and cardiovascular disorders.

In pivotal Study PA-CL-05A, there was one serious TEAE of myocardial infarction and one cardiac arrest in the same subject in the PA21 group, events which led to withdrawal from the study and death. There were no reported cardiac ischaemic events with sevelamer in the study. Acute cardiac ischaemic events occurred in 27 subjects (3.8%) in the PA21 group and 9 subjects (2.6%) in the sevelamer group. No acute cardiac ischaemic events were considered related to treatment. Overall, the acute cardiac ischaemic events were serious in 26 subjects (2.5%) and led to withdrawal in 5 subjects (0.7%). Acute cardiac ischaemic events were fatal in 4 subjects: 3 in the PA21 group and 1 in the sevelamer group.

Unwanted immunological events

Four cases of potential immunological reactions have been reported following administration of PA21. A review of case narratives suggestive of hypersensitivity reactions to PA21 has been performed on the four subjects and all of these TEAEs were considered (and re-confirmed) as unrelated to study treatment by the Investigator. The

majority of these events resolved on the same day they started. None of the events caused temporary interruption or permanent withdrawal of study treatment, as in all these cases, the PA21 dose was maintained or increased. All subjects had a good or plausible medical explanation for their TEAEs[38].

Postmarketing data

None.

Evaluator's conclusions on safety

Evaluator's overall conclusions on clinical safety

A total of 1,500 subjects participated in the 10 completed studies and of these, 1,112 received PA21 (210 of whom also received a comparator as part of the DDI studies), 374 received sevelamer, and 14 received placebo. The Phase II and III safety population comprised 1,209 subjects, of whom 835 received PA21 and 374 received sevelamer. Overall, majority of the subjects (healthy volunteers and patients) were < 65 years of age, but the studies in patients with ESRD, included subjects > 65 and > 75 years of age, which is broadly representative of the dialysis patient population. The demographic and baseline characteristics were similar between treatment groups in the PA-CL-05A/05B combined studies. There were slightly more male (58.1%) versus female (41.9%) subjects, and subjects were predominantly White (77.0%). The dialysis modality was comparable between treatment groups with 91.8% subjects on haemodialysis and 8.2% subjects on peritoneal dialysis.

In the Phase III studies (Studies PA-CL-05A/05B combined), duration of exposure to treatment was similar between treatment groups: exposure to PA21 ranged from 1 to 420 days. Duration of exposure to PA21 was at least 24 weeks in 513 (72.6%) subjects, and 319 (45.1%) subjects completed 52 weeks of treatment, exceeding the extent of exposure for the ICH E1 guidance[39]. A total of 610 subjects (86.3%) were exposed to >7.5 g/day (the proposed starting dose for PA21) for an average duration of 223.7 days. In addition, a further 61 subjects received 7.5 g/day for 6 weeks in the Phase 2 dose-ranging studies. Treatment compliance was high (> 85%) and similar in both treatment groups.

The most common TEAEs observed with PA21 occurred in the Gastrointestinal and Metabolism and Nutritional Disorders system organ classes (SOCs). Discoloured faeces, resulting from the iron content of the product, was commonly reported with PA21 but was not dose related. These events were generally mild, non-serious, did not lead to treatment withdrawal, and were observed early after the initiation of PA21 treatment. Diarrhoea was also a common TEAE which occurred early after initiation of PA21 treatment, being reported by 23.6% of subjects in the Phase III studies (Studies PA-CL-05A/05B combined) compared to 11.5% in the comparator group. In most subjects, diarrhoea events were mild in severity, and resolved with continued use of PA21. Diarrhoea was rarely dose or treatment limiting, as few diarrhoea events led to dose changes or withdrawal from treatment. Reporting of diarrhoea in the PA21 group was substantially lower in the safety extension study PA-CL-05B, providing further support for the early onset and transient nature of these events. The incidence of diarrhoea and other GI AEs reported for sevelamer in Study PA-CL-05A/05B was surprisingly low, and contrasts with the incidence seen in previously reported studies with sevelamer (Renagel PI). This may also be at least

[38] one subject had a medical history of allergies to several drugs, another subject's TEAE was confirmed by the Investigator to be due to an antibiotic sensitivity, another subject had a chronic history of itching, and for the last subject, the TEAE was attributed to seasonal allergies.
[39] ICH Topic E 1. Note for Guidance on Population Exposure: The Extent of Population Exposure to Assess Clinical Safety.

partly due to approximately 38.0% of subjects having been treated with sevelamer before entering the study, thereby creating a certain selection bias.

In the Metabolism and Nutritional Disorders SOC, hyperphosphataemia, hypophosphataemia, and hypercalcaemia were common (particularly in the Phase II dose ranging studies where a fixed dose of PA21 was employed with no opportunity to alter doses). These events are expected bearing in mind the intended action of the drug and the disease under investigation and, in the Phase III studies, were reported with similar frequencies in the PA21 treated subjects compared to the sevelamer treated subjects. Other common TEAEs included nausea, constipation, vomiting, dyspepsia and abdominal pain, flatulence, tooth discolouration, and product taste abnormal.

Constipation is a concern in CKD patients on dialysis and is also commonly reported with the use of oral iron medications. The incidence of constipation with PA21 was low, at 5.1% over 52 weeks in Study PA-CL-05A/05B (compared with 8.3% in the sevelamer group) and the majority of reported events were mild in severity. With the exception of common GI events of faeces discolouration and diarrhoea, the overall AE profile of PA21 was broadly similar to sevelamer, and consistent with the background disease.

In Studies PA-CL-05A/05B combined, over 1 year, there were a relatively high number of withdrawals from both treatment groups (48.2% of the subjects receiving PA21 compared to 35.0% of subjects receiving sevelamer) and the main reasons for withdrawal were inadequate treatment effect and TEAEs.

Overall there were 21 deaths in subjects treated with PA21 during the Phase II and III studies, none of which were considered related to treatment. In keeping with the ESRD population, most of the deaths involved cardiac or cardiorespiratory events, and the overall death rate was similar to sevelamer, and consistent with background incidence in this population. Very few serious TEAEs were attributed to treatment, and those which were, were exclusively in the Gastrointestinal Disorders SOC.

No safety signals were detected with respect to clinical chemistry, haematological, or vitamin levels. No changes in ECG parameters or vital signs were seen. No changes in bone markers were apparent in Study PA-CL-03A. In Study PA-CL-05A/05B, there were significant decreases in fibroblast growth factor 23 (FGF-23) in both treatment groups, with no significant difference between treatment groups. There were also significant increases in bone-specific alkaline phosphatase (BAP) in both treatment groups, but there was a significantly higher increase in the sevelamer group. However, given that serum iPTH, calcium, Vitamin D and 1,25-hydroxy Vitamin D levels remained relatively stable, the small changes in BAP which occurred concurrently with the control of serum phosphorus levels during long-term treatment with PA21 are not considered to be clinically relevant.

Bicarbonate levels (which, if decreasing, could indicate the onset of metabolic acidosis, a problem that has been reported with sevelamer HCl) remained basically unchanged with the introduction of PA21 treatment. In these studies, reduction in bicarbonate levels was not observed in the sevelamer treated group. Serum lipid levels showed no significant changes during treatment with PA21, although, consistent with previous reports, sevelamer did show modest reductions in Total-C and LDL-C levels.

Throughout the studies, a high incidence of anaemia was seen, as would be expected in this population, and this is reflected in the number of subjects receiving concomitant treatment with IV iron and erythropoiesis stimulating agent. The lack of relative change associated with study treatment allocation and the low level of AEs relating to haematology parameters support the conclusion that PA21 has no adverse effect on haematology parameters during early or longer term exposure. There was no indication that PA21 had any demonstrable effect on coagulation at the population level, as measured by mean activated partial thromboplastin time and prothrombin time, low incidence of

coagulation parameter-related AEs, and the absence of consistent patterns of change in the shift tables.

Subjects with ESRD generally have low iron stores, and most subjects receive regular IV iron administration to achieve an iron uptake of approximately 5 to 7 mg per day. In Study Q-24120, subjects on haemodialysis had a median uptake of 0.02% of iron from PA21. This would equate to absorption of 0.6 mg iron/day following administration of the maximum proposed daily clinical dose of 15.0 g/day PA21, and an iron content of 20% m/m. Consequently, the risk that uptake of iron from PA21 should lead to iron overload during long term treatment can be considered low.

The iron status of the subjects enrolled in these studies, with relatively high ferritin and relatively low transferrin saturation (TSAT), is in line with their underlying ESRD and the widespread use of iron supplementation. The use of an iron-based phosphorus binder could, theoretically, adversely affect that status through iron overload. Data from the radiolabelled iron absorption study indicated that absorption was minimal in volunteers (0.16% to 1.25%) and ESRD subjects on dialysis (0% to 0.44%). The data generated in the clinical studies support the minimal iron absorption from PA21 and indicate that it has no adverse effect on iron status parameters during early or longer term exposure. Furthermore there was no evidence of any adverse effect upon a primary target organ for toxicity in the event of iron accumulation, the liver.

There were few changes in physical examination findings and no clinically relevant patterns for shifts in findings that would indicate any treatment differences for the systems evaluated. Electrocardiogram changes from baseline were not statistically significant in the PA21 and sevelamer treatment groups, and there were no differences between treatment groups. There is no evidence that PA21 has an effect on QT intervals.

All TEAEs were analysed by the intrinsic factors of sex, age, and race, and by the extrinsic factors of geographic region and dialysis modality. These analyses did not reveal clinically meaningful differences from the overall population for PA21 versus sevelamer.

As PA21 is not absorbed, it is unlikely that there will be significant interaction between PA21 and systemically acting drugs. Specific DDI studies in healthy volunteers and an assessment of concomitant medications in Studies PA–CL–05A/05B combined showed no interaction between PA21 and the typical variety of concomitant medications also taken by subjects with ESRD.

The PA21 clinical development programme has provided a robust safety database. A thorough analysis of all clinical safety data was performed across all studies and included subjects treated with a range of doses for up to 52 weeks. The PA21 safety review has considered the nonclinical findings, as well as the well-known safety characteristics of the phosphate binder class of drugs. Overall, the long term safety profile of PA21, in the proposed clinical dose range of 7.5 g/day to 15.0 g/day, supports its use in patients with ESRD undergoing dialysis.

The safety aspects of the proposed PI are satisfactory.

First round benefit-risk assessment

First round assessment of benefits

The benefits of Velphoro (PA21) in the proposed usage are:

- Lower pill burden when compared to currently available phosphate binders such as sevelamer.

- PA21 has demonstrated superiority over the non-effective (PA21 low dose) dose, both in initially lowering, and then maintaining, serum phosphorus levels.
- The efficacy of PA21 was further demonstrated to be non-inferior to sevelamer in reducing serum phosphorus levels in subjects on haemodialysis and peritoneal dialysis after 12 weeks of treatment.
- Long term maintenance of control of serum phosphorus levels with PA21 treatment for up to 12 months has also been demonstrated.
- The efficacy of PA21 is robust and consistent across all sub-groups (sex, age, race, ethnicity, geographic region, haemodialysis or peritoneal dialysis), and was not affected by other baseline or disease characteristics.
- PA21 was well tolerated at the proposed doses and majority of TEAEs were attributable to the intended pharmacological action of PA21 (such as changes in serum phosphorus levels) or to its physicochemical composition (for example, discoloured faeces). With the exception of higher incidence of common GI events of faeces discolouration and diarrhoea, the overall AE profile of PA21 was broadly similar to sevelamer.

First round assessment of risks

The risks of Velphoro (PA21) in the proposed usage are:

- Increased incidence of GI AEs.
- Higher incidence of TEAEs and withdrawals due to AEs, but these were mainly related to GI AEs such as discoloured faeces and diarrhoea.
- Potential risk of iron overload, although studies did not reveal significant absorption or any adverse effects on the liver.
- Efficacy and safety in combination with other phosphate binders has not been evaluated.
- Lack of evaluation in patients < 18 years of age.

First round assessment of benefit-risk balance

Following oral administration, sucroferric oxyhydroxide adsorbs the dietary phosphate in the GI tract, preventing its uptake into the blood, and thereby reducing the serum level of phosphorous. The phosphoric bound to sucroferric oxyhydroxide is subsequently eliminated in the faeces. Sucroferric oxyhydroxide is stable in the GI tract yielding minimal iron release and absorption, and has a low potential for interaction with co-administered drugs and dietary components.

The effectiveness of PA21 in lowering serum phosphorus levels in adult patients with CKD on dialysis has been confirmed in 2 adequate and well controlled studies. Subjects enrolled were representative of the adult population of CKD patients on dialysis (haemodialysis and peritoneal dialysis). PA21 and sevelamer treatment groups in Stage 1 and the PA21 maintenance dose and low dose groups in Stage 2 were generally well matched between treatment groups, and across regions and the subgroups. Of note, 38% of subjects had prior exposure to sevelamer within the past 12 months, 71.8% were on concomitant iron replacement treatment and 85.6% were receiving concomitant erythropoiesis stimulating agent. However, the proposed indication needs to be specific in that Velphoro is indicated for treatment in adult patients with ESRD on dialysis (see section on *Clinical questions*, below).

PA21 has demonstrated superiority over the non-effective (PA21 low dose) dose, both in initially lowering, and then maintaining, serum phosphorus levels. The efficacy of PA21 was also shown to be non-inferior to sevelamer, an approved and standard treatment, after 12 weeks of treatment. The serum phosphorus lowering effects of sevelamer were consistent with previous studies, thereby providing assay sensitivity and supporting the clinical relevance of the efficacy results.

The long term maintenance of control of serum phosphorus levels with PA21 treatment for up to 12 months has also been demonstrated. The efficacy of PA21 is robust and consistent across all sub-groups (sex, age, race, ethnicity, geographic region, haemodialysis or peritoneal dialysis), and was not affected by other baseline or disease characteristics.

Although the proposed starting dose of 1500 mg/day was not used in the pivotal Phase III study (which used 1000 mg/day), there was adequate data to support the proposed starting dose of 3 tablets/day (1500 mg/day), as discussed under *Efficacy*, above. A starting dose of 3 tablets per day would also allow more flexibility and better distribution of drug administration during the day, thus ensuring that more meals can be consumed with a PA21 tablet.

Throughout all the studies in the clinical development programme, PA21 was well tolerated at the proposed clinical doses. The profile of TEAEs exhibited by PA21 was consistent with what might be expected for a phosphate binding agent designed to be used by patients with ESRD undergoing dialysis. The majority of TEAEs were attributable to the intended pharmacological action of PA21 (such as changes in serum phosphorus levels) or to its physicochemical composition (for example, discoloured faeces). With the exception of common GI events of faeces discolouration and diarrhoea, the overall AE profile of PA21 was broadly similar to sevelamer, and consistent with the background disease.

The majority of these diarrhoea AEs occurred early after starting treatment, were mild in severity, and resolved with continued use of PA21. No new or significant safety signals have emerged with long term treatment in the analysis of the safety extension study, and the findings from this study support the continuing maintenance of efficacy and favourable tolerability of PA21. The incidence of the more common GI events observed in the pivotal efficacy studies was substantially reduced in the extension long term study.

No safety concerns were raised by a comprehensive assessment of laboratory tests which includes ECGs, haematology and chemistry tests. PA21 has been shown not to affect the blood levels of fat soluble vitamins or interfere with the PK of several commonly used concomitant medications (losartan, furosemide, omeprazole, digoxin and warfarin). In the post-hoc analysis of lipid levels in Studies PA-CL-05A/05B, no clinically relevant impact on lipid levels was observed when PA21 treated subjects were co-administered atorvastatin, simvastatin or other statins. Administration of PA21 at proposed doses did not appear to have any significant effect on iron status parameters or haematology parameters. However, when administering any medicinal product that is known to interact with iron, the medicinal product should be administered at least 1 hour before or 2 hours after PA21.

Velphoro (PA21) is an efficacious well tolerated, calcium- and aluminium-free phosphate binder which provides a safe and effective therapeutic option with a reduced pill burden compared to other available products for the control of serum phosphorus in adult patients with ESRD on dialysis. Overall, the benefit-risk balance of Velphoro (PA21) is favourable.

First round recommendation regarding authorisation

It is recommended that approval of the submission be granted subject to the following conditions:

Approval is granted for the modified indication of:

> *Velphoro is indicated for the control of serum phosphorus levels in adult patients with end-stage renal disease (ESRD) on dialysis.*

Approval is subject to incorporation of changes to PI[40] and adequate response to the clinical questions (below).

Clinical questions

Efficacy

1. The sponsors have provided the following justification for selecting the non-inferiority margin of 0.19 mmol (0.6 mg/dL) in the pivotal Phase III Study PA-CL-05A:

   The number of randomised clinical trials comparing sevelamer (sevelamer carbonate or sevelamer HCl) against placebo is very limited (Tonelli, 2007[41]; Navaneethan, 2009[42]). The estimation of the non-inferiority margin could not be assessed by conducting a systematic review and meta-analysis to evaluate the confirmed effect of sevelamer against placebo in the reduction of serum phosphorus and the CI of this effect. Several published clinical trials of sevelamer compared against active comparators indicated an absolute change from baseline in serum phosphorus of around 2 mg/dL (range from 1.8 mg/dL to 2.2 mg/dL) with a consistent standard deviation (SD) of around 2.2 mg/dL (range from 2.1 mg/dL to 2.4 mg/dL) (Bleyer, 1999[43]; Braun, 2004[44]; Chertow, 1999[45]). Given the size of these studies, the lower bounds of the 95% CI of the absolute change from baseline in serum phosphorus could be estimated to be around 1.5 mg/dL (range from 1.25 mg/dL to 1.86 mg/dL). Similar information on the absolute change from baseline in serum phosphorus was also extracted from the published label of sevelamer with a mean absolute change from baseline of -2 mg/dL (95% CI: -2.5, -1.5) (page 12 of PI for sevelamer). Hence, the lower bound of the 95% CI was around 1.5 mg/dL. The sponsors state that given the consistency of the published results, the choice of a margin of 0.6 mg/dL (0.19 mmol/L) appears to be reasonable as it is approximately a third of the lower

[40] Details of recommended revisions to the product literature are generally beyond the scope of the AusPAR

[41] identified 14 primary publications of randomized trials (3193 participants) that were eligible for efficacy analysis. In analyses pooling, the 10 studies reporting on serum phosphate and calcium (2501 participants), serum phosphate was significantly lower with calcium-based phosphate binders by 0.12 mmol/l [95% confidence interval (CI) 0.05–0.19], compared with sevelamer.

[42] 40 trials (6,406 patients) were included. There was no significant decrease in all-cause mortality (10 randomised controlled trials; 3,079 patients; relative risk [RR], 0.73; 95% confidence interval [CI], 0.46 to 1.16), hospitalisation, or end-of-treatment serum calcium-phosphorus product levels with sevelamer compared with calcium based agents. There was a significant decrease in end-of-treatment phosphorus and parathyroid hormone levels with calcium salts compared with sevelamer and a significant decrease in risk of hypercalcemia (relative risk (RR), 0.47; 95% CI, 0.36 to 0.62) with sevelamer compared with calcium-based agents. There was a significant increase in risk of gastrointestinal adverse events with sevelamer in comparison to calcium salts (RR, 1.39; 95% CI, 1.04 to 1.87). Compared with calcium-based agents, lanthanum significantly decreased end-of-treatment serum calcium and calcium-phosphorus product levels, but with similar end-of treatment phosphorus levels.

[43] Bleyer AJ, Burke SK, Dillion M, Garrett B, Kant KS, Lynch D, et al. A comparison of the calcium-free phosphate binder sevelamer hydrochloride with calcium acetate in the treatment of hyperphosphatemia in hemodialysis patients. *Am J Kid Dis*. 1999; Apr;33(4):694-701.

[44] Braun J, Asmus HG, Holzer H, Brunkhorst R, Krause R, Schulz W, et al. Long-term comparison of a calcium-free phosphate binder and calcium carbonate--phosphorus metabolism and cardiovascular calcification. *Clin Nephrol*. 2004;62(2):104-115.

[45] Chertow GM, Burke SK, Dillon MA, Slatopolsky E; RenaGel Study Group. Long-term effects of sevelamer hydrochloride on the calcium x phosphate product and lipid profile of haemodialysis patients. *Nephrol Dial Transplant* 1999;14:2907-2914.

bound of the 95% CI of the absolute change in serum phosphorus seen with sevelamer.

Notwithstanding the lack of adequate placebo controlled data with sevelamer, there is a slight chance that the non-inferiority margin chosen will not be able to demonstrate that the effect of size seen with PA21 will be significantly greater than zero (or placebo); however, this may have been partly addressed by the demonstration of superiority of the PA21 maintenance dose group versus the non-effective low dose control group which essentially functions as a placebo control group. It is conventional, however, to state confidence intervals with 95%, not 97.5% boundaries and the sponsors have not justified use of the 97.5% one-sided CI for defining the non-inferiority margin between PA21 and sevelamer. This is especially relevant considering the fact that at 12 weeks, sevelamer was actually found to be superior to PA21 in terms of reduction in serum phosphorous levels. Could the sponsors please clarify this.

Safety

1. Were any cases of intestinal obstructions, ileus, perforation or of difficulty swallowing seen on either PA21 or sevelamer treatments?

Product Information

Indications

1. The *Indications* in the proposed PI are: *Velphoro is indicated for the control of serum phosphorus levels in patients with end stage renal disease (ESRD).*

   End stage renal disease includes patients treated by dialysis or transplantation, irrespective of the level of GFR. The pivotal Phase III study in this submission included only patients who were currently on dialysis. Although about 8% of the patients had received prior renal transplant, all of them were currently on dialysis. Furthermore, the efficacy and safety of Velphoro has not been evaluated in patients < 18 years of age.

   Hence, it is recommended that the proposed Indication be changed to reflect the patient population evaluated in the pivotal studies:

   > *Velphoro is indicated for the control of serum phosphorus levels in adult patients with end-stage renal disease (ESRD) on dialysis.*

Interactions with other medicines

1. The proposed US PI for Velphoro mentions the following: *"Take alendronate and doxycycline at least 1 hour before Velphoro. Velphoro should not be prescribed with oral levothyroxine and oral vitamin D analogs".*

   Could the sponsors please specify why the same precautions have not been added to the proposed Australian PI.

[Note: other questions and comments regarding the PI are beyond the scope of the AusPAR.]

Second round evaluation of clinical data submitted in response to questions

Data on Interactions with vitamin D analogues

In addition to responses to the *Clinical questions*, above, the sponsor's response to the TGA request for information included an additional study: *Supplementary report of analyses to assess pharmacodynamic interaction of Velphoro with oral Vitamin D analogues*, to support proposed amendments to the DDI statements in the PI (see also *Sponsor's response to question on Interactions with other medicines*, below).

Oral Vitamin D analogues are commonly taken to treat or prevent secondary hyperparathyroidism in CKD patients by reducing serum iPTH levels. Post-hoc analyses of pooled data from Studies PA-CL-05A and PA-CL-05B (PA-CL-05A/05B) were conducted to further investigate any possible PD interaction between Velphoro and oral Vitamin D analogues, with respect to their effects in controlling serum iPTH levels.

These analyses were conducted to support a labelling supplement [in the US] to remove the restriction on the prescribing of oral Vitamin D analogues with Velphoro and evaluated the possible impact of Velphoro and sevelamer, given concomitantly with stable doses of oral Vitamin D analogues, on the levels of serum iPTH.

Details of this study are found in AusPAR Attachment 2, Extract from the CER.

Evaluator's conclusion

Overall, the evidence provided in the study is not adequate to justify removal of the labelling restriction in the PI on the prescribing of oral Vitamin D analogues with Velphoro.

Evaluation of responses to clinical questions

Sponsor's response to efficacy question 1 and 2

Acceptable responses were provided (see AusPAR Attachment 2, Extract from the CER, for details).

Sponsor's response to safety question 1

The sponsor advised that in the combined PA-CL-05A/05B Studies, 2 subjects (0.3%) reported difficulty swallowing (dysphagia) in the PA21 treatment group compared with 3 subjects (0.9%) in the sevelamer treatment group. One sevelamer treated subject experienced intestinal obstruction, with none in the PA21 treatment group. There were no cases of either intestinal perforation or ileus in either treatment group throughout the 52 weeks of treatment.

Evaluator's comments on sponsor's response:

The above response by the sponsor is acceptable.

Sponsor's response to question on PI: Indications

In response to the evaluator's comments, the sponsor has modified the proposed *Indications* to:

> *Velphoro is indicated for the control of serum phosphorus levels in adult patients with end-stage renal disease (ESRD) on dialysis.*

Evaluator's comments on sponsor's response:

The response by the sponsor is acceptable.

Sponsor's response to question on interactions with other medicines

The sponsor provided data and analyses to support the following changes (shown in bold and strikethrough font) to the text on DDIs in the proposed PI:

> '**In addition, clinical studies demonstrated no impact of Velphoro on iPTH lowering effect of oral Vitamin D analogues.** Vitamin D and 1,25-dihydroxy Vitamin D levels remained unchanged.'
>
> 'In vitro studies with the following drugs showed an interaction: alendronate, cephalexin, doxycycline **and,** levothyroxine~~, atorvastatin, doxercalciferol and paricalcitol~~'

Data and pooled analyses to support these amendments were provided (see AusPAR Attachment 2, Extract from the CER, for details).

In addition, the sponsor provided a Supplementary study on Interactions between Velphoro and Vitamin D analogues (see above and AusPAR Attachment 2) to support the proposal that it is unnecessary to restrict the concomitant administration of Vitamin D analogues.

Evaluator's conclusion on sponsor's response:

Overall the evidence is not adequate to support the changes to the DDI information proposed by the sponsors (above).

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Velphoro in the proposed usage are unchanged from those identified in the *First round assessment of benefits*, above.

Second round assessment of risks

After consideration of the responses to clinical questions, the benefits of Velphoro in the proposed usage are unchanged from those identified in the *First round assessment of risks,* above.

Second round assessment of benefit-risk balance

The benefit-risk balance of Velphoro given the proposed usage is favourable.

Second round recommendation regarding authorisation

It is recommended that the submission for marketing of Velphoro be approved for the following indication:

> *Velphoro is indicated for the control of serum phosphorus levels in adult patients with end-stage renal disease (ESRD) on dialysis.*

However, the approval is subject to incorporation of changes to PI as suggested (see *Sponsor's response to question on Interactions with other medicines*[46]).

[46] Other recommended revisions to the PI are beyond the scope of the AusPAR.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan EU-RMP Version 2.0 (dated 26 July 2013) with an Australian Specific Annex (ASA) dated 11 October 2013 which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 12.

Table 12: Summary of Ongoing Safety Concerns

Ongoing safety concerns	
Important Potential Risk	Masking of potential GI bleeding due to PA21 induced discoloured (black) faeces
Important Potential Risk	Potential iron accumulation in predisposed patient population
Important Missing Information	Use in paediatric population < 18 years Use in pregnant and lactating women Long-term usage beyond 1 year Use in patient population with CKD Stage 1-4 Use in patient population with HIV and HBV and/or HCV infections Use in patient population with concurrent severe hepatic disorders Use in patient population with a history or evidence of significant GI disorders Use in patient population with history of haemochromatosis, or any other iron accumulation disorders Use in patient population receiving PA21 concomitantly with other PBs Use in patient population receiving aluminium-, calcium- or magnesium-containing antacids and/or oral iron preparations

CKD = Chronic kidney disease; GI = Gastrointestinal; HBV = Hepatitis B virus; HCV = Hepatitis C virus; HIV = Human immunodeficiency virus; PB = Phosphate binder.

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities to monitor all the specified ongoing safety concerns. Additional pharmacovigilance activities, in the form of a paediatric clinical trial, are proposed to further monitor and characterise the important missing information: 'Use in paediatric population < 18 years'

Risk minimisation activities

The sponsor has concluded that routine risk minimisation activities for all the specified ongoing safety concerns are sufficient, except for the important missing information: 'Long-term usage beyond 1 year', 'Use in patient population with HIV and HBV and/or HCV infections', 'Use in patient population receiving PA21 concomitantly with other PBs' and 'Use in patient population receiving aluminium-, calcium- or magnesium-containing antacids and/or oral iron preparations', for which no routine risk minimisation activities are proposed.

Routine risk minimisation activities will include indications, contraindications, clinical trial data, and precautionary statements (including interaction, instructions for use and/or notification of undesirable effects) in the Australian PI.

Reconciliation of issues outlined in the RMP report

Table 13 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

Table 13: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
Safety considerations may be raised by the nonclinical and clinical evaluators through the TGA consolidated request for information and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP. Consequently comments in the nonclinical evaluation report regarding exposure margins in the RMP, and statements on genotoxicity should be addressed.	The sponsor has responded to comments in the nonclinical evaluation report and agrees to make appropriate amendments in the next version of a revised RMP.	The Toxicology area of the Office of Scientific Evaluation (OSE) of the TGA advised as that this response is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
Module S.VII.5: 'Pharmacological Class Effects' of the EU-RMP states inter alia: *"Similar to other approved PBs, GI events (such as nausea, vomiting, diarrhoea, and constipation) are the most common adverse events reported"* and *"There are no pharmacological class effects considered as important identified or potential risks."* Nevertheless the sponsor indicates that in the pivotal studies Velphoro had no marked differences in safety profile compared to sevelamer. Consequently the sponsor should provide compelling justification as to why the following ongoing safety concerns associated with sevelamer should not be adopted for Velphoro: the important identified risks: 'Vitamin Deficiency', 'Peritonitis' & 'Worsening of metabolic acidosis' the important potential risks: 'Intestinal Obstruction/ileus', 'Hyperphosphataemic CKD patients on peritoneal dialysis', 'AV fistula site adverse reactions' and 'Increased sodium chloride levels'. If the sponsor decides to include these ongoing safety concerns in Australia for Velphoro, then consideration must be given as to what pharmacovigilance and risk minimisation activities will be proposed for them and the ASA should be revised accordingly.	The sponsor has provided justification as to why none of the specified pharmacological class effects should be considered as ongoing safety concerns (see 'Outstanding Issues' below).	It would appear that the clinical data indicate that the incidence of 'Vitamin deficiency' in the Velphoro treatment arm (2.26%) is comparable if not slightly higher than the incidence from the sevelamer carbonate group (1.72%). Consequently it is recommended that the pharmacological class effect: 'Vitamin Deficiency' be adopted for Velphoro as an important potential risk which may be monitored by routine pharmacovigilance. Given the background routine risk minimisation will not be required for this ongoing safety concern. These changes need only be reflected in a revised ASA before this application is approved.
Notwithstanding the evaluation of the nonclinical and clinical aspects of the Safety Specifications, it is recommended that the sponsor consider the following amendments (shown in the following row) to this list of ongoing safety concerns:	The sponsor has provided justification as to why none of the proposed important potential risks should be considered as ongoing safety concerns.	See cell below.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
Module S.VII.4: 'Identified and Potential Interactions' of the EU-RMP states: *"with PA21's mode of action and chemical composition there is potential for interactions through altering the absorption of other medications administered orally"* and *"All reported adverse reactions with PA21 and any adverse reaction which is suspected to be caused due to a drug interaction with PA21 or is suspected to be related to any PA21 drug interaction will be properly evaluated and closely monitored by the existing routine pharmacovigilance activities (see also Part III of this RMP). This will include close monitoring of any reports from the post-marketing environment, standard case report follow-up activities, literature review, generation of Periodic Safety Update Reports, and an ongoing evaluation of the benefit/risk ratio of PA21. Those activities are sufficient to ensure close monitoring of any potential drug interaction with PA21."* Consequently it is suggested that the important potential risk: 'Drug interactions' be included as a new ongoing safety concern. The 'Interactions with Other Medicines' section of the proposed PI states: "In vitro studies with the following drugs showed an interaction: alendronate, cephalexin, doxycycline, levothyroxine, atorvastatin, doxercalciferol and paricalcitol." Consequently it is suggested that the important potential risk: 'Increased thyroid stimulating hormone levels/Hypothyroidism' be included as a new ongoing	The sponsor has opposed this recommendation on the basis that *"the potential for interactions with medicinal products seems low"*. (See *Outstanding issues* below)	This justification is considered inadequate and it is reiterated that the important potential risk: 'Drug interactions' should be included as a new ongoing safety concern for which routine pharmacovigilance and routine risk minimisation are already proposed. These changes need only be reflected in a revised ASA before this application is approved.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
safety concern. If the sponsor decides to include these ongoing safety concerns in Australia for Velphoro, then consideration must be given as to what pharmacovigilance and risk minimisation activities will be proposed for them and the ASA should be revised accordingly.		
The sponsor should provide details of the qualified person responsible for pharmacovigilance (PRP) within CEPL and include this information in a revised ASA.	The sponsor has provided details of the qualified person responsible for pharmacovigilance (PRP) within CEPL and an assurance to include these contact details in the next version of the revised ASA.	The sponsor should now make such changes and submit a revised ASA before this application is approved.
The sponsor should update the [RMP] Table: 'Overview of Ongoing Studies' of the ASA and provide at least a draft protocol for the planned paediatric clinical trial to the TGA for review, as an attachment to the revised ASA. If this document is not yet available, the sponsor should provide an assurance that it will be submitted to the TGA once it becomes available	The sponsor states: *"The applicant will include an updated Table [on] 'Overview of Ongoing Studies' in the next version of the revised ASA. The currently available version of the study protocol (Version 1; dated 6 June 2014) of the planned paediatric clinical trial PA-CL-PED-01 is included in this submission."*	The sponsor should now make such changes and submit a revised ASA before this application is approved.
At this time the specified ongoing safety concerns would not appear to warrant additional risk minimisation activities.	The sponsor agrees that, based on the specified ongoing identified safety concerns, currently no additional risk minimisation activities are warranted.	n/a

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
The sponsor's handling of the potential for medication errors using routine pharmacovigilance and routine risk minimisation activities is considered satisfactory.	The sponsor agrees that routine pharmacovigilance and routine risk minimisation activities are considered satisfactory for the handling of the potential for medication errors.	n/a
'Risk Minimisation Activities Referenced in the EU-RMP' of the ASA states: *"In addition to routine pharmacovigilance measures, the following additional pharmacovigilance activity will occur. 1. Evaluation of the PIP* [paediatric investigation plan] *will monitor the safety profile of Velphoro in children and adolescents."* The sponsor should amend this section of the ASA as it is inappropriate to refer to pharmacovigilance activities in the Risk Minimisation Plan.	The sponsor states: *"The applicant will provide an amended statement in the next version of the revised ASA for Section 3.1 'Risk Minimisation Activities Referenced in the EU-RMP'."*	The sponsor should now make such changes and submit a revised ASA before this application is approved.
The sponsor should provide a table summarising the pharmacovigilance plan and risk minimisation plan proposed for Australia in the ASA. Wording pertaining to all the specified ongoing safety concerns in the proposed Australian PI and CMI should be included in the table.	The sponsor states: "To summarise the pharmacovigilance plan and risk minimisation plan planned for Australia for the ongoing safety concerns, the applicant will include [a] Table into the next version of the revised ASA. The proposed text in the table below is presenting the current wording of the proposed Australian Reference Safety Information."	The sponsor should now make such changes, taking into account 'Outstanding issues' (see above), and submit a revised ASA before this application is approved.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
Notwithstanding the recommendations made in regard to the specified list of ongoing safety concerns, the proposed routine risk minimisation activities in the draft product information document are considered satisfactory. Similarly in regard to the proposed routine risk minimisation activities, the draft CMI is considered satisfactory.	The sponsor agrees that the proposed routine risk minimisation activities are sufficient for the specified list of ongoing safety concerns.	n/a

Summary and recommendation

Outstanding issues

The sponsor's correspondence dated 10 July 2014 states: "*It is proposed to submit an updated EU-RMP and revised version of the ASA to the TGA after registration of the product in the EU and in agreement with the TGA. This is expected in the coming months.*" Given the outstanding issues specified below, this proposal is only acceptable if the sponsor is prepared to delay any decision being made in regard to this application until any updated RMP documentation is submitted and then evaluated.

Alternatively the sponsor should address the following outstanding issues:

- The sponsor was asked to provide compelling justification as to why the important identified risk: 'Vitamin Deficiency' associated with sevelamer should not be adopted for Velphoro. The sponsor states: *"From 707 patients treated with Velphoro, 16 patients reported events falling into this defined pool. From 348 patients treated with sevelamer carbonate, 6 patients reported such events. These results show that the incidence of "Vitamin deficiency" was very low in the Velphoro treatment arm (2.26%) and comparable to the incidence from the sevelamer carbonate group (1.72%). As outlined in the CSR for PA-CL-05A/05B, transitory Vitamin D decreases were observed in both treatment groups. Decreases appeared to be slightly greater in the sevelamer groups and were more pronounced in female subjects."* and *"Based on these clinical results from the studied patient population on dialysis, there is no suspicion that "Vitamin deficiency" should be considered as an ongoing safety concern for Velphoro in Australia."* However, it would appear that the clinical data indicate that the incidence of 'Vitamin deficiency' in the Velphoro treatment arm (2.26%) is comparable if not slightly higher than the incidence from the sevelamer carbonate group (1.72%). Consequently it is recommended that the pharmacological class effect: 'Vitamin Deficiency' be adopted for Velphoro as an important potential risk which may be monitored by routine pharmacovigilance. Given the background routine risk minimisation will not be required for this ongoing safety concern. These changes need only be reflected in a revised ASA before this application is approved.
- Module S.VII.4: 'Identified and Potential Interactions' of the EU-RMP states: "*with PA21's mode of action and chemical composition there is potential for interactions through altering the absorption of other medications administered orally*" and "*All reported adverse reactions with PA21 and any adverse reaction which is suspected to be caused due to a drug interaction with PA21 or is suspected to be related to any PA21*

drug interaction will be properly evaluated and closely monitored by the existing routine pharmacovigilance activities (see also Part III of this RMP). This will include close monitoring of any reports from the post-marketing environment, standard case report follow-up activities, literature review, generation of Periodic Safety Update Reports, and an ongoing evaluation of the benefit/risk ratio of PA21. Those activities are sufficient to ensure close monitoring of any potential drug interaction with PA21." Consequently it was suggested that the important potential risk: 'Drug interactions' be included as a new ongoing safety concern. The sponsor has opposed this recommendation on the basis that "*the potential for interactions with medicinal products seems low*". This justification is considered inadequate and it is reiterated that the important potential risk: 'Drug interactions' should be included as a new ongoing safety concern for which routine pharmacovigilance and routine risk minimisation are already proposed. These changes need only be reflected in a revised ASA before this application is approved.

- In response to other recommendations the sponsor has provided satisfactory responses and/or an assurance to amend and/or update the next version of the ASA accordingly. Consequently the sponsor should now make such changes, taking into account the above outstanding issues, and submit a revised ASA before this application is approved.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Comments on the safety specification of the RMP

Clinical evaluation report

- The Safety Specifications identified in the draft RMP are consistent with AEs/safety profile of Velphoro (PA21) in the clinical trials.

Nonclinical evaluation report

- Where reference is made to the exposure margin in the RMP, the error from the non-clinical overview has been carried across and the margins refer to comparison with a 75 kg rather than a 70 kg patient.
- The statements in the RMP: *"The outcome ….. was negative" "There was no evidence of genotoxic potential ….."* are not strictly true. Overall the genotoxic potential of PA21 appeared to be low but there were some inconsistent, equivocal results obtained in the chromosomal aberration tests.

These matters have been satisfactorily addressed (see Table above).

Recommended conditions of registration

- The European Risk Management Plan (Version 2.0, dated 26 July 2013) with an Australian Specific Annex (dated 11 October 2013), to be revised as specified in the sponsor's correspondence dated 10 July 2014 and as agreed by the TGA, must be implemented.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Background

This is a submission to register an iron containing new chemical entity, sucroferric oxyhydroxide (Velphoro; code PA21), that is a mixture of 'core' polynuclear iron(III)-oxyhydroxide active moiety (polynuclear iron(III)-oxyhydroxide) "wrapped" with sucrose and starches.

Velphoro is intended for oral administration and acts locally in the gut lumen as a phosphate binder. Following completion of the first clinical evaluation round, the sponsor agreed to the following modified indication:

> *Velphoro is indicated for the control of serum phosphorus levels in adult patients with end stage renal disease (ESRD) on dialysis.*

The finished product will be presented as 2.5 gram oral tablets but the proposed labelling is based on its iron content rather than the quantity of sucroferric oxyhydroxide, that is, Velphoro 500 mg chewable tablets (each chewable tablet contains 500 mg iron as sucroferric oxyhydroxide).

The currently approved GI phosphate binders include calcium salts (carbonate, citrate, acetate), aluminium salts (mostly hydroxides), a lanthanum salt (lanthanum carbonate) and a cationic polymer (sevelamer HCl; note, the carbonate salt of sevelamer used in the pivotal trial for Velphoro is not registered in Australia).

Quality

The active moiety of Velphoro, polynuclear iron(III)-oxyhydroxide, is insoluble and not absorbed. Bioavailability and conventional PK studies were therefore not performed.

The submission was not referred to the PSC. The TGA Pharmaceutical Chemistry area recommends approval.

Drug substance and the finished product

The drug substance, sucroferric oxyhydroxide, is obtained by basifying ferric chloride solution to produce a polynuclear iron(III)-oxyhydroxide suspension. This is mixed with potato and maize starches and sucrose. The particle size of polynuclear iron(III)-oxyhydroxide is difficult to measure directly. The size of sucroferric oxyhydroxide is established but does not correlate well with phosphate adsorption. The drug substance specification includes a phosphate adsorption test. As polynuclear iron(III)-oxyhydroxide is insoluble, a dissolution test is not appropriate. A disintegration test is used to test batch consistency.

Sucroferric oxyhydroxide dissolves in strong acid, destroying the phosphate binding capacity and release of iron which can be absorbed. Tablets are tested (solubilisation) in vitro at pH 3.

The formulation is intended to disintegrate even if the tablets are not properly chewed. The daily sucrose exposure is 2.25 to 4.5 grams.

The formulation contains a number of excipients including 2 new entities (neohesperidin dihydrochalcone and woodberry flavour). The Toxicology area of TGA considers their use acceptable.

The proposed shelf-life is 18 months for the unopened product (bottle or blister) with optimal storage (below 30˚C; keep in original container; protect from moisture). A 45 day in-use shelf-life is recommended for the bottle presentation.

Formulations

A 250 mg iron formulation was used in Phase I studies. A modified 250 mg iron formulation was used in Phase II studies. Later a 500 mg iron formulation was used in Phase IIIA studies, and a modified version was used in Phase IIIB studies. A formulation similar to this is proposed for commercialisation. The Quality evaluators inform that because of the inapplicability of conventional dissolution tests, it is not possible to conclude that different formulations are equivalent in vivo. However, in vitro phosphate binding was broadly similar.

Nonclinical

There are no nonclinical objections to registration of sucroferric oxyhydroxide for the proposed indication.

Mechanism of action

The drug effect does not rely on systemic absorption. The phosphate adsorption takes place in the GI tract by ligand exchange between hydroxyl groups and/or water in sucroferric oxyhydroxide and the dietary phosphate. The bound phosphate (and iron) is excreted with faeces.

In vivo, small amounts of iron derived from the drug were detected in red blood cells of nonclinical species and in humans. The percentages of administered dose detected in blood cells were very low (< 2% in animals and < 0.5% in humans).

In vitro studies of iron release from the PA21 drug product indicated a very low propensity for iron release in acidic environment except in the absence of phosphate. Therefore, the systemic absorption of iron derived from PA21 is expected to be lower in patients with hyperphosphataemic, such as those with CKD on dialysis. The sucrose and starch components of the PA21 drug product can be digested to glucose and fructose, and maltose and glucose respectively and systemically absorbed.

In toxicity studies, Velphoro was administered with diet or by oral gavage. In repeated dose toxicity studies, the likely adaptive (administration in normophosphataemic animals) effects included elevated ALP, increased serum calcium and phosphorus, elevated urine calcium, decreased urinary phosphorus, elevated serum osteocalcin and urinary DPD and increased serum Vitamin D metabolites. There were also small increases in the iron content of the kidney, liver and spleen and evidence of iron deposition particularly in the reticuloendothelial system.

Hyperplasia, mutagenesis and carcinogenesis

At high doses used in the rodent studies, PA21 caused thyroid c-cell adenomas, hyperplastic changes in the GI tract and hyperplastic changes in the urinary bladder. These effects are considered likely related to the pharmacological and local effects of the drug. PA21 does not appear to be mutagenic. Carcinogenicity studies were done in mice and rats. The balance of evidence suggests that PA21 is not directly carcinogenic. However, prolonged exposure to very high doses has the potential to induce hyperplastic change which may progress to neoplastic change. Such effects are considered unlikely in humans at clinically relevant doses.

Genotoxicity, effects on fertility and embryofetal development

PA21 was negative in the Ames test and in a modified Comet assays assessing DNA damage in the stomach, duodenum and colon of rats. The results from tests for mutagenic

potential in vitro in Chinese hamster lung cells were equivocal at 5000mg/mL. The weight of evidence suggests that PA21 does not pose a genotoxic concern.

PA21 had no effects on fertility, embryofetal or post-natal development in rats. However, PA21 did cause some reductions in fetal bodyweight in rabbits (5 x maximum recommended clinical dose) and a trend towards incomplete ossification at this maternotoxic dose. Pregnancy category B3 is recommended based on this finding and text proposed for inclusion in the PI.

Clinical

The clinical dossier consisted of 7 pharmacology studies (including 5 drug interaction (DDI) studies), one Phase II dose ranging study and one pivotal Phase III study including its controlled safety extension. There were 2 Japanese studies (a Phase I and a Phase II study) for which full reports were not provided.

In general in efficacy studies the serum phosphorus level at end of treatment and at various timepoints, serum calcium and iPTH were used as endpoints whereas iron studies were undertaken as part of safety outcomes. Both the pivotal (Phase III) and the supporting (Phase II dose finding study) were open label trials, due to chewed or crushed ingestion of Velphoro compared to whole tablet ingestion of the active comparator phosphate binder sevelamer. Faecal discolouration with the iron based PA21 precluded double blinding.

Pharmacokinetics

The radiolabelled (^{59}Fe) sucroferric oxyhydroxide Study Q-24120 was conducted in 16 patients with chronic kidney disease (8 pre-dialysis and 8 haemodialysis patients) and 8 healthy volunteers with low iron stores (serum ferritin < 100 µg/L), using a suspension preparation of sucroferric oxyhydroxide (2 g iron in one day) in water. The (Quality) evaluators state that it is unclear if this labelled sample can be considered representative of the commercial tablets or whether results reflect the worst case scenario for systemic iron absorption. In healthy subjects, the median uptake of radiolabelled iron in the blood was 0.43% on Day 21 compared to a much lower median of 0.04% on Day 21 in patients with chronic renal disease.

Drug-drug interaction studies

In vitro assessment of drug interactions (adsorption by PA21) indicated extensive adsorption by PA21 of furosemide, losartan, atorvastatin, alendronate, levothyroxine, paricalcitol, doxercalciferol, doxycycline and cephalexin.

In vitro, significant interaction (adsorption by PA21) was not detected with ciprofloxacin, digoxin, enalapril, metoprolol, nifedipine, warfarin, hydrochlorothiazide, metformin, quinidine, clopidogrel and simvastatin. Similarly no adsorption was found for cinacalcet or glipizide, but results were inconclusive at some pH values whereas moderate adsorption to PA21 was noted for pioglitazone.

However, in vivo studies in healthy volunteers demonstrated lack of interaction in terms of bioavailability (AUC) between PA21 and losartan (Study PA-DDI-001), furosemide (PA-DDI-002), digoxin (PA-DDI-004), warfarin (PA-DDI-005) and omeprazole (PA-DDI-003).

In addition, post-hoc analysis of data from the pivotal efficacy Study PA-CL-05A/05B did not show significant alteration in serum lipid profile in PA21 treated patients who were taking 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (atorvastatin and simvastatin) in this study.

The data from this pivotal clinical trial also showed significant reduction in Vitamin D levels at 24 Weeks with both PA21 and sevelamer. However, the levels returned to baseline values at 52 Weeks. A post-hoc analysis of 187 patients (127 PA21 patients; 60 sevelamer patients) who were on stable doses of oral Vitamin D analogues during this study was also performed and indicated that there was no loss of control of serum iPTH. However, the clinical evaluator points out that the mean iPTH values remained above the recommended target range of 150-300 pg/mL. Note that the KDOQI clinical guidelines provide that ESRD patients on dialysis patients with iPTH levels above this recommended range should receive active Vitamin D analogues. The PA21 serum P lowering effect was not impaired.

Note also that in PD studies in healthy volunteers, no consistent effect was seen with ascending single and multiple doses of PA21 on serum levels of Vitamins A, D, E and K.

Pharmacodynamics:

Primary and secondary PD effects are discussed in the CER (see Attachment 2 of this AusPAR).

Dose response

The Phase II study (PA-CL-03A) investigated dose response using 5 dose levels of PA21 (1.25 g, 5.0 g, 7.5 g, 10.0 g, 12.5 g per day with meals in divided doses) and one dose level of sevelamer HCl (4.8 g per day; taken whole with meals in divided doses).

The studied population was adult patients with CKD who were on maintenance haemodialysis three times a week for at least 3 months, receiving stable doses of phosphate binder (with or without Vitamin D) and having stable calcium content in dialysate for at least 1 month. The serum phosphorus levels at the time of screening were required to be > 1.78 mmol/L (> 5.5mg/dL).

The exclusion criteria included, among others, Uncontrolled hyperphosphataemia (> 2.5 mmol/L (> 7.75 mg/dL)) on phosphate binders, hypercalcaemia (serum calcium > 2.5 mmol/L (> 10.0mg/dL), hypocalcaemia (serum calcium < 1.9mmol/L (< 7.6mg/dL)), severe hyperparathyroidism (iPTH levels > 600 ng/L), intention to initiate therapy with Vitamin D, Vitamin D metabolites or calcimimetics during the study or receiving non-stable therapy with these agents, iron deficiency anaemia (haemoglobin < 10g/dL and ferritin < 100 ng/mL) or history of haemochromatosis (or ferritin > 800g/L) or other iron storage disorders.

Antacids containing aluminium or magnesium, iron preparations (IV iron preparations were permitted until the end of screening), phosphate binders (addition to the study drugs), antibiotics, anti-arrhythmic and anti-seizure medication if prescribed for moderate to severe arrhythmic and seizure disorders were not allowed during the course of study.

PA21 was dispensed as 1.25 g tablets (PA21-1 formulation). Sevelamer was dispensed as 800 mg tablets. The patients underwent a 2 week period of washout for the existing phosphate binders before initiation of treatment in the study. The patients were to be withdrawn if serum phosphorus level exceeded the upper safety limit of 2.75 mmol/L (8.5 mg/dL) at any time from 2 weeks after the start of treatment, or decreased below the lower safety limit of 1.13 mmol/L (3.5 mg/dL) at any time after the start of treatment.

The trial design was multicentre, open label, randomised, parallel groups for a treatment period of 6 weeks. The sample size was calculated based on the need to detect a difference (from baseline to a post-baseline time-point) in serum phosphorus level of 0.65 mmol/L (2 mg/dL).

The primary efficacy endpoint was change from baseline in serum phosphorus (P) at the end of treatment (Week 7). A total of 154 patients were randomised equally to 6 groups. The groups were broadly comparable, including baseline serum P. The overall mean age was 60-61 years overall. All patients received study medications and 103/154 (67%) completed the study.

The response was dose dependent with maximum response obtained with the 10 g and 12.5 g PA21 daily dosing. The clinically relevant (based on the assumption used in sample calculation) change of 0.65 mmol/L (2 mg/dL) was achieved with the 10 g PA21 daily dosing. The treatment comparison of the two highest doses (12.5 g and 10 g PA21) was statistically significant compared to the lowest PA21 dose (1.25 g). The treatment comparison between the 7.5 g and 5 g doses with the 1.25 g dose was not statistically significant (controlling for multiplicity). The statistical comparison with sevelamer was not performed but the 4.8 g sevelamer dose (informally) appeared similar to the 5 g PA21 dose. The results are depicted in the table below:

Table 14: Analysis of serum phosphorous (mmol/L (mg/dL)): Absolute change from baseline at end of treatment (FAS)

Variable	PA21					Sevelamer (HCl) (N=24)
	1.25 g/Day (N=26)	5.0 g/Day (N=26)	7.5 g/Day (N=25)	10.0 g/Day (N=25)	12.5 g/Day (N=24)	
Baseline, mmol/L (mg/dL)						
Mean	2.203 (6.822)	2.135 (6.609)	2.212 (6.847)	2.186 (6.767)	2.089 (6.468)	2.242 (6.940)
SD	0.531 (1.644)	0.348 (1.078)	0.372 (1.152)	0.565 (1.750)	0.383 (1.186)	0.519 (1.606)
Minimum	1.11 (3.44)	1.36 (4.21)	1.46 (4.52)	1.38 (4.27)	1.34 (4.15)	1.31 (4.06)
Median	2.250 (6.966)	2.120 (6.563)	2.170 (6.718)	2.170 (6.718)	2.135 (6.610)	2.275 (7.043)
Maximum	3.32 (10.28)	2.68 (8.30)	2.92 (9.04)	2.99 (9.26)	2.96 (9.16)	3.89 (12.04)
End of treatment, mmol/L (mg/dL)						
Mean	2.162 (6.692)	1.787 (5.532)	1.808 (5.598)	1.541 (4.772)	1.543 (4.776)	1.901 (5.885)
SD	0.661 (2.047)	0.625 (1.936)	0.382 (1.183)	0.620 (1.918)	0.540 (1.672)	0.474 (1.468)
Minimum	0.24 (0.74)	0.38 (1.18)	0.95 (2.94)	0.23 (0.71)	0.65 (2.01)	1.23 (3.81)
Median	2.200 (6.811)	1.770 (5.480)	1.840 (5.697)	1.470 (4.551)	1.500 (4.644)	1.865 (5.774)
Maximum	3.40 (10.53)	3.17 (9.81)	2.37 (7.34)	3.02 (9.35)	2.58 (7.99)	3.16 (9.78)
Change from baseline to end of treatment, mmol/L (mg/dL)						
Mean	-0.042 (-0.130)	-0.348 (-1.076)	-0.404 (-1.250)	-0.644 (-1.995)	-0.547 (-1.692)	-0.341 (-1.055)
SD	0.650 (2.011)	0.684 (2.118)	0.391 (1.210)	0.551 (1.706)	0.584 (1.807)	0.436 (1.349)
Minimum	-1.66 (-5.14)	-2.07 (-6.41)	-1.26 (-3.90)	-1.85 (-5.73)	-1.85 (-5.73)	-1.22 (-3.78)
Median	-0.010 (-0.031)	-0.340 (-1.053)	-0.510 (-1.579)	-0.660 (-2.043)	-0.465 (-1.440)	-0.375 (-1.161)
Maximum	1.04 (3.22)	0.78 (2.41)	0.28 (0.87)	0.68 (2.11)	0.56 (1.73)	0.58 (1.80)
p-value[1]	0.7448	0.0157*	<0.001*	<0.001*	<0.001*	<0.001

1 Two-sided single sample t-test; PA21 only p-values≤0.05 flagged * according to the hierarchical procedure (descending dose) of PA21.
Notes: End of treatment values based on value at Week 7 or last observation carried forward for missing data.
FAS = full analysis set, SD = standard deviation

The proportion of patients with controlled serum phosphorous levels at Weeks 7 (defined as serum Phosphorus ≥ 1.13 to ≤ 1.78 mmol/L (≥ 3.5 to ≤5.5 mg/dL)] was achieved by 4/19 (21%), 7/17 (41%), 7/20 (35%), 6/14 (43%), 9/15 (60%) and 8/19 (42%) patients in the PA21 1.25 g/day, 5 g/day, 7.5 g/day, 10 g/day, 12.5 g/day and sevelamer groups respectively. The median time to reach controlled Phosphorus level was 36, 14, 8, 14, 8, and 15 days in PA21 1.25 g, 5 g, 7.5 g, 10 g, 12.5 g groups and sevelamer group respectively.

Generally the higher Velphoro doses led to more premature discontinuations and instances of severe hypophosphataemia as shown below:

Table 15: Premature discontinuations and instances of severe hypophosphataemia with Velphoro

Study PA-CL-03A	PA21 (g/day)					Sevelamer
	1.25	5	7.5	10	12.5	
· Prematurely withdrawn	8/26 (31%)	9/26 (35%)	5/25 (20%)	12/27 (44%)	9/24 (38%)	8/26 (31%)

Study PA-CL-03A	PA21 (g/day)					Sevelamer
	1.25	5	7.5	10	12.5	
· Due to serum P below safety limit	1/26 (4%)	3/26 (12%)	3/25 (12%)	7/27 (26%)	6/24 (25%)	1/26 (4%)
· Due to serum P above safety limit	4/26 (15%)	2/26 (8%)	0/25 (0%)	2/27 (7%)	0/24 (0%)	2/26 (8%)
· Due to serum Ca above safety limit	2/26 (8%)	2/26 (8%)	0/25 (0%)	0/27 (0%)	0/24 (0%)	0/26 (8%)
· Due to Adverse Event	0/26 (0%)	0/26 (0%)	0/25 (0%)	1/27 (4%)	1/24 (4%)	2/26 (8%)

Secondary outcomes included various timepoint: serum calcium; serum Ca x P product and serum iPTH.

A placebo controlled dose ranging study (PA1201) in Japanese patients (N = 183; on haemodialysis) was also provided.

Clinical efficacy (Pivotal Study PA-CL-05A and safety extension PA-CL-05B)

The Phase III Study PA-CL-05A is considered pivotal for the purposes of this submission. This was an open label, multicentre, randomised, active controlled, parallel group study to investigate the efficacy and safety of PA21 compared with sevelamer carbonate. The study involved a 2-Stage re-randomisation as follows:

Stage 1: Following a 2-4 week washout period after stopping the currently administered phosphate binders, the eligible patients were randomised (open label) to 2 parallel treatment groups, that is, PA21 and sevelamer for a treatment period of 24 weeks consisting of initial 8 weeks for dose titration and followed by maintenance of treatment to Week 24.

The starting dose for PA21 patients was 5 g/day and the dose was to be titrated for efficacy (target serum phosphorus of 0.81 to 1.78 mmol/L, that is, 2.5 to 5.5 mg/dL) or tolerability during the first 8 weeks. Dose increments of 2.5 g/day every 2 weeks were allowed. The allowed PA21 dose range was 5 g/day to 15 g/day.

The starting dose for sevelamer patients was 4.8 g/day and the dose was to be titrated for efficacy or tolerability during the first 8 weeks. Dose increments (or decrease) of 2.4 g/day every 2 weeks were allowed. The allowed sevelamer dose range was 2.4 g/day to 14.4 g/day.

After the first 8 weeks in which dose titration was completed, the patients continued on individualised doses of the respective drug for a further 4 weeks. Titration for reasons of tolerability was allowed during this period. A non-inferiority efficacy comparison for PA21 versus sevelamer was a pre-specified secondary outcome at this time-point (Week 12).

From Week 12 to 24, dose titrations were allowed for both tolerability and efficacy reasons. Safety analysis and efficacy data for the PA21 versus sevelamer comparison at this time-point (Week 24) were provided in the dossier.

Stage 2: This was a (partial) withdrawal study in a subset (n = 100) in which a control group was transferred to a low dose of PA21 compared to the maintenance dose reached at the end or Week 24. This was done by undertaking re-randomisation (open label) at Week 24 among PA21 patients on haemodialysis who had completed Week 24 and had achieved serum phosphorus < 1.78 mmol/L (< 5.5 mg/dL) earlier at Week 20. The two randomised groups were PA21 maintenance dose versus PA21 lower dose (lower dose 1.25 g/day). The two PA21 groups (maintenance dose and lower dose) were to be treated for a period of 3 weeks and a superiority comparison was planned at Week 27 as a prespecified primary efficacy endpoint. The baseline values for this analysis were the end of Week 24 values.

Long term extension (study PA-CL-05B): At Week 27, the Stage 2 PA21 maintenance dose patients could move directly into a 6 month (24 weeks) extended treatment study for continuing controlled comparison with the sevelamer group. The Stage 2 PA21 lower dose patients were not eligible to participate in the extension phase.

The eligible population (Study PA-CL-05A) was adults (aged ≥ 18 years; male or female) on maintenance haemodialysis 3 times per week with Kt/V[47] of ≥ 1.2 or peritoneal dialysis with a Kt/V of ≥ 1.7 over the last 3 months prior to the study and receiving stable doses of a phosphate binder.

The patients were required to have serum phosphorus ≥ 1.94mmol/L (≥ 6.0mg/dL) during a minimum 2 weeks washout period for existing phosphate binding therapy. No home haemodialysis or nocturnal haemodialysis overnight stay at site was allowed.

The exclusion criteria, among others, were iPTH level > 800ng/L (> 800 pg/mL or 88 pmol/L), serum ferritin >2,000 µg/L (4,494 pmol/L), hypercalcaemia (total serum calcium > 2.60 mmol/L (> 10.50 mg/dL)) on non-calcium based phosphate binders, hypocalcaemia (total serum calcium < 1.9 mmol/L (< 7.6 mg/dL)), patients taking more than 2 phosphate binders concomitantly prior to screening and phosphate binder naïve patients. IV iron supplementation was allowed during the study.

The study drugs were dispensed as PA21 2.5 g chewable tablets, PA21 1.25 g chewable tablets and sevelamer carbonate 800 mg tablet (Renvela).

The sample size for Stage 1 was based on an assumption of mean decrease in serum P level of 0.65 mmol/L (2.0 mg/dL) in both of the treatment groups and SD of 0.63 mmol/L (1.96 mg/dL). The pre-specified non-inferiority margin was treatment difference no worse than 0.19 mmol/L (0.6 mg/dL) using upper bound of 97.5% CI. The sample size for Stage 2 assumed a treatment difference between the groups of 0.42 mmol/L (1.30 mg/dL) and SD of 0.63 mmol/L (1.96 mg/dL).

A total of 1,059 patients were randomised (2:1) in Stage 1 (n = 710 in PA21 and n = 349 in sevelamer group). Of these 1,055 received at least one dose of study drugs, and 808/1059 (76%) completed Stage 1. A total of 659/1059 (62%) were included in the extension study. During Stage 1, 251/1059 (24%) patients prematurely discontinued the study with a higher withdrawal rate in the PA21 group (195/710; 27.5%) compared to sevelamer (56/349; 16%).

A subset of 99/710 (14%) PA21 haemodialysis patients participated in Stage 2 from Week 24 to Week 27 as a part of partial treatment withdrawal for comparison between PA21 maintenance dose versusPA21 lower dose. Of these, 94 were treated and 88 completed Stage 2. During Stage 2, 11 patients prematurely discontinued the study comprising of 8/50 (16%) PA21 maintenance dose patients and 3/49 (6%) PA21 lower dose patients.

The randomised treatment groups in Stage 1 (PA21 and sevelamer) were broadly comparable (as were PA21 maintenance dose and PA21 lower dose groups in Stage 2).

[47] K = Dialyser clearance of urea; t = dialysis time; V = patient's total body water

The overall mean age of Stage 1 participants was 56 ± 13 years (range 21 to 89 years) with 42% females and 58% males. Most (77%) were Caucasian. The mean time from diagnosis of ESRD was 65 ± 64 months (median 45 months) with 92% on haemodialysis and 8% on peritoneal dialysis. A total of 8% had previous renal transplant at baseline. Most were taking one phosphate binder (83%) with calcium based binder the most common product (65%) followed by sevelamer (35%). Nearly 72% had been taking an iron supplemental product at baseline.

Stage 1 (Week 12): PA21 versus sevelamer non-inferiority comparison: At baseline (using FAS population), the mean serum P was 2.5 ± 0.59 mmol/L (7.7 ± 1.81 mg/dL) in PA21 group compared to 2.4 ± 0.57 mmol/L (7.5 ± 1.77 mg/dL) in the sevelamer group.

Table 16: Summary of mean serum phosphorous levels (SI and CV Units) and mean change from baseline in Stage 1 (FAS (n = 1,041))

Time Point	Statistic	PA21 (N=694)					Sevelamer (N=347)				
		Serum Phosphorus					Serum Phosphorus				
		mmol/L			mg/dL		mmol/L			mg/dL	
		Mean Dose	Actual	Change	Actual	Change	Mean Dose	Actual	Change	Actual	Change
Stage 1 baseline[1]	n		694		694			347		347	
	Mean	N/A	2.5		7.7		N/D	2.4		7.5	
	SD		0.59		1.81			0.57		1.77	
Week 4	n		651	651	651	651		334	334	334	334
	Mean	N/A	2.0	-0.5	6.2	-1.5	N/D	1.8	-0.6	5.6	-1.8
	SD		0.55	0.55	1.70	1.71		0.48	0.57	1.48	1.76
Week 8	n		607	607	607	607		318	318	318	318
	Mean	9.1	1.9	-0.6	5.8	-1.9	7.0	1.7	-0.7	5.4	-2.1
	SD	2.65	0.49	0.59	1.50	1.84	2.50	0.49	0.59	1.51	1.84
Week 12	n		589	589	589	589		318	318	318	318
	Mean	10.0	1.8	-0.7	5.6	-2.1	8.2	1.7	-0.7	5.3	-2.2
	SD	3.21	0.46	0.62	1.43	1.92	3.16	0.44	0.63	1.35	1.95
Endpoint Week 12[2]	n		694	694	694	694		347	347	347	347
	Mean	N/A	1.8	-0.7	5.7	-2.0	N/D	1.7	-0.7	5.3	-2.1
	SD		0.47	0.63	1.44	1.94		0.42	0.64	1.29	1.97
Week 24	n		496	496	496	496		285	285	285	285
	Mean	11.0	1.7	-0.7	5.4	-2.3	9.0	1.7	-0.7	5.2	-2.2
	SD	3.46	0.47	0.65	1.46	2.02	3.55	0.45	0.62	1.38	1.92
Endpoint Week 24[3]	n		694	694	694	694		347	347	347	347
	Mean	N/A	1.8	-0.7	5.6	-2.1	N/D	1.7	-0.7	5.3	-2.1
	SD		0.51	0.66	1.59	2.05		0.45	0.63	1.40	1.94

3 Endpoint was Week 24 or includes the latest measurement after baseline prior to withdrawal.
Notes: Week 1, 3, 5, 7: Only HD subjects were evaluated.
FAS = Full analysis set; HD = Haemodialysis; N/A = Not applicable; N/D = No data; SD = Standard deviation.

At Week 12, the mean serum P was 1.8 ± 0.46 mmol/L (5.6 ± 1.43 mg/dL) in PA21 group compared to 1.7 ± 0.44 mmol/L (5.3 ± 1.35 mg/dL) the in the sevelamer group.

In the Per Protocol (PP) analysis set (N = 685), used for non-inferiority comparison, the mean (least squares (LS)) change from baseline was -0.71 (-2.19 mg/dL) and -0.79 mmol/L (-2.45 mg/dL) in the PA21 and sevelamer groups respectively. The treatment difference (PA21 versus sevelamer) was 0.08 mmol/L (0.26 mg/dL) with 97.5% CI upper limit of 0.15 mmol/L (0.46 mg/dL) which was below the 0.19 mmol/L (0.6 mg/dL) predefined margin.

A superiority comparison of PA21 versus sevelamer at this Week 12 timepoint, using FAS population (N = 1,041) indicated that the result was statistically significant (p = 0.013) in favour of sevelamer (LS mean difference 0.08 mmol/L (0.23 mg/dL); 95% CI 0.02 to 0.14 mmol/L (0.05 to 0.42 mg/dL).

Stage 2 (Week 24-27): PA21 maintenance dose versus PA21 lower dose;primary outcome (primary efficacy set; N = 93): The mean serum P level at the Stage 2 baseline (Week 24) was 1.5 ± 0.33 mmol/L (4.7 ± 1.03 mg/dL) in the PA21 maintenance dose group compared to 1.6 ± 0.37 mmol/L (5.0 ± 1.14 mg/dL) in the PA21 lower dose group.

At Week 27, the mean serum P level was 1.6 ± 0.34 mmol/L (5.1 ± 1.05 mg/dL) in PA21 maintenance dose group indicating maintenance of effect compared to 2.2 ± 0.50 mmol/L (6.7 ± 1.55 mg/dL) in the PA21 lower dose group.

The mean (LS) treatment effect for change in serum P level (PA21 low dose versus PA21 maintenance dose) was 0.54 mmol/L (95% CI 0.37 to 0.71 mmol/L) [1.67 mg/dL; 95% CI 1.15 to 2.19] indicating loss of control with significant ($p < 0.001$) rise in serum P level in the lower dose group compared to maintenance dose group.

The proportion of patients who achieved controlled serum P levels according to KDOQI[48] was 32/44 (73%) at Week 24 and 24/38 (63%) at Week 27 in PA21 maintenance dose group [(15/44 (34%), and 12/38 (32%) at Weeks 24 and 27 respectively according to KDIGO[49])].

The proportion of patients who achieved controlled serum P levels according to KDOQI was 30/49 (61%) at Week 24 and 7/46 (15%) at Week 27 in the PA21 lower dose group [(14/49 (29%) and 2/46 (4%) at Weeks 24 and 27 respectively according to KDIGO)].

Changes in serum calcium, Ca x P product, serum iPTH were documented.

Baseline to Week 24: PA21 versus sevelamer (FAS; N = 1,041): At 'Week 24 Endpoint' (Table above), the mean serum P level was 1.8 ± 0.51 mmol/L (5.6 ± 1.59 mg/dL) in the PA21 group compared to 1.7 ± 0.45 mmol/L (5.3 ± 1.40 mg/dL) in the sevelamer group. The (LS) mean treatment difference for PA21 versus sevelamer was 0.05 mmol/L (0.15 mg/dL) with 95% CI of -0.02 to 0.12 mmol/L (-0.05 to 0.36 mg/dL).

PA21 and sevelamer demonstrated similar serum phosphorus lowering effects in patients on haemodialysis and peritoneal dialysis.

At Week 24, the proportion of patients who achieved controlled serum P levels was 261/496 (53%) versus 155/285 (54%) according to KDOQI criteria for PA21 versus sevelamer group, respectively, and was 119/496 (24%) versus 85/285 (30%) according to KDIGO criteria for PA21 versus sevelamer, respectively.

The median time to achieve controlled serum P based on KDOQI was 23 days with PA21 and 18.6 days with sevelamer, and was 81.8 days versus 49 days respectively based on KDIGO criteria. The mean duration of control was 72 days versus 81 days with PA21 and sevelamer, respectively, based on KDOQI criteria, and was 40 days versus 51 days for PA21 and sevelamer, respectively, based on KDIGO criteria.

Changes in serum calcium, Ca-P product, serum iPTH, pill burden, Quality of Life measures, patient preferences and body weight are documented.

Week 24 to 52-55 extension (Study PA-CL-05B): The patients who completed treatment in PA-CL-05A (including PA21 maintenance dose patients completing Stage 2) and met all eligibility criteria were enrolled in this 24-28 week extended treatment. The patients continued to receive PA21 or sevelamer according to their randomisation in the base study.

A total of 658 patients received treatment in the extension phase (391 PA21 patients and 267 sevelamer patients). Dose modifications for tolerability and efficacy were allowed during the study. A total of 549/658 (83%) patients completed the study (322 PA21 patients and 227 sevelamer patients).

The serum P levels were maintained with continuing treatment in both groups from Week 24 to Weeks 52-55. The changes in serum P were minimal and the differences between the two groups were not significant at any timepoint.

[48] KDIGO (Kidney Disease Improving Global Outcomes) range 1.13-1.78 mmol/L (3.5-5.5 mg/dL)
[49] KDOQI (Kidney Disease Outcomes Quality Initiative) range 0.81-1.45 mmol/L (2.5-4.5 mg/dL)

Overall, using a combined endpoint[50] (FAS; N = 1,041), the proportion of patients who achieved controlled serum P level according to the KDOQI criteria was 311/694 (45%) versus 181/347 (52%) for PA21 versus sevelamer group, respectively.

Additional outcomes were noted.

Clinical safety

As sucroferric oxyhydroxide is not absorbed systemically, the anticipated adverse effects mainly relate to the GI tract, to physical or chemical interactions with concomitantly administered medications or dietary components (such as vitamins) and consequences of any iron absorption. Some effects such as hyperplasia noted in the animal studies, possibly adaptive responses to local irritation caused by repeated high oral load of drug, were not considered relevant to the expected human use.

A total of 1,500 subjects participated in 10 studies (including 5 DDI studies in healthy volunteers). Of these, 1,112 received PA21, 374 received sevelamer, and 14 received placebo.

The pivotal Phase III Study PA-CL-5A/05B and the Phase II dose ranging Study PA-CL-03A evaluated adult ESRD patient on dialysis, who were either assigned to a fixed (PA-CL-03A) or a dose-titration (PA-CL-05A/05B) PA21 regimen. The Phase II and III safety population comprised of 1,209 patients. Of these 835 received PA21 and 374 received sevelamer. PA21 was administered in the dose range 1.25-15 g/day (divided doses with meals). Both studies included active comparator sevelamer (HCl in PA-CL-03A (6 weeks study) and carbonate in PA-CL-05/05B) for a period of up to 52 weeks (PA-CL-05B).

In Studies PA-CL-05A/05B, the mean duration of exposure to PA21 was 243 days (SD = 130 days) compared with 294 days (SD = 112 days) in sevelamer group. In PA-CL-05A, the average daily dose was 8.2 g/day (SD = 3 days) for PA21 patients and 6.9 g/day (SD = 2.8 days) for sevelamer patients. There was an increase in average daily dose during the PA-CL-05B extension: mean daily dose was 10 g/day (SD = 3.7 days) for PA21 patients and 8 g/day (SD = 5 days) for sevelamer patients.

A total of 513 (73%) patients were treated with PA21 for at least 24 weeks in PA-CL-05A Stage 1 and 319 (45%) PA21 patients completed at least 52 weeks of treatment in PA-CL-05B. The 46 patients in the lower dose arm in Stage 2 were not eligible to enter PA-CL-05B.

In Study PA-CL-05A, the PA21 patients commenced with PA21 5 g/day dose. At the end of 8 weeks dose titration, the distribution of PA21 patients by dose was 17% (5 g/day), 26.5% (7.5 g/day), 30.5% (10 g/day), 25% (12.5 g/day) and 0.8% (15 g/day). At 24 weeks, the distribution was 12% (5 g/day), 17% (7.5 g/day), 22% (10 g/day), 18% (12.5 g/day) and 31% (15 g/day). At 52 weeks in Study PA-CL-05B, the dose distribution of PA21 patients was 11% (5 g/day), 16% (7.5 g/day), 15% (10 g/day), 15% (12.5 g/day) 43% (15 g/day).

The most common TEAE observed with PA21 treatment occurred in the GI Tract SOC. Discoloured faeces were commonly reported with PA21 but were not dose related. Diarrhoea was also a common TEAE which tended to occur early in the course of PA21 treatment and was reported by 23.6% PA21 patients in Studies PA-CL-05A/05B compared to 11.5% in the sevelamer group.

In the Metabolism and Nutritional Disorders SOC, drug pharmacology related effects such as hyperphosphataemia, hypophosphataemia, and hypercalcaemia were reported with similar frequencies in the PA21 patients compared to the sevelamer patients.

[50] Defined as the last post-baseline, non-missing value across study PA-CL-05A (Stage 1) or Study PA-CL-05B

Other common TEAEs included nausea, constipation, vomiting, dyspepsia and abdominal pain, flatulence, tooth discolouration, and product taste. The incidence of constipation with PA21 was 5.1% in Study PA-CL-05A/05B compared to 8.3% in the sevelamer group.

With the exception of GI tract events of faecal discolouration and diarrhoea, the overall AE profile of PA21 was broadly similar to sevelamer. TEAEs analysed by age, sex, race, region and dialysis modality (haemodialysis or peritoneal dialysis) did not reveal clinically meaningful differences from the overall analysis.

However, note that AEs and adverse drug reactions (ADRs) with PA21 treatment were found to be significantly higher against placebo comparison in a dose-related manner as reported in the Phase II dose ranging Japanese study.

Based on data included in this dossier, no safety signals have so far been detected with respect to clinical chemistry or haematology. No clinically meaningful changes in ECG or vital signs were reported. Significant increases in BAP were reported with both treatments (PA21 and sevelamer). Serum calcium levels remained relatively stable during the efficacy studies whereas serum iPTH levels were more variable. Bicarbonate levels also remained unchanged. Serum lipid levels did not show significant changes during treatment with PA21. No immunogenicity events considered drug related have been reported.

The data indicated minimal iron absorption from PA21 with no clinically meaningful effect on iron studies performed during the 52 Week study. There was also no reported evidence of target organ toxicity due to iron accumulation or clinically relevant effect on liver function tests. There was no demonstrable effect on coagulation.

One sevelamer treated patient experienced intestinal obstruction. No instance of intestinal obstruction was reported in the PA21 treatment group. There were no reported cases of intestinal perforation or ileus in either treatment group in any study.

Thirty-five patients experienced fatal TEAEs during the PA-CL-05A/05B Study or within 30 days of the last dose of study drugs. These included 21 (3.0%) PA21 treated patients and 14 (4.0%) sevelamer treated patients. Fatal TEAEs occurred in 32 (3.3%) patients on haemodialysis and in 3 (3.5%) patients on peritoneal dialysis. The causes of death were generally consistent with the ESRD on dialysis related morbidity and majority were attributed (42.9%) to cardiac disorders. There was no indication of major differences in cause of death between treatment groups and there was no association between the incidence of fatal TEAEs and the maximum daily dose. One death was also reported in the PA21 5 g/day group in the dose ranging Phase II study and was also not considered related to the study drug.

Clinical evaluator's recommendation

The clinical evaluator recommended approval of Velphoro for the following indication

> *Velphoro is indicated for the control of serum phosphorus levels in adult patients with end-stage renal disease (ESRD) on dialysis.*

Recommended revisions to the PI were noted.

Risk management plan

This submission was not referred to ACSOM. The European RPM (Version 2.0, dated 26 July 2013) and Australian Specific Annex (dated 11 October 2013), to be revised as specified in the sponsor's correspondence dated 10 July 2014 and as agreed by the TGA and any subsequent mutually agreed changes/updates, apply to this submission (proposed condition of registration).

The finalisation of the PI, in regard to the recommendation of the RMP evaluation area, was pending.

The incidence of 'vitamin deficiency' was 2.26% (16/707) in the PA21 group and 1.72% (6/348) in sevelamer treated patients (RMP evaluation report). In the response to the Delegate's Overview, the sponsor was requested to provide comment in respect of issues raised in the RMP evaluation report, namely potential risk and need for monitoring for 'vitamin deficiency' and 'drug interactions'.

Risk-benefit analysis

Delegate's considerations

1. Sucroferric oxyhydroxide (Velphoro; code PA21) is an iron containing phosphate binder which provides another therapeutic option of a non-calcium and aluminium based product for the control of hyperphosphataemia in ESRD.
2. It is not systemically absorbed but degradation in the gut can release iron which can be systemically absorbed especially in acidic environment such as stomach. However, based on the radiolabelled Study Q-24120 and the iron studies included as safety outcomes in the efficacy/safety trials, the risk of toxic or clinically meaningful iron absorption is considered very low in the intended ESRD patients on dialysis. The chewable tablets are intended for administration with meals.
3. Adequately dose finding and efficacy data were presented, consisting of one Phase II study (6 week dose ranging study using 5 fixed dose levels of PA21 and one dose level of active control sevelamer HCl; placebo group not included) and one Phase III pivotal trial (titration based dosing with PA21 dose range 5 g to 15 g per day in divided doses with meals; up to 52 weeks extension in eligible patients at Week 24; active comparator sevelamer carbonate).
4. Although the proposed starting dose (7.5 g/day) for registration was not the starting dose in the pivotal efficacy trial (5 g/day was the starting dose in the titration phase), the Delegate accepted the argument that overall there is sufficient data (including its use in the dose ranging Phase II study) to support the use of 7.5 g/day starting dose.
5. At Week 12 in the 52 weeks pivotal efficacy trial, the titration-based PA21 regimen was shown to be non-inferior to the titration-based sevelamer regimen according to a predefined margin [PA21 versus sevelamer (LS) mean treatment difference = 0.08 mmol/L (0.26 mg/dL); 97.5% CI upper limit = 0.15 mmol/L (0.46 mg/dL) based on per protocol set].

   The use of an upper limit of 97.5% in this context was correct and is equivalent to a 2 sided 95% CI. The predefined non-inferiority margin for serum phosphorus 0.19 mmol/L (0.6 mg/dL) could arguably have been more conservative.

   Another modelling approach at this timepoint (Week 12) showed that this result indicated statistically superior efficacy of sevelamer (LS mean treatment difference = 0.08 mmol/L (0.23 mg/dL); p = 0.013; 95% CI 0.02, 0.14 mmol/L (0.05, 0.42 mg/dL) based on FAS population).

   At Week 24, the PA21 versus sevelamer (LS) mean treatment difference treatment difference was 0.05 mmol/L (0.15 mg/dL); 95% CI of -0.02 to 0.12 mmol/L (-0.05 to 0.36 mg/dL).

   Given that the upper limit of 95% CI at Week 24 was 0.12 mmoL and appeared to be maintained to Week 52 (not formally tested), the two drugs can be considered to have

similarly meaningful clinical efficacy with respect to the serum phosphorus lowering capacity.

6. The safety profile was consistent with that expected for a drug which is not systemically absorbed and acts in the gut lumen on dietary phosphate. The incidence of diarrhoea was higher and the incidence of constipation lower with PA21 compared to sevelamer. These effects were not always dose related but tended to occur early after the start of therapy with decreasing frequency over time with continued use. Effects particular to PA21 included faecal discolouration due to iron content. Tooth discolouration was also reported. Pharmacological effects such as clinically significant hypophosphataemia were dose related. At this early stage of clinical experience with PA12 (513 patients exposed for 24 weeks and 319 patients exposed for 52 weeks) no safety signals were identifiable with respect to systemic effects, including iron overload or target organ toxicity including liver.
7. Given the observed efficacy and the adverse effects profile, the net risk-benefit balance for the proposed use of sucroferric oxyhydroxide is considered favourable.
8. *Product Information:* In view of the observed results for various drug interactions referred to earlier, the Delegate was of the view that it is appropriate that oral Vitamin D analogues and levothyroxine be not included in the list of drugs not allowed with PA21. In addition, a recommendation regarding alendronate along the lines in the US approved label was also appropriate. The ACPM advice would be requested in regard to the proposed text in the PI.

   In the response to the Overview, the sponsor was requested to comment on whether any clinical studies (PK or PD) are underway or planned to confirm the lack of adsorption noted for a number of drugs in in vitro studies, in particular clopidogrel, metformin and pioglitazone.
9. The proposed product label will show the quantity of elemental iron per table (500 mg) in place of the quantity of the active ingredient sucroferric oxyhydroxide (2.5 g). The ACPM advice would be sought on whether this was clinically appropriate.
10. A 45 day shelf-life (after opening) is proposed for the bottle presentation due to exposure to atmospheric moisture which reduces the desiccated inner iron core and impairs the phosphate binding potency of the product. The ACPM advice would be sought whether availability of this presentation is satisfactory from a clinical point of view.

Proposed action

The Delegate had no reason to say, at this time, that the application for sucroferric oxyhydroxide (Velphoro) 2.5 g (containing 500 mg iron) chewable oral tablet should not be approved for registration.

The data support the following therapeutic indication. The dosing, as proposed, is also supported:

> *Velphoro is indicated for the control of serum phosphorus levels in adult patients with end-stage renal disease (ESRD) on dialysis*

Request for ACPM advice

The Delegate proposed to seek general advice on this application from the ACPM and to request the committee provide advice on the following specific issues:

1. The proposed product label will show quantity of iron per table (500 mg) rather than the quantity of the active ingredient sucroferric oxyhydroxide (2.5 g). Advice is requested from ACPM whether this is considered clinically appropriate.
2. A 45 day shelf-life is proposed for the bottle presentation after opening. This is due to exposure to the atmospheric moisture which reduces the phosphate binding potency of the product. Advice is requested from ACPM whether this is considered clinically appropriate.
3. Advice is also sought from ACPM regarding the appropriate recommendations for concomitant use of Velphoro with a number of drugs, in particular oral Vitamin D analogues, levothyroxine and alendronate.

Response from Sponsor

Introduction

Hyperphosphataemia is a common and serious complication in patients with CKD, particularly those in ESRD requiring dialysis. Chronic kidney disease is a major public health concern worldwide and is associated with decreased quality of life, significant increased morbidity and (premature) mortality. Despite many medical advances, the mortality rate for patients with CKD receiving dialysis is in excess of 20% per year. Mortality due to cardiovascular disease is 10 to 20 times greater in haemodialysis patients compared to the general population after adjusting for age, race, gender and the presence of diabetes.

Vifor (International) Inc. has developed a new oral phosphate binder, PA21, chewable tablet, for the control of serum phosphorus levels in patients with ESRD.

The drug product PA21 is presented as a chewable tablet with a content of approximately 2,500 mg PA21 drug substance, adjusted to the strength of 500 mg iron. The tablet also contains the conventional excipients.

Following oral administration, PA21 adsorbs the dietary phosphate in the GI tract, preventing its uptake into the blood, thereby reducing the serum level of phosphorus. The phosphate bound to PA21 is subsequently eliminated in the faeces.

Clinical studies performed with Velphoro demonstrated the safety and efficacy of PA21 in the control and maintenance of serum phosphorus levels in ESRD patients undergoing maintenance haemodialysis or peritoneal dialysis. The robustness of the efficacy and safety of PA21 was further demonstrated in PA-CL-05A/05B altogether with a markedly reduced pill burden in comparison to sevelamer.

Given the observed efficacy and the adverse effects profile, the Delegates' Overview has concluded that the net risk-benefit balance for the proposed use of sucroferric oxyhydroxide is considered favourable.

Sponsors Response to Issues raised by the Delegate for ACPM advice

The sponsor commented on the following Delegate's recommendations and comments:

Delegate's comment: It is appropriate that oral vitamin D analogues and levothyroxine be not included in the list of drugs not allowed with PA21.

The sponsor agrees with the Delegate that oral Vitamin D analogues should be allowed to be prescribed concomitantly with PA21.

The sponsor respectfully believes that the clinical evaluator has misinterpreted the results of the post-hoc analysis of iPTH levels in patients taking stable doses of oral Vitamin D analogues and PA21. This analysis was performed to investigate whether or not the concomitant use of PA21 can affect the primary efficacy of oral Vitamin D analogues,

namely their iPTH lowering effects. If such an interaction was present, iPTH levels would increase (from baseline) when patients taking stable doses of oral Vitamin D analogues were started on PA21 during the study. Many patients with ESRD have secondary hyperparathyroidism with elevated iPTH levels despite treatment with Vitamin D analogues and/or calcimimetics. It should be noted that PA21 does not primarily affect iPTH levels. Hence, it is not relevant that the mean values of iPTH during the study were still above the recommended KDOQI target range (150 to 300 pg/mL [16.5 to 33.0 pmol/L]). Similarly, data on the proportion of Velphoro treated patients who achieved the target iPTH values or even a 50% reduction from baseline following treatment with Vitamin D analogues is also not relevant to the interpretation of the results of this analysis.

The analyses clearly show that the concomitant use of PA21 did not affect the iPTH lowering effects of oral Vitamin D analogues. Indeed, iPTH levels declined during the study in the PA21 treated patients, and to a greater extent than in the sevelamer treated patients. This result confirms that there is no clinically meaningful interaction between PA21 and oral Vitamin D analogues.

The FDA has recently completed their review of this post-hoc analysis submitted as an supplemental new drug application (sNDA), and have advised that oral Vitamin D analogues can be removed from the list of oral drugs that should not be prescribed with PA21. The sponsor commits to providing TGA with FDA's approval once available.

A recommendation regarding alendronate along the lines in the US approved label will also be appropriate.

Under the *Drug Interaction* section in the US Product Insert (USPI), it is stipulated that alendronate should be taken at least 1 hour before Velphoro. As recommended in the Delegate's overview, the sponsor agrees to include into the PI the following statement:

> *It is recommended that these drugs should be administrated at least 1 hour before or at least 2 hours after intake of Velphoro.*

Delegate's comment: The sponsor is requested to comment on whether any clinical study (PK or PD) are underway or planned to confirm the lack of adsorption noted for a number of drugs in in vitro studies, in particular clopidogrel, metformin and pioglitazone.

To date no clinical studies (PK or PD) are planned or underway to confirm the lack of adsorption noted in particular clopidogrel, metformin and pioglitazone.

Delegate's comment: The proposed product label will show the quantity of elemental iron per tablet (500 mg) in place of the quantity of the active ingredient sucroferric oxyhydroxide (2.5 g). The ACPM advice would be sought on whether this is considered clinically appropriate.

The expression of the dose and tablet strength was changed from the amount of the drug substance (DS) (mixture of iron(III)-oxyhydroxide, sucrose and starches) to the amount of iron in the DS. The rationale for this change was based on the following.

First, iron is the component that is quantified in the tablet and not the polynuclear iron(III)-oxyhydroxide or the total mass of the tablet. According to the stoichiometry of the iron(III)-oxyhydroxide core, a PA21 tablet contains 500 mg iron. Secondly, the mode of action of PA21 is such that iron is the component that binds phosphate. This reference to the iron content is more pharmacologically correct and is consistent with the phosphate binder lanthanum carbonate.

Furthermore it should be noted that the iron content is also used in the USPI and the approved EU Summary of Product Characteristic (SmPC) to express the strength of the tablets.

The sponsor believes the expression of dose and strength with the iron content provides the most suitable dose information and avoids any potential confusion in dosing in Australia.

In accordance with the TGA labelling guidelines, the sponsor has included the active ingredient name "sucroferric oxyhydroxide" on the product label but proposes to express the dose as "500 mg iron as sucroferric oxyhydroxide."

Delegate's comment: A 45 day shelf-life (after opening) is proposed for the bottle presentation due to exposure to atmospheric moisture which reduces the desiccated inner iron core and impairs the phosphate binding potency of the product. The ACPM advice would be s sought on whether availability of this presentation is satisfactory from a clinical point of view.

An in-use stability study was conducted using 90-count drug product in 400 mL HDPE bottles. The selected sample presentation for in-use evaluation represents worst-case based on opening and closing bottles. Considering the lowest effective dosage used during clinical development (2 tablets a day in, for example, PA-CL-05A/B; PA-CL-03A), the 90 tablets contained into the bottle should be used up in 45 days. The maximal shelf-life (after opening) has been designed to simulate the use of the product in practice which in that case should not exceed 45 days. Therefore the 45 day in use shelf life nominated is based on criteria applied to the study design rather than any potential instability of the product.

Furthermore it should be noted that all tests results remained within acceptance criteria with no significant change after 45 days of simulated patient use of bottles and support a 45 day in-use shelf-life after drug product packaged in an HDPE bottle is opened and stored as recommended.

Response to issue raised in the second round clinical evaluation report

Evaluator's comments:

The following changes proposed by the sponsors [in bold and strikethrough font] are not approved:

*'**In addition, clinical studies demonstrated no impact of Velphoro on iPTH lowering effect of oral Vitamin D analogues.** Vitamin D and 1,25-dihydroxy Vitamin D levels remained unchanged.'*

*'In vitro studies with the following drugs showed an interaction: alendronate, cephalexin, doxycycline **and**, levothyroxine~~, atorvastatin, doxercalciferol and paricalcitol~~'*

Based on the response above, the sponsor believes that the proposed addition of the sentence regarding Velphoro impact on the iPTH lowering effects of oral Vitamin D analogues is appropriate.

Comments on the Product Information

The PI has been updated taken into consideration the Delegate's overview recommendations. The PI has also been revised in order to be consistent with the safety information listed in the CMI.

Comments on the Consumer Medicine Information (CMI)

Based on the revised PI, the CMI has been updated accordingly.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register a new chemical entity.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Velphoro, chewable oral tablet, containing 2.5 g (equivalent to 500 mg iron) of sucroferric oxyhydroxide to have an overall positive benefit–risk profile for the amended indication;

> *Velphoro is indicated for the control of serum phosphorus levels in adult patients with chronic kidney disease (CKD) on dialysis.*

In making this recommendation the ACPM noted;

- There were no data submitted in patients under 18 years.
- The need for consistency and accuracy in CKD terminology.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- Negotiation of Product Information and Consumer Medicines Information to the satisfaction of the TGA.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the amendments contained in the Specific Advice section below.

Specific advice

The ACPM advised the following in response to the delegate's specific questions on this submission:

1. The proposed product label will show quantity of iron per table (500 mg) rather than the quantity of the active ingredient sucroferric oxyhydroxide (2.5 g). Advice is requested from ACPM whether this is considered clinically appropriate.

The ACPM advised that iron is the quantified and active component and the statement: "500 mg iron as sucroferric oxyhydroxide" covers both aspects adequately.

2. A 45 day shelf-life is proposed for the bottle presentation after opening. This is due to exposure to the atmospheric moisture which reduces the phosphate binding potency of the product. Advice is requested from ACPM whether this is considered clinically appropriate.

The ACPM was of the view that the 45 day shelf life was probably acceptable and noted similar results between different packaging methods. However, it was also noted that the relevant study only opened containers bd whereas the medicine is to be used tds. The ACPM suggested more prominent display of shelf life on the bottle presentation and inclusion of a statement in the CMI.

3. Advice is also sought from ACPM regarding the appropriate recommendations for concomitant use of Velphoro with a number of drugs, in particular oral vitamin D analogues, levothyroxine and alendronate.

The ACPM agreed with the Delegate's recommendations with respect to the drug interactions for inclusion in the PI.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Velphoro chewable tablet, containing the new chemical entity sucroferric oxyhydroxide in 2500 mg strength (equivalent to 500 mg iron), Velphoro, sucroferric oxyhydroxide 2500 mg (equivalent to iron 500 mg) chewable tablet blister and bottle, indicated for:

> *Velphoro is indicated for the control of serum phosphorus levels in adult patients with chronic kidney disease (CKD) on dialysis.*

Specific conditions of registration applying to these goods

- Implementation in Australia of the Velphoro, sucroferric oxyhydroxide European Risk Management Plan (Version: 5.1, dated 8 September 2014, revised as specified by the Australian Specific Annex (dated 11 November 2014), included with submission 2013-03249-1-3, and any future updates, as agreed with the TGA's Office of Product Review.

Attachment 1. Product Information

The Product Information approved for Velphoro at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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