Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Sucroferric oxyhydroxide

Proprietary Product Name: Velphoro

Sponsor: Vifor Pharma Pty Ltd

Date of CER:
First round: 26 March 2014
Second round: 21 August 2014

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 the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
ANCOVA	Analysis of covariance
AUC_{0-24}	Area under the plasma concentration time curve from time zero to24 hours
AUC_{0-inf}	Area under the plasma concentration time curve from time zero to infinity
BAP	Bone-specific alkaline phosphatase
BL	Baseline
Ca × P	Calcium-phosphorus product
CI	Confidence interval
CKD	Chronic kidney disease
Cmax	Maximum plasma drug concentration
CSR	Clinical Study Report
CTX	Carboxy-terminal cross-linking telepeptide
CVD	Cardiovascular disease
D1	First dialysis session of the week
D2	Second dialysis session of the week
D3	Third dialysis session of the week
DDI	Drug-drug interaction
DOPPS	International Dialysis Outcomes and Practice Patterns Study
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ESA	Erythropoiesis stimulating agent
ESRD	End-stage renal disease

Abbreviation	Meaning
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FGF-23	Fibroblast growth factor 23
FUP	Follow up period
GFR	Glomerular filtration rate
GI	Gastrointestinal
HD	Haemodialysis
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
ICH	International Conference on Harmonisation
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
LD	Low dose
mcg	Microgram
MD	Maintenance dose
PD	Peritoneal dialysis
PEPPS	Primary efficacy per-protocol set
PES	Primary efficacy set
PK	Pharmacokinetics
PPS	Per-protocol set
PTH	Parathyroid hormone
ROW	Rest of the world

Abbreviation	Meaning
SAE	Serious adverse event
SD	Standard deviation
SEM	Standard error of the mean
SF-36	36-item short-form health survey
SI	International System (of Units) (Systèm International d'Unités)
SOC	System organ class
SHPT	Secondary hyperparathyroidism
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

1. Introduction

This is a Category 1 submission to register a new chemical entity Velphoro- sucroferric oxyhydroxide (equivalent to 500mg iron) chewable tablet.

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 gastrointestinal tract.

The proposed indication is

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

2. 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. M, 2002]. Declining kidney function is also associated with a progressive deterioration of mineral homeostasis, including that of phosphorus and calcium [KDOQI, 2003]. 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 F, 2008; Kestenbaum B, 2005; Block, 2004). Hyperphosphataemia contributes to 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; Jono, 2000). 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 S, 2011). 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 (i.e., loss of GFR) (Kanbray M, 2009). 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% CI: 1.12,1.25) (Palmer SC, 2011). 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) 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 FK, 2006) and suggests that suboptimal use of phosphate binder therapy is at least partially responsible for this high rate of hyperphosphataemia. 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, sevelamer carbonate) and a lanthanum salt (lanthanum carbonate).

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 HD receiving calcium-based phosphate binders (Meric F, 1990). In conjunction with raised phosphorus levels, this may contribute to cardiovascular calcification, with potentially fatal consequences [Block GA, 2001). It has been suggested that calcium-based phosphate binders should be avoided in many, if not most patients who are undergoing dialysis (Moe Sm, 2006).

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 MR, 1983; Alfrey AC, 1976).

Sevelamer (available as hydrochloride and carbonate) is a non-absorbable, cationic polymer capable of reversibly binding anions such as phosphate (Chertow GM, 1997; Burke SK, 1997), and is currently widely regarded as the phosphate binder of choice. Gastrointestinal problems are the most frequently reported adverse events (Renagel Tablet PI, 2011; Renvala PI, 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 IA, 2008). The most common AEs are GI events such as nausea and vomiting. Low, but measurable absorption of lanthanum has been observed (Pennick M, 2006; Damment, 2008), and further studies are needed to address the longer-term toxic effect on bone and other organs.

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 P, 2009). It consists of a mixture of polynuclear iron(III)-oxyhydroxide (about 33% m/m), stabilised by sucrose (about 30% mass/mass (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.

2.1.1. Guidance

The sponsor provided the following information from the pre-submission planning forms:-

- As per the Pre Submission Planning Form, the sponsors have provided the EMA Day 120 questions and sponsor responses in Module 1, Annex II to assist in the TGA review.
- The responses relating to the clinical aspects of the EU submission were reviewed by the evaluators.

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

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- Module 5
  - 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).
  - 1 Phase 2 dose-ranging study PA-CL-03A.
  - 1 pivotal efficacy/safety Phase 3 study PA-CL-05A.
  - Long-term safety extension study PA-CL-05B.
  - Other studies: Synopses of 2 additional studies (a Phase 1 study PA1101 and a Phase 2 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.
  - other, e.g. pooled analyses, meta-analyses, PSURs, Integrated Summary of Safety, etc.
- Module 1
  - Application letter, application form, draft Australian PI and CMI.
  - RMP
- Module 2
  - Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

3.2. Paediatric data

The submission did not include paediatric data.

3.3. Good clinical practice

The PA21 development programme adhered to the principles outlined in the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice.

4. Pharmacokinetics

4.1. 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 pharmacokinetic studies can be carried out, e.g., determination of the distribution volume, area under the curve,

or mean residence time. The Phase 1 clinical programme, therefore, focussed on measures for phosphate-binding capacity, iron release and absorption, and drug interactions.

> **Comments**: Given the characteristics of Velphoro and its mechanism of action, the lack of conventional pharmacokinetic studies in the submission is acceptable.

Table 1. 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 vs. 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
Population PK analyses	Healthy subjects	None
	Target population	None
	Other	None

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

4.2. Summary of pharmacokinetics

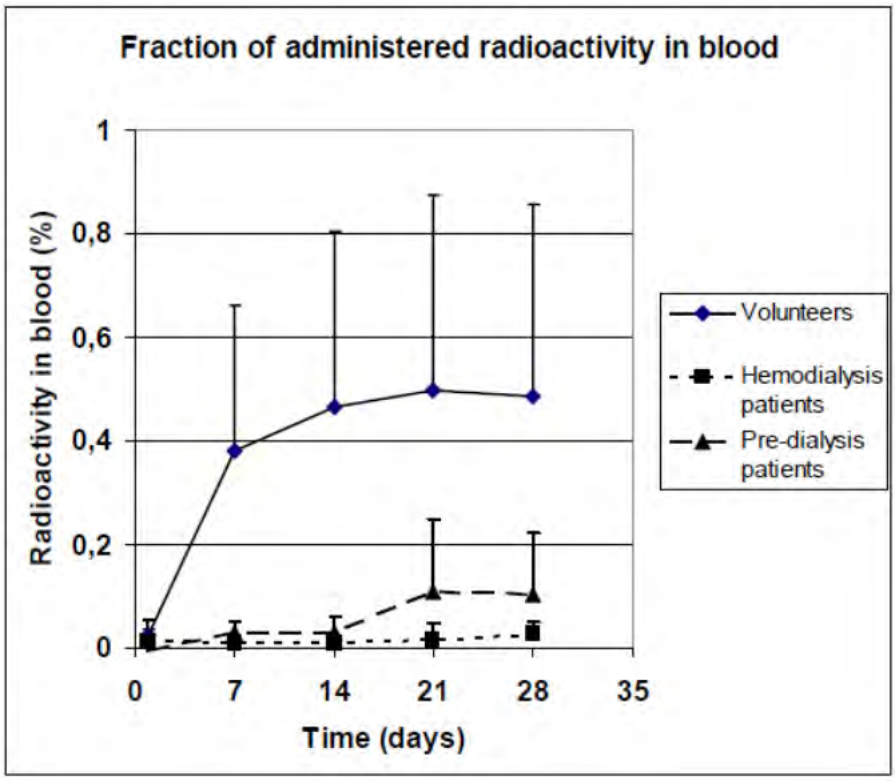
Given the insolubility and degradation characteristics of PA21, and the minimal absorption of the active moiety, iron(III)-oxyhydroxide, no classical pharmacokinetic studies can be carried out, e.g., determination of the distribution volume, area under the curve, or mean residence time. The Phase 1 clinical programme, therefore, focussed on measures for phosphate-binding capacity, iron release and absorption, and drug interactions.

4.2.1. Pharmacokinetics in healthy subjects

4.2.1.1. Absorption

The active moiety of Velphoro, pn-FeOOH, is practically insoluble and therefore not absorbed. However, its degradation product, mononuclear iron species can be released from the surface of pn-FeOOH and be absorbed. The iron uptake from radiolabelled Velphoro drug substance, 2,000 mg in 1 day was investigated in 16 CKD patients (8 pre-dialysis and 8 haemodialysis patients) and 8 healthy volunteers with low iron stores (serum ferritin <100 mcg/L) (study Q24120). The uptake of ^{59}Fe in blood showed the same pattern in all healthy volunteers, with an increase over time that levelled out after approximately 2 weeks (Figure 1). The uptake was in the range of 0.16 to 1.25% with a median value of 0.43% on Day 21. In chronic kidney disease patients, the median uptake was minimal, 0.04% on Day 21. Blood levels of radiolabelled iron were very low and confined to the erythrocytes in both healthy subjects and CKD patients.

Figure 1: Circulating radioactivity in blood as a function of time after administration of radiolabelled Velphoro



PA1101 was a single-centre, randomised, double-blind, placebo-controlled, stepwise dose-escalation (250, 500, and 1,000mg) study in 30 healthy Japanese male volunteers. The changes in serum iron levels observed in all PA21 groups were similar to those observed with placebo.

> **Comments**: The process of erythropoiesis takes 3 to 4 weeks such that iron utilisation from the time of administration only peaks after approximately 2 to 3 weeks, and short-term AUC values of serum iron are of much less relevance than long-term values for iron uptake by erythrocytes. The amount of iron in the serum represents only a small part of

the iron that is transferred to the site of action, which is not proportional to the Cmax or to the AUC values but to the rates of transfer and elimination to and from the serum. Measurement of the uptake of radioactive isotopes (e.g., ^{59}Fe), either in the whole body or only in the erythrocytes, represents the reference method for assessing iron bioavailability. Hence results from the Japanese study PA1101 do not provide any relevant data about iron absorption following administration of PA21.

Whole body counting determines the total amount of labelled iron retained in the body, including iron temporarily stored in the RES or deposited in liver ferritin, and as such is the most comprehensive measurement of iron utilisation. However, whole body counting cannot be measured with non-radioactive isotopes, and in the case of using ^{59}Fe, needs higher radioactivity dosages compared to erythrocyte incorporation measurements. Therefore, erythrocyte counting represents a good measure of how much administered iron is utilised for erythropoiesis, especially if only small amounts (e.g., less than 5 mg iron) are absorbed as it is the case with PA21 in CKD. The pharmacodynamic characteristics of iron possibly released from PA21 are clinically more relevant than its PK. The methods used to measure these characteristics are the most appropriate for this study. In addition, for the long-term pharmacodynamic characterisation of PA21, serum ferritin, and TSAT levels were monitored over 1 year in the 05A/05B studies.

Overall, the absorption/uptake of iron based on measurement of radioactivity in the blood in the Q-24120 study provides an accurate estimation of the total amount of iron that may be absorbed and distributed throughout the body from PA21. The low iron absorption from PA21 shown in this study is further supported by the nonclinical and clinical studies. The lack of tissue distribution data for the absorbed iron in this clinical study (Q-24120) is compensated by the fact that in the long-term studies 05A/05B, serum ferritin and TSAT levels were monitored over 1 year.

4.2.1.2. Bioavailability

4.2.1.2.1. Absolute bioavailability

Not applicable.

4.2.1.2.2. Bioavailability relative to an oral solution or micronised suspension

Not applicable.

4.2.1.2.3. Bioequivalence of clinical trial and market formulations

PA21-1 drug substance was used in the manufacture of the tablet utilised in the Phase 1 clinical studies (Q-24120 and VIT-CI-01/2), Phase 2 study (PA-CL-03A) and as the low dose treatment in the Phase 3 study (PA-CL-05A). The PA21-2 drug substance was used to manufacture the chewable tablets used in the Phase 3 studies (PA-CL-05A and PA-CL-05B) and in the 5 in vivo DDI studies (PA-DDI-001, PA-DDI-002, PA-DDI-003, PA-DDI-004, and PA-DDI-005).

The comparability of the 2 drug substance formulations was demonstrated by comparison of iron release, structure, oxidative state, hydration state, particle size and batch analysis, and stability data. A limited programme of nonclinical “bridging” studies showed that PA21-2 behaved in a similar manner to PA21-1 in terms of toxicity profile, genotoxic potential, and iron uptake/absorption (Quality Overall Summary, and Nonclinical Toxicology Summary).

Allowing for the differences in study designs, the serum phosphorus lowering effects of PA21 in the PA-CL-03A study (using tablets made with PA21-1 drug substance) were broadly similar to Study PA-CL-05A/05B (using tablets made with PA21-2 drug substance). The AEs seen in both studies were also broadly similar, notably with AEs relating to the GI tract. These findings, together with the in vitro and nonclinical studies, confirm the comparability in the clinic of PA21 tablets made from these 2 drug substance formulations.

Comments: Although there were no direct bioequivalence studies to compare the 2 drug substance formulations, the clinical and non-clinical data submitted appear to be adequate.

4.2.1.2.4. Bioequivalence of different dosage forms and strengths

Not applicable.

4.2.1.2.5. Bioequivalence to relevant registered products

Not applicable.

4.2.1.2.6. Influence of food

No formal food interaction studies with PA21 were performed. Nonclinical studies have shown that very little iron is released from PA21 in simulated gastrointestinal (GI) conditions representative of the fed state. Maximum release of iron (approximately 6%) has been shown to occur at pH <2, and in humans, pH levels <2 in the GI tract are normally observed in an empty stomach, i.e., in a fasting state. However, PA21 has to be taken with food otherwise the reaction with phosphate cannot occur. If some Fe(III) is released from PA21, it will be precipitated again as pn-FeOOH during the transport through the GI tract. The possible absorption of the released Fe(III) is also inhibited by hepcidin, which is elevated in ESRD patients. The low absorption of iron was shown in the long-term Phase 3 studies 05A/05B in which serum ferritin and TSAT levels were monitored over 1 year.

4.2.1.2.7. Dose proportionality

Not evaluated.

4.2.1.2.8. Bioavailability during multiple-dosing

Not evaluated.

4.2.1.2.9. Effect of administration timing

Maximal release of iron (approximately 6%) has been shown to occur at pH<2 and in humans, pH<2 in the GI tract are normally observed in the fasting state, i.e., empty stomach. However, PA21 is to be administered with food and so a pH<2 is not likely to be encountered in the normal clinical sue of PA21.

Comments: The proposed PI has adequate instructions to emphasise that the Velphoro tablet is to be administered with meals only and not in a fasting state thus minimising the absorption of iron.

4.2.1.3. Distribution

Due to the insolubility and degradation characteristics of Velphoro, no classical pharmacokinetic studies can be carried out. Therefore, there is no data to determine the distribution of the drug.

4.2.1.4. Metabolism

The active moiety of Velphoro, pn-FeOOH, is not metabolised. However, the degradation product of Velphoro, mononuclear iron species, can be released from the surface of polynuclear iron(III)-oxyhydroxide and be absorbed. Clinical studies have demonstrated that the systemic absorption of iron from Velphoro is low.

In vitro data suggest that the sucrose and starch components of the drug substance can be digested to glucose and fructose, and maltose and glucose, respectively. These compounds can be absorbed in the blood. One tablet is equivalent to 1.4 g of carbohydrates.

4.2.1.5. Excretion

4.2.1.5.1. Routes and mechanisms of excretion

In animal studies with rats and dogs administered ^{59}Fe-Velphoro drug substance orally, radiolabelled iron was recovered in the faeces but not the urine.

4.2.1.5.2. Mass balance studies

None.

4.2.1.5.3. Renal clearance

Not applicable.

4.2.1.6. Intra- and inter-individual variability of pharmacokinetics

The degree of iron uptake in the targeted CKD patient population is dependent on the degree of renal impairment as expressed by the CKD stage (i.e. GFR), the status of hemodialysis treatment and also on the iron status (e.g. serum ferritin). For this reason the uptake of PA-21 was assessed in 2 distinct groups of CKD patients (hemodialysis patients on maintenance therapy and pre-dialysis patients). Compared to the healthy control group, the absorption levels in the CKD patient groups might show slightly larger intra-individual variations and lower absorption levels which was observed in the Phase 1 study Q24120.

4.2.2. Pharmacokinetics in the target population

The active moiety of Velphoro, pn-FeOOH, is practically insoluble and therefore not absorbed. However, its degradation product, mononuclear iron species can be released from the surface of pn-FeOOH and be absorbed. The iron uptake from radiolabelled Velphoro drug substance, 2,000 mg in 1 day was investigated in 16 CKD patients (8 pre-dialysis and 8 haemodialysis patients) and 8 healthy volunteers with low iron stores (serum ferritin <100 mcg/L) (study Q24120). The uptake of ^{59}Fe in blood showed the same pattern in all healthy volunteers, with an increase over time that levelled out after approximately 2 weeks (Figure 1 above). The uptake was in the range of 0.16 to 1.25% with a median value of 0.43% on Day 21. The plasma values were all very low, which suggests that the radioactivity in the blood is confined to the erythrocytes. A lower uptake of administered ^{59}Fe in the blood was seen in the patients with CKD compared to the healthy volunteers with low iron stores (Figure 1). In the CKD patients, the uptake ranged from 0 to 0.44%, with a median of 0.04% on Day 21, which is approximately 10 times lower than in the healthy volunteers [median value 0.43% (range 0.16 to 1.25%)]. Only 2 CKD patients (both pre-dialysis) had values above 0.1%. The median uptake values in the dialysis and pre-dialysis patients were 0.02% (range 0 to 0.04%) and 0.06% (range 0.008 to 0.44%), respectively. As seen in the healthy volunteers, plasma ^{59}Fe levels were also low in the CKD patients. These results indicate that the potential for iron overload with PA21 is expected to be low.

4.2.3. Pharmacokinetics in other special populations

4.2.3.1. Pharmacokinetics in subjects with impaired hepatic function

Not evaluated.

4.2.3.2. Pharmacokinetics in subjects with impaired renal function

PA21 is indicated in subjects with ESRD on dialysis and so studies in patients with mild or moderate renal impairment were not conducted.

4.2.3.3. Pharmacokinetics according to age

Not evaluated.

4.2.3.4. Pharmacokinetics related to genetic factors

Not applicable.

4.2.3.5. Pharmacokinetics {in other special population / according to other population characteristics}

Not applicable.

4.2.4. Pharmacokinetic interactions

4.2.4.1. Pharmacokinetic interactions demonstrated in human studies

Unlike other drugs which act systemically and might therefore interact systemically with other drugs, with or without metabolic activation, PA21 remains and acts locally in the GI tract. Hence, systemic interactions are considered unlikely, although they might occur in the GI tract. For this reason, in vivo experiments which comprise absorption and systemic pathways were not considered necessary. Hence, adsorption to PA21 and/or degradation of concomitant drugs in the presence of PA21 in vitro under physiologically relevant conditions was evaluated. The basic experimental set-up represents worst-case conditions, since no phosphate was present, thereby offering the whole surface of iron(III)-oxyhydroxide to the concomitant drug for potential adsorption. Therefore, in this setting, interactions are over-estimated. If no significant adsorption is observed, a clinically relevant interaction is unlikely; i.e., the systemic absorption and further metabolism of the given concomitant drug is not likely to be influenced by PA21. Using this approach, and together with nonclinical in vivo studies, the low potential for PA21 to bind to or interact with an extensive number of commonly co-administered drugs and dietary components (including vitamins) has been demonstrated, and selected drugs were identified for clinical study in vivo.

A Phase 1 DDI clinical programme in healthy volunteers has been conducted to assess the effects of PA21 on the pharmacokinetics (PK) of some drugs shown to bind extensively with PA21. Human DDI studies were conducted for furosemide and losartan, as well as for drugs where there were no clear in vitro interactions, but where a narrow therapeutic margin exists (i.e., warfarin and digoxin). The observed adsorption of levothyroxine, paricalcitol and atorvastatin was less pronounced in the presence of phosphate which competes for binding to PA21. A human DDI study has also been conducted for omeprazole, as increased solubility was observed in the in vitro study. In addition, a post-hoc analysis of lipid levels in subjects co-administered PA21 and 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (i.e., statins) was conducted using data from the Phase 3 studies PA-CL-5A/05B.

Five DDI studies (PA-DDI-001 (losartan), PA-DDI-002 (furosemide), PA-DDI-003 (omeprazole), PA-DDI-004 (digoxin), and PA-DDI-005 (warfarin)) were conducted with identical designs. These were randomised, open-label, 3-period crossover studies in male and female healthy volunteers, aged 20 to 50 years. Each study had at least 12 evaluable subjects in each treatment group. A PA21 dose of 3,000 mg/day was given for 1 day in 2 of the 3 treatment periods in all studies. This dose is the maximum daily dose of PA21 that will be used in clinical practice. Subjects were randomised to 1 of 3 groups and followed the period dosing schedule for that group, with a 7 day washout period between dosing for each period. The PK sampling schedule reflected the known PK profiles of each test drug so that the endpoint parameters of $AUC_{0\text{-}24}$, $AUC_{0\text{-}inf}$, Cmax, Tmax, and t½ could be calculated to determine the effect of PA21 for all periods. The bioequivalence criteria for log-transformed parameters were defined as 80% to 125%. When the 90% CI for exposure ratios fell within these bioequivalence criteria, it was concluded that no clinically significant differences were present.

Results of study pa-ddi-001 showed that the geometric means of $AUC_{0\text{-}24}$, AUC+, and $AUC_{0\text{-}infinity}$ for losartan were lower by 1-7% when co-administered with PA21 and by 3-5% when administered 2 hours after PA21, but bioequivalence was confirmed (geometric means ratio were contained within the bioequivalence range of 80-125%). Cmax of losartan was decreased

by 7% when PA21 was co-administered but increased by 22% when PA21 was administered 2 hours earlier. In both cases, bioequivalence was not confirmed statistically as the 90% CIs of the geometric least square mean ratio were partially outside the bioequivalence range (80-125%). This effect is consistent with the known food-drug effect of losartan potassium. Tmax of losartan was significantly reduced by PA21 when co-administered (p=0.0021) with losartan potassium and when PA21 was administered 2 hours earlier (p<0.0001). The t½ of losartan and its active metabolite (EXP 3174) was significantly reduced (p=0.0154 and p=0.0415, respectively) when PA21 was co-administered with losartan potassium but not when PA21 was administered 2 hours earlier than losartan potassium. Cmax of the active metabolite were unaffected by PA21 when co-administered with losartan potassium or when administered 2 hours earlier. Tmax of the active metabolite was significantly reduced (p=0.0019) when PA21 was administered 2 hours earlier than losartan potassium but not when co-administered. The extent of formation of EXP 3174, the active metabolite of losartan, was not affected by PA21, regardless of whether PA21 was administered immediately (Trt 1) or 2 hours prior to losartan potassium (Trt 3).The Cmax ratio of losartan metabolite to losartan parent was about 2.0 in the absence of PA21 and did not vary when PA21 was administered either immediately (Trt 1) or 2 hours prior to losartan potassium (Trt 3). The area under curve ratio (regardless of whether it was $AUC_{0\text{-}24}$, $AUC_{0\text{-}t}$ or $AUC_{0\text{-}infinity}$) of EXP 3174 to losartan was about 5.6 in the absence of PA21 and did not vary when PA21 was administered either immediately (Trt 1) or 2 hours prior to losartan potassium (Trt 3).

Results from study pa-ddi-002 showed that the geometric means of $AUC_{0\text{-}24}$, and $AUC_{0\text{-}infinity}$ for furosemide were slightly lower by 6-11% when co-administered with PA21 and by 3-6% when administered 2 hours after PA21, but bioequivalence was confirmed as all 90% CIs on the geometric means ratio were contained within the range (0.80-1.25). Cmax of furosemide was decreased by 15% when co-administered with PA21 but increased by 17% when PA21 was administered 2 hours earlier and bioequivalence in terms of Cmax was not confirmed statistically as the 90% CIs of the least squares mean ratio were partially outside the bioequivalence range (80-125%). Tmax of furosemide was significantly reduced when PA21 was administered 2 hours prior to furosemide (p<0.0001) but not when co-administered. These changes in Cmax and Tmax are characteristic of a food effect and consistent with the food effect described for furosemide. The t½ of furosemide was significantly increased when co-administered with PA21 (p=0.0044) but was not affected when PA21 was administered 2 hours prior to furosemide.

Results of study pa-ddi-003 showed that the $AUC_{0\text{-}8}$, and $AUC_{0\text{-}infinity}$ of omeprazole were not affected or were moderately affected by the presence of PA21, regardless of whether omeprazole was administered immediately or 2 hours following PA21 administration. The Cmax of omeprazole decreased by 14% when co-administered with PA21 and breakfast, but increased by 30% when omeprazole was administered 2 hours after PA21 and breakfast; bioequivalence in terms of Cmax was not confirmed. The Tmax of omeprazole was significantly reduced by 2.5 hours when PA21 was administered 2 hours prior to omeprazole (p≤0.0001) but not when co-administered (increased by 1 hour). Together with the Cmax data, this is consistent with a food-drug effect for omeprazole. The t½ of omeprazole was unchanged in any of the treatment groups. Overall, PA21 co-administered with omeprazole or administered 2 hours prior to omeprazole does not appear to have a clinically relevant effect on systemic exposure to omeprazole.

> **Comments**: One possible explanation for the different effect on omeprazole Cmax is that when administered together, there may be some degree of binding of omeprazole to PA21 in vivo, just as was observed in vitro, leading to a lesser degree of omeprazole absorption. However, when omeprazole was administered 2 hours after PA21, the bolus of PA21 had moved distally down the gastrointestinal tract, and omeprazole was able to be absorbed in the proximal segments of the intestinal tract without interference. An alternate explanation for the apparently inconsistent effect of PA21 on omeprazole

Cmax may be the presence of a food effect. It has been shown that food slows the absorption of omeprazole and decreases Cmax. Following a high-calorie and high-fat meal, there was a significant reduction in rate and extent of systemic exposure for 2 enteric coated omeprazole products.

Results from study pa-ddi-004 showed that the Cmax of digoxin increased slightly when co-administered with PA21 and breakfast but increased even more when digoxin was administered 2 hours after PA21 and breakfast. Digoxin $AUC_{0\text{-}24}$ and $AUC_{0\text{-}infinity}$ were not different from the reference group whether digoxin was administered with PA21 and food or administered 2 hours after PA21 and food. The Tmax of digoxin was slightly shorter when PA21 was administered with breakfast 2 hours prior to digoxin compared to when digoxin was administered immediately with PA21 and breakfast. The half-life of digoxin was about the same whether PA21 was administered with digoxin or not, but it was slightly decreased when it was administered 2 hours prior to PA21 with breakfast, although this difference was not significant.

Comments: When PA21 and digoxin were administered together with breakfast (Trt 1), Cmax was about 10% lower and Tmax was delayed by 0.5 hours compared to when digoxin was administered 2 hours after PA21 with breakfast (Trt 3). These changes in Cmax and Tmax are characteristic of a food effect, although the effect is not a large one, nor can it be established with certainty because Trt 3 and Trt 1 were not compared statistically.

Results from study pa-ddi-005 showed that the Cmax of R- and S-warfarin was essentially the same whether PA21 was administered with or without warfarin. The Cmax of R- and S-warfarin increased slightly when warfarin was administered 2 hours after PA21 and breakfast compared to when warfarin was administered alone with breakfast, or concurrently with PA21 and breakfast. R- and S-warfarin $AUC_{0\text{-}24}$ and $AUC_{0\text{-}infinity}$ were not different from the reference group regardless of whether warfarin was administered with PA21 and food or administered 2 hours after PA21 and food. The Tmax of R- and S-warfarin was reached sooner when warfarin was administered 2 hours after PA21 with breakfast. The t½ of R- and S-warfarin was unchanged in all of the 3 treatment groups.

4.2.4.2. Clinical implications of in vitro findings

In a series of analytical in vitro studies, potential adsorption to PA21 in an aqueous solution was assessed for a range of drugs commonly used in CKD patients. Possible interactions were tested by the quantification of the respective analytes in a validated liquid chromatography assay with ultraviolet, mass spectrometry or fluorescence detection. No significant binding/interaction of PA21 was revealed with a number of drugs which may be co-administered with the compound (ciprofloxacin, digoxin, enalapril, metoprolol, nifedipine, warfarin, hydrochlorothiazide, metformin, quinidine, clopidogrel and simvastatin). No adsorption was found for cinacalcet or glipizide, but results were inconclusive at some pH values. Moderate adsorption to PA21 was noted for pioglitazone. Extensive binding was observed for furosemide, losartan, atorvastatin, doxycycline, alendronate, levothyroxine, paricalcitol, cephalexin and doxercalciferol.

4.3. Evaluator's overall 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 pharmacokinetic studies can be carried out, e.g., 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 gastrointestinal (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, i.e., in a fasting state, but PA21 has to be taken with

food and the proposed PI and CMI has adequate instructions to ensure it is administered with food. Hence, the lack of conventional BA, BA vs 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 1 clinical programme, therefore, focussed on measures for phosphate-binding capacity, iron release and absorption, and DDIs.

The iron uptake from radiolabelled Velphoro drug substance, 2,000 mg in 1 day, was investigated in 16 chronic kidney disease patients (8 pre-dialysis and 8 haemodialysis patients) and 8 healthy volunteers with low iron stores (serum ferritin <100 mcg/L) in the open-label ADME study Q-24120. In healthy subjects, the median uptake of radiolabelled iron in the blood was 0.43% on Day 21. In chronic kidney disease patients the median uptake 0.04% on Day 21, which was approximately 10 times lower than in the healthy volunteers. Hence, subjects on HD 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[1]. In the Phase 3 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 3 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 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, as noted above, 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 (i.e., 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.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

Table 2 shows the studies relating to each pharmacodynamic topic.

[1] Among iron-treated patients in the US between August 2010 and July 2011, the median prescribed dose of intravenous (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.

Table 2. 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.
Population PD and PK-PD analyses	Healthy subjects	None
	Target population	None

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

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

5.2.1. Mechanism of action

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 gastrointestinal tract. Serum phosphorus levels are reduced as a consequence of the reduced dietary phosphate absorption.

In vitro data suggest that PA21 is an effective phosphate binder with a relatively specific, high phosphate binding potency, which is stable, and exhibits minimal release of iron across the range of pH values found in the GI tract. In the aqueous environment of the GI tract, phosphate binding takes place by ligand exchange between hydroxyl groups and/or water and the phosphate ions. PA21 has an optimised binding affinity at pH 3 to 8, and a high phosphate binding capacity in vitro. A dose of 500 mg (iron) binds a minimum of 105 mg of inorganic phosphate under validated laboratory conditions at pH 3.During the development of PA21, the expression of the dose and tablet strength was changed from the amount of the drug substance (mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches) to the amount of iron in the drug substance.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

The pharmacodynamics of PA21 was investigated in the ADME Study Q-24120. An increase in serum phosphorus level was seen in the CKD patients during the 1-week washout period (i.e., when no phosphate-binding agents were administered). During the 1-week treatment with PA21, a reduction of the phosphate level was apparent in all but 1 HD patient. The mean change in serum phosphorus during the treatment period was -0.34 mmol/L (-1.05 mg/dL) in the pre-dialysis patients, -0.60 mmol/L (-1.86 mg/dL) in the dialysis patients and -0.08 mmol/L (-0.25 mg/dL) in the healthy volunteers.

In Study VIT-CI-01/2 no remarkable differences in serum phosphorus concentrations were observed between active treatment groups and the placebo group after 8 days of treatment with PA21 (750 to 2,500 mg/day). Mean serum phosphorus concentrations increased over time in all treatment groups from 1.0 to 1.2 mmol/L (3.1 to 3.7 mg/dL) at baseline (BL) to mean values of 1.2 to 1.3 mmol/L (3.7 to 4.0 mg/dL) on Day 10, likely as a result of the standardised phosphorus-rich diet. Urinary phosphorus concentrations tended to decrease over time in treated subjects, when compared with subjects in the placebo group. This decrease was most pronounced in the 2,500 mg/day PA21 dose group, which may indicate an effect of the drug, although the difference tested via analysis of covariance (ANCOVA) failed to show statistical significance.

In the Japanese study PA1101 no changes in serum phosphorus, serum calcium, serum iron or urinary calcium excretion were detected following either single- or repeat-dose administration of PA21 (250, 500 and 1,000 mg) when compared with placebo. Urinary phosphorus levels, following orally administered repeat doses (3 times daily) for 7 days, showed a dose-dependent trend toward lower elimination when compared to placebo. PA21 was well tolerated. No serious treatment-emergent adverse events (TEAE) or TEAEs leading to discontinuation from the study were reported. All reported TEAEs were mild. The most frequently reported treatment-related TEAEs were diarrhoea and discoloured faeces.

> **Comments**: The lack of clinically significant findings in the above 2 studies (VI-CO-01/2 and PA1101) is not unexpected as it was performed in healthy volunteers whose normal homeostatic mechanisms would have been activated to prevent marked changes in serum or urinary phosphorus levels.

5.2.2.2. Secondary pharmacodynamic effects

Effects of ascending single and multiple doses of PA-21 on serum vitamins (A, D, E and K), calcium metabolism as well as of iron parameters were evaluated in 57 healthy subjects in the Phase 1 study VIT-CI-01/02. Among the parameters iron, ferritin, haemoglobin, transferrin and transferrin saturation, some differences between PA21 dose groups and placebo were statistically significant ($p<0.05$), but these were mainly confined to the lower dose groups. Moreover, there were no consistent trends to higher or lower values across the PA21 dose groups compared with placebo for any of these parameters. The more pronounced increases in ferritin in the two lower dose groups appeared to be influenced by the occurrence of infections in some subjects. The subjects' calcium concentrations in 24 hour urine appeared to increase with the dose on Day 10 compared with placebo up to a dose-level of 11.25 g PA21, but these differences were biased by an accidentally large decrease in the placebo group ($p=0.0004$). No relevant differences between PA21 dose groups and the placebo group were found for calcium concentrations in blood. AP and PTH activities in the higher dose groups appeared to be lower than after placebo administration, but these differences were biased by increases from baseline in the placebo group. Moreover, there was no clear dose-relationship and none of the differences tested via ANCOVA showed a p-value <0.05. For vitamins A, D [25(OH)D], D [1,25(OH)2D], E and K, no consistent trends to higher or lower values were observed after dosing with PA21 compared to placebo. Although vitamin A and vitamin E levels after 12.5-g

PA21 were statistically significantly lower than after placebo administration, but changes were not consistent across other PA21 dose groups.

5.2.3. Time course of pharmacodynamic effects

In study Q24120 the reduction in serum phosphorous was observed within 1 week of start of dosing with similar results observed in the Phase 2 and 3 studies (PA-CL-03A, PA-CL-05A).

5.2.4. Relationship between drug concentration and pharmacodynamic effects

Not applicable.

5.2.5. Genetic-, gender- and age-related differences in pharmacodynamic response

Not applicable.

5.2.6. Pharmacodynamic interactions

The 5 DDI studies evaluated effect of PA21 on the PKs of losartan, omeprazole, furosemide, digoxin and warfarin. However, effect of PA21 co-administration on PDs of each of these drugs was not evaluated (for eg. Effect of PA21 co-administration on coagulation tests was not evaluated for warfarin).

Together, studies PA-CL-05A/05B provided data on over 1,000 subjects treated for up to 12 months, and of these subjects, 40.6% were taking concomitant HMG-CoA reductase inhibitors (statins), the most common being atorvastatin or simvastatin. Post-hoc analyses were conducted on the pooled PA-CL-05A/05B data to determine if there were any pharmacodynamic interactions between PA21 and either atorvastatin, simvastatin, or other statins administered concomitantly in CKD patients on dialysis, specifically to evaluate the potential of PA21 to affect the lipid-lowering effects of these drugs.

Two analysis populations were derived from the safety set (SS) (N=1,055) in PA-CL-05A/05B: the atorvastatin set (AS) (N=1,010) and the simvastatin set (SmS) (N=1,010). Each of these sets included all subjects from the SS with at least 1 BL evaluable LDL-C value and 1 post-BL evaluable LDL-C value. The subjects in each of these sets were analysed based on their study drug treatment in PA-CL-05A/05B (i.e., PA21 or sevelamer) and on the type of statin co-administered: i.e., atorvastatin, “other statin”, or no statin for the AS; and simvastatin, “other statin”, or no statin for the SmS. Changes from BL over time in LDL-C (primary parameter), Total-C, and triglyceride levels were compared for each of these 3 statin groups within the AS or SmS.

The observed results for these post-hoc analyses were consistent with the results in the combined PA-CL-05A/05B studies. In sevelamer-treated subjects, the lipid-lowering effect was seen for both LDL-C and Total-C in all groups in both the AS and SmS, i.e., regardless of statin use at BL. No effect was observed on triglycerides, which is consistent with the known effect of sevelamer on this lipid parameter. These observations indicate that the post-hoc analyses of the AS and SmS have sufficient assay sensitivity to detect an effect of PA21 on the lipid-lowering properties of atorvastatin, simvastatin and other statins, should this effect be present. The LDL-C and Total-C lowering effect observed in the sevelamer group was not seen in the PA21-treated subjects. As also seen in the sevelamer group, no effect was observed on triglycerides.

5.3. Evaluator’s overall conclusions on pharmacodynamics

5.3.1. Primary PD 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 BL 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 2 and 3 studies (PA-CL-03A, PA-CL-05A).

5.3.2. Secondary PD effects

In the Phase 1 study VIT-CI-01/02 involving 57 healthy subjects, administration of ascending single and multiple doses of PA-21 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 [Chertow et al 1999]. This pharmacodynamic effect was observed after 4 weeks of treatment and was maintained for the duration of studies PA-CL-05A/05B. No similar pharmacodynamic 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.

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

6. Dosage selection for the pivotal studies

6.1. Study PA-CL-03A

6.1.1. Study design, objectives, methodology

PA-CL-03A was a Phase 2, parallel group, randomised, open-label, active-controlled, multicentre dose ranging study. It was conducted from 28 Jan, 2009 to 13 Oct, 2009 at 50 study centres, 44 in Europe (Bulgaria, Croatia, Czech Republic, Germany, Poland, Romania, Russia and Switzerland) and 6 in US. The primary objective was to investigate the ability of different doses of PA21 to lower serum phosphorus levels in patients with chronic kidney disease (CKD) on maintenance haemodialysis. The secondary objective was to assess the efficacy/safety profiles of the different doses of PA21.

This 9-week study compared 5 dosage regimens of PA21 with a single dosage regimen of sevelamer hydrochloride (HCl). The study consisted of a screening phase (up to 1 week), a washout phase of 2 weeks, a 6-week treatment phase, and a 2-week run-out phase. The study visits took place on the day of the subject's dialysis sessions. Enrolled subjects underwent a washout of their previous phosphate binders for 2 weeks. After the washout period, study visits took place on the day of the first dialysis session of the week. Subjects were withdrawn if their

serum phosphorus levels exceeded the upper safety limit of 2.75 mmol/L (8.5 mg/dL) at any time as of 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. After the last dose of study treatment, subjects underwent a 2-week run-out phase, during which time they did not receive treatment with a phosphate binder. The run-out phase was stopped prematurely if a subject's serum phosphorus level exceeded the upper safety limit of 2.75 mmol/L (8.5 mg/dL).

6.1.2. Inclusion/exclusion criteria:

The main inclusion criteria were: Adult subjects receiving maintenance haemodialysis 3 times a week for ≥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 before screening serum phosphorus levels were >1.78 mmol/L (>5.5 mg/dL) in the blood sample from Week -1, D2 or D3.

The main exclusion criteria were: Uncontrolled hyperphosphataemia [>2.5 mmol/L (>7.75 mg/dL)] while subject was on conventional phosphate binders; Hypercalcaemia [serum calcium >2.5 mmol/L (>10.0 mg/dL)]; Hypocalcaemia [serum calcium <1.9 mmol/L (<7.6 mg/dL)]; Severe hyperparathyroidism [intact parathyroid hormone (iPTH) levels >600 ng/L at screening]; Intention to initiate therapy with Vitamin D, Vitamin D metabolites or calcimimetics during the study or receiving non-stable therapy with these agents; Known history of non-response to phosphate binders; known hypersensitivity to PA21, sevelamer or any of its excipients, or iron allergy; Pregnancy or lactation[2]; Iron deficiency anaemia at screening (haemoglobin <10 g/dL and ferritin <100 ng/mL) or history of haemochromatosis (or ferritin >800 g/L) or other iron storage disorders; Foreseen concomitant medication changes or intention to change diet during the study and/or known or suspected non-compliance with dietary phosphate restrictions; Significant disorders/medical conditions (e.g., gastrointestinal or hepatic disorders), history of major gastrointestinal surgery within 5 years before screening, planned major surgery, active hepatitis, known seropositivity to human immunodeficiency virus, active infection, history of drug or alcohol abuse within 2 years of screening; treatment with medication for moderate to severe arrhythmic or seizure disorders, had been treated with lanthanum carbonate (Fosrenol) at any time, or sevelamer (Renagel or Renvela) within 3 months of screening, had received antacids containing aluminium or magnesium or oral iron preparations within 1 month of screening; known sensitivity to any of the study products to be administered.

6.1.3. Study treatments

After a washout period from their previous phosphate binder treatment, suitable subjects were randomised to receive either PA21 or sevelamer (HCl) for 6 weeks[3]. PA21 was dispensed as tablets containing 1.25 g of PA21-1. 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).

[2] If of child-bearing potential, subject was not using adequate contraceptive precautions. Subject must have agreed to use adequate contraception during the study and for 1 month after the last dose of study medication. A highly effective method of birth control must have been used.

[3] The study treatment was taken from the first meal after the visit on dialysis day D1 in Week 1 (when the study treatment was first dispensed) until the last meal before the visit on the dialysis day D1 in Week 7. On the dialysis day D1 in Week 1, the subject took only one-third or two-thirds of the full daily dose, depending on the number of meals the subject had after he or she had left the study centre. On the dialysis day D1 in Week 7, the subject took only one-third or two-thirds of the full daily dose, depending on the number of meals the subject had on the dialysis day D1 in Week 1 after he or she had left the study centre. On the days of all other study visits, the number of tablets to be taken prior to the visit depended on the meals a subject had before the study visit. The subjects were instructed to take the study treatment, PA21 or sevelamer (HCl), with meals and with no additional water.

- 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.

Sevelamer (HCl) was dispensed as tablets containing 800 mg of sevelamer (HCl). The subjects received 4.8 g (i.e., 6 tablets) of sevelamer (HCl) per day[4]. There were no dose adjustments during the study. No concomitant medication was to be administered between 2 hours before and 2 hours after the study treatment. The following medications were prohibited during the study: Antacids containing aluminium or magnesium; Iron preparations (intravenous iron preparations were permitted until end of screening); Phosphate binders (except for study treatment); Antibiotics; Anti-arrhythmic and anti-seizure medication if prescribed for moderate to severe arrhythmic and seizure disorders.

> **Comments**: The dose of sevelamer (HCl) used in this study was 4.8 g/day; this dose was chosen as it is an approved dose for this product and is commonly used. However, it is important to note that the PA21-1 formulation used in this study is not the one proposed for marketing (PA21-2); the proposed marketing formulation was only used in the pivotal Phase 3 study PA-CL-05A/05B.

6.1.4. Efficacy variables and outcomes:

The primary efficacy endpoint was change from baseline in serum phosphorus levels at the end of treatment. Secondary efficacy endpoints were Change from baseline in serum phosphorus levels at each time point (apart from end of treatment); Percentage of patients achieving controlled serum phosphorus levels [i.e., ≥1.13 to ≤1.78 mmol/L (≥3.5 to ≤5.5 mg/dL)] after 1, 2, 3, 4, 5 and 6 weeks of treatment, separately; Time to reach the first controlled serum phosphorus level; Serum phosphorus and calcium level at each time point; Change in serum calcium and phosphorus products from baseline at each time point; Serum iPTH levels at each time point; Change in serum iPTH levels from baseline at each time point.

The primary safety endpoints were Adverse events (AEs), Clinical safety laboratory parameters (haematology, clinical chemistry, vitamins, iron status and bone markers were measured at a central laboratory and blood pH was measured locally) and secondary safety endpoints were Vital signs (blood pressure, heart rate, temperature) and body weight, physical examination and standard 12-lead electrocardiogram.

6.1.5. Randomisation and blinding methods

Subjects eligible for treatment were randomised at Week 1, first dialysis session (D1) via an interactive voice response system (IVRS). Subjects were randomised on a 1:1:1:1:1:1 basis to PA21 1.25 g, 5.0 g, 7.5 g, 10.0 g, or 12.5 g or sevelamer (HCl) in an open-label setting. Randomisation was stratified by geographic region, i.e., Europe versus the US.

An open-label design was employed throughout the study because of the impracticability of maintaining blinding of the study treatment due to following reasons:- (1) obtaining and/or manufacturing placebos to sevelamer and PA21 are impractical due to immediate unblinding because of differences in the stool colour of subjects taking PA21 (which will be discoloured because of the iron content in PA21); (2) Sevelamer tablets must be swallowed whole, while PA21 is administered as a chewable tablet and, therefore, a double dummy procedure would require subjects to take an unreasonably high number of tablets. Moreover, the open-label

[4] Sevelamer (HCl) tablets were swallowed whole. During 6 weeks, the daily dose, divided in 3 doses, was taken orally with meals and with no additional water except for the amount usually taken by the subject for the meals.

design did not bias the primary efficacy endpoint of serum phosphorus, which is an objective laboratory measurement.

6.1.6. Analysis populations, sample size, statistical methods

The efficacy analyses were performed on the FAS, i.e., on randomised patients who received at least 1 dose of study treatment and had at least 1 post-baseline efficacy evaluation, and on the PPS i.e., those patients of the FAS without major protocol violations.

A sample size of 19 subjects per group, with at least 1 post-baseline efficacy measurement, was determined to be sufficient for an alpha of 0.05 and 90% power to detect a 2 mg/dL (0.65 mmol/L) change in serum phosphorus, assuming an SD of 2.5 mg/dL using a 2-sided single sample t-test and testing treatment doses from the highest to lowest in an hierarchical manner[5].

The change from baseline in serum phosphorus levels at the end of treatment was analysed with a single sample t-test within each treatment group. Comparisons of the change from baseline in serum phosphorus levels for each of the higher PA21 doses to the lowest PA21 dose (1.25 g/day) were done using an analysis of covariance (ANCOVA) with the baseline serum phosphorus level as a covariate and adjusted for the multiple comparisons (Dunnett). The proportion of patients with controlled serum phosphorus levels [i.e., ≥1.13 to ≤1.78 mmol/L (≥3.5 to ≤5.5 mg/dL)] in the 5 PA21 groups were analysed for an increasing dose effect using a 2-sided Cochran-Armitage test at a 5% significance level. PA21 dose groups were also compared pair-wise to the lowest PA21 dose group as a reference using a chi-squared test (2-sided, 5% significance level). These analyses were done after 1, 2, 3, 4, 5 and 6 weeks of treatment, separately. In addition, 95% confidence intervals were calculated for the percentages of patients with controlled serum phosphorus levels within each group and also for the differences between each of the higher PA21 dose levels and the lowest PA21 levels. Kaplan-Meier estimates were provided for the time to reach the first controlled serum phosphorus level. Log-rank tests were performed for pair-wise comparisons of the different PA21 dose levels to the lowest dose level.

Other efficacy variables were summarised per treatment group by means of tabulated descriptive statistics for measured values and for absolute changes from baseline.

6.1.7. Participant flow

Overall, 417 subjects were screened, 263 subjects were not eligible for the study and 154 subjects were randomised, all of which received study medication. The most common reason for screening failure was non-fulfilment of the inclusion criteria. Of the 154 randomised subjects, 103 subjects (66.9%) completed the study and 51 subjects (33.1%) were withdrawn from the study. The proportions of withdrawn subjects were highest in the PA21 10.0 g/day and 12.5 g/day groups, and lowest in the PA21 7.5 g/day group. The higher withdrawal rates in the 2 highest PA21 dose groups were mainly due to higher incidences of hypophosphataemia which was a pre-defined withdrawal criterion (25.9% for the 10.0 g/day group and 25.0% for the 12.5 g/day group). This observation was anticipated in part due to the known pharmacological effect of the treatment (i.e., lowering serum phosphorus) and also due to the fixed dose design of the study, which would not allow down titration as would be conducted in clinical practice. The second most common reason for withdrawal was a serum phosphorus level above the upper safety limit [serum phosphorus >2.75 mmol/L (>8.5 mg/dL)] recorded at any time from 2 weeks after the start of treatment. As expected, the proportion of subjects who were withdrawn because of hyperphosphataemia was highest in the PA21 lowest dose (1.25 g/day) group (15.4% of subjects). Very few subjects were withdrawn from the study due to serum calcium levels above the safety limit [i.e., hypercalcaemia: serum calcium >2.5 mmol/L (>10 mg/dL)].

[5] To preserve the overall alpha level, a hierarchical testing procedure was applied, testing from the highest PA21 dose (12.5 g/day) to the lowest dose (1.25 g/day) until all doses were tested or the first p-value above 0.05 was observed.

6.1.8. Major protocol violations/deviations

Major protocol deviations were identified for 34 (22.1%) of the 154 randomised subjects. The most common major protocol deviation was "non-compliance to study treatment", occurring in 23 subjects (14.9%) overall. However, for 6 subjects (3.9%), the classification of non-compliance was assigned because compliance data was missing. The proportion of subjects who did not comply with treatment was highest in the PA21 10.0 g/day group (6 subjects, 22.2%).

6.1.9. Baseline data

There were no notable differences between the treatment groups regarding age, height and race; the majority of the subjects were White males from Eastern European countries. The underlying causes of CKD in the pooled PA21 group and in the sevelamer (HCl) group were broadly comparable. In the pooled PA21 group, the most common cause of CKD was reported as "other" (42.1%), followed by glomerulopathy (23.9%). Within the PA21 groups, the most notable differences were in the proportions of subjects whose CKD was caused by glomerulopathy, which was highest in the PA21 10.0 g/day group (8 subjects, 32.0%) and lowest in the PA21 5.0g/ day group (4 subjects, 15.4%); vascular nephropathy, which was highest in the PA21 1.25 g/day group (7 subjects, 26.9%) and lowest in the PA21 12.5 g/day group (3 subjects, 12.5%). T

he median duration of CKD in the pooled PA21 group was 54.2 months whilst for the sevelamer (HCl) group it was 65 months. Within the PA21 groups, the median duration of CKD was longest in the PA21 12.5 g/day group (74.0 months). Hypertension (75.8% and 69.2% in the pooled PA21 group and sevelamer groups, respectively) and diabetes (32% and 38.5%, respectively) were most frequently recorded as underlying history relevant to CKD. In the FAS, 145 subjects (96.7%) had relevant medical and/or surgical history in addition to CKD, as would be expected in this population of severely ill patients with multiple co-morbidities. The MedDRA SOC most commonly associated with relevant medical and/or surgical histories was Vascular Disorders SOC (118 subjects, 78.7%), followed by Blood and Lymphatic System Disorders (101 subjects, 67.3%) and Metabolism and Nutrition Disorders (89 subjects, 59.3%).

All patients had used prior medications and the most commonly used prior medications were calcium supplements (90.5% and 91.7% in the pooled PA21 and sevelamer groups, respectively), followed by "other anti-anaemic preparations" such as ESA (81% and 70.8%, respectively) and heparin products (62.7% and 54.2%, respectively). Platelet aggregation inhibitors excluding heparin were used by 68 (54%) of the pooled PA21 group and 9 (37.5%) of the sevelamer (HCl) group. Parenteral iron preparations were used by 62 (49.2%) of the subjects in the pooled PA21 group and by 9 (37.5%) of the sevelamer (HCl) group. The proportion of subjects using most of the drug classes was similar across the PA21 treatment groups and the sevelamer (HCl) group. Mean treatment compliance was 94.1% in the pooled PA21 group (ranging from 89.4% in the PA21 12.5 g/day group to 100.5% in the PA21 1.25 g/day group) and 92% in the sevelamer (HCl) group.

6.1.10. Results for the primary efficacy outcome

All PA21 treatment groups >5.0 g/day, and the sevelamer (HCl) 4.8 g/day group showed a statistically significant decrease in serum phosphorus levels from baseline to end of treatment in both the FAS and PPS (<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 (-0.348mmol/L)

For the PA21 dose groups, the decrease in serum phosphorus levels appeared to be dose-dependent. For the FAS, ANCOVA comparisons of the lowest PA21 dose (1.25 g/day) to the PA21 10.0 g/day and 12.5 g/day doses for the primary endpoint were statistically significant ($p \leq 0.001$). For the PPS, all PA21 doses >5.0 g/day showed a statistically significantly greater

reduction from baseline in serum phosphorus when compared to the PA21 1.25 g/day group (p≤0.011).

6.1.11. Results for other efficacy outcomes

PA21 treatment resulted in a rapid decrease of serum phosphorus levels in all but the lowest dose group. In the FAS, mean serum phosphorus levels had decreased after 1 week of treatment in all treatment groups, except for the PA21 1.25 g/day group, where little change from baseline was seen throughout the treatment period. In general, the mean decreases from baseline over time were larger in the PA21 10.0 g/day and 12.5 g/day groups than in the PA21 5.0 g/day and 7.5 g/day groups at most time points. In the sevelamer (HCl) group, mean changes from baseline in serum phosphorus were similar to those seen in the PA21 5.0 g/day and 7.5 g/day dose groups throughout the study. Furthermore the higher doses of PA21 had an early and potent effect on phosphorus levels leading to hypophosphataemia in some subjects who consequently discontinued the study early. Mean serum phosphorus levels returned towards baseline levels after subjects entered the 2-week run-out phase (FUP) during which they did not receive treatment with a phosphate binder.

In the FAS at baseline, i.e., before the start of treatment, about 25% of subjects overall had controlled serum phosphorus levels (≥1.13 to ≤1.78 mmol/L; ≥3.5 to ≤5.5 mg/dL), as specified in the KDOQI guidelines despite having a level >1.78 mmol/L (>5.5 mg/dL) during the final week of the washout period, as required for eligibility into the study. In the PA21 groups, the proportions of subjects with controlled serum phosphorus levels at baseline ranged from 11.5% (PA21 5.0 g/day) to 32.0% (PA21 10.0 g/day). At most time points from Week 2 onwards, the proportions of subjects with controlled serum phosphorus levels exceeded the proportions at baseline in all PA21 groups apart from the PA21 1.25 g/day group. The proportions of subjects with controlled serum phosphorus levels varied over time, with the highest proportions seen in the PA21 12.5 g/day group and the lowest proportions seen in the PA21 1.25 g/day group. At week 7 (end of treatment period), the proportion of patients with controlled serum phosphorous levels was 21.1%, 41.2%, 35%, 42.9%, 60% and 42.1% in the PA21 1.25g/day, 5.0g/day, 7.5g/day, 10g/day, 12.5g/day and sevelamer 4.5g/day groups, respectively. At Weeks 3 and 6, the Fisher's exact test for pair- wise comparison of the 4 higher PA21 dose groups to the PA21 1.25 g/day group was statistically significant for most comparisons, indicating a higher proportion of subjects with controlled serum phosphorus levels for the higher PA21 doses compared to the lowest PA21 dose. The median time to first controlled serum phosphorus level [≥1.13 to ≤1.78 mmol/L (≥3.5 to ≤5.5 mg/dL)] was broadly dose-dependent in the PA21 groups with the lowest dose group taking a longer time to achieve first controlled serum phosphorus compared to the higher dose groups (36, 14, 8, 14 and 8 days in the PA21 1.25, 5.0, 7.5, 10 and 12.5g/day groups, respectively); it was 15 days in the sevelamer (HCl) group.

In the FAS, baseline mean serum calcium levels were comparable in the 6 treatment groups (2.10 to 2.16 mmol/L; 8.39 to 8.63 mg/dL). Mean changes from baseline in serum calcium at each time point were small and variable for all of the PA21 treatment groups, ranging from -0.08 to 0.14 mmol/L (-0.30 to 0.56 mg/dL). In the sevelamer (HCl) group, mean changes from baseline were also small [0.02 to 0.12 mmol/L (0.06 to 0.49 mg/dL)] over the study period.

In the FAS, the baseline mean serum calcium × phosphorus products were comparable in the 6 treatment groups. The mean changes from baseline in serum calcium × phosphorus product over time were broadly dose-dependent and consistent with the mean changes in serum phosphorus levels. Mean serum calcium × phosphorus product had decreased after 1 week of treatment in the 4 high-dose PA21 groups and the sevelamer (HCl) group, and this effect was sustained during the whole treatment period. Mean serum calcium × phosphorus product returned towards baseline levels after subjects entered the 2-week run-out phase, during which time they did not receive treatment with a phosphorus binder.

In the FAS, mean serum iPTH levels at baseline ranged from 222.38 ng/L in the PA21 12.5 g/day group to 271.60 ng/L in the PA21 7.5 g/day group. The mean serum iPTH levels were variable over time and across the treatment groups, but were generally lower than baseline for the 3 highest PA21 dose groups and the sevelamer (HCl) group, reflecting the greater serum phosphorus lowering seen in these groups.

> **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 2 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 Kidney Disease Quality Outcomes Initiative was also good during treatment.

6.2. Japanese phase 2 dose-ranging study PA1201

6.2.1. Study design, objectives, treatments

PA1201 was a Phase 2, dose-ranging study in 183 haemodialysis patients with hyperphosphataemia. The study was conducted at 14 centres in Japan from 11 Jan 2012 to 3 July 2012. The main objective was to investigate dose-response efficacy and safety, when orally administering PA21 at single doses of 1.25, 2.5, 3.75 or 5 g, 3 times daily immediately prior to meals for 6 weeks. Following a washout period of 3 weeks (for any phosphate binders that have been taken before study start), the patients were randomised to PA21 3.75g, PA21 7.5g, PA21 11.25g, PA21 15g and placebo (39, 36, 35, 36 and 37 subjects, respectively). The study treatment was chewable brown tablets each containing 1.25 g PA21 and matching placebo tablets. Placebo or PA21 doses of 1.25, 2.5, 3.75 or 5 g are to be orally administered 3 times per 1 day, immediately prior to meals for 6 weeks.

6.2.2. Inclusion/exclusion criteria

The main inclusion criteria were: Patients aged > 20years who have been receiving stable maintenance haemodialysis 3 times weekly for 12 weeks or more before start of observation period and who were planning to continue HD during their treatment period; whose serum phosphate concentration was >6.0 and <10.0 mg/dL, at the week's first dialysis session of observation period week -1. Information on other inclusion and exclusion criteria were provided in the CSR.

6.2.3. Efficacy endpoints and statistical considerations

The primary efficacy variable in this study was serum phosphate concentration, the primary endpoint being change from baseline in serum phosphate concentration at final evaluation. The primary endpoint will be compared between the PA21 and placebo treatment groups using Analysis of covariance (ANCOVA) with treatment and baseline serum phosphate concentration as covariates. The following closed testing procedure is used to adjust the type I error rate at the 0.05 level: PA21 15 g group superiority over placebo; PA21 11.25 g group superiority over placebo; PA21 7.5 g group superiority over placebo and PA21 3.75 g group superiority over placebo.

The following analyses were done, as additional evaluations of the primary endpoint: Analyses of serum phosphate concentration at each time-point; Cumulative achievement rates for target serum phosphate concentrations (≥3.5 to ≤6.0 mg/dL) and Kaplan-Meier plots to evaluate for target serum phosphate concentration achievement times.

Secondary efficacy endpoints were serum phosphate concentration, serum calcium ×phosphate product, and serum intact-PTH concentration.

6.2.4. Patient disposition, analysis sets, baseline characteristics

Overall, 82%, 95%, 86%, 66% and 42% of the patients in the placebo, PA21 3.75 g, 7.5 g, 11.25 g and 15 g groups, respectively completed the study. The number of discontinuations was much higher in the PA21 groups, especially the 11.25 and 15g/day dose groups mainly due to increased incidence of hypophosphatemia. The Per protocol analysis set differed significantly from the FAS with significant differences between the PA21 groups and placebo group in the proportion of FAS patients included in the PP analysis (92%, 83%, 60%, 39% and 76% in the placebo, PA21 3.75 g, 7.5 g, 11.25 g and 15 g groups, respectively). The baseline demographics and disease characteristics were generally similar across treatment groups. The most commonly used previous phosphate binders was calcium carbonate (76% to 85%) followed by sevelamer HCl and lanthanum carbonate hydrate. Treatment compliance was generally similar across treatment groups with exception of lower compliance in the PA21 15g group.

6.2.5. Primary efficacy results

Change from baseline in serum phosphate levels at final evaluation showed dose dependent statistically significant ($p<0.001$) reduction for all PA21 doses compared with placebo (0.14, −1.84, −2.59, −3.17 and −3.78 mg/dL in the placebo, PA21 3.75 g, 7.5 g, 11.25 g and 15 g groups, respectively). The reduction in serum phosphorous was observed by first week of treatment and maintained for the 6 week duration of treatment.

Cumulative achievement rate were statistically significantly ($p<0.001$, Fisher's exact tests) greater in all PA21 dose groups compared with placebo (35.5%, 80.6%, 93.8%, 96.9% and 100.0% in the placebo, PA21 3.75 g, 7.5 g, 11.25 g and 15 g groups, respectively).

6.2.6. Secondary efficacy results

Corrected serum calcium levels showed a reduction in all PA21 dose groups compared with placebo. Serum calcium × phosphate product also showed similar reduction in all PA21 dose groups. Serum intact-PTH levels also showed reduction from baseline in all PA21 groups while there was no change in the placebo groups.

> **Comments**: The use of placebo control in this Japanese study was not appropriate considering 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 to 15g/day).

7. Clinical efficacy

7.1. Indication 1: Control of serum phosphorus levels in patients with end stage renal disease (ESRD)

7.1.1. Pivotal efficacy studies

7.1.1.1. Study PA-CL-05A

7.1.1.1.1. Study design, objectives, locations and dates

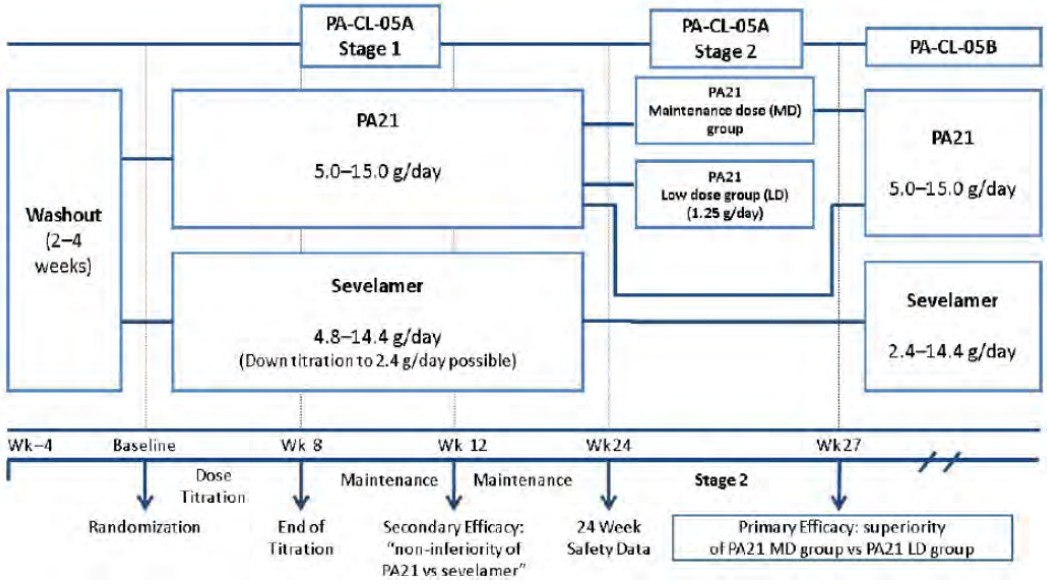
PA-CL-05A was an open-label, randomised, active-controlled, parallel group, multicentre, Phase 3 study to investigate the safety and efficacy of PA21 compared with Sevelamer Carbonate followed by a randomised comparison of PA21 Maintenance Dose versus PA21 Low Dose in 1059 dialysis patients with hyperphosphataemia. The study was conducted from 7 Mar, 2011 to

9 April 2012 at 174 active centres in 14 countries (Austria, Belgium, Croatia, Czech Republic, Latvia, Lithuania, Poland, Romania, Russia, Serbia, South Africa, Ukraine, UK and US).

The primary efficacy objective was to establish the superiority of PA21 maintenance dose (MD) versus PA21 low dose (LD) control in maintaining the phosphorus lowering effect in patients undergoing haemodialysis (HD), 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.

This was a 2-stage re-randomisation study: After a 2-4 week washout period, eligible subjects were randomised and entered Stage 1. Stage 1 was a prospective, randomised, parallel group, open-label, active controlled, 24-week study of PA21 compared with sevelamer. Subjects received an individualised MD of PA21 or sevelamer after an 8-week titration period. The objective of this stage was to compare the efficacy (in a non-inferiority analysis at 12 weeks) and safety (at 24 weeks) of PA21 versus sevelamer. Stage 2, starting at Week 24, was a prospective, randomised, parallel group, open-label, 3-week comparison of PA21 MD (dose previously titrated for efficacy) versus PA21 LD control (fixed dose of 1.25 g/day) (Figure 2).

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



The objective of this stage was to compare (in a superiority analysis) the efficacy of the PA21 MD group to the PA21 LD control group using a treatment withdrawal approach. Subjects on HD had weekly study visits for the first 8 weeks of treatment, and then every 4 weeks until Week 24. Subjects on PD had study visits every second week for the first 8 weeks of treatment, and then every 4 weeks until Week 24. For subjects on HD, study visits were planned to coincide with the first dialysis session of the week (i.e., D1). Subjects on PD were free to select a weekday for the study visits that coincided best with their weekly routine.

Follow-up and extension study: At the end of the 3-week treatment period in Stage 2 (Week 27), subjects from the Stage 2 PA21 MD treatment group moved directly into Study PA-CL-05B (a 6-month extension study). Subjects who were randomised in Stage 2 to the PA21 LD control group completed the study after 27 weeks of treatment and were not eligible for Study PA-CL-05B. Subjects who did not participate in Stage 2 completed the study after 24 weeks of treatment and moved directly into Study PA-CL-05B (6-month extension study).

7.1.1.1.2. Inclusion and exclusion criteria

The main inclusion criteria were: Male and female adult subjects (aged ≥18 years at time of consent) receiving maintenance HD 3 times/week with a Kt/V of ≥1.2 or peritoneal dialysis (PD) with a Kt/V of ≥1.7 within the last 3 months prior to screening (No home HD or nocturnal HD- overnight stay at site, was allowed); history of hyperphosphataemia and receiving stable doses of a phosphate binder(s) for at least 1 month prior to screening. Subjects may be on stable doses of 1 or 2 phosphate binders; Subjects with serum phosphorus levels ≥1.94 mmol/L (≥6.0 mg/dL) during the washout period (a minimum of 2 weeks washout period was obligatory); subjects with the ability to understand the requirements of the study and abide by the study restrictions and give written informed consent.

The main exclusion criteria were: Subjects with intact parathyroid hormone (iPTH) levels >800 ng/L (>800 pg/mL or 88 pmol/L) at screening. Subjects with iPTH >600 ng/L (>600 pg/mL or 66 pmol/L) at screening must be considered stable in the Investigator's opinion; planned or expected parathyroidectomy within the next 12 months; anticipated need for major surgery during the study that may be associated with increased risk to the subject, or may interfere with study assessments or outcomes, or the ability to provide written informed consent or comply with study procedures; history (within 3 years of screening) of major gastrointestinal (GI) surgery likely to influence the outcome of treatment with phosphate binders and/ or significant GI or hepatic disorders; Subjects currently with: Unstable angina, Unstable hypertension, Uncontrolled diabetes, Estimated life expectancy of less than 12 months, Anticipated renal transplantation during study participation; Subjects with known seropositivity to human immunodeficiency virus, hepatitis B surface antigen positivity and/or hepatitis C virus ribonucleic acid positivity at screening; Subjects with significant medical conditions; history of haemochromatosis or other iron accumulation disturbances that might lead to iron overload; Serum ferritin >2,000 mcg/L (4,494 pmol/L) at screening.; Subjects on PD with a history of peritonitis in the last 3 months or ≥3 episodes in the last 12 months; on non-calcium based phosphate binders with hypercalcaemia [serum total calcium >2.60 mmol/L (>10.50 mg/dL)] at screening; hypocalcaemia [serum total calcium <1.9 mmol/L (<7.6 mg/dL)] at screening; raised alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of the normal range at screening; taking any prohibited medications; Subjects taking more than 2 phosphate binders concomitantly prior to screening or subjects who are phosphate binder naïve prior to screening; history of drug or alcohol abuse within 2 years prior to screening; Subjects currently enrolled in or who have completed any other investigational device or drug study <30 days prior to screening, or subjects receiving other investigational agents; pregnancy/ lactation known sensitivity to any of the study products to be administered during dosing; Subjects previously randomised to or received treatment with PA21 in this or any other PA21 study.

Subjects entering Stage 2 must be on HD, must complete Stage 1, must be on PA21 in Stage 1, and must have a controlled serum phosphorus level of <1.78 mmol/L (<5.5 mg/dL) at Week 20.

7.1.1.1.3. Study treatments

The study investigational treatments 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). Two formulations of PA21 (PA21-1 and PA21-2) were used in this study. The PA21-1 formulation which was also used in the completed Phase 2 study (PA-CL-03A), was used in Stage 2 by subjects who were randomised to the LD control group (fixed dose of 1.25 g/day). The PA21-2 formulation was used in Stage 1 by subjects who were randomised to PA21 and in Stage 2 by subjects who are randomised to the PA21 MD group.

Subjects randomised to PA21 commenced treatment at a dose of 5.0 g/day. Dose titrations with single 2.5 g/day dose adjustments at every 2 weeks were allowed for efficacy (target serum

phosphorus levels between 0.81 to 1.78 mmol/L (2.5 to 5.5 mg/dL)) or for tolerability reasons during the first 8 weeks of treatment. The maximum dose of PA21 was 15.0 g/day (6 tablets/day) and the minimum dose was 5.0 g/day (2 tablets/day). The starting dose for Sevelamer was 4.8 g/day and the dose was titrated for efficacy and tolerability reasons. Dose increases or decreases of 2.4 g/day (3 tablets/day- 1 tablet per meal) every 2 weeks were permitted. The maximum dose of sevelamer was 14.4 g/day (18 tablets/day) and the minimum dose was 2.4 g/day (3 tablets/day) (see Table 3 below).

Table 3: 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.

After the first 8 weeks dose titration period, the subject continued on a stable dose of either PA21 or sevelamer for a further 4 weeks maintenance period. However, dose titrations for tolerability reasons throughout this period were allowed. Subjects continued their study medication from Week 12 to Week 24, during which time dose titrations were allowed for both tolerability and efficacy reasons. During this period, dose titrations for efficacy were based on central laboratory values taken at regular study visits (every 4 weeks)[6]. At Week 24, 100 subjects on HD from the Stage 1 PA21 treatment group who had completed Stage 1 and who had a controlled serum phosphorus level of <1.78 mmol/L (<5.5 mg/dL) at Week 20, were randomised via IVRS in a 1:1 ratio to the PA21 MD group or the PA21 LD group (50 to the PA21 MD group and 50 to the PA21 LD group). Subjects randomised to the PA21 MD group continued with the same dose they were receiving at the end of Stage 1 (Week 24), and no dose adjustments were allowed for the next 3 weeks, until Stage 2 was complete. Subjects randomised to the PA21 LD group were switched from the dose they were receiving at the end of Stage 1 (Week 24) to PA21 1.25 g/day, with no dose adjustments allowed for the next 3 weeks, until Stage 2 was complete.

At the end of the 3-week Stage 2 period (Week 27), subjects from the PA21 MD group moved directly into Study PA-CL-05B (6-month extension study). Subjects who were randomised in Stage 2 to the PA21 LD group completed the study after 27 weeks treatment and were not eligible for study PA-CL-05B. Subjects who did not participate in Stage 2 completed the study after 24 weeks treatment in Stage 1 and moved directly into Study PA-CL-05B.

Prohibited therapies in this study included the following: Antacids containing aluminium, calcium or magnesium; phosphate binders (i.e., phosphate binders in addition to the study medications PA21 or sevelamer); Oral iron therapies[7] and oral iron supplements specifically intended to increase iron intake.

Concomitant medications that have a direct influence on serum phosphorus levels (e.g., Vitamin D, Vitamin D analogues and calcimimetics), dietary restrictions (e.g., phosphorus and calcium intake) and dialysis regimens (e.g., duration of dialysis, number of HD sessions per week, number of PD exchanges/day, modality of dialysis) remained unchanged as far as possible in

[6] If a dose adjustment was indicated, i.e., if the serum phosphorus level was outside the target serum phosphorus levels of 0.81 to 1.78 mmol/L (2.5 to 5.5 mg/dL), the Investigator informed the subject (either directly or by phone) whether a dose increase or a dose decrease was indicated.

[7] Intravenous iron treatment during the course of the study was allowed, and was recorded in the eCRF and source documentation for each visit, including trade name, dosage, start and stop dates and reason for use

both the PA21 and sevelamer groups throughout the study in accordance with local clinical practice. This did not apply if changes were indicated for safety and tolerability reasons.

7.1.1.1.4. Efficacy variables and outcomes

The primary efficacy endpoint (Stage 2) was Change from Week 24, D1[8] in serum phosphorus levels at Week 27, D1 – a superiority comparison between the PA21 MD group and the PA21 LD control group (fixed dose of 1.25 g/day) in the primary efficacy set (PES) of subjects on HD. Serum phosphorus is routinely measured in clinical practice by automated calorimetric methods and generally recognised to be precise and reproducible. It has been used as the primary objective measure of efficacy in studies of other approved phosphate binders.

The key secondary efficacy endpoint was Change from baseline in serum phosphorus levels at Week 12 – a non-inferiority comparison between PA21 and sevelamer (per-protocol set (PPS) and full analysis set (FAS)).

Other secondary endpoints included Change from baseline in serum phosphorus levels at Week 1 through to Week 8, Week 12, 16, 20, and 24 (PPS and FAS using a mixed model repeated measure analysis); Achievement of response (serum phosphorus control[9]) at Week 12 and Week 24; Duration of serum phosphorus levels in the KDIGO normal range 0.81 to 1.45 mmol/L (2.5 to 4.5 mg/dL); Duration of serum phosphorus levels in the KDOQI target range of 1.13 to 1.78 mmol/L (3.5 to 5.5 mg/dL).

Secondary endpoints related to both safety and efficacy were: Serum calcium (total, corrected and ionised), Serum calcium-phosphorus product and Serum iPTH levels at each time point and change from baseline; Proportion of subjects that develops hypo/hyperphosphataemia.

Additional assessments included:- Pill burden (summarised by treatment group for each treatment period in Stage 1 and for Stage 2); Quality of life was assessed using the standard SF-36 (Version 2.0) quality of life questionnaire. patient preference and patient satisfaction assessments (using traditional Likert scale); Changes in dietary habits[10], including fluid intake; Changes in dialysis parameters[11].

Efficacy endpoints were also evaluated for subgroups based on dialysis status (PD, HD), region (EU, US, ROW), age (<65, ≥65), sex, race (White, Black, Other), ethnicity (Hispanic, Non-hispanic), and prior sevelamer treatment within 12 months prior to screening.

Treatment Compliance[12] was calculated by dividing the number of pills taken by the number of pills expected to be taken based on dose.

7.1.1.1.5. Randomisation and blinding methods

An open-label design was employed throughout the study because of the impracticability of maintaining blinding of the study treatment. In addition, obtaining and/or manufacturing placebos to sevelamer and PA21 are impractical and/or technically challenging. Sevelamer tablets must be swallowed whole, while PA21 is administered as a chewable tablet and,

[8] D1 refers to the first dialysis session of the week

[9] defined as: – Percentage of subjects with serum phosphorus within the Kidney Disease Outcomes Quality Initiative (KDOQI) guideline target range of 1.13 to 1.78 mmol/L (3.5 to 5.5 mg/dL); – Percentage of subjects with serum phosphorus within the Kidney Disease Improving Global Outcomes (KDIGO) guideline normal range of 0.81 to 1.45 mmol/L (2.5 to 4.5 mg/dL).

[10] The parameters recorded were the intake of fluid, potassium, lipids, sodium chloride, phosphorus, protein, calcium, and other changes

[11] Dialysis modality and dose were to remain as stable as possible during the study.Kt/V was recorded by the Investigator at screening (from historical data), and derived from the dialysis parameters at baseline and Weeks 12, 24 and 27 (Visits 4, 13, 16, and 19).

[12] Investigator ensured that adequate records of the receipt, preparation, administration and return of the study drug were kept and that the study drug was used only for subjects enrolled in the study. Each study centre maintained a drug inventory/dispensing record for all drugs dispensed and returned.

therefore, a double dummy procedure in Stage 1 would require subjects to take an unreasonably high number of tablets. A placebo would have led to immediate unblinding in Stage 1 and Stage 2 due to differences in the stool colour of subjects taking PA21 (which will be discoloured because of the iron content in PA21 tablets). Moreover, the open-label design did not bias the primary efficacy endpoint of serum phosphorus, which is an objective laboratory measurement and was analysed by 1 of 2 central laboratories.

Subjects who were eligible were randomised via an interactive voice response system (IVRS) in a 2:1 ratio to either PA21 or sevelamer, respectively, and entered the treatment period.

Stage 2: At Week 24, 100 subjects on HD from the Stage 1 PA21 treatment group who had completed Stage 1 and who had a controlled serum phosphorus level of <1.78 mmol/L (<5.5 mg/dL) at Week 20, were randomised via IVRS in a 1:1 ratio to the PA21 MD group or the PA21 LD group (50 to the PA21 MD group and 50 to the PA21 LD group).

7.1.1.1.6. Analysis populations

A total of 1,840 subjects were screened, 1,059 subjects (57.6%) were randomised to treatment in Stage 1 and 1,055 received treatment. A subset of 99 subjects was randomised to treatment in Stage 2. Subject analysis sets described in the protocol were:

- FAS, which consisted of all subjects randomised to treatment who received at least 1 dose of randomised study medication and had at least 1 post-baseline evaluable efficacy assessment.
- PPS, which consisted of all subjects who, in addition to the FAS criteria, had completed the analysis dose titration period (baseline to Week 12) and had at least 1 evaluable serum phosphorus result at or after Week 12, and had no major protocol deviations.
- Safety set (SS), which consisted of all randomised subjects who took at least 1 dose of study medication.

Additional analysis sets described in the Statistical Analysis Plan were:

- PES, which consisted of subjects who were randomised to Stage 2 and received at least 1 dose of study medication during Stage 2 and had at least 1 evaluable post-baseline (Stage 2) efficacy assessment in Stage 2.
- Primary efficacy per-protocol set (PEPPS), which consisted of all subjects who were randomised to Stage 2 and had no major protocol deviations.
- Safety set for Stage 2 (SS2), which consisted of all subjects who received at least 1 dose of study medication during Stage 2.

Summary of analysis sets in Stage 1 and Stage 2 are provided in Table 4.

Table 4: Summary of analysis sets in Stage 1 and Stage 2

Summary of Analysis Sets in Stage 1 - All Subjects Randomised (N=1,059)

Parameter	PA21 (N=710) n (%)	Sevelamer (N=349) n (%)	Total (N=1,059) n (%)
Safety set	707 (99.6%)	348 (99.7%)	1,055 (99.6%)
Full analysis set	694 (97.7%)	347 (99.4%)	1,041 (98.3%)
Per-protocol set	461 (64.9%)	224 (64.2%)	685 (64.7%)

Summary of Analysis Sets in Stage 2 - All Subjects Randomised to Stage 2 (N=99)

Parameter	PA21 MD (N=50) n (%)	PA21 LD (N=49) n (%)	Total (N=99) n (%)
Safety set for Stage 2	45 (90.0%)	49 (100%)	94 (94.9%)
Primary efficacy set	44 (88.0%)	49 (100%)	93 (93.9%)
Primary efficacy per-protocol set	31 (62.0%)	27 (55.1%)	58(58.6%)

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

7.1.1.1.7. Sample size

The sample size for Stage 1 of the study was based on the secondary efficacy endpoint: change from baseline in serum phosphorus levels at Week 12 – a non-inferiority comparison between PA21 and sevelamer. Assuming a mean decrease in serum phosphorus levels of 0.65 mmol/L (2.0 mg/dL) in both treatment groups with a standard deviation (SD) of 0.63 mmol/L (1.96 mg/dL), a power of 90%, a non-inferiority margin of 0.19 mmol/L (0.6 mg/dL), and a randomisation ratio of 2:1 (PA21:sevelamer), a total of 507 PPS subjects were required (338 subjects in the PA21 group and 169 subjects in the sevelamer group). To account for a 20% rate of subjects being excluded from the PPS, a minimum of 636 subjects was required (424 in the PA21 group and 212 in the sevelamer group).

The sample size for Stage 2 of the study was based on the primary efficacy endpoint: change from Week 24, D1 in serum phosphorus levels at Week 27, D1 – a superiority comparison between the PA21 MD group and the PA21 LD control group. The number of subjects needed for this analysis was 50 per group, assuming a difference between the groups of 0.42 mmol/L (1.30 mg/dL), SD of 0.63 mmol/L (1.96 mg/dL), a power of 90% and a 2-sided significance value of 0.05. Therefore, for Stage 2 it was planned to randomise a total of 100 subjects from the subjects on HD who completed 24 weeks on PA21 in Stage 1 and had a controlled serum phosphorus level of <1.78 mmol/L (<5.5 mg/dL) at Week 20.

7.1.1.1.8. Statistical methods

The primary superiority efficacy analysis compared the change from Week 24 in serum phosphorus levels at Week 27 in the PA21 MD group to the PA21 LD control group, after 24 weeks of treatment with PA21 (HD subjects only). The comparison was assessed using an analysis of covariance (ANCOVA) with Week 24 serum phosphorus level and region as covariates for the PES.

A secondary non-inferiority efficacy analysis compared the change from baseline in serum phosphorus levels at Week 12 in the PA21 group to the sevelamer group on the PPS. The ANCOVA analysis was conducted using a mixed model with baseline serum phosphorus level, dialysis status and region as fixed effects. The 97.5% 1-sided CI for mean change differences between treatment groups was presented and compared to the non-inferiority margin of 0.19

mmol/L (0.6 mg/dL). If the upper bound of the 97.5% 1-sided CI fell below 0.19 mmol/L (0.6 mg/dL), then the non-inferiority of PA21 against sevelamer was concluded. The same analysis was conducted for the FAS as a secondary and supportive analysis. A mixed model for repeated measures was used to compare the trends in changes from baseline in serum phosphorus levels between the PA21 and sevelamer treatment groups for both the PPS and FAS sets at Week 1 through to Week 8, Week 12, 16, 20, and 24. In addition to the overall analyses sets, efficacy endpoints were also evaluated for subgroups based on dialysis status (PD, HD), region (EU, US, ROW), age (≤65, >65), sex, race (White, Black, Other), ethnicity (Hispanic, Non-hispanic), and prior sevelamer treatment within 12 months prior to screening. Changes from baseline in quality of life scores and patient preference and patient satisfaction scores were analysed only for the FAS and were summarised by treatment. Changes in dietary habits and dialysis parameters were summarised by treatment group and maximum daily dose using summary statistics and shift tables.

Comments: The sponsors have provided the following justification for selecting the non-inferiority margin of 0.19mmol (0.6mg/dl):

The number of randomised clinical trials comparing sevelamer (sevelamer carbonate or sevelamer hydrochloride) against placebo is very limited (Tonelli M, 2007[13]; Navaneethan SD[14], 2009). 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 SD of around 2.2 mg/dL (range from 2.1 mg/dL to 2.4 mg/dL) (Bleyer AJ, 1999; Braun J, 2004; Chertow GM, 1999) . 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 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 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 MD group versus the non-effective LD control group which essentially functions as a placebo control group.

[13] 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.

[14] 40 trials (6,406 patients) were included. There was no significant decrease in all-cause mortality (10 randomized controlled trials; 3,079 patients; relative risk [RR], 0.73; 95% confidence interval [CI], 0.46 to 1.16), hospitalization, 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 (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.

It is conventional, however, to state confidence intervals with 95%, not 97.5% 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 under *Clinical questions*, below.

7.1.1.1.9. Participant flow

Stage 1: A total of 1,840 subjects were screened and 1,059 subjects were randomised to treatment in Stage 1 (710 randomised to PA21 and 349 to sevelamer). A total of 1,059 subjects were randomised to treatment in Stage 1, 1,055 (99.6%) were treated, and 808 (76.3%) completed Stage 1. Of the subjects that completed Stage 1, 659 (62.2%) enrolled in the PA-CL-05B study extension and 99 subjects (14.0% of subjects in the PA21 group) who were on HD enrolled in Stage 2. During Stage 1, 251 subjects (23.7%) prematurely discontinued the study with higher withdrawal rate in PA21 group (195 subjects (27.5%)] compared with sevelamer [56 (16.1%)]. The primary reasons for withdrawal in Stage 1 (excluding deaths) were non-fatal AEs for other than phosphorus or calcium levels (45.8% of all withdrawals), and withdrawal of consent (18.7%), renal transplant (9.2%), protocol deviation (2.8%), Investigator decision (2.4%, all for non-compliance), hyperphosphataemia (4.8%), and Sponsor decision (3.6%, all due to closure of site 701). Less frequent reasons were hypercalcaemia (0.8%), prohibited medications (0.8%) and hypophosphataemia (0.4%).

Stage 2: Of the 99 subjects randomised to Stage 2, 94 were treated and 88 completed Stage 2. During Stage 2, 11 subjects prematurely discontinued the study (8 of 50 subjects or 16% in the PA21 MD group and 3 of 49 subjects or 6.1% in the PA21 LD group). The withdrawals during Stage 2 in the PA21 MD were not related to safety. The reason for withdrawal for all subjects in the PA21 MD group was a protocol deviation. Of these 8 subjects, 5 were dispensed PA-CL-05B study drug in error and 3 were non-compliant with the protocol. There was 1 death in the PA21 LD group (complications from a renal transplant) which was not attributed to treatment.

7.1.1.1.10. Major protocol violations/deviations

In Stage 1, major protocol deviations were identified for 361 (34.1%) of the randomised subjects, with a similar proportion in both treatment groups (33.7% in the PA21 group and 34.1% in the sevelamer group). The most common major protocol deviations in Stage 1 were non-compliance (206 subjects overall, 19.5%), treatment duration <11 weeks (140 subjects overall, 13.2%), and prohibited use of phosphate binders before treatment or during titration (59 subjects overall, 5.6%). Protocol deviations resulted in premature withdrawal from the study for 7 PA21-treated subjects during Stage 1.

In Stage 2, major protocol deviations were identified for 41 subjects (41.4%) of the randomised subjects. The frequency of major protocol deviations was similar for both treatment groups. The most common major protocol deviation in Stage 2 was non-compliance with study medication (in 28 subjects overall, 28.3%). However, non-compliance issues were most often related to improper recording of treatment rather than to subjects who did not take the amount of study medication as prescribed. For these subjects, the drug records did not contain sufficient information to confirm compliance. In addition, 5 subjects (4 in the PA21 LD and 1 in the PA21 MD group) received phosphate binders other than the study treatment during Stage 2. Protocol deviations resulted in premature withdrawal from the study for 3 subjects in the PA21 MD group during Stage 2.

7.1.1.1.11. Baseline data

In the Stage 1 FAS, 504 subjects (48.4%) came from the US, 232 (22.3%) from the EU and 305 (29.3%) from the ROW region. At Stage 1 randomisation, the mean age of subjects was 56.1 years (range 21 to 89), mean weight was 83.4 kg (range 38.9 to 168.0). The majority were male (57.8%) and White (76.8%; 19.4% were Black/ African and 12.1% were Hispanic) and 91.8%

were on HD. The Stage 1 treatment groups were generally comparable with minor differences between PA21 and sevelamer treatments groups with exception of fact that there were more female subjects in the PA21 group (44.8%) than in the sevelamer group (36.9%). In Stage 2 PES, 70 subjects (75.3%) came from US, 15 (16.1%) from the EU and 8 (8.6%) from the ROW region. In Stage 2 compared with Stage 1 there were more Black/African American subjects and more Hispanic subjects, related to the large proportion of subjects from the US enrolled in Stage 2.

There were no notable demographic differences between the PA21 MD and PA21 LD treatment groups.

The most common reasons for ESRD in the FAS overall and in both treatment groups, were diabetes mellitus, hypertension and glomerulonephritis. The mean time from diagnosis of ESRD (65 months, SD=64.44) and the mean time from the first dialysis to randomisation (52.1 months, SD=50.93) varied widely among subjects. A relatively small portion of subjects (8.3%) had undergone a renal transplant and only 85 subjects (8.2% of the FAS) who were on PD. Similar ESRD characteristics were observed in Stage 2 for both PA21 MD and LD treatment groups.

Overall, 82.7% of subjects in Stage 1 used 1 phosphate binder, and 14.6% used 2 or more phosphate binders prior to the study. The use of phosphate binders prior to the study was not notably different between the PA21 and sevelamer treatment groups with the majority using calcium based phosphate binders (PA21 vs sevelamer: 65.6% vs 64.8%) or sevelamer (34.3% vs 35.7%). There were no notable differences in previous phosphate binder use observed in the PPS or SS. There were notable regional differences in prior use of phosphate binders in the FAS as the use of sevelamer was higher in the US (56.2%) compared with the EU (23.1%) and ROW (8.2%) and the use of calcium-based phosphate binders was higher in the EU (79.7%) and ROW (91.1%) compared with the US (46.6%). The use of phosphate binders prior to the study for subjects in Stage 2 did not differ significantly between the PA21 MD and LD groups. Overall, 81.7% of subjects in the PES had used 1 phosphate binder, and 15.1% had used 2 or more phosphate binders.

The incidence of relevant medical conditions was similar in both treatment groups in Stage 1 and hypertension, anaemia and secondary hyperparathyroidism being most common. The overall medical history profile for the subset of subjects that entered Stage 2 was similar to the medical history profile for the Stage 1 subjects. Prior medications excluding phosphate binders were similar for the PA21 and sevelamer treatment groups. Antianaemic preparations including iron supplements and erythropoiesis stimulating agents (ESA) were taken previously by 91.8% of subjects overall. The other most common types of medications previously taken were antithrombotic agents, calcium channel blockers, medications maintaining calcium homeostasis, agents acting on the renin-angiotensin system, lipid modifying agents, treatments for GI acid related disorders, beta blockers and vitamin supplements.

Prior medication use by subjects participating in Stage 2 did not differ substantially from the overall Stage 1 PA21 treatment group with no notable differences between the PA21 MD and PA21 LD groups. Concomitant medication use was similar for the 2 treatment groups overall with antianaemic preparations taken by 88.0% of subjects overall, and by a similar proportion of subjects in both treatment groups. These antianaemic preparations included iron products (taken by >70%) and ESAs (taken by >80%).

The other most common types of concomitant medications taken during Stage 1 were antithrombotic agents, calcium channel blockers, medications maintaining calcium homeostasis, agents acting on the renin-angiotensin system, lipid modifying agents, treatments for GI acid related disorders, beta blockers and vitamin supplements. The overall use of antianaemics was lower in subjects on PD compared with those on HD, particularly marked with the use of iron preparations (35.6% versus 75.0%, respectively). The use of ESAs was more similar (73.6% for subjects on PD versus 86.7% for subjects on HD). There were notable differences in the

concomitant medications that were started in Stage 2 between the 2 groups. More subjects started concomitant medications in the LD group compared with the MD group (65.3% versus 15.6%). Noticeably more subjects in the LD group started drugs used to treat hyperphosphataemia, such as antianaemic preparations (ESAs) and anti-parathyroid preparations (paricalcitol). It appears that more subjects in the LD group either re-started or had dose increases in ESAs compared to the MD group.

In Stage 1, more than 70% of subjects in both treatment groups were taking concomitant iron products. No substantial differences were observed in the overall percentage of subjects who received concomitant iron medications in the PA21 group versus sevelamer group (70.6% versus 74.1%) nor for any specific iron medications. The most commonly used iron medications overall were saccharated iron oxide, ferric sodium gluconate complex and iron dextran (53.2%, 10.9% and 7.4% of subjects, respectively). Oral iron products (prohibited by protocol) were taken by 2 subjects on PA21 (0.2%, ferrous sulphate and saccharated iron oxide) and 2 subjects on sevelamer (0.6%, ferrous fumarate and ferrous gluconate). Concomitant intravenous iron products were received by 66.3% of subjects on HD and 28.7% on PD. In Stage 2, a higher proportion of subjects in the PA21 LD required the addition of concomitant iron products or an increase in dose compared with subjects in the MD group (16.3% versus 2.2%, respectively). All subjects that required added iron preparations received saccharated iron oxide.

Based on the tablet counts, more subjects in the PA21 group were compliant with study drug treatment. The proportion of subjects compliant at 70 to 120% expected in Stage 1 was higher in the PA21 group compared with the sevelamer group (82.6% versus 77.2%). Furthermore, low compliance (<70% expected) was more common in the sevelamer group (21.3% versus 15.1%). The mean compliance was 89.0% in the PA21 group versus 86.2% in the sevelamer group. Compliance levels with PA21 treatment were generally lower in Stage 2 for subjects in both the MD and LD groups than in Stage 1. The proportion of subjects who were compliant at 70 to 120% was 68.2% in the PA21 MD and 55.1% in the LD group. Non-compliance issues were most often related to improper recording of treatment rather than to subjects who did not take the amount of study medication as prescribed. The proportion compliant at 70 to 120% was 13% higher in the MD compared with the LD group. Mean compliance was notably higher in the PA21 LD, likely related to a proportionately larger number of subjects who took >120% of the expected dose.

7.1.1.1.12. Results for the primary efficacy outcome

The primary efficacy endpoint was the change from Week 24 in serum phosphorus levels at Week 27 – a superiority comparison between the PA21 MD group and the PA21 LD control group (fixed dose of 1.25 g/day) in the PES. In the PES, baseline (Week 24) mean serum phosphorus levels were comparable for the 2 treatment groups: 1.5 mmol/L (4.7 mg/dL) in the MD group and 1.6 mmol/L (5.0 mg/dL) in the LD group. In the PA21 MD group, mean serum phosphorus values showed little change during Stage 2, indicating continued control of serum phosphorus. However, in the PA21 LD group mean values increased to 2.0 mmol/L (6.3 mg/dL) at Week 25 and continued to increase. At endpoint, mean values in the PA21 LD group had increased to 2.2 mmol/L (6.8 mg/dL) which was 0.6 mmol/L (1.8 mg/dL) higher than baseline, indicating loss of control (Table 5 and Table 6).

Table 5: Summary of serum phosphorous levels (SI and CV units) and change from baseline in Stage 2 (PES (N=93))

Time Point	Statistic	PA21 MD (N=44)				PA21 LD (N=49)			
		Serum Phosphorus				Serum Phosphorus			
		mmol/L		mg/dL		mmol/L		mg/dL	
		Actual	Change	Actual	Change	Actual	Change	Actual	Change
Week 20[1]	n	44		44		49		49	
	Mean	1.4		4.4		1.5		4.6	
	SD	0.22		0.68		0.36		1.13	
Stage 2 baseline[1]	n	44		44		49		49	
	Mean	1.5		4.7		1.6		5.0	
	SD	0.33		1.03		0.37		1.14	
Week 25	n	42	42	42	42	46	46	46	46
	Mean	1.5	0.0	4.7	0.0	2.0	0.4	6.3	1.3
	SD	0.30	0.30	0.91	0.94	0.46	0.43	1.44	1.33
Week 26	n	42	42	42	42	45	45	45	45
	Mean	1.5	0.0	4.7	0.0	2.1	0.5	6.6	1.7
	SD	0.39	0.37	1.21	1.13	0.62	0.60	1.91	1.87
Week 27	n	38	38	38	38	46	46	46	46
	Mean	1.6	0.1	5.1	0.3	2.2	0.6	6.7	1.7
	SD	0.34	0.42	1.05	1.30	0.50	0.47	1.55	1.46
LOCF endpoint[2]	n	44	44	44	44	49	49	49	49
	Mean	1.6	0.1	5.0	0.3	2.2	0.6	6.8	1.8
	SD	0.35	0.40	1.07	1.22	0.53	0.47	1.63	1.47

1 Week 20 values were used to qualify subjects for Stage 2. Stage 2 baseline was Week 24 or latest value available before Week 24 when Week 24 result was missing.
2 LOCF endpoint was Week 27 or includes the latest evaluable measurement after Week 24.
Notes: LD = Low dose; LOCF = Last observation carried forward; MD = Maintenance dose; PES = Primary efficacy set.

Table 6: Summary of serum phosphorous levels (SI and CV units) and change from baseline in Stage 2 (PEPPS (N=58))

Time point	Statistic	PA21 MD (N=31)				PA21 LD (N=27)			
		Serum Phosphorus				Serum Phosphorus			
		mmol/L		mg/dL		mmol/L		mg/dL	
		Actual	Change	Actual	Change	Actual	Change	Actual	Change
Stage 2 baseline[1]	n	31		31		27		27	
	Mean	1.5		4.6		1.6		5.0	
	SD	0.32		0.99		0.41		1.27	
Week 25	n	31	31	31	31	26	26	26	26
	Mean	1.5	0.0	4.7	0.1	2.1	0.5	6.5	1.5
	SD	0.31	0.30	0.95	0.92	0.52	0.43	1.62	1.33
Week 26	n	31	31	31	31	26	26	26	26
	Mean	1.5	0.0	4.7	0.1	2.2	0.6	6.8	1.9
	SD	0.40	0.32	1.23	1.00	0.75	0.72	2.31	2.22
Week 27	n	28	28	28	28	26	26	26	26
	Mean	1.6	0.1	5.0	0.2	2.2	0.6	6.9	1.9
	SD	0.30	0.38	0.94	1.17	0.59	0.49	1.82	1.53
LOCF endpoint[2]	n	31	31	31	31	27	27	27	27
	Mean	1.6	0.1	4.9	0.2	2.3	0.7	7.1	2.1
	SD	0.33	0.36	1.01	1.11	0.61	0.50	1.89	1.56

1 Stage 2 baseline was Week 24 or latest value available before Week 24 when Week 24 result was missing.
2 LOCF endpoint was Week 27 or includes the latest evaluable measurement after Week 24.
Notes: LD = Low dose; LOCF = Last observation carried forward; MD = Maintenance dose; PEPPS = Primary efficacy per-protocol set.

The primary efficacy analysis confirmed that the PA21 MD was statistically significantly ($p<0.001$) superior to the PA21 LD in the PES and these results were confirmed in the PEEPS analysis. Robustness of the results was also confirmed in the sensitivity analyses.

7.1.1.1.13. Results for other efficacy outcomes

Secondary efficacy endpoints for Stage 2: At Stage 2 baseline (Week 24), 72.7% of subjects in the MD group and 61.2% in the LD were within the KDOQI target range. At Week 27, 63.2% subjects in the MD group were within the target range, versus only 15.2% in the LD group. The differences between the MD and LD groups were highly statistically significant ($p\leq0.004$) for both the KDOQI target and KDIGO normal ranges. The Kaplan-Meier analysis demonstrates that the first serum phosphorus values outside the KDOQI target range occurred significantly more quickly in the PA21 LD group compared with the MD group ($p<0.001$).

The median time for subjects in the PA21 LD to lose control was 8 days versus a median of 15 days in the MD group. The duration of serum phosphorus control in Stage 2 was analysed using both the KDOQI target range and the KDIGO normal range, but was not conclusive due to the

short duration of treatment, the natural fluctuation of serum phosphorus values within individuals and the low number of subjects.

No statistically significant difference between treatment groups (p=0.075) and no changes over time in serum total calcium levels were observed in the PES. Consistent with the superiority of PA21 MD over LD for control of serum phosphorus, the calcium-phosphorus product was statistically significantly higher in the PA21 LD group compared with the MD group (p<0.001). Mean serum iPTH values were similar for the MD and LD group at Stage 2 baseline (Week 24). Mean serum iPTH increased during Stage 2 in both groups, and there was considerable variability among subjects (standard deviations were high). At Week 27 and endpoint, mean increases were notably greater in the PA21 LD group compared with the MD group, although the difference at endpoint was not statistically significant (p=0.067). Increases in the LD group following withdrawal from the PA21 dose titrated to efficacy in Stage 1 were consistent with the known physiology regarding the relationship of hyperphosphataemia and iPTH.

Stage 1- secondary efficacy analysis comparing PA21 with sevelamer: Key secondary efficacy analysis: Non-inferiority of PA21 vs sevelamer: For the ANCOVA model, the predefined non-inferiority margin for mean change differences between treatment groups was 0.19 mmol/L (0.6 mg/dL) based on 97.5% 1-sided CIs. The model included treatment, dialysis status, region and baseline serum phosphorus level as fixed effects.

The baseline serum phosphorus effect was significant. As would be expected, higher baseline serum phosphorus levels correlated with higher endpoint values. In the PPS, the least square (LS) mean change from baseline was -0.71 and -0.79 mmol/L in the PA21 and sevelamer groups, respectively (diff=0.8, SE=0.3); the upper bound of the 97.5% CI was 0.15 mmol/L (0.46 mg/dL), which was below the 0.19 mmol/L (0.6 mg/dL) predefined margin. Therefore, PA21 is non-inferior to sevelamer. Results of the ANCOVA-LOCF for the FAS were consistent with PPS results and supported the non-inferiority of PA21 versus sevelamer.

A sensitivity analysis was also performed on the FAS using the ANCOVA-OC model which was based on the endpoint results (OC at Week 12 without replacement of missing values) which confirms the primary ANCOVA-LOCF analysis and supports the non-inferiority of PA21 versus sevelamer for control of serum phosphorus levels. The LS mean was within the 97.5% 1-sided CI and the upper bound of the CI was 0.14 mmol/L (0.42 mg/dL) which was below the 0.19 mmol/L (0.6 mg/dL) pre-defined margin.

PA21 and sevelamer demonstrated consistent serum phosphorus lowering effects in Stage 1 PPS subgroups for dialysis status, sex, age, race, ethnicity, geographic region and prior use of sevelamer suggesting that the results of the non-inferiority analysis were robust. Following the non-inferiority analysis, a superiority analysis of the comparison of PA21 against sevelamer was tested. The results indicated a significant difference in the change from baseline which was greater with sevelamer than PA21 (p=0.011).

Other Stage 1 efficacy endpoints: In the FAS, the mean serum phosphorus level had dropped below 5.5 mg/dL (within the KDOQI target range) by Week 6 in the sevelamer group and by Week 16 in the PA21 group. The serum phosphorus lowering effects were slightly greater for sevelamer compared with PA21. For the Week 12 endpoint (end of titration), the mean change in serum phosphorus level was -0.7 mmol/L (-2.0 mg/dL) and -0.7 mmol/L (-2.1 mg/dL) in the PA21 and sevelamer groups, respectively. The phosphorus lowering effect was maintained through Week 24 with both treatments. At the Week 24 endpoint, the mean change in serum phosphorus level was -0.7 mmol/L (-2.1 mg/dL) and -0.7 mmol/L (-2.1 mg/dL), respectively.

PA21 and sevelamer demonstrated similar serum phosphorus lowering effects in subjects on HD and subjects on PD at generally similar doses. In the larger number of subjects on HD, mean baseline levels were equivalent and levels reached the KDOQI target level at Week 12 with PA21 and Week 8 with sevelamer, consistent with results in the total PPS. In the smaller group of subjects on PD, mean baseline serum phosphorus levels were higher in the PA21 group, and

mean decreases were slightly larger with PA21 versus sevelamer at Weeks 4, 8, and 24 and endpoint (by approximately 0.1 mg/dL). The KDOQI target level was achieved at Week 12 in the PA21 group and Week 4 in the sevelamer group.

The MMRM-MAR model was used as a sensitivity analysis for the main non-inferiority efficacy analysis comparing the change in serum phosphorus levels in the PA21 versus sevelamer at Stage 1 visits. In this model there were significant differences between treatment groups up to Week 12; however, from Week 16 there were no statistically significant differences in the FAS. Results for the PPS were generally consistent with the FAS; however the differences between treatment groups were statistically significant at later time points.

A greater proportion of subjects in the sevelamer group compared with the PA21 group had serum phosphorus levels within the KDOQI range at Week 12 (54.7% versus 44.8%, respectively). However, by Week 24, there was only a slight difference between treatment groups (54.4% versus 52.6%). The treatment differences were statistically significant at Week 12 (p=0.010) but not at Week 24 (p=0.949).

In both treatment groups, the mean and median daily doses were generally lower in the controlled subjects compared with the uncontrolled subjects and the doses appeared to increase slightly over time in both treatments.

The median time for subjects to achieve control based on KDOQI was 23.0 days with PA21 and 18.6 days with sevelamer. The difference in time to control was statistically significant favouring sevelamer (p=0.004). The time to control was notably longer with PA21 compared to sevelamer based on the KDIGO range. The earlier onset of control was reflected in the longer duration of control in the sevelamer group. The mean duration of control based on KDOQI was 71.8 days for the PA21 group and 81.4 days for the sevelamer group.

There were no clinically relevant changes in serum total calcium over time and no difference between treatment groups (p=0.901). As expected, decreases in calcium-phosphorus product were consistent with changes seen in serum phosphorus and were slightly greater in the sevelamer treatment group through Week 16. Decreases were greater with PA21 at the Week 20 and 24 time points and equal at endpoint. The calcium-phosphorus product was below the KDOQI target level (55 mg/dL) by Week 4 in both treatment groups. Although differences between the groups were small, ANCOVA-LOCF indicated they were statistically significant (p=0.030) and favoured sevelamer. Mean serum iPTH levels decreased during Stage 1 in the FAS, although there was considerable variability among subjects. There was a trend toward greater decreases in iPTH with PA21 versus sevelamer, although this was not statistically significant (p=0.314). Decreases in iPTH were generally larger in the PA21 group compared with the sevelamer group for all subgroups. Decreases in iPTH in subjects on HD were generally larger compared with subjects on PD in both treatment groups.

Subjects treated with PA21 in Stage 1 had a considerably lower pill burden compared with those treated with sevelamer overall (3.1 versus 8.1 tablets per day, respectively) and during the titration (2.8 versus 7.6) and maintenance period (3.6 versus 8.7). Subjects in the Stage 2 PA21 MD group maintained control of serum phosphorus with an average pill burden of 2.9 tablets/day.

Changes from baseline in quality of life scores were generally small overall with no trends observed and no significant differences between treatment groups for any SF-36 components.

There were only small differences between treatment groups for preference of the phosphate binder they were receiving at Week 12, overall, or with respect to number of pills, ease of intake and side effects. Generally subjects preferred their study drugs compared with their previous phosphate binder in both treatment groups. More than 80% of subjects in the PA21 group found their treatment preferable or equal to their previous phosphate binder. The patient preferences responses summarised by dialysis status and region showed generally consistent results with

the total FAS. However, subjects on PD treated with PA21 showed a slightly higher overall preference for their current phosphate binder than subjects treated with sevelamer.

The baseline patient satisfaction scores for their current phosphate binder for number of pills, ease of intake and overall satisfaction were similar for the PA21 and sevelamer treatment groups. Scores at Week 12 and Week 24 showed small improvements in patient satisfaction parameters in both treatment groups, but there were no relevant differences observed between the 2 groups.

Kt/V ratios were comparable at baseline for the PA21 and sevelamer groups (mean ratios were 0.8 versus 0.7, respectively). Mean/median changes from baseline were small in both groups and not clinically significant and the differences between groups were not clinically relevant. Overall, the Kt/V ratios indicate that the dialysis dose remained relatively constant during the study for both subjects on HD and subjects on PD.

There were small changes (≤0.4 kg) in mean weight in patients on both HD and PD, but the changes were not meaningful with no remarkable differences between the PA21 and sevelamer treatment groups.

7.1.2. Other efficacy studies

7.1.2.1. Study PA-CL-05B

7.1.2.1.1. Study design, objectives, location and dates

PA-CL-05B was a Phase 3, 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 MD[15]) 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. The extension study was conducted from 20 Sept, 2011 to 25 Oct, 2012 at 143 of the 174 centres that conducted PA-CL-05A.

7.1.2.1.2. Study treatments

In PA-CL-05B, continued treatment was administered to 658 subjects (659 enrolled): 391 received PA21 and 267 received sevelamer. Subjects continued at their established dose as given at Week 24 (or Week 27 for subjects in the Stage 2 MD group) in PA-CL-05A. Dose modifications for both tolerability and efficacy reasons were allowed [target serum phosphorus levels between 0.81 to 1.78 mmol/L (2.5 to 5.5 mg/dL)]. Dose adjustments for efficacy were based on central laboratory values taken at regular study visits. If a dose adjustment was indicated, the Investigator informed the subjects (either directly or by phone) whether to increase or decrease the dose. The maximum dose of PA21 was 15.0 g/day (6 tablets/day) and the minimum dose was 5.0 g/day (2 tablets/day). The maximum dose of sevelamer was 14.4 g/day (18 tablets/day) and the minimum dose was 2.4 g/day (3 tablets/day).

7.1.2.1.3. Efficacy endpoints

The main efficacy endpoints were: Change from baseline (entry to PA-CL-05B) and levels at each time point for serum phosphorus, serum calcium (total, corrected and ionised), serum iPTH.

[15] Subjects randomised to the PA21 LD group of the Stage 2 primary efficacy assessment of Protocol PA–CL-05A were excluded from this extension study.

7.1.2.1.4. Patient disposition, protocol violations

Of the 659 subjects enrolled in PA-CL-05B, 549 (83.3%) completed the study and 110 (16.7%) prematurely discontinued. Overall, the primary reasons for premature discontinuation during PA-CL-05B were "TEAEs other than phosphorus or calcium level TEAEs" (19.1%), hyperphosphataemia (17.3%), renal transplant (16.4%), withdrawn consent (15.5%), and death (10.0%, all unrelated to treatment). The overall percentage of subjects withdrawn and the percentage withdrawn for hyperphosphataemia were similar for the 2 groups. However, a higher proportion of the withdrawals in PA21-treated subjects were for AEs other than phosphorus or calcium TEAEs (PA21 vs sevelamer: 24.6% vs 9.8%) and a higher proportion of withdrawals in sevelamer-treated subjects were due to withdrawal of consent (13.0% vs 19.5%).

Major protocol violations were identified for 156 (23.7%) subjects enrolled in PA-CL-05B. The most common major protocol deviations overall were non-compliance (95 subjects, 14.4%) and use of other phosphate binders (55 subjects, 8.3%). Major protocol violations occurred at a greater incidence in the sevelamer group (80 subjects, 29.9%) compared with the PA21 group (76 subjects, 19.4%). The higher number of major protocol violations in sevelamer-treated subjects were mostly due to the higher incidences of non-compliance and use of other phosphate binders during the study. Overall, 314/384 (80%) and 185/260 (69%) patients in the PA21 and sevelamer groups, respectively were included in the per-protocol set for study PA-CL-05B.

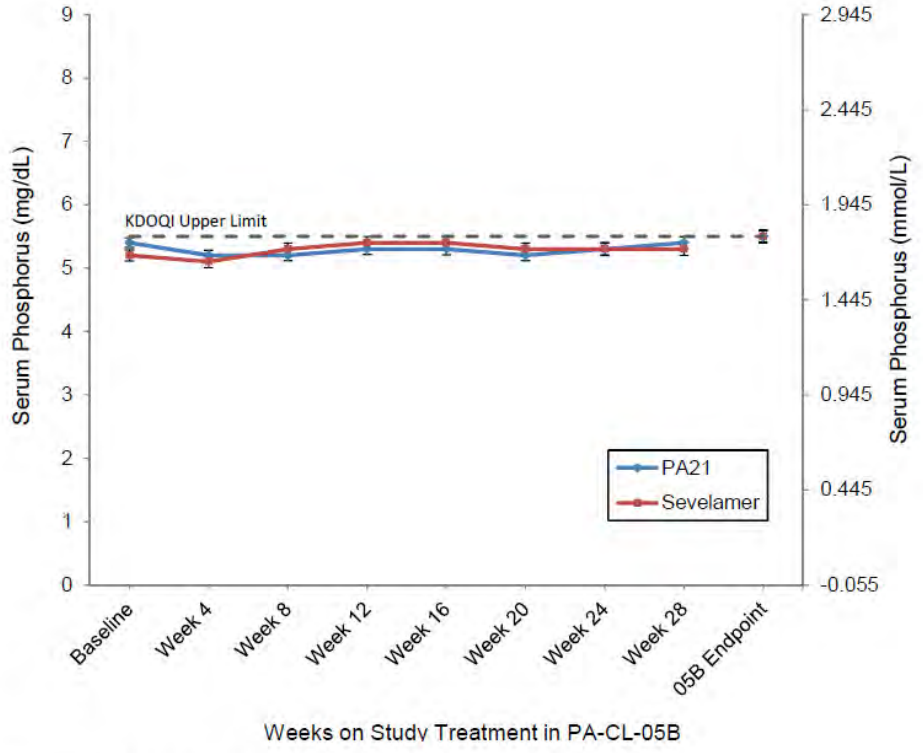
7.1.2.1.5. Baseline demographics and characteristics

The baseline demographics and disease characteristics were generally similar to those observed in study PA-CL-05A with no significant difference between the PA21 and sevelamer groups. The proportion of subjects compliant at 70-120% expected in the FAS5B was higher (by 9.3%) in the PA21 group compared with the sevelamer group (86.2% versus 76.9%, respectively). Furthermore, low compliance (<70% expected) in the FAS5B was even more prevalent in the sevelamer group (21.2%) compared with the PA21 group (13.3%). The mean overall compliance in the FAS5B was 89.2% in the PA21 group and 85.6% in the sevelamer group.

7.1.2.1.6. Efficacy results

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. Serum phosphorus levels were consistent during the PA-CL-05B long-term extension with similar levels at the end of PA-CL-05A, week 24, PA-CL-05B Week 28 (PA 21 vs sevelamer: 1.8 vs 1.7 mmol/L at both time points); minimal changes during the long-term extension indicated good control of serum phosphorus over time by both treatments through 52 weeks (Figure 3).

Figure 3: Mean ± SEM serum phosphorous levels at each time point in PA-CL-05B. FAS5B (N=644)



Notes: FAS5B = Full analysis set for PA-CL-05B; SEM = Standard error of the mean.

The change in serum phosphorus from the PA-CL-05B baseline did not differ statistically significantly over time between treatment groups (p=0.121). Control of serum phosphorus based on the KDOQI target was maintained during the additional 28 weeks of treatment. The proportion of subjects responding to treatment was 53.1% and 53.6% for PA21 and sevelamer, respectively at Week 24 and 51.9% and 55.2%, respectively at Week 52. For 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 throughout the extension study.

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.

The pill burden remained lower with PA21 during the PA-CL-05B extension study (mean 4.0/ median 4.0 for PA21 versus mean 10.1/median 8.9 for sevelamer), consistent with results from the PA-CL-05A study data.

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. In completers, changes in serum total calcium×phosphorus product were no different from those in the FAS. Changes in Serum iPTH: There was significant variability of serum iPTH levels among subjects in both treatment groups throughout the 52 weeks of treatment. There were no clinically relevant mean changes from baseline in iPTH at Week 52 and no differences between treatment groups. In completers, changes in iPTH were no different from those in the FAS.

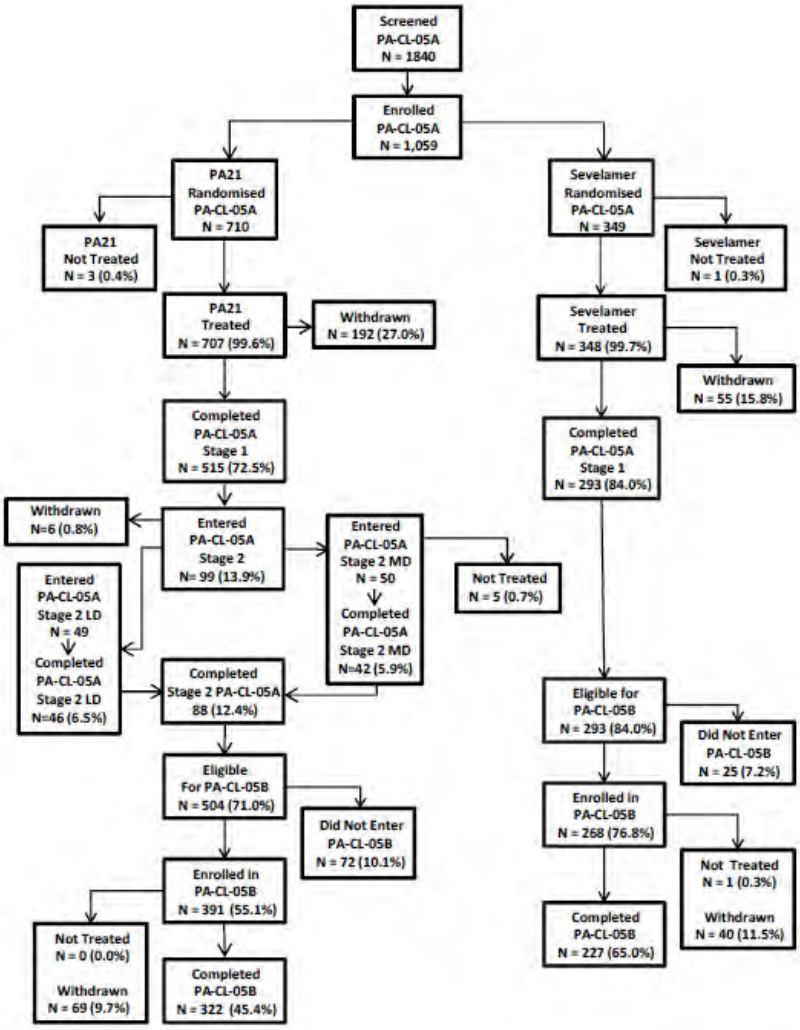
Dietary habits and dialysis parameters generally remained unchanged in both treatment groups and no clinically relevant differences between groups were observed.

7.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

7.1.3.1. Integrated analysis (PA-CL-05A/PA-CL-05B Pooled Data)

Of the 1,059 subjects randomised, 808 (76.3%) subjects completed the first 24 weeks of PA-CL-05A (515 on PA21 and 293 on sevelamer) and were potentially eligible to be enrolled into PA-CL-05B. A total of 659 (62.2%) subjects (391 on PA21 and 268 on sevelamer) were enrolled in PA-CL-05B (Figure 4).

Figure 4: Disposition of subjects in PA-CL-05A and PA-CL-05B



Of the 1,059 subjects randomised into the PA-CL-05A study, 808 subjects (76.3%) completed Stage 1 of Study PA-CL-05A (24 weeks treatment), and 549 (51.8%) completed at least 52 weeks treatment, i.e., both Study PA-CL-05A and Study PA-CL-05B. Overall, there were 464 subjects (43.8%) who prematurely discontinued the study treatment in either PA-CL-05A or PA-CL-05B. In subjects randomised to PA21 (n=710), 515 (72.5%) completed PA-CL-05A Stage 1 and 322 (45.4%) completed PA-CL-05B. Overall, 342 (48.2%) subjects prematurely discontinued study treatment in either PA-CL-05A or PA-CL-05B. The primary reasons for premature discontinuation of PA21 during the combined studies were TEAEs other than

phosphorus or calcium levels TEAEs (33.2% of withdrawals), withdrawn consent (12.2%), renal transplant (8.3%), and hyperphosphataemia (7.1%). In subjects randomised to sevelamer (n=349), 293 (84.0%) completed PA-CL-05A and 227 (65.0%) completed PA-CL-05B.

Overall, 122 (35.0%) subjects prematurely discontinued either PA-CL-05A or PA-CL-05B. The primary reasons for premature discontinuation of sevelamer-treated subjects during the combined studies (excluding deaths) were TEAEs other than phosphorus or calcium level TEAEs (19.7% of withdrawals), withdrawn consent (18.9%), renal transplant (10.7%), and hyperphosphataemia (5.7%). The percentage of subjects withdrawn prematurely was higher in the PA21 group compared with the sevelamer group during the combined studies, although the difference was much less pronounced in Study PA-CL-05B (PA21 vs sevelamer: 17.6% vs 15.3%) than in Study PA-CL-05A (27% vs 15.8%); this difference was primarily because of the higher percentage of subjects in the PA21 group withdrawn for TEAEs other than hypo/hyperphosphataemia or hypercalcaemia. Gastrointestinal TEAEs accounted for 47.0% of withdrawals for PA21 and 30.6% for sevelamer.

Overall, the number of subjects withdrawn from PA-CL-05A or PA-CL-05B was slightly lower in the younger group (32.6% <65 years; 38.9% ≥65 years). In both treatment groups, subjects ≥65 years were more likely to die (12.7% versus 4.5%), were more likely to have TEAEs leading to withdrawal (46.6 versus 32.7%), had fewer TEAEs related to high serum phosphorus levels (5.1% versus 10.2%) and a smaller proportion received a renal transplant (5.1% versus 13.9%) when compared to those subjects that were <65 years. These results are not unexpected because older subjects suffering from CKD are more likely to have additional comorbidities.

In both the PA21 and sevelamer treated groups, there were no notable racial differences in subject disposition across the three race groups examined (White, Black and Other), although interpretation of results is limited by the small numbers in the "Other" race category. The mean age of subjects in the FAS was 56.1 years (range 21 to 89 years), and mean weight was 83.4 kg (range 38.9 to 168.0 kg). The majority were male (57.8%) and white (76.9%), and 91.9% were on HD. There was a good representation of the Black/African American race (19.4%) and subjects of Hispanic ethnicity (12.1%). Demographic characteristics were generally similar for the FAS and FAS5B.

The treatment groups were generally comparable in the analysis sets with minor differences between PA21 and sevelamer treatments subgroups regarding age, race, height, weight or body mass index. There was, however, an imbalance in the sex groups, with a slightly greater proportion of female subjects in the PA21 group (44.8%) than in the sevelamer group (36.9%) for the FAS. The most common underlying diseases contributing to ESRD in the FAS overall, were diabetes mellitus (27.9%), hypertension (23.6%) and glomerulonephritis (23.2%). Other underlying causes occurred in less than 10% of subjects in each group. The distribution of underlying disease was very similar in each treatment group. The nature of underlying diseases contributing to ESRD in this pooled population is representative of the ESRD population as a whole.

The mean time from diagnosis of ESRD to randomisation in PA-CL-05A was 65.0 months and varied widely among subjects (SD=64.44). The time from the first dialysis to randomisation in PA-CL-05A averaged 52.2 months and also varied widely among subjects (SD=50.97). The overall history of ESRD in the FAS5B was similar to that in the FAS. There were 84 subjects (8.1%) in the FAS and 60 subjects (9.3%) in the FAS5B on PD. There were no notable differences between treatment groups relative to underlying conditions for ESRD, time to start of ESRD, time to first dialysis, and baseline Kt/V values. Kt/V ratios were in compliance with entry criteria and indicate subjects were generally being adequately dialysed.

Concomitant medication use was similar for the 2 treatment groups overall in the SS and SS5B and antianaemic preparations were used by >89% of subjects in the SS and >84% in the SS5B overall, and by a similar proportion of subjects in both treatment groups. These antianaemic

preparations included ESAs, taken by >86.0% in the SS and >83% in the SS5B. The other most common types of concomitant medications taken by subjects in the SS were antithrombotic agents (80.5%), vitamin supplements (64.9%), beta blockers (60.7%), calcium homeostasis agents (60.4%), renin-angiotensin system agents (53.6%), calcium channel blockers (49.7%), GI acid related disorder agents (46.3%), lipid modifying agents (46.2%), and analgesics (41.4%). Common concomitant medications used by the 2 treatment groups were not notably different. Concomitant iron products were taken by >74% in the SS (pooled PA-CL-05A/ PA-CL-05B data) and >62% in the SS5B. No substantial differences were observed in the overall percentage of subjects who received concomitant iron medications in the PA21 group versus sevelamer group (72.8% versus 77.3%) nor for any specific iron medications.

The main efficacy endpoints evaluated in this integrated analysis were: Serum phosphorus, serum calcium (total, corrected and ionised), serum total calcium-phosphorus product, serum iPTH levels at each time point and change from entry into both PA-CL-05A and PA-CL-05B studies separately; Percentage of subjects with serum phosphorus within the target range recommended in the KDOQI guidelines [1.13 to 1.78 mmol/L (3.5 to 5.5 mg/dL)]. Additional endpoints included Pill burden (tablets/day); Change in dialysis parameters and Kt/V as a marker of dialysis adequacy and Change in dietary habits.

7.1.3.2. Results

The serum phosphorus lowering effects were slightly greater for sevelamer compared with PA21 during the titration period of study PA-CL-05A. However mean changes were similar for the 2 treatments by PA-CL-05A Week 12 [–0.7 mmol/L (-2.1 mg/dL) in the PA21 and -0.7 mmol/L (-2.2 mg/dL) in the sevelamer group]. The effects were maintained through Week 24 [-0.7 mmol/L (-2.3 mg/dL) in the PA21 and -0.7 mmol/L (-2.2 mg/dL) in the sevelamer group]. For subjects who entered the PA-CL-05B study extension, the mean change from the PA-CL-05A baseline after 52 weeks treatment (PA-CL-05B Week 28) was maintained; mean change was -0.7 mmol/L (-2.2 mg/dL) in the PA21 and -0.7 mmol/L (-2.1 mg/dL) in the sevelamer group and were still within the KDOQI target range. In the larger group of subjects on HD, mean baseline levels in the 2 treatment groups were equivalent and changes from baseline were consistent with results in the total FAS. In the smaller group of subjects on PD, mean baseline serum phosphorus levels were higher in the PA21 group, and mean decreases were slightly larger with PA21 versus sevelamer (by approximately 0.1 mmol/L) during both studies. The change from baseline at the combined endpoint was -0.7 mmol/L versus -0.5 mmol/L for PA21 versus sevelamer. By Week 12, values had dropped below the KDOQI target level in both treatment groups and remained in the target range throughout the studies. Over 52 weeks, there were no remarkable differences in treatment effect on the change from baseline in serum phosphorus across region, sex, age, race or dialysis status (Table 7).

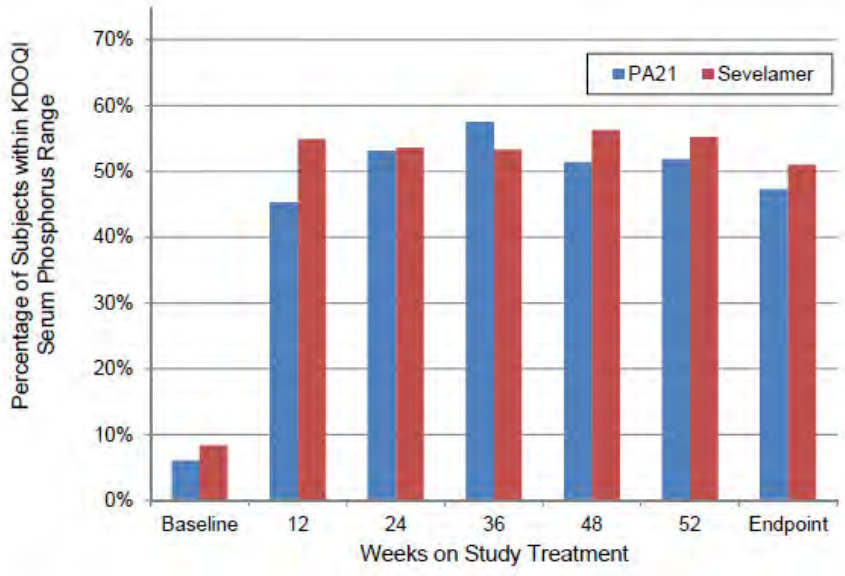
Table 7: Mean change from baseline in serum phosphorous – All subgroups, FAS pooled 05A/05B (N=1,041)

Subgroups			PA21 N=694 Mean (SD) Change from Baseline in Serum Phosphorus		Sevelamer N=347 Mean (SD) Change from Baseline in Serum Phosphorus	
			Week 24/Endpoint	Combined Endpoint	Week 24/Endpoint	Combined Endpoint
Region	EU	mmol/L	-0.8 (0.66)	-0.7 (0.64)	-0.7 (0.62)	-0.6 (0.71)
		mg/dL	-2.4 (2.03)	-2.2(1.98)	-2.1 (1.92)	-1.8 (2.20)
	US	mmol/L	-0.6 (0.68)	-0.6 (0.70)	-0.7(0.55)	-0.7 (0.59)
		mg/dL	-2.0 (2.09)	-1.8 (2.16)	-2.1 (1.72)	-2.1 (1.84)
	ROW	mmol/L	-0.7 (0.67)	-0.6 (0.66)	-0.8 (0.72)	-0.6 (0.80)
		mg/dL	-2.1 (2.07)	-1.9 (2.03)	-2.4 (2.21)	-1.8 (2.49
Sex	Male	mmol/L	-0.7 (0.67)	-0.6 (0.67)	-0.7 (0.60)	-0.6 (0.65)
		mg/dL	-2.0 (2.07)	-1.9 (2.09)	-2.0 (1.85)	-1.9 (2.03
	Female	mmol/L	-0.7 (0.67)	-0.6 (0.67)	-0.8 (0.65)	-0.7 (0.74)
		mg/dL	-2.2 (2.07)	-2.0 (2.09)	-2.4 (2.02)	-2.1 (2.29)
Age, years	<65	mmol/L	-0.7 (0.69)	-0.6 (0.68)	-0.7 (0.65)	-0.7 (0.74)
		mg/dL	-2.1 (2.15)	-1.9 (2.11)	-2.3 (2.00)	-2.0 (2.29)
	≥65	mmol/L	-0.6 (0.60)	-0.6 (0.66)	-0.6 (0.54)	-0.6 (0.55)
		mg/dL	-2.0 (1.87)	-1.9 (2.03)	-1.8 (1.69)	-1.8 (1.70)
Race	White	mmol/L	-0.7 (0.66)	-0.6 (0.66)	-0.7(0.64)	-0.6 (0.73)
		mg/dL	-2.2 (2.03)	-2.0 (2.04)	-2.2 (1.98)	-1.9 (2.27)
	Black	mmol/L	-0.7 (0.72)	-0.6 (0.74)	-0.6 (0.57)	-0.6 (0.52)
		mg/dL	-2.0 (2.22)	-1.8 (2.31)	-1.9 (1.77)	-1.9 (1.60)
	Other	mmol/L	-0.5 (0.69)	-0.5 (0.63)	-0.8 (0.37)	-1.0 (0.47)
		mg/dL	-1.5 (2.14)	-1.6 (1.94)	-2.4 (1.16)	-3.1 (1.45)
Dialysis type	HD	mmol/L	-0.7 (0.68)	-0.6 (0.68)	-0.7 (0.63)	-0.6 (0.69)
		mg/dL	-2.1 (2.09)	-1.9 (2.10)	-2.2 (1.94)	-2.0 (2.15)
	PD	mmol/L	-0.7 (0.60)	-0.7 (0.61)	-0.5 (0.49)	-0.5 (0.60)
		mg/dL	-2.0 (1.85)	-2.1 (1.89)	-1.6 (1.53)	-1.5 (1.84)

Notes: EU = European Union; FAS = Full analysis set; HD = Haemodialysis; PD = Peritoneal dialysis; ROW = Rest of world; SD = Standard deviation

The proportion of subjects responding to PA21 and sevelamer increased during PA-CL-05A, and at Week 24 >53% of subjects in both groups were controlled based on the KDOQI target range (Figure 5).

Figure 5: Control of serum phosphorous based on KDOQI target range. FAS (N = 1,041)



Notes: FAS = Full analysis set; KDOQI = Kidney Disease Outcomes Quality Initiative.

Once a subject's serum phosphorus level had reached the KDOQI target range, there was no requirement for Investigators to further increase the dose of study medication to achieve a lower serum phosphorus level. Although the serum phosphorus fluctuated in both treatment groups during PA-CL-05B, >51% of subjects in both groups were maintaining control of serum phosphorus at Week 52. At Week 52, 40.1% and 38.1% of subjects in the PA21 and sevelamer groups, respectively, had serum phosphorus values >1.78 mmol/L (>5.5 mg/dL).

As expected, changes in serum total calcium-phosphorus product mirrored the changes in serum phosphorus during the PA-CL-05A and PA-CL-05B studies. Differences between the 2 treatment groups were small. Mean serum total calcium-phosphorus product decreased in both groups during the dose titration phase of the PA-CL-05A study and then remained relatively unchanged during the PA-CL-05A maintenance period and during continued treatment in PA-CL-05B. Mean values and change from baseline in total calcium-phosphorus product in the completers were not notably different from those in the FAS.

Mean iPTH values were high in both treatment groups at baseline. Changes in serum iPTH were quite variable among subjects in both treatment groups throughout the studies. In the FAS, there were no clinical relevant changes from baseline at Week 52 and no difference between treatment groups.

Subjects treated with PA21 had a considerably lower mean daily pill burden compared with those treated with sevelamer during the combined PA–CL–05A/ PA-CL-05B (PA21 vs sevelamer: mean 3.3/median 3.1 versus mean 8.7/median 8.1 tablets per day). As expected pill burden remained lower with PA21 during the PA-CL-05B extension study (mean 4.0/median 4.0 vs mean 10.1/median 8.9) consistent with results from PA-CL-05A.

Subjects' dietary habits (including calcium, lipid, phosphorus, potassium, protein, or sodium chloride intake) remained generally unchanged throughout the PA-CL-05A and PA-CL-05B studies and there were no differences observed between treatment groups with the exception of fluid intake with meals. Overall average daily fluid intake with meals was slightly higher in sevelamer-treated subjects than PA21-treated subjects over the combined study periods (101.8 vs 92.2 mL, respectively). There were no significant differences between groups in the dialysis parameters. The absences of significant changes in weight and Kt/V ratio indicate that the dialysis dose remained unchanged during the studies; and therefore, changes in serum phosphorus can be attributed to the study treatments and not to changes in dialysis dose.

7.2. Evaluator's conclusions on clinical efficacy for the control of serum phosphorus levels in patients with end stage renal disease (ESRD)

The dosing recommendations 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 250mg iron (equivalent to 1250mg sucroferric oxyhydroxide) was used and hence the following Table 8 has been provided to clarify the conversion between the component and parent for each strength of VELPHORO tablets used in the clinical studies.

Table 8: Component and parent strengths for VELPHORO tablets used in clinical studies

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

The main evidence for efficacy of PA21 for reduction of serum phosphorous was provided by the Phase 2 study PA-CL-03A and the Phase 3 studies PA-CL-05A/ 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[16] 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. A sevelamer (HCl) group was added to assess assay sensitivity and to provide an active control group for comparability of efficacy and tolerability. The patient population in studies PA-CL-03A and PA-CL-05A was representative of the target patient population for PA21 with majority on HD (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 Kidney Disease Outcomes Quality Initiative (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 iPTH at various time points, as high or low levels of these parameters are critical risks for this patient population.

Results of the Phase 2, dose-ranging study PA-CL-03 involving 154 CKD patients on haemodialysis showed that the 1.25g/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 FAS and PPS (<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 (-0.348mmol/L). Control of serum phosphorus levels, to the levels defined by the Kidney Disease Quality Outcomes Initiative was good: observed in 21.1%, 41.2%, 35%, 42.9%, 60% and 42.1% in the PA21 1.25g/day, 5.0g/day, 7.5g/day, 10g/day, 12.5g/day and sevelamer 4.5g/day groups, respectively. Although this Phase 2 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 3 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 MD over the LD control (p<0.001; 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 HD and PD 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 MD group versus the non-effective LD control group which essentially functions as a placebo control group. It is conventional, however, to state

[16] 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).

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. 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 3 study was 1000mg/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 2 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 3 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) recommendation which considers 300-600 subjects as adequate for an assessment of common 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 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 vs sevelamer) 2.8 vs 7.6 tablets/day during the titration period (Week 0 to Week 12) and 3.6 vs 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 end-stage renal disease, 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 vs sevelamer: 1.8 vs 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 vs sevelamer: 53.1% vs 53.6% at Week 24 and 51.9% vs 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.

The “Clinical trials” and “Indications” section of the proposed PI is not satisfactory and recommended revisions are provided[17].

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data: 7 Phase 1 studies, a single pivotal Phase 2 dose ranging study (PA-CL-03A), and a pivotal Phase 3 efficacy and safety study with a long-term safety extension (PA-CL-05A and PA-CL-05B). Two Japanese studies (Phase 1 study PA1101 and Phase 2 study PA1201) have been completed by Kissei Pharmaceutical Co. Ltd. as

[17] The sections discussing recommended revisions to Product Information and Consumer Medicines information are not included in the Extract from the Clinical Evaluation Report

part of a strategic partnership; however, only translations of the study synopsis were provided in the submitted dossier (CSRs not provided).

The safety results of the completed studies have been discussed individually, apart from:

- The 5 pooled Phase 1 drug-drug interaction (DDI) studies in 210 healthy subjects.
- The combined Phase 3 studies (Study PA-CL-05A and its long-term extension study, Study PA-CL-05B) in patients with end-stage renal disease (ESRD) undergoing dialysis (total: 1,055; treated with PA21: 707).

The Phase 2 (PA-CL-03A) and 3 (PA-CL-05A/05B combined) studies evaluated subjects 18 years of age or older in which subjects were either assigned to a fixed-dose (Phase 2 study PA-CL-03A) or to a dose-titration (Phase 3 study PA-CL-05A) regimen. PA21 was administered in the dose range 1.25 to 15.0 g/day, and each study included an active comparator, sevelamer, either as the hydrochloride (in study PA-CL-03A) or carbonate (in study PA-CL-05) salts for a period of up to 52 weeks.

These Phase 2 and 3 studies included the following safety assessments: adverse events (AEs), physical examination, vital signs, electrocardiogram, and laboratory parameters (haematology, coagulation, clinical chemistry, liver enzymes, iron metabolism, vitamins, calcium, phosphorus, intact parathyroid hormone, and other markers of bone metabolism). These safety data have considered nonclinical safety observations for PA21 and the well-characterised safety profile of other phosphate binders, particularly with respect to gastrointestinal (GI) and metabolic TEAEs.

Pooled analysis of the studies PA-CL-03A and PA-CL-05A/05B was not done because of the differences in their study designs: i.e., 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 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 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 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 using the following definitions:

- Hypophosphataemia serum phosphorus <0.81 mmol/L or <2.5 mg/dL
- Hyperphosphataemia serum phosphorus >2.75 mmol/L or >8.5 mg/dL
- Hypocalcaemia total serum calcium <1.9 mmol/L or <7.6 mg/dL
- Hypercalcaemia total serum calcium >2.75 mmol/L or >11.00 mg/dL
- Hyperparathyroidism iPTH value >600 ng/L (>600 pg/ml or >66.0 pmol/L)

8.1.1. Pivotal studies that assessed safety as a primary outcome

PA-CL-05B was a long-term extension of pivotal Phase 3 study PA-CL-05A that assessed safety as a primary outcome.

8.1.2. Dose-response and non-pivotal efficacy studies

The dose-response, Phase 2 study PA-CL-03A and Phase 2 Japanese study PA1201. Safety data from the integrated analysis of pivotal study PA-CL-05A and its extension PA-CL-05B was also evaluated.

8.1.3. Clinical pharmacology studies

Seven Phase 1 studies including the 5 DDI studies which all have an identical design, and the data from these studies have been pooled for the analysis; the 2 remaining Phase 1 studies (Studies VIT-CI-01/2, Q-24120) are described individually.

8.2. Pivotal studies that assessed safety as a primary outcome

8.2.1. Study PA-CL-05B

The study design, treatments, objectives, patient characteristics were discussed in detail in section 7.1.2.1 above. Main Safety Endpoints were Comparison between PA21 and sevelamer of the TEAE profiles, haematology and biochemical laboratory parameters, iron parameters, bone markers, vitamins, vital signs and ECGs.

> **Comments**: The results of the safety endpoints for extension study PA-CL-05B were provided in the integrated report of studies PA-CL-05A and PA-CL-05B and have been discussed in subsequent sections.

8.3. 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 9.

Table 9: 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.

The majority of the subjects (285/291; 97.9%) in the PK trials were <65 years. The age distribution in the controlled trials was broadly representative of the dialysis patient

population, with the majority (845/1,209; 69.9%) being aged <65 years and few (8/1,209; 0.7%) being ≥85 years.

In each of the DDI studies (which were of a 3-way cross-over design), each subject received a maximum of 8 doses of PA21 (4 for each of the two PA21 dosing periods) and 3 doses of the reference drug; the reference drugs administered were either losartan, furosemide, omeprazole, digoxin, or warfarin.

In Study PA-CL-03A, median treatment duration and median average daily dose were consistent with the protocol in all treatment groups.

In Studies PA-CL-05A/05B combined, the total overall exposure to PA21 was 470.5 subject-years and the overall exposure to sevelamer was 280.2 subject-years. In PA21-treated subjects, the overall duration of exposure for the PA-CL-05A/ PA-CL-05B combined studies ranged from 1 to 420 days, with a mean of 243.1 days (SD=130.59) compared with 294.1 days (SD=112.45) in sevelamer-treated subjects (range: 13.0 to 413.0 days). The average daily dose for the PA-CL-05A/PA-CL-05B combined studies was 8.2 g/day (SD=3.15) for PA21-treated subjects and 6.9 g/day (SD=2.84) for sevelamer-treated subjects. There was only a small increase in average daily dose during the PA-CL-05B study; the average daily dose was 10.1 g/day (SD=3.69) for PA21-treated subjects and 8.1 g/day (SD=5.27) for sevelamer-treated subjects (Table 10). The average daily number of tablets taken for the PA-CL-05A/PA-CL-05B combined studies was 3.3 tablets/day (SD=1.26) and 8.7 tablets/day (SD=3.56) for PA21- and sevelamer-treated subjects, respectively.

Table 10: Summary of extent of exposure to study treatments in studies PA-CL-05A/05B combined (SS)

Parameter	Pooled PA-CL-05A/PA-CL-05B (SS)	
	PA21 (N=707)	Sevelamer (N=348)
Overall duration of exposure (days)[1]		
Mean (SD)	243.1 (130.59)	294.1 (112.45)
Median	253.0	364.0
Min/max	1.0/420.0	13.0/413.0
Total overall exposure (subject-years)[2]	470.5	280.2
Overall total number of tablets taken		
Mean (SD)	864.3 (617.94)	2,633.5 (1,556.42)
Median	750.0	2,405.0
Min/max	2.0/2,125.0	53.0/6,782.0
Overall average daily number of tablets taken		
Mean (SD)	3.3 (1.26)	8.7 (3.56)
Median	3.1	8.1
Min/max	0.4/6.3	1.9/18.6
Average daily dose (g/day)		
n	698	348
Mean (SD)	8.2 (3.15)	6.9 (2.84)
Median	7.8	6.5
Min/max	1.0/15.8	1.5/14.8
Subjects with at least 1 dose adjustment for efficacy, n (%)	607 (85.9%)	299 (85.9%)
Subjects with at least 1 dose adjustment for tolerability, n (%)	86 (12.2%)	49 (14.1%)
Subjects with at least 1 dose adjustment for efficacy and tolerability, n (%)	23 (3.3%)	17 (4.9%)

1 Duration of exposure is calculated as the date of last study drug intake minus the date of the first dose intake plus 1 day.
2 The sum of the duration of exposures for all subjects in the particular treatment group.

A total of 513 (72.6%) subjects were treated with PA21 for at least 24 weeks (approximately 6 months) which was the maximum expected duration of treatment for PA-CL-05A Stage 1. With continued treatment in PA-CL-05B, 319 (45.1%) PA21-treated subjects completed at least 52

weeks of treatment (approximately 12 months) while 226 (64.9%) of sevelamer-treated subjects completed that duration of treatment. It should be noted that 46 subjects in the LD arm of Study PA-CL-05A Stage 2 did not continue and were excluded from study PA-CL-05B as required by the study protocol.

In Study 05A, all subjects commenced treatment on Day 1 with PA21 5.0 g/day, or sevelamer. At 2-weekly intervals dosage could be adjusted on the basis of clinical response. By the end of the first 4 weeks, 30.9% of subjects were maintained on their starting dose of 5.0 g/day PA21, the remainder being increased to at least 7.5 g/day. At 8 weeks, the distribution of subjects by dose of PA21 was more even, with 107 subjects (17.3%) remaining on the 5.0 g/day starting dose, 164 (26.5%) on 7.5 g/day, 189 (30.5%) on 10.0 g/day, 155 (25.0%) on 12.5 g/day, and 5 (0.8%) on 15.0 g/day. After 24 weeks, 61 subjects (11.9%) remained on 5.0 g/day, 86 (16.8%) were on 7.5 g/day, 115 (22.4%) were on 10.0 g/day, 92 (17.9%) were on 12.5 g/day, and 159 (31.0%) were on the maximum permitted dose of PA21 15.0 g/day.

In Study 05B, this pattern continued, with the highest proportion of subjects maintained at the 15.0 g/day dose. By 52 weeks after the start of Study 05A (Week 28 of Study PA-CL-05B), 36 subjects (11.3%) remained on 5.0 g/day, 52 (16.3%) were on 7.5 g/day, 47 (14.7%) were on 10.0 g/day, 47 (14.7%) were on 12.5 g/day, and 137 (42.9%) were on 15.0 g/day.

> **Comments**: These subject numbers exceed the extent of exposure set out in the ICH E1 guidance on extent of population exposure to assess clinical safety. Furthermore, by 12 months, most subjects receiving PA21 were maintained on a 3–times daily dose regimen (i.e., coinciding with meal times), which is optimal for preventing the absorption of dietary phosphate. The data on dose distribution during the Studies PA-CL-05A/05B combined illustrate the dose titration that would occur with PA21 during clinical practice, designed to achieve optimal efficacy and tolerability for each individual patient.

The starting dose proposed in the Summary of Product Characteristics (SmPC) is 7.5 g/day, which was not included as a starting dose in the Phase 3 studies.

In the Phase 2 study PA-CL-03A, 128 subjects received PA21 and 26 received sevelamer. Of the 128 subjects treated with PA21, 25 (19.5%) received a fixed dose of 7.5 g/day for up to 6 weeks, and 23 (92.0%) of these subjects were compliant within 80 to 120% of their intended dose over the course of the trial. The average daily dose was 7.0 g/day ± 0.98 g/day. In the Phase 2 study PA1201, 36 Japanese subjects with ESRD received PA21 7.5 g/day for 6 weeks. Overall, a total of 61 subjects from the Phase 2 studies received a starting dose of 7.5 g/day.

In Studies PA-CL-05A/05B combined, mean (± SD) overall exposure to PA21 (all doses) was 243.1 ± 130.6 days for 707 subjects. The number of subjects who received 7.5 g/day at some point in the trial was 609 (86.1%), and their average duration of exposure to the 7.5 g/day dose was 57.6 ± 82.7 days. The number of subjects who received PA21 doses >7.5 g/day was 610 (86.3%)[18] (Table 11). Of the 365 subjects who completed 12 months continuous treatment with PA21 in the combined studies PA-CL-05A/05B, 36 (11.3%) remained on their starting dose of 5.0 g/day, 52 (16.3%) were on 7.5 g/day, 47 (14.7%) were on 10.0 g/day, 47 (14.7%) were on 12.5 g/day, and 137 (42.9%) were on 15.0 g/day at the end of the studies.

[18] For one subject, the dose escalation was from 5.0 g/day to 10.0 g/day, without receiving the 7.5 g/day dose, hence the difference between the first and second numbers.

Table 11: Overall extent of exposure to at least 7.5 g/day PA21 in studies PA-CL-05A/05B combined (SS)

Parameter	PA21 (N=707)
Overall duration of exposure (days)	
n	707
Mean (SD)	243.1 (130.59)
Median	253.0
Min/max	1.0/420.0
Total overall exposure (subject-years)[1]	470.5
Number of subjects receiving 7.5 g PA21, n (%)	609 (86.1%)
Duration of exposure to 7.5 g PA21 (days)	
n	609
Mean (SD)	57.6 (82.65)
Median	18.0
Min/max	2.0/353.0
Subjects receiving at least 7.5 g PA21, n (%)	610 (86.3%)
Subjects receiving at least 7.5 g PA21 for more than 6 months, n (%)	335 (54.9%)
Duration of exposure to at least 7.5 g PA21 (days)	
n	610
Mean (SD)	223.7 (123.61)
Median	226.5
Min/max	2.0/406.0
Subjects receiving 15.0 g PA21, n (%)	240 (33.9%)
Duration of exposure to 15.0 g PA21 (days)	
n	240
Mean (SD)	172.6 (102.24)
Median	181.0
Min/max	2.0/332.0

1 The sum of the duration of exposures for all subjects in the particular treatment group.
Notes: Duration of exposure is calculated as the date of last study drug intake minus the date of the first dose intake plus 1 day.
Max = Maximum; Min = Minimum; SD = Standard deviation; SS = Safety set.

Comments: The proposed starting dose of 7.5g/day was not evaluated in the pivotal Phase 3 study PA-CL-05A (starting dose was 5g/day). However, in the Phase 2 dose-ranging studies, 61 subjects received a starting dose of 7.5 g/day, and were maintained at this dose for 6 weeks. In the Phase 3 trials, a total of 609 subjects (86.1%) received the proposed starting dose of 7.5g/day at some point in the study and the mean duration of exposure at this proposed starting dose was 58 days. Overall, 610 (86.3%) were exposed to >7.5 g/day for an average duration of 223.7 days (Table 11 above). The number of exposures at the intended starting dose is in line with the ICH Guideline (CHMP/ICH/375/95) recommendation which considers 300-600 subjects as adequate for an assessment of common AEs.

8.3.1. Treatment compliance:

In study PA-CL-03A, the majority of subjects (84.4%) showed treatment compliance of between 80 and 120% with a mean compliance of 92.97% for PA21; the compliance was similar for

sevelamer with 88.5% of subjects showing compliance between 80 and 120%, and a mean treatment compliance of 89.3%.

In the combined PA-CL-05A/05B studies, the proportion of subjects compliant at 70 to 120%[19] expected in the SS was slightly higher in the PA21 group (82.5%) compared with the sevelamer group (79.6%). Furthermore, low compliance (<70% expected) was more prevalent in the sevelamer group (19%) compared with the PA21 group (15.7%). The mean overall compliance in the SS was 88.4% in the PA21 group versus 86.0% in the sevelamer group. No case of PA21 or sevelamer overdose was reported as a TEAE. In the PA21 group, compliance was calculated at more than 120% for 13 subjects during the PA-CL-05A and PA-CL-05B studies combined. These instances did not result in excessive dosing and were mostly related to discrepancies in recording of tablet dispensing and returns.

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Pivotal study PA-CL-05A

Overall, 853 subjects (80.9%) who participated in Stage 1 of the study reported at least 1 TEAE: 588 (83.2%) in the group treated with PA21 and 265 (76.1%) in the group treated with sevelamer. The overall incidence of TEAEs was higher in the PA21 group and this difference was driven by a higher incidence of GI events, primarily discoloured faeces and mild diarrhoea. Severe TEAEs were reported by 11.3% of subjects in Stage 1, with a similar incidence in the PA21 and sevelamer group (11.5 versus 10.9%, respectively).

The majority of subjects in Stage 1 were on HD (968 or 91.7%) and the overall incidence of TEAEs was slightly higher in subjects on HD compared with PD (81.5% vs 73.6%). The proportions of subjects who had serious or severe TEAEs, who were withdrawn for TEAEs, or died during Stage 1 were similar for the HD and PD groups. In subjects on HD, the overall incidence of TEAEs was higher in PA21-treated subjects compared to sevelamer (84.3% vs 75.8%). The incidence of withdrawals due to TEAEs was also higher in the PA21 group (15.8% vs 6.3%).

In subjects on PD, the overall incidence of TEAEs was higher in the sevelamer-group (80%) versus the PA21 group (70.2%), but the incidence of severe and serious TEAEs and withdrawals for TEAEs was higher for PA21-treated subjects on PD. However, the differences between treatment groups for the most common TEAEs were similar in subjects on HD versus PD. However, the incidence of diarrhoea in PA21-treated subjects on PD (10.5%) was lower than in PA21-treated subjects on HD (20.9%), while the incidence of nausea (20.0%) and vomiting (10.0%) was much higher in sevelamer-treated subjects on PD compared to sevelamer-treated subjects on HD (10.4% and 5.0%, respectively). There did not appear to be any relationship between dose and incidence of TEAEs in subjects on HD or PD, although interpretation is compromised by the open dose titration study design.

Overall, 26 subjects (27.7%) who participated in Stage 2 of the study reported at least 1 TEAE. A higher proportion of subjects in the LD group (n=22, 44.9%) had TEAEs compared with the MD group (n=4, 8.9%). In the LD group, notably more subjects had serious or severe TEAEs, and more were withdrawn because of TEAEs compared with subjects in the MD group. Hyperphosphataemia was the primary TEAE reported in the LD group. The majority of TEAEs in both groups were mild or moderate in severity and the incidence of severe AEs was similar in the PA21 (11.5%) and sevelamer (10.9%) groups.

[19] The analysis for this study used <70%, 70 to 120%, and >120% as compliance categories. The compliance categories were changed from those used in Study PA-CL-03A for the Phase 3 studies to allow flexibility, and to accommodate missed meals as the dose was not to be taken if a meal was missed. This was based on the experience from Study PA-CL-03A, and is more clinically relevant.

The highest incidence of TEAEs by SOC in both the PA21-treated and sevelamer-treated groups was GI Disorders. TEAEs in the GI Disorders SOC were more common in the PA21 group (319 subjects, 45.1%) compared with the sevelamer group (117 subjects, 33.6%). The incidence for other most commonly affected SOCs was similar in both treatment groups. Subjects commonly experienced TEAEs classified to the Metabolic and Nutrition Disorders SOC (PA21 vs sevelamer: 27.6% vs. 26.7%) and to the Infections and Infestations SOC (22.2% vs. 21.3%).

The highest incidence of TEAEs by preferred term in the PA21 group was diarrhoea (20.1%), discoloured faeces (15.4%), hyperphosphataemia (11.2%), nausea (7.2%) and hypertension (6.4%). The highest incidence of TEAEs by preferred term in the sevelamer group was nausea (11.2%), hyperphosphataemia (7.8%), hypertension (7.5%), diarrhoea (7.5%), and constipation (7.2%). The following TEAEs were reported by a larger proportion (difference ≥2%) in subjects treated with PA21 compared with sevelamer: diarrhoea, discoloured faeces, hyperphosphataemia, and abnormal product taste. Nausea, constipation, anaemia and decreased appetite were reported by a larger proportion of subjects in the sevelamer group. The higher proportion of PA21-treated subjects experiencing TEAEs in the GI SOC compared with sevelamer-treated subjects, was driven by the higher incidence of diarrhoea and discoloured faeces. Only 2 cases of diarrhoea with PA21 and 1 case with sevelamer were classified as serious. The diarrhoea events were generally mild and short in duration. The onset of diarrhoea was generally soon after starting treatment.

Upper respiratory tract infection, bronchitis and nasopharyngitis TEAEs were reported in both groups at an incidence of no more than 4%; none of these events was treatment-related and none resulted in withdrawal. However, 5 subjects (4 in the PA21 group and 1 in the sevelamer group) had events classified as serious. Abnormal product taste was generally related to treatment and was reported more commonly by subjects treated with PA21 compared with sevelamer (3.3% vs 0.6%). Eleven subjects (1.6%) in the PA21 group and 1 subject (0.3%) in the sevelamer group withdrew for abnormal product taste. Chest pain was reported in 2.4% of subjects in the PA21 group versus 3.7% in the sevelamer group. Chest pain was not treatment-related, but was classified as serious in 13 subjects: 8 (1.1%) in the PA21 group (one who was withdrawn) and 5 subjects (1.4%) in the sevelamer group. The incidence of asthenia, pyrexia and other musculoskeletal/ connective tissue AEs was similar in the PA21 and sevelamer groups (<3.5%). Vascular Disorders, including hypertension and hypotension were reported in a similar proportion of both treatment groups. Reports of hypertension and hypotension were generally mild, and rarely were considered treatment-related or serious, or led to withdrawal. Both headache and dizziness[20] were reported in a similar proportion of subjects in both groups.

The overall incidence of subjects experiencing TEAEs in the titration phase was higher in the PA21 group. This difference was predominantly driven by a higher incidence of GI events, primarily discoloured faeces and mild diarrhoea. Overall in the maintenance phase, considerably fewer subjects experienced TEAEs (55.2%) and the proportion of subjects was similar between the 2 treatment groups: 323 (55.6%) in the PA21-treated group and 169 (54.3%) in the sevelamer-treated group. The overall proportion of subjects with severe or serious TEAEs during Stage 1 remained constant. Severe TEAEs were experienced by 71 subjects (6.7%) in the titration period and 55 (6.2%) in the maintenance period. Serious TEAEs were experienced by 116 subjects (11.0%) in the titration period and 106 (11.9%) subjects in the maintenance period. Further, the proportion of subjects experiencing severe and serious TEAEs were similar in the PA21 and sevelamer treatment groups in both Stage 1 titration and maintenance periods.

[20] Headaches were considered treatment-related in 3 subjects in the PA21 group and in 1 subject in the sevelamer group. Dizziness was considered treatment-related in 2 subjects in the PA21 group; 1 of them was withdrawn for dizziness. In 1 subject in the sevelamer group dizziness was considered treatment-related

In Stage 2, the overall incidence of subjects experiencing TEAEs in the PA21 LD group (44.9%) was much higher than in the PA21 MD group (8.9%). The proportion of subjects with TEAEs in Stage 2 was highest in the Metabolism and Nutrition Disorders SOC. The majority of these TEAEs were events of hyperphosphataemia involving 7 subjects (14.3%) in the PA21 LD group. There were only 4 subjects that had GI TEAEs in Stage 2, 1 subject (2.2%) in the MD group and 3 subjects (6.1%) in the LD group. The commonly reported TEAEs that occurred in the PA21 LD group only were hyperphosphataemia in 7 subjects (14.3%), pruritus in 3 subjects (6.1%) and increased blood phosphorus in 2 subjects (4.1%). No single events were reported by more than 1 subject in the PA21 MD group. The TEAEs of hyperphosphataemia and increased blood phosphorus reported in Stage 2 represented the loss of control following withdrawal of the established Stage 1 MD.

8.4.1.2. Other studies

8.4.1.2.1. Integrated analysis of PA-CL-05A and PA-CL-05B

Overall, the proportion of subjects reporting at least 1 TEAE during the combined PA-CL-05A and PA-CL-05B studies was 88.7%, with a similar proportion in the PA21 and sevelamer groups (PA21 vs sevelamer, 88.8% vs 88.5%); a slightly lower proportion of subjects reported TEAEs in the extension study PA-CL-05B (494 subjects, 75.1%). Although a larger proportion of subjects in the PA21 group compared with the sevelamer group had reported TEAEs during PA-CL-05A (PA21 vs sevelamer 83.2% vs 76.1%), the proportion of subjects with TEAEs in PA-CL-05B was similar for the 2 treatment groups (73.9% vs 76.8%). The majority of TEAEs in both treatment groups in the pooled PA−CL−05A/PA−CL−05B data were mild or moderate in severity with similar incidence of severe AEs in PA21 and sevelamer groups (16.0% vs 17.5%). Similarly, the majority of TEAEs in both treatment groups in PA-CL-05B were mild or moderate with similar incidence of severe AEs in both treatment groups (10.2% vs 10.1%).

Overall, the most common TEAEs in the pooled PA-CL-05A/PA-CL-05B data were in the GI Disorders SOC (PA21 vs sevelamer: 52.5% vs 42.8%), the Metabolism and Nutritional Disorders SOC (37.8% vs 39.7%) and the Infections and Infestations SOC (29.7% vs 32.5%). The incidence of TEAEs in all SOCs was similar (difference ≤5.0%) for both treatment groups with the exception of the GI Disorders, Blood and Lymphatic Disorders and Endocrine Disorders SOCs. There was a higher incidence of GI Disorders with PA21 and a slightly higher incidence with sevelamar of Blood and Lymphatic Disorders (6.9% vs 12.1%) and Endocrine Disorders SOC (6.6% vs 11.8%). The distribution of TEAEs by SOCs was similar for PA-CL-05A and PA-CL-05B except for the GI TEAEs. The incidence of TEAEs in the GI SOC was notably lower in PA-CL-05B in both treatment groups, and particularly in the PA21 treatment group (45.1% in PA-CL-05A versus 25.6% in PA-CL-05B) (Table 12).

Table 12: Summary of Treatment Emergent Adverse Events by SOC, SS (N = 1,055) and SS5B (N = 658)

MedDRA SOC	Pooled PA-CL-05A/PA-CL-05B (SS)[1]		PA-CL-05B (SS5B)	
	PA21 (N=707) n (%) E	Sevelamer (N=348) n (%) E	PA21 (N=391) n (%) E	Sevelamer (N=267) n (%) E
Any TEAE	628 (88.8%) 3,821	308 (88.5%) 2,033	289 (73.9%) 1,232	205 (76.8%) 939
Gastrointestinal Disorders	371 (52.5%) 811	149 (42.8%) 310	100 (25.6%) 170	51 (19.1%) 95
Metabolism and Nutrition Disorders	267 (37.8%) 531	138 (39.7%) 269	120 (30.7%) 201	79 (29.6%) 133
Infections and Infestations	210 (29.7%) 373	113 (32.5%) 224	90 (23.0%) 125	67 (25.1%) 102
General Disorders and Administration Site Conditions	149 (21.1%) 213	87 (25.0%) 127	48 (12.3%) 58	41 (15.4%) 59
Vascular Disorders	149 (21.1%) 244	84 (24.1%) 154	69 (17.6%) 115	47 (17.6%) 82
Musculoskeletal and Connective Tissue Disorders	140 (19.8%) 229	74 (21.3%) 119	62 (15.9%) 93	42 (15.7%) 60
Injury, Poisoning and Procedural Complications	129 (18.2%) 224	79 (22.7%) 137	48 (12.3%) 79	47 (17.6%) 64
Investigations	126 (17.8%) 279	76 (21.8%) 146	50 (12.8%) 77	43 (16.1%) 69
Nervous System Disorders	106 (15.0%) 161	61 (17.5%) 99	47 (12.0%) 63	29 (10.9%) 45
Respiratory, Thoracic and Mediastinal Disorders	102 (14.4%) 159	59 (17.0%) 91	38 (9.7%) 53	33 (12.4%) 45
Cardiac Disorders	93 (13.2%) 148	51 (14.7%) 89	33 (8.4%) 45	23 (8.6%) 31
Skin and Subcutaneous Tissue Disorders	76 (10.7%) 108	43 (12.4%) 53	18 (4.6%) 25	20 (7.5%) 26
Blood and Lymphatic System Disorders	49 (6.9%) 72	42 (12.1%) 62	23 (5.9%) 27	28 (10.5%) 38
Endocrine Disorders	47 (6.6%) 50	41 (11.8%) 53	23 (5.9%) 23	29 (10.9%) 33
Psychiatric Disorders	39 (5.5%) 43	18 (5.2%) 19	12 (3.1%) 12	9 (3.4%) 9
Surgical and Medical Procedures	35 (5.0%) 37	9 (2.6%) 10	12 (3.1%) 12	4 (1.5%) 5
Eye Disorders	27 (3.8%) 34	12 (3.4%) 20	12 (3.1%) 17	7 (2.6%) 13
Renal And Urinary Disorders	20 (2.8%) 25	16 (4.6%) 18	4 (1.0%) 4	9 (3.4%) 10
Hepatobiliary Disorders	15 (2.1%) 22	8 (2.3%) 11	5 (1.3%) 8	6 (2.2%) 8
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	14 (2.0%) 19	7 (2.0%) 7	6 (1.5%) 7	5 (1.9%) 5
Reproductive System and Breast Disorders	14 (2.0%) 16	5 (1.4%) 5	6 (1.5%) 8	2 (0.7%) 2
Ear and Labyrinth Disorders	12 (1.7%) 13	3 (0.9%) 5	5 (1.3%) 5	1 0.4%) 1
Immune System Disorders	6 (0.8%) 8	4 (1.1%) 4	3 (0.8%) 4	3 (1.1%) 3
Congenital, Familial and Genetic Disorders	2 (0.3%) 2	1 (0.3%) 1	1 (0.3%) 1	1 (0.4%) 1

1 PA21 treatment group also includes adverse events occurring in PA-CL-05A Stage 2.
Notes: E = Total number of adverse events; MedDRA = Medical Dictionary for Regulatory Activities; n = Number of subjects, each subject counts only once for each adverse event; SOC = System organ class; SS = Safety set; SS5B = Safety set for PA-CL-05B; TEAE = Treatment-emergent adverse event.

In the SS (pooled PA-CL-05A/PA-CL-05B data) the most commonly reported TEAEs by PT in the PA21 group were diarrhoea (23.6%), hyperphosphataemia (16.0%), discoloured faeces (16.1%), hypertension (11.2%), and arteriovenous (AV) fistula or graft complications (4.5%). The TEAEs most commonly reported in the sevelamer group were nausea (14.4%), hyperphosphataemia (12.6%), AV fistula or graft complications (7.5%), hypertension (11.8%), diarrhoea (11.5%) and hyperparathyroidism (2.9%). Diarrhoea, hyperphosphataemia, discoloured faeces, and abnormal product taste were reported at a ≥2% higher incidence with PA21 compared with sevelamer. Atrioventricular (A/V) fistula or graft complications, AV fistula thrombosis, nausea, hyperparathyroidism, hypophosphataemia, vomiting, hypotension, anaemia, constipation, chest pain, and decreased appetite were reported at ≥2% higher incidence with sevelamer compared with PA21.

The most commonly reported TEAEs (incidence ≥7.5%) in the PA21 group in PA-CL-05B were hyperphosphataemia (12.0%), hypertension (9.7%), and diarrhoea (8.2%).The most commonly reported TEAEs in the sevelamer group in PA-CL-05B were hyperphosphataemia (10.9%), secondary hyperparathyroidism (8.6%), hypotension (7.9%) and hypertension (7.5%). The TEAEs reported by a larger proportion (difference ≥2%) in subjects treated with PA21 compared to sevelamer during the PA-CL-05B treatment period were hypertension, diarrhoea, and headache. Secondary hyperparathyroidism, A/V fistula or graft complications, hypotension, pyrexia, and upper urinary tract infection were reported by a larger proportion of subjects in the sevelamer group. AEs most likely to be associated with study medication, particularly GI events, occurred early during treatment in both groups. However, the occurrence of most events likely associated with ESRD and other co-morbidities were generally more evenly distributed.

The analysis of TEAEs by maximum dose does not indicate any obvious increase in the incidence of TEAEs with increasing dose with no apparent increase in the overall incidence of AEs, withdrawals due to AEs, severity or seriousness of AEs or relationship to treatment in subjects who received the higher maximum daily doses.

Comments: It is difficult to draw conclusions regarding any dose relationship of TEAEs from these studies, as all subjects initially received the starting dose, with increases in dose permitted for tolerability or safety reasons. Results from the analyses by maximum dose should be treated with caution as the start of the TEAE may have been earlier in the study while receiving PA21 or sevelamer at a lower dose.

8.4.1.2.2. Phase 2 dose-ranging studies

In study PA-CL-03A, more than half the subjects reported TEAEs, but there was no PA21 dose-dependent trend in severe TEAEs or serious TEAEs, including death. The proportions of subjects with TEAEs were highest in the PA21 10.0 g/day (66.7%) and PA21 12.5 g/day groups (70.8%), mainly due to increased incidences of hypophosphataemia, reflecting the stronger potency of the 2 highest PA21 doses, and also reflecting the fixed dose nature of the study design, such that down titration of dose was not done. The proportion of subjects with any TEAE in the sevelamer (HCl) group (57.7%) was similar to that in the 3 lower-dose PA21 treatment groups (52.0% to 61.5%). The most common TEAEs by PT in the pooled PA21 group were hypophosphataemia (18.0%), faeces discoloured (11.7%), hyperphosphataemia (7.8%) and muscle spasms (6.3%). The most common TEAEs by PT in the sevelamer (HCl) group were hypophosphataemia, diarrhoea and hypotension (11.5% for each event), followed by hyperphosphataemia and hypercalcaemia (7.7% for each event). Very few of the TEAEs were severe, with a total of 4 (3.1%) in the pooled PA21 group, compared to 1 (3.8%) in the sevelamer (HCl) group.

In the Japanese Phase 2 study PA1201 the incidence of TEAEs was 69.2%, 61.1%, 82.9%, 75% and 54.1% in subjects receiving PA21 3.75, 7.5, 11.25, 15.0 g/day and placebo, respectively. The most frequent TEAEs occurred in the GI Disorders SOC 38.5%, 61.1% and 27% in subjects receiving PA21 3.75g/day, PA21 15.0 g/day and placebo, respectively. This was the only SOC to show any dose relationship regarding TEAEs. The number of subjects experiencing GI TEAEs at the proposed starting dose of 7.5 g/day (41.7%) was similar to the lowest dose tested, 3.75 g/day (38.5%). Above 7.5 g/day the frequency of GI TEAEs increased from around 40% to 60%. TEAEs from other SOCs were generally infrequent. No reported TEAEs were considered severe.

8.4.1.2.3. Phase 1 non-pooled studies

In study VIT-CI-01/2 single day and multiple dose administration of placebo or 3.75 to 12.5 g/day PA21 for up to 8 days was well tolerated by 57 healthy male and female subjects. In total, 48 subjects (84.2%) experienced 143 TEAEs across all dose groups in this study. Study Q-24120 was conducted in 8 healthy volunteers, 8 pre-dialysis subjects and 8 HD subjects, all of whom received PA21 10.0 g/day for 7 days. There were a total of 41 TEAEs across all dose groups. Study PA1101 in 30 healthy Japanese males, 3 groups of 8 subjects were administered PA21 for 7 days in the dose range 3.75 to 15.0 g/day, and 6 subjects received placebo. TEAEs were experienced by 62.5%, 87.5%, 75.0% and 66.7% of subjects receiving PA21 3.75g/day, 7.5g/day, 15g/day and placebo, respectively.

8.4.1.2.4. Phase 1 pooled studies

The safety results of the 5 DDI studies are discussed in section 8.8.2.1.

8.4.2. Treatment-related adverse events (adverse drug reactions)

8.4.2.1. Pivotal study PA-CL-05A

In Stage 1 of study PA-CL-05A, more subjects in the PA21 group had treatment-related TEAEs than in the sevelamer group (39.6% vs 19.8%), driven primarily by the number of subjects who had discoloured faeces (14.9% vs 0.3%), diarrhoea (12.7% vs 2.1%) and abnormal product taste (3.1% vs 0.6%). Subjects in the sevelamer group had a higher incidence of treatment-related nausea (PA21 vs sevelamer: 3.5% vs 5.2%) and constipation (2.4% vs 4.6%) (Table 13).

Table 13: Treatment-related treatment emergent adverse events occurring in ≥ 0.5% of subjects in Stage 1 by SOC and Preferred Term (SS (N = 1,055))

MedDRA SOC and Preferred Term	PA21 (N=707) n (%) E	Sevelamer (N=348) n (%) E
Any treatment-related TEAE	280 (39.6%) 509	69 (19.8%) 122
Gastrointestinal Disorders	223 (31.5%) 383	53 (15.2%) 86
Faeces discoloured	105 (14.9%) 106	1 (0.3%) 1
Diarrhoea	90 (12.7%) 121	8 (2.3%) 9
Nausea	25 (3.5%) 27	8 (5.2%) 18
Constipation	17 (2.4%) 19	16 (4.6%) 17
Dyspepsia	13 (1.8%) 16	5 (1.4%) 5
Vomiting	13 (1.8%) 14	4 (1.1%) 4
Abdominal pain	11 (1.6%) 12	4 (1.1%) 4
Tooth discolouration	9 (1.3%) 9	0 (0.0%) 0
Abdominal pain upper	7 (1.0%) 8	5 (1.4%) 5
Flatulence	7 (1.0%) 7	6 (1.7%) 7
Abdominal distension	5 (0.7%) 5	3 (0.9%) 3
Frequent bowel movements	5 (0.7%) 6	0 (0.0%) 0
Gastritis	4 (0.6%) 4	2 (0.6%) 2
Tongue discolouration	4 (0.6%) 4	0 (0.0%) 0
Abdominal discomfort	3 (0.4%) 4	3 (0.9%) 3
Dysphagia	2 (0.3%) 2	2 (0.6%) 2
Metabolism and Nutrition Disorders	41 (5.8%) 48	15 (4.3%) 18
Hypophosphataemia	14 (2.0%) 17	6 (1.7%) 8
Hyperphosphataemia	13 (1.8%) 16	3 (0.9%) 3
Hypocalcaemia	4 (0.6%) 4	2 (0.6%) 2
Decreased appetite	3 (0.4%) 3	4 (1.1%) 5
General Disorders and Administration Site Conditions	34 (4.8%) 38	4 (1.1%) 5
Product taste abnormal	22 (3.1%) 22	2 (0.6%) 2
Oral administration complication	7 (1.0%) 7	1 (0.3%) 1
Skin and Subcutaneous Tissue Disorders	11 (1.6%) 13	0 (0.0%) 0
Pruritus	6 (0.8%) 7	0 (0.0%) 0
Investigations	7 (1.0%) 7	4 (1.1%) 4
Blood phosphorus decreased	2 (0.3%) 2	3 (0.9%) 3

Notes: E = Total number of adverse events; MedDRA = Medical Dictionary for Regulatory Activities; n = Number of subjects; each subject counts only once for each adverse event; SOC = System organ class; SS = Safety set; TEAE = Treatment-emergent adverse event.

No treatment-related TEAEs were reported for Stage 2 subjects in the PA21 MD group. In the PA21 LD group, 6 subjects had hyperphosphataemia that was attributed to treatment and these increases in phosphorus levels represented the loss of control following withdrawal from the MD reached in Stage 1.

8.4.2.2. Other studies

8.4.2.2.1. Integrated analysis of PA-CL-05A and PA-CL-05B

Overall (pooled PA-CL-05A/PA-CL-05B data), more subjects in the PA21 group had treatment-related TEAEs than in the sevelamer group (PA21 vs sevelamer: 45.3% vs 24.7%), driven primarily by the number of subjects who had GI TEAEs. The most notable differences (≥2.0% incidence) in specific treatment-related TEAEs between treatment groups were the higher proportion of subjects in the PA21 group with treatment-related discoloured faeces (15.6% vs 0.3%), diarrhoea (13.0% vs 2.3%) and abnormal product taste (3.8% vs 0.6%). In study PA-CL-

05B, there was a higher incidence of treatment-related AEs in the PA21 group compared with the sevelamer group (14.6% vs 9.0%) mainly due to higher incidence of GI-related AEs in the PA21 group. However, the difference in treatment-related TEAEs between groups was smaller in PA-CL-05B compared to PA-CL-05A, as there was a significantly lower incidence of treatment-related GI TEAEs reported during PA-CL-05B in PA21-treated subjects. Majority of treatment-related TEAEs were mild in both treatment groups (67.2% vs 66.3%). All except 1 severe treatment-related TEAEs occurred during the PA-CL-05A treatment period and the majority of severe treatment-related TEAEs were in the GI Disorders SOC.

8.4.2.2.2. Phase 2 dose-ranging study PA-CL-03A

In the pooled PA21 group, 44 subjects (34.4%) reported at least 1 treatment-related TEAE. The proportion of subjects with treatment-related TEAEs was highest in the PA21 10.0 g/day (44%) and 12.5 g/day (41.7%) groups due to a higher incidence of treatment-related hypophosphataemia in the 2 highest-dose PA21 groups (25.9% and 20.8% in the PA21 10.0 g/day and 12.5 g/day groups, respectively). The proportion of subjects with treatment-related TEAEs was lowest in the PA21 1.25 g/day group (19.2%) and that in the sevelamer (HCl) (30.8%) group was similar to that in the PA21 5.0 g/day (34.6%) and 7.5 g/day (32%) groups. No subject reported a severe or serious treatment-related TEAE.

In the Japanese study PA1201, the incidence of treatment-related AEs was 38.5%, 36.1%, 54.3%, 55.6% and 10.8% in PA21 3.75g/day, 7.5g/day, 11.25g/day, 15g/day and placebo groups, respectively.

8.4.3. Deaths and other serious adverse events

8.4.3.1. Pivotal studies PA-CL-05A

There were 21 subjects that experienced fatal TEAEs during the pivotal study (Stage 1 and Stage 2) or within 30 days of the last dose of study medication, 14 (2.0%) in the PA21-treated subjects and 7 (2.0%) in the sevelamer-treated subjects. The onset of fatal TEAEs occurred during Stage 1 in 20 subjects and during Stage 2 in 1 subject. None of the deaths was considered related to study treatment. Only 2 of the 21 subjects (1 in each treatment group) were on PD. The overall number of deaths was the same in the titration and maintenance periods (9 deaths in both periods). In the titration period, the number of deaths was slightly higher in the PA21 group; 7 subjects (1.0%), while the number of deaths was slightly higher in the sevelamer group (5 subjects, 1.6%) in the maintenance period. The majority of deaths were related to Cardiac Disorders and there was no indication of major differences in the reasons for death between treatment groups. There was no association between the incidence of fatal TEAEs and maximum daily dose. No notable differences in the incidence or SOC association of fatal TEAEs were observed for dialysis subgroups.

The overall proportion of subjects with serious TEAEs during Stage 1 was 18.8% with no major difference between the overall PA21 and sevelamer groups (18.2% vs 19.8%). The largest proportions of serious TEAEs were infections and cardiac event, followed by GI Disorders, procedural complications, respiratory disorders, and vascular disorders. SAEs were reported for 8 subjects total in Stage 2: 2 subjects in the PA21 MD group and 6 subjects in the PA21 LD group (including a fatal SAE reported in a PA21 LD subject- renal transplant / tubular necrosis).

8.4.3.2. Other studies

8.4.3.2.1. Integrated analysis of PA-CL-05A and PA-CL-05B

Thirty-five subjects experienced fatal TEAEs during the PA-CL-05A and PA-CL-05B combined studies or within 30 days of the last dose of study medication: 21 (3.0%) of PA21-treated subjects and 14 (4.0%) of sevelamer-treated subjects. The onset of the fatal TEAEs occurred during PA-CL-05A in 21 subjects and during PA-CL-05B in 14 subjects. None of the deaths was considered related to study treatment. Fatal TEAEs occurred in 32 (3.3%) of subjects on HD and in 3 (3.5%) of subjects on PD. The causes of death were generally consistent with the medical

conditions of ESRD patients on dialysis and majority of deaths (42.9%) were related 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 maximum daily dose.

In the pooled PA-CL-05A/PA-CL-05B data, SAEs were reported by 26.6% and 29.6% in the PA21 and sevelamer groups, respectively. In PA-CL-05B, serious TEAEs were reported in 19.9% and 19.5%, respectively. The largest proportions of SAEs in the integrated PA-CL-05A/PA-CL-05B analysis were associated with the SOCs of Infections and Infestations and Cardiac Disorders, followed by Injury, Poisoning and Procedural Complications, Vascular Disorders, GI Disorders, Respiratory, Thoracic and Mediastinal Disorders, and Metabolism and Nutrition Disorders. There were only 4 subjects overall who experienced SAEs that were treatment-related; all of the treatment-related SAEs during the 2 studies were in the GI Disorders SOC, 4 events (3 subjects) in the PA21 group and 1 event (1 subject) in the sevelamer group and all 4 subjects were on HD.

8.4.3.2.2. Phase 2 dose-ranging study PA-CL-03A

One subject in the PA21 5.0 g/day group died[21] during the study. Eight subjects (6.3%) in the pooled PA21 treatment group experienced a total of 13 serious TEAEs and 2 subjects (7.7%) in the sevelamer (HCl) treatment group experienced a total of 3 serious TEAEs. The only serious TEAE reported by more than 1 subject was staphylococcal sepsis, reported by 1 subject in each of the PA21 5.0 g/day and 12.5 g/day groups (3.8% and 4.2%, respectively). The number of subjects with serious TEAEs was comparable across all treatment groups (1 to 2 subjects).

In the Phase 2, Japanese dose-ranging study PA1201, there were no deaths in any treatment group. There were 8 serious TEAEs reported by 7 (3.8%) subjects, none of which were considered treatment-related.

8.4.3.2.3. Phase 1 non-pooled studies

There were no deaths or SAEs in the Phase 1 non-pooled studies VIT-CI-01, Q-24120 and PA1101 with exception of 1 unrelated SAE[22] in study Q24120.

8.4.4. Discontinuations due to adverse events

8.4.4.1. Pivotal studies PA-CL-05A

More subjects in the PA21 group compared with the sevelamer group were withdrawn from treatment for TEAEs (15.7% vs 6.6%). Gastrointestinal TEAEs were the most common class of TEAEs leading to withdrawal in both groups, accounting for 60 of 111 withdrawals (54%) in the PA21 group and 10 of 23 (43.5%) in the sevelamer group. In Stage 1 in the PA21 group, the most common AEs leading to withdrawal were diarrhoea, nausea, constipation, vomiting, abdominal pain, discoloured faeces, dyspepsia, flatulence, abnormal product taste and hyperphosphataemia. In the sevelamer group, common AEs leading to withdrawal were diarrhoea, nausea, constipation, and vomiting.

Only 3 subjects were withdrawn as a result of TEAEs in Stage 2. All 3 subjects withdrawn in Stage 2 were in the PA21 LD group[23].

[21] This subject, who had a medical history of diabetes mellitus, hypertension and myocardial infarction, experienced a gastrointestinal haemorrhage and cardiac arrest approximately 4 weeks after first intake of study treatment
[22] serious TEAE (MI in a dialysis subject), which occurred after discontinuation of PA21 treatment and was considered not related to treatment.
[23] 2 subjects were withdrawn because of hyperphosphataemia and 1 was withdrawn because subject underwent a renal transplant (the subject had renal tubular necrosis and subsequently died).

8.4.4.2. Other studies

8.4.4.2.1. Integrated analysis of PA-CL-05A and PA-CL-05B

In the integrated analysis, more subjects in the PA21 group compared with the sevelamer group were withdrawn from treatment for TEAEs (20.9% vs 10.3%). Gastrointestinal TEAEs were the most common class of TEAEs leading to withdrawal in both groups, accounting for 70 of 148 withdrawals (47.3%) in the PA21 group and 11 of 36 (30.6%) in the sevelamer group. The GI TEAEs leading to withdrawal were severe in only 6 subjects in the PA21 group and 6 subjects in the sevelamer group. In the PA21 group, diarrhoea, nausea, constipation, vomiting, abdominal pain, discoloured faeces, and dyspepsia led to withdrawal in ≥0.5% of subjects. Other than GI events, the only TEAEs with an incidence ≥0.5% in the PA21 group were abnormal product taste in 13 subjects (1.8%) and hyperphosphataemia in 23 subjects (3.3%). In the sevelamer group, diarrhoea, nausea, constipation, vomiting, flatulence, and product dosage form issue led to withdrawal in ≥0.5% of subjects.

A significantly lower proportion of subjects were withdrawn for TEAEs during PA-CL-05B compared with the combined studies, suggesting that a smaller proportion of subjects would be expected to experience TEAEs leading to withdrawal during long-term treatment (PA21 vs sevelamer: 8.2% vs 4.9%) and the most common reason for discontinuation in both treatment groups was hyperphosphataemia (2.8% vs 2.6%), which reflects the predefined withdrawal criteria for the study. A similar proportion of subjects had serious TEAEs that led to withdrawal in the 2 treatment groups: 26 subjects (3.7%) in the PA21 group and 16 subjects (4.6%) in the sevelamer group. Serious TEAEs leading to withdrawal were mostly in the Cardiac Disorders, GI Disorders, and Infection and Infestations SOCs. There were no remarkable differences between treatment groups in the combined PA-CL-05A and PA-CL-05B studies or in PA-CL-05B alone.

The time of onset of TEAEs leading to withdrawal are consistent with the time of onset of other TEAEs. In the PA21 group, TEAEs leading to withdrawal tended to occur during the early part of the combined studies whereas, in the sevelamer group, these TEAEs were more evenly distributed throughout the combined studies.

8.4.4.2.2. Phase 2 dose-ranging study PA-CL-03A

The proportion of subjects who were withdrawn from study treatment and/or the study because of TEAEs was 21.1% in the pooled PA21 treatment group and 23.1% in the sevelamer treatment group. The proportion was higher in the PA21 10.0 g/day group (29.6%) than in the remaining PA21 groups; hypophosphataemia was the most frequent cause of permanent discontinuation, occurring in 10.2% (13/128) of the pooled PA21 group and 7.7% of the sevelamer (HCl) group. Within the PA21 group there was a dose relationship with more subjects withdrawing due to hypophosphataemia in the 2 highest dose groups: 6 subjects (22.2%) in the 10.0 g/day group and 4 subjects (16.7%) in the PA21 12.5 g/day group.

In the Phase 2, Japanese dose-ranging study PA1201, there were 21 TEAEs reported by 17 subjects (9.3%) that resulted in a temporary or permanent discontinuation of dosing.

There were no withdrawals due to AEs in the Phase 1 non-pooled studies VIT-CI-01, Q-24120 and PA1101.

8.5. Laboratory tests

8.5.1. Liver function

8.5.1.1. Pivotal study PA-CL-05A

In study PA-CL-05A, alkaline phosphatase increased significantly from baseline in both treatment groups and the increase in the sevelamer group was significantly higher than the PA21 group. The changes in the subjects on HD and PD were also similar. These changes were driven by changes in bone-specific alkaline phosphatase. Although there were several

statistically significant changes from baseline in the other liver enzyme test (aspartate transaminase, alanine transaminase, lactate dehydrogenase, and gamma-glutamyl transpeptidase), these changes were generally small and not different between treatment groups. The changes in the subjects on HD and PD were also similar. Five subjects (3 treated with PA21 and 2 treated with sevelamer) had elevated liver enzymes or abnormal liver function tests reported as a TEAE. However, none of the 5 events were considered serious or led to withdrawal.

8.5.1.2. Other studies

In the Combined PA-CL-05A/05B studies, alkaline phosphatase increased from BL in both treatment groups, and the increases in the sevelamer group were significantly higher than in the PA21 group and were mainly driven by changes in bone-specific alkaline phosphatase (BAP). Although there were several statistically significant changes from BL in the other liver enzyme tests (AST, ALT, lactate dehydrogenase, and GGT), these changes were generally small and not different between treatment groups. There were no clinically relevant differences in shifts of liver enzymes between treatment groups. Eleven subjects (6 treated with PA21 and 5 treated with sevelamer) had elevated liver enzymes or abnormal liver function tests reported as a TEAE. None of these were considered serious or led to withdrawal.

In Phase 2 study PA-CL-03A, mean changes from BL to Week 4, and FUP in ALT, AST, alkaline phosphatase, GGT, and lactate dehydrogenase were not statistically significant, and no parameters displayed an apparent pattern across the treatment groups. In general, the proportions of patients whose liver enzymes values shifted to outside the normal range after BL were low. Occasional differences between the treatment groups did not correlate with PA21 dose.

8.5.2. Kidney function

There were no clinically relevant changes in renal function parameters (refer section 8.5.3 below).

8.5.3. Other clinical chemistry

8.5.3.1. Pivotal study PA-CL-05A

Mean changes from baseline in bicarbonate, bilirubin, BUN, C-reactive protein, chloride, creatine kinase, creatinine, glucose, cholesterol (total, low density lipoproteins and high density lipoproteins), potassium, sodium, total protein, and urate were not clinically significant and the differences between PA21 and sevelamer treatment groups were not statistically significant.

As expected, subjects most commonly experienced TEAEs related to increases or decreases in serum phosphorus, calcium or hyperparathyroid hormone levels. PA21-treated subjects had a slightly lower incidence of sustained hypophosphataemia compared with sevelamer-treated subjects (0.1% vs 1.1%) and a higher incidence of sustained hyperphosphataemia (9.9% vs 6.3%). The incidence of hyperphosphataemia was much higher during the dose titration period than the maintenance period, which is not unexpected as subjects were uptitrated to target levels. The incidence of sustained hypercalcaemia was very low and similar in both groups.

There were 10 subjects (1.4%) with 13 SAEs related to clinical laboratory values in the PA21 group and 4 subjects (1.2%) with 4 SAEs in the sevelamer group. These SAEs were not clustered in any SOC and none was considered treatment-related. None resulted in withdrawal from treatment with the exception of one case of severe anaemia in a PA21 subject. There were 18 subjects with 20 TEAEs leading to withdrawal in the PA21 group and 1 subject with 1 event in the sevelamer group.

There were no clinically relevant mean changes in activated partial thromboplastin time and prothrombin time, and no notable differences between treatment groups.

8.5.3.2. Other studies

In the Combined PA-CL-05A/05B studies, mean changes from BL in bicarbonate, bilirubin, blood urea nitrogen, HDL cholesterol, chloride, creatine kinase, creatinine, glucose, potassium, sodium, total protein, and urate were overall not clinically relevant, and the differences in changes were not statistically significant between PA21 and sevelamer treatment groups.

In Phase 2 dose-ranging study PA-CL-03A, although several individual changes from baseline were observed, clinically significant abnormalities showed no trends or clinically relevant changes except for the expected and previously described changes in serum phosphorus; hypophosphataemia was seen more frequently in subjects receiving higher doses of PA21 whereas hyperphosphataemia was more commonly associated with low doses of PA21.

8.5.4. Haematology

8.5.4.1. Pivotal study PA-CL-05A

The mean changes from baseline in haematology parameters were not clinically relevant and the differences between PA21 and sevelamer treatment groups were not statistically significant. Anaemia was reported as an AE in 13 subjects (1.8%) in the PA21 group and in 16 subjects (4.6%) in the sevelamer group. Similar results for haematology parameters were observed during stage 2 of the pivotal study.

8.5.4.2. Other studies

In the Combined PA-CL-05A/05B studies, mean changes from BL in basophils / eosinophils / monocytes / neutrophils (absolute and %), haematocrit, mean corpuscular Hb concentration and mean corpuscular volume, platelets; reticulocytes and leucocytes were not clinically relevant and the differences between PA21 and sevelamer treatment groups were not statistically significant. Mean changes in Hb were small in both treatment groups in the SS. There were occasional statistically significant changes from BL and between treatments, but these were not clinically meaningful. No relationship between Hb values and the maximum dose level of PA21 received was observed. Anaemia was reported as an AE in 37 subjects (5.2%) in the PA21 group and in 35 subjects (10.1%) in the sevelamer group. Abnormal white blood cell counts (usually increases) were reported in >4.0% of subjects during the study, but there were no distinct patterns in either treatment group, and the events were generally not serious and were not related to treatment.

In the Phase 2 study PA-CL-03A, mean changes from BL to Week 4, were not statistically significant in the pooled PA21 treatment group or any of the individual PA21 treatment groups for all parameters; there was no pattern of clinically significant change observed for any parameter across the individual PA21 groups and the sevelamer group. Mean changes from BL to Week 4, in activated partial thromboplastin time (aPTT), INR and prothrombin time were not statistically significant in the pooled PA21 treatment group. No pattern was observed in mean changes from BL to FUP across the PA21 groups and the sevelamer (HCl) group.

8.5.5. Iron status parameters

The iron status of subjects with ESRD is usually abnormal, reflecting both the inherent anaemia of the condition and the widespread use of iron supplementation and ESAs. The use of an iron-based phosphorus binder like PA21 could, theoretically, improve some aspects of that status (for example, increasing iron levels) but could also adversely affect that status, perhaps through iron accumulation. A careful assessment of the potential impact of study medications on iron status parameters was conducted by the sponsors.

In the pivotal study PA-CL-05A, serum ferritin was elevated at baseline in both treatment groups, presumably reflecting the regular concomitant iron replacement and ESA therapy that subjects were given during the study. More than 70% of subjects in both groups were receiving concomitant iron products and more than 80% were receiving concomitant ESAs during the

study. Statistically significant increases from baseline to Week 24 endpoint in serum ferritin [+277.4 pmol/L (+123.5 ng/mL)] and transferrin saturation (+4.8%) and significant decreases from baseline in transferrin (-0.5 g/L) were observed in the PA21 group. These differences were also statistically significantly different from results with sevelamer (+92.0 pmol/L ferritin, -0.5% transferrin saturation, and +1.8 g/L transferrin). There was no apparent relationship with maximum daily doses, but interpretation of dose relationship is limited in this study because of the open dose titration study design. There were also significant increases from baseline in serum iron in both groups, but no significant differences between treatment groups. Subjects on HD had higher baseline serum ferritin compared with subjects on PD. The changes in these iron parameters were generally similar. The changes in iron parameters (especially ferritin and transferrin saturation) suggest that there may be low iron absorption from PA21, which is consistent with the nonclinical data and the Phase 1 data. The changes in iron parameters did not result in any effects on haemoglobin and/or haematocrit values. TEAEs related to iron status (increased serum ferritin, increased blood iron, iron overload or increased haemoglobin) were reported as TEAEs in a similar proportion of subjects in both treatment groups: 14 subjects (2.0%) treated with PA21 and 8 subjects (2.3%) treated with sevelamer. None of these events was considered severe or serious and none led to withdrawal. However, iron overload in one PA21-treated subject[24] was considered related to treatment by the Investigator.

In the combined PA-CL-05A/05B studies, BL mean serum ferritin levels were significantly above the ULN, while mean iron and TSAT levels were around the lower quartile of normal, and mean ferritin levels were just below the lower limit of normal. In contrast to Study PA–CL–03A, IV iron was allowed during these studies. Mean changes from BL in serum ferritin and TSAT showed significantly larger increases in the PA21 group compared with the sevelamer group, especially during the first 24 weeks of treatment. Thereafter, the differences in ferritin and TSAT between treatments groups were maintained. Mean transferrin levels decreased slightly from BL in the PA21 group, and mean values increased slightly in the sevelamer group. Iron level increases from BL were not meaningful and did not differ significantly between treatment groups.

A comparison of iron parameters between subjects in Studies PA-CL-05A/05B combined who were receiving IV iron supplementation (70.2% of subjects in the PA21 group and 73.6% for sevelamer) and not receiving supplementation reveals that, at BL, mean serum ferritin, TSAT, and Hb levels were slightly lower in those patients not receiving IV iron supplementation. Through the first 24 weeks of treatment, mean serum ferritin levels rose substantially in both treatment groups in subjects treated with IV iron, though the increase was slightly greater in the PA21-treated subjects. In subjects not receiving IV iron, mean serum ferritin levels fell slightly across the 52 weeks of treatment. At the individual subject level, TEAEs related to iron parameters (serum ferritin increase, transferrin saturation increase, iron overload, transferrin decrease, and Hb increase) were reported by a similar proportion of subjects in both treatment groups: 20 (2.8%) subjects for PA21 and 10 (2.9%) subjects for sevelamer. None of these events was severe, considered serious or led to withdrawal.

In study PA-CL-03A, mean serum ferritin levels at baseline were at or just above the ULN, while mean iron and ferritin levels were at or below the lower limit of normal (expected in a population in which the majority were receiving IV iron supplementation). It should be noted that no oral or IV iron preparations were allowed during the study. Mean changes from BL to Week 4 and FUP in ferritin, iron, transferrin, and TSAT were not statistically significant at either

[24] On Day 168, whilst taking PA21 12.5 g/day, the serum laboratory results for a Subject depicted elevated transferrin saturation (80%) and iron (48.1 µmol/L), but ferritin remained within normal range (70 pmol/L (31.15 ng/mL)). The subject was diagnosed with iron overload but did not receive treatment for the event. The subject remained on the PA21 dose until the end of the study. The iron overload resolved without sequelae on Day 182. The Investigator considered the iron overload to be related to study treatment.

time point in any treatment group/dose level, except for the decrease in transferrin at FUP in the PA21 5.0 g/day group. Iron parameter results were similar between the PA21 treatment groups and the sevelamer group. At the individual subject level, the shift tables show that the proportions of patients with shifts in ferritin, iron and transferrin values to outside the normal range were generally low, and there were no apparent differences across the treatment or PA21 dose groups.

8.5.6. Vitamins A, K, E, D, bone markers and FGF-23

In the combined studies PA-CL-05A/ 05B, mean levels of Vitamin D decreased significantly in both treatment groups during the first 24 weeks of treatment, and values recovered during the latter weeks of treatment. Decreases appeared to be slightly greater in the sevelamer groups, but were not statistically significantly different between groups. At the individual subject level, Vitamin D decreases were reported as TEAEs in 18 subjects (2.5%) in the PA21 group and 7 subjects (2.0%) in the sevelamer group. The majority of Vitamin D deficiencies were mild, and none was considered serious or related to treatment. Some subjects were treated with supplements, but none were withdrawn from treatment. Shifts from BL in Vitamin A, Vitamin D, 1,25 hydroxy Vitamin D, Vitamin E, and Vitamin K were not clinically significant (NCS), and the differences in shifts were not noticeably different between treatment groups.

Significant increases from BL in BAP were observed in both treatment groups during treatment, but values returned to near BL at the end of the studies. Increases were generally greater in the sevelamer group, but differences between groups were not statistically significant except at the combined endpoint. At the individual subject level, there were no noticeable differences between treatment groups in shifts of BAP.

Osteocalcin increased slightly during the first 24 weeks in both treatment groups; increases were larger during the subsequent weeks, reaching or exceeding the ULN (approximately 22 ng/mL) by the end of the studies. Although increases were larger in the sevelamer group, there was no significant difference between groups.

Tartrate-Resistant Acid Phosphatase (TRAcP) values showed statistically significantly decreases from BL throughout the studies in both treatment groups with no significant difference between groups.

CTX levels increased during the first 24 weeks of treatment – the increases were comparable between treatment groups. CTX values levelled off during PA-CL-05B and had returned to near BL at Week 52.

Significant decreases from BL in FGF-23 were observed during PA-CL-05A and sustained in PA-CL-05B, but the differences between treatment groups were not significant.

> **Comments**: The data from these studies show gradual, but significant, reductions in Vitamin D levels over the six months (24 weeks) following initiation of treatment with both PA21 and sevelamer. However, these levels gradually increased over the ensuing months to return to BL values at 52 weeks. No significant changes in total, HDL- or LDL-C, or triglyceride levels were seen during treatment with PA21. Consistent with this lack of effect on fat absorption, no effects were seen in the levels of the other fat-soluble Vitamins A, E, and K, and only a very few TEAEs relating to these vitamins were reported. Overall, the data indicate that PA21 has no adverse effect on vitamin A, K, E and D levels during early or longer-term exposure.

8.5.7. Electrocardiograph

Baseline in Study PA-CL-03A was the pre-dose ECG assessment at Week 1. Baseline in Studies PA-CL-05A/05B combined was the latest assessment performed prior to the first study drug intake in Study PA-CL-05A. Increases from BL in QTcB and QTcF were summarised over time using the categories 30 to 60 ms and >60 ms. Absolute values of QTcB and QTcF were

summarised over time using the categories ≤450 ms, >450 to <480 ms, >480 to <500 ms, and >500 ms.

8.5.7.1. Pivotal studies

The mean changes from baseline to Week 12, Week 24, and endpoint in PQ, QRS, QT, and RR intervals and HR were not statistically significant (i.e., the 95% CIs of the mean changes included zero) in the PA21 and sevelamer treatment groups and there were no differences between treatment groups. A significant proportion (>38%) of subjects in both treatment groups had prolonged QTcB intervals (>450 msec) at baseline; however, no significant changes in the proportion of subjects that had prolonged QTcB intervals were observed in either group at any time point during Stage 1 treatment. Shifts in overall ECG results did not differ between treatment groups.

8.5.7.2. Other studies

In the combined studies PA-CL-05A/05B, none of the mean changes from the PA-CL-05A or PA-CL-05B BLs in QTcB and/or QTcF intervals were statistically significant (i.e., the 95% CIs of the mean changes included zero) in the PA21 or sevelamer treatment groups, with the exception of Week 52 for the PA21 group. A significant proportion (>38%) of subjects in both treatment groups had prolonged QTcB intervals (>450 ms) at BL: PA21, 266 of 694 subjects (38.3%); sevelamer 138 of 343 subjects (40.2%). In addition, 47 (6.8%) PA21 and 13 (3.8%) sevelamer subjects had QTcB intervals >500 ms at BL. No significant increases in the proportion of subjects that had prolonged QTcB intervals were observed in either treatment group at any time point compared to BL, for either >450 ms or >500 ms with similar results for QTcF. In the PA21 group, 14.9% of subjects had increases in QTcB ≥30 ms at Week 24, 17.7% at Week 52 and 15.8% at the combined Endpoint. Intervals determined by the Fredericia method showed similar increases. Corrected QT interval increases were observed in the sevelamer group with a pattern similar to increases in the PA21 group. One PA21-treated subject had an arrhythmia that was reported as a TEAE in Study PA-CL-05A and considered related to treatment, but was not serious; arrhythmia was again reported for this subject in Study PA-CL-05B and was considered unrelated at that time. Mild first-degree AV block in another PA21-treated subject was considered related to treatment; however, the event was not serious and did not lead to withdrawal. Another PA21-treated subject was withdrawn because of increased HR, unrelated to treatment and not serious. Several other subjects (8 in the PA21[25] group and 8 in the sevelamer[26] group) had serious TEAEs related to ECG findings; however none of these serious events were considered related to treatment and none led to withdrawal.

In study PA-CL-03A, majority (90%) of subjects in all groups showed no significant increases in QTc; using the QTc Bazett and QTc Fredericia, there was no significant increase in 91.1% and 92.0% of the pooled PA21 groups respectively, while in the sevelamer group the comparable figures were 81.0% and 85.7%, respectively. There was no evidence of a dose related effect between the PA21 dose groups, either in the increase of >30 msec or >60 msec.

There were no clinically significant changes in ECGs in the Phase 1 studies including the 5 pooled DDI studies.

8.5.8. Vital signs

The vital signs data were presented for absolute values and the change from BL by study treatment group.

[25] 3 PA21-treated Subjects had serious atrial fibrillation; 1 subject had serious atrial flutter; 2 subjects had serious ventricular tachycardia; 1 subject each had had a complete AV block and serious bradycardia.
[26] 5 sevelamer subjects had serious atrial fibrillation (1 with fatal cardiac tamponade); 2 had serious bradycardia and 1 subject each had serious SVT and ventricular extrasystoles.

8.5.8.1. Pivotal study PA-CL-05A

Hypertension (PA21 vs sevelamer: 6.4% vs 7.5%) and hypotension (3.1% vs 3.2%) were among the most commonly reported TEAE in Stage 1, with a similar proportion of subjects reporting these events in both treatment groups. No subjects were withdrawn from treatment for hypertension or hypotension. The mean changes from baseline in diastolic and systolic BP, HR and body temperature at Week 24/endpoint were not clinical relevant and did not differ between treatments.

8.5.8.2. Other studies

In the combined studies PA-CL-05A/05B, although several changes from BL were observed in BP, HR, and body temperature, few were clinically significant and there were no notable differences between treatment groups. The mean changes from BL in diastolic and systolic BP were not clinically relevant and did not differ between treatments. Hypertension and hypotension were among the most commonly reported TEAEs, with a similar proportion of subjects reporting these events in both treatment groups. No subjects were withdrawn from treatment for hypertension. One subject treated with sevelamer was withdrawn for hypotension. In the PA21 group, 6 subjects (0.8%) had serious hypertension and 3 subjects (0.4%) had serious hypertensive crisis; none of these were considered related to treatment and none of the subjects were withdrawn. Serious hypotension was reported in 3 PA21-treated subjects (0.4%) and in 3 sevelamer-treated subjects (0.9%). There were few changes in physical examination[27] findings and no clinically relevant patterns for shifts in findings indicating any treatment differences for the systems evaluated.

In study PA-CL-03A, there were no statistically significant changes in systolic BP, diastolic BP, HR and body temperature in the pooled PA21 group, in the individual PA21 groups and in the sevelamer (HCl) group.

There were no clinically significant changes in vital signs or physical examination in the Phase 1 studies including the 5 pooled DDI studies.

8.5.9. AEs of special interest

8.5.9.1. Gastrointestinal AEs

The incidence of GI AEs in the Phase 2 study PA-CL-03A was similar in the PA21 (22.7%) and sevelamer (26.9%) groups. In PA-CL-05A/05B, however, the incidence of GI TEAEs was higher in the PA21 group (52.5%) than in the sevelamer (42.8%) group.

In Studies PA-CL-05A/05B combined, the most common GI events (occurring in >5.0%) in the PA21 group were diarrhoea (167 subjects, 23.6%), discoloured faeces (114 subjects, 16.1%), nausea (69 subjects, 9.8%), vomiting (42 subjects, 5.9%) and constipation (36 subjects, 5.1%). In the sevelamer group, the most common GI events were nausea (50 subjects, 14.4%), diarrhoea (40 subjects, 11.5%), vomiting (32 subjects, 9.2%), and constipation (29 subjects, 8.3%). The higher proportion of PA21-treated subjects experiencing TEAEs in the GI Disorders SOC compared with sevelamer-treated subjects was driven by the higher incidence of diarrhoea and discoloured faeces, particularly during the first stage of study PA-CL-05A.

The incidence of other important GI AEs (constipation, nausea, vomiting, flatulence and abdominal pain/discomfort) was generally lower in the PA21 group compared with the sevelamer group.

Gastrointestinal events (including diarrhoea) with both PA21 and sevelamer generally occurred early after the start of treatment. In Study PA-CL-05A, the overall incidence of TEAEs was higher in the dose titration period (first 12 weeks) of the study, than in the maintenance period (Weeks

[27] Physical examinations included the following evaluations: abdomen, cardiovascular, general appearance, head, lymph nodes, musculoskeletal, neurological, respiratory, and skin

12 to 24). During the maintenance period and throughout the extension study, the incidence rates for overall and GI TEAEs in particular were similar between the PA21- and sevelamer-treated groups. Similarly, the incidence of GI TEAEs in both groups was much lower in Study PA-CL-05B when compared with Study PA-CL-05A, supporting the evidence of early onset of such events. The incidence of GI TEAEs during Study PA-CL-05B was 25.6% for PA21 and 19.1% for sevelamer, compared with 45.1% for PA21 and 33.6% for sevelamer in Study PA-CL-05A. In particular, the incidence of diarrhoea in the PA21 group was much lower and was more comparable with sevelamer in the extension study (8.2% PA21 and 5.6% sevelamer) than in Study PA-CL-05A (20.1% PA21 and 7.5% sevelamer.

Overall, more subjects in the PA21 group had treatment-related TEAEs than in the sevelamer group (39.6% vs 19.8%), driven primarily by the number of subjects who had discoloured faeces (14.9% vs 0.3%), diarrhoea (12.7% vs 2.1%) and abnormal product taste (3.1% vs 0.6%).

In the pooled PA-CL-05A/PA-CL-05B data, SAEs were reported by 26.6% and 29.6% in the PA21 and sevelamer groups, respectively and the largest proportions of SAEs were associated with the SOCs of Infections and Infestations and Cardiac Disorders, followed by Injury, Poisoning and Procedural Complications, Vascular Disorders, GI Disorders, Respiratory, Thoracic and Mediastinal Disorders, and Metabolism and Nutrition Disorders.There were only 4 subjects overall (3 subjects during PA-CL-05A and 2 during PA-CL-05B) who experienced SAEs that were treatment-related; all of the treatment-related SAEs during the 2 studies were in the GI Disorders SOC, 4 events (3 subjects) in the PA21 group and 1 event (1 subject) in the sevelamer group and all 4 subjects were on HD.

In the pivotal study PA-CL-05A, more subjects in the PA21 group compared with the sevelamer group were withdrawn from treatment for TEAEs (15.7% vs 6.6%) and gastrointestinal TEAEs were the most common class of TEAEs leading to withdrawal in both groups, accounting for 60 of 111 withdrawals (54%) in the PA21 group and 10 of 23 (43.5%) in the sevelamer group. In Stage 1 in the PA21 group; the most common AEs leading to withdrawal in the PA21 group were diarrhoea, nausea, constipation, vomiting, abdominal pain, discoloured faeces, dyspepsia, flatulence abnormal product taste and hyperphosphataemia. In the integrated analysis, more subjects in the PA21 group compared with the sevelamer group were withdrawn from treatment for TEAEs (20.9% vs 10.3%). Gastrointestinal TEAEs were the most common class of TEAEs leading to withdrawal in both groups, accounting for 70 of 148 withdrawals (47.3%) in the PA21 group and 11 of 36 (30.6%) in the sevelamer group. The GI TEAEs leading to withdrawal were severe in only 6 subjects in the PA21 group and 6 subjects in the sevelamer group. In the PA21 group, diarrhoea, nausea, constipation, vomiting, abdominal pain, discoloured faeces, and dyspepsia led to withdrawal in ≥0.5% of subjects.

One key difference between the tolerability profiles of PA21 and sevelamer is the occurrence of discoloured faeces with PA21 treatment, which contributes to the incidence of GI TEAEs reported with PA21. This is an expected event for an oral iron-based compound, and has been seen consistently throughout all studies in the development programme. It should be expected that most subjects will experience discoloured faeces with PA21 treatment. However, only a minority of PA21-treated subjects reported discoloured faeces as an AE: 15 subjects (11.7%) and 114 subjects (16.1%) in studies PA-CL-03A and PA-CL-05A/05B, respectively. It was generally mild with no medically important consequences. None of these events were described as severe and they rarely led to discontinuation of treatment (none in PA-CL-03A and 5 subjects (0.7%) in PA-CL-05A/05B). In the occurrences of TEAEs of gastrointestinal bleeding, it appears that the presence of dark stool did not mask the diagnosis of bleeding. In PA-CL-05A, a few cases of temporary discolouration of the teeth (10 subjects, 1.4%) and tongue (5 subjects, 0.7%) were also reported with the use of PA21.

Diarrhoea was also commonly reported in both treatment groups. In PA-CL-03A, diarrhoea was reported by 5.5% of PA21-treated subjects and 11.5% of sevelamer-treated subjects. In PA-CL-05A/05B, diarrhoea was more frequently reported with PA21 treatment (23.6%) than with

sevelamer treatment (11.5%). In this study, although diarrhoea was often reported to be related to PA21 treatment, the diarrhoea events with PA21 were generally mild, occurred early after initiation of treatment and were transient, with >80% resolving with continued treatment. The terms used to describe these events often refer to "looser or softer stools", and the reporting of "watery diarrhoea" is very rare. The reporting of severe (2 subjects, 0.3%) diarrhoea was very rare, and diarrhoea rarely led to discontinuation of treatment (25 subjects, 3.5%).

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.

> **Comments**: It is important to note that 38.0% of subjects were treated with sevelamer within the 12 months before screening; hence, the lower reporting rates of AEs, especially diarrhoea in the sevelamer group may be at least partly attributable to Investigator and subject familiarity with this drug. In selecting subjects for the study, it is likely that only subjects who had previously tolerated sevelamer would be considered for screening and randomisation, thereby creating a certain selection bias.

8.6. Post-marketing experience

Not applicable.

8.7. Safety issues with the potential for major regulatory impact

8.7.1. 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.

8.7.2. Haematological toxicity

No clinically relevant changes were observed in haematological parameters.

8.7.3. Serious skin reactions

None.

8.7.4. 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 2 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 HD or PD 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.

8.7.5. 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[28].

8.8. Other safety issues

8.8.1. Safety in special populations

Adverse events that occurred in the total population were evaluated by the intrinsic factors of sex, age, and race, and the extrinsic factors of geographical region and dialysis modality. Since the Phase 1 and DDI studies mainly involved healthy volunteers (treated in relatively small numbers for short periods), TEAEs from the Phase 3 studies were used for the analysis of safety in special populations.

8.8.1.1. AEs by sex

In the combined studies PA-CL-05A/ 05B, the incidence of TEAEs was the same across treatments by sex for PA21 (male vs female: 88.8%vs 88.8%) and slightly higher in females than males for sevelamer (85.8% vs 93.0%). The incidence of TEAEs leading to withdrawal was similar in the males and females in the PA21 treatment group (20.3% vs 21.7%), but in the sevelamer group, more females withdrew due to TEAEs than males (8.7% vs 13.2%). The incidence of treatment-related TEAEs, serious TEAEs and severe TEAEs were all essentially similar when compared across the treatments and the sexes. However, deaths in the females treated with sevelamer (7 subjects, 5.4%) were noticeably higher than females treated with PA21 (8 subjects, 2.6%), and also higher than males treated with either PA21 or sevelamer (13 subjects, 3.3% and 7 subjects, 3.2%, respectively).

In the GI Disorders SOC, the overall incidence of TEAEs in male subjects receiving PA21 was similar to female subjects in Study PA-CL-03A, (males vs females: 23.2% vs 21.7%); however, in Studies PA–CL-05A/05B combined, slightly fewer males in the PA21 group experienced GI TEAEs compared to females (males vs females: 49.7% vs 55.9%). Compared to males,

[28] 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.

proportionately more sevelamer-treated females experienced GI TEAEs in both Study PA-CL-03A (20.0%, vs 36.4%), and Studies PA-CL-05A/05B combined, (39.3% vs 48.8%). The reporting of diarrhoea, the most common GI TEAE overall, was similar between men and women receiving PA21 in Studies PA-CL-05A/05B combined (22.1% vs 25.6%), and higher than the diarrhoea rate following sevelamer (13.2% vs 8.5%). Similarly, the reporting of discoloured faeces, which was uncommon with sevelamer, showed no apparent sex difference in the PA21 groups (16.2% vs 16.0% in Studies PA−CL-05A/05B combined). Nausea was more common in the sevelamer-treated groups in Studies PA−CL−05A/05B combined, but showed little difference between sexes. Constipation was marginally more common in both males and females receiving sevelamer in Studies PA−CL−05A/05B combined (males vs females: PA21: 4.1% vs 6.4%; sevelamer: 8.2% vs 8.5%).

TEAEs of hyperphosphataemia in PA21-treated males in Studies PA-CL-05A/05B combined were higher than in females (males vs females: 18.0% vs 13.4%); however, this was reversed in sevelamer treated subjects (11.0% vs 15.5%). Overall, the reporting of hyperphosphataemia was similar between PA21 and sevelamer groups and did not show a consistent sex difference. In Studies PA-CL-05A/05B combined, the rates of hypophosphatemia were low overall, and slightly higher with sevelamer (males vs females: 8.7% vs 7.8%) compared to PA21(5.1% vs 6.4%). Hypercalcaemia was reported in Studies PA-CL-05A/05B combined by 3.6% of males and 4.2% of females on PA21 compared to 0.9% of males and 6.2% of females who received sevelamer. The apparent discrepancy between the sexes with regard to hypercalcaemia in sevelamer subjects is unexplained. Some minor differences between the sexes were noted in other SOCs, with higher overall incidence of TEAEs in Infections and Infestations, and Musculoskeletal and Connective Tissue Disorders SOCs in females compared to males in both the PA21 and the sevelamer groups across the studies. In PA-CL- 05A/05B combined, abnormal product taste (General Disorders and Administration Site Conditions) was reported predominantly by men following PA21 (PA21, 4.6% versus none for sevelamer), but female reporting of abnormal product taste was more evenly distributed (PA21, 3.2% versus sevelamer, 2.3%).

8.8.1.2. AEs by age

There was no meaningful difference in the frequency of TEAEs overall by age, and no difference between PA21 and sevelamer, although interpretation for the very elderly age group (>85 years) was limited by small number of patients. As with the overall population, there were more related TEAEs associated with PA21 across the age groups compared to sevelamer, but there were no significant differences in severe or serious TEAEs with age. Withdrawals due to TEAEs were also higher in the PA21 group as a whole (compared to sevelamer) and were proportionately higher in the 65−74 (27.4%) and 75-84 (22.1%) year groups compared to the <65 year (18.7%) category.

Overall, the number of subjects withdrawn from PA-CL-05A or PA-CL-05B was slightly lower in the younger group (32.6% <65 years; 38.9% ≥65 years). In both treatment groups, subjects ≥65 years were more likely to die (12.7% versus 4.5%), were more likely to have TEAEs leading to withdrawal (46.6 versus 32.7%), had fewer TEAEs related to high serum phosphorus levels (5.1% versus 10.2%) and a smaller proportion received a renal transplant (5.1% versus 13.9%) when compared to those subjects that were <65 years. These results are not unexpected because older subjects suffering from CKD are more likely to have additional comorbidities.

Some PTs to which elderly subjects might be vulnerable were selected for further investigation including selected central nervous system (CNS) events (extrapyramidal syndrome SMQ plus confusional state), PTs relating to falls, cardiovascular (CV) events (acute cardiac ischaemia), and cerebrovascular events. Across studies PA-CL-05A and 05B, the reporting of PTs of confusion and dyskinesia was limited to 1 or 2 subjects only in the <65 and ≥65 year age categories, with no particular pattern, and no difference between PA21 and sevelamer. Similarly cerebrovascular events, which were generally infrequent, did not reveal any age-associated

pattern or difference between treatments. TEAEs relating to falls were higher in the PA21 groups but were similar in elderly subjects compared to younger ones, with the possible exception of the 75-84 year group (4.6%, 2.3%, 8.8% and 0% in <65 years, 65-74 years, 75-84 years and ≥85 years, respectively). Similarly, CV events were more frequent with PA21 but also showed no age relationship (3.6%, 2.9%, 4.4% and 0%, respectively).

Of the TEAEs broken down by age, only TEAEs in the Infections and Infestations SOC showed a modest potential for an impact of age in both the PA21 and sevelamer groups. There does not appear to be any pattern with regard to deaths in the more elderly subjects receiving PA21 or sevelamer in these trials. None of the deaths was thought by Investigators to be causally related to PA21 or sevelamer. In PA−CL−05A/PA−CL-05B combined, the overall incidences of TEAEs in the GI Disorders SOC in the PA21 and sevelamer treatment groups was 49.2% and 39.7%, respectively in the <65 year age group compared 60.9% and 50.0%, respectively in the ≥65 year age group suggesting a slightly higher susceptibility to GI TEAEs in the elderly compared to the young.

The frequency of nausea and constipation TEAEs was similar across the age groups in PA21 subjects; however, the reporting of diarrhoea (21.0% in <65 years versus 30.5% in ≥65 year groups) and faeces discoloured (13.3% in <65 years versus 23.4% in ≥65 year groups) was higher in the older >65 years group. There was a similar pattern with sevelamer with the exception that reporting of discoloured faeces was rare with sevelamer in both age categories. TEAEs in the Metabolism and Nutritional Disorders SOC had a similar frequency in PA21 and sevelamer subjects in the <65 year group (PA21 versus sevelamer: 39.0% vs. 41.7%), and were actually slightly lower overall in the ≥65 year old subjects (34.5% vs. 34.9%). This difference was primarily driven by hyperphosphataemia, which was lower in the ≥65 year group compared to the <65 year age group for both PA21 (<65 years vs. ≥65 years: 18.0% vs. 10.7%) and sevelamer (15.3% vs. 6.6%).

Cardiac Disorders were, as expected, more common in the elderly, but not greatly different between treatments. Slightly more subjects reported hypertension in PA21-treated subjects in the <65 year population (PA21 vs sevelamer: 11.8% vs 13.6%) than in the ≥65 year population (9.6%, vs 7.5%); however, hypotension was more frequent in the older group ≥65 years (8.1% vs 11.3%) compared with <65 years (4.9% vs 7.9%). From other SOCs, product taste abnormal following PA21 was more common in the ≥65 year group (7.1%) compared to subjects aged <65 years (2.7%).

> **Comments**: Overall frequency of TEAEs was similar in the elderly compared to the younger age subjects. Related TEAEs were marginally higher in the ≥65 age group compared to the <65 year group for both PA21 and sevelamer, and withdrawals due to TEAEs and deaths were more common in the elderly. Common GI TEAEs associated with PA21 such as diarrhoea and discoloured faeces were more common in elderly subjects compared to young subjects, and TEAEs in the cardiac Disorders SOC such as atrial fibrillation, hypotension and congestive cardiac failure were also more common in the elderly, regardless of which phosphate binder was used. Similarly, infections/infestations were more common in older subjects, presumably as a consequence of reduced immune function with age. Falls and CV events, although marginally more frequent with PA21 compared to sevelamer, did not show a clear age relationship, nor did some selected CNS and cerebrovascular events. Hyperphosphataemia was reported less frequently in elderly subjects treated with either PA21 or sevelamer, possibly reflecting a reduced dietary intake of phosphate by this group. Overall, the safety of PA21 was broadly comparable across the age groups studied.

8.8.1.3. AEs by race

In Studies PA-CL-05A/05B combined, the incidence of TEAEs in Black subjects (PA21 vs sevelamer: 93.1% vs 88.0%) was similar to that of White subjects (87.8% vs 88.6%). In the PA21 treatment group, 27.7% of Black subjects experienced serious events compared to 26.3% of White subjects. The respective rates for serious events with sevelamer in Black and White subjects were 30.7% and 29.9%. Furthermore, there was no meaningful difference between the Black and White racial groups for severe TEAEs, TEAEs leading to withdrawal, or Deaths. In the GI Disorders SOC, there was a slightly higher overall incidence of TEAEs in the White group (54.6%) compared to the Black group (43.1%) in PA21–treated subjects. Gastrointestinal TEAEs following sevelamer were reported by 44.0% Black subjects and 42.8% White, respectively. The difference in GI TEAEs by race was partly attributable to a higher incidence of diarrhoea in the White subjects (25.5%) compared to Black subjects (15.4%). Diarrhoea reported following sevelamer was lower in both race groups (Black, 10.7% versus White, 11.7%); there was no effect of race on other common GI TEAEs such as discoloured faeces, nausea and constipation for either PA21- or sevelamer-treated subjects. In the Metabolism and Nutritional Disorders SOC, the reporting of TEAEs was very similar between Black and White subjects in both treatment groups; Black subjects were less likely to experience TEAEs of hyperphosphataemia, regardless of treatment. In the PA21 group, hyperphosphataemia was experienced by 16.6% of White subjects compared to 12.3% of Black subjects; however, the situation was reversed for hypophosphataemia reported by 4.6% of White subjects and 9.2% of Black subjects. A similar trend was seen following sevelamer treatment. The overall incidence of TEAEs in the Vascular Disorders SOC was also higher in the Black group (25.4%) than in the White group (19.9%) for the PA21-treated subjects. However, hypertension (Black vs White: 11.5% vs 10.8%), and hypotension (6.9% vs 5.7%) were similar. Sevelamer subjects had slightly higher rates of hypertension in both races compared to PA21.

In the Cardiac Disorders SOC, Black subjects in the PA21 group experienced a slightly higher incidence of TEAEs overall (14.6%) compared to the White group (12.4%). For sevelamer, the pattern was reversed in this SOC, with more of the White group (16.7%) reporting TEAEs compared to the Black group (9.3%); however, the frequency of congestive cardiac failure was higher in both PA21- and sevelamer-treated Black subjects (PA21, 3.8% and sevelamer 2.7%) compared to White subjects (PA21, 0.9% and sevelamer, 0.8%). Overall, 156 subjects were treated with PA21 in the Asian population in Studies PA-CL-03A, PA-CL-05A/05B combined, and in the Phase 2 clinical trial in Japan (PA1201). Asian subjects showed no obvious difference in TEAE profile compared to other races.

> **Comments**: Some minor differences in TEAE profile were noted between Black and White subjects. White subjects were more likely to report diarrhoea following PA21 treatment, and more likely to withdraw from treatment as a consequence. Black subjects were marginally less likely to experience hyperphosphataemia as a TEAE and more likely to experience hypophosphataemia, but the differences were relatively modest. Overall, race does not seem to have a significant effect on the safety of PA21.

8.8.1.3.1. Safety in the Japanese Phase 2 study PA1201

The overall incidence of AEs was higher in the PA21 groups compared with placebo (54.1%, 69.2%, 61.1%, 82.9% and 75% in the placebo, PA3.75g, 7.5g, 10g and 15g/day groups, respectively); the incidence of adverse drug reaction 10.8%, 38.5%, 36.1%, 54.3% and 55.6%, respectively. The most frequently noted adverse drug reactions (with an incidence of 5% or more in any PA21 group) were: Diarrhoea (8.1%, 10.3%, 11.1%, 34.3% and 33.3%, respectively), faeces discoloured (2.7%, 25.6%, 30.6%, 28.6% and 27.8%, respectively), constipation (0.0%, 0.0%, 2.8%, 5.7% and 2.8%, respectively) and tongue discolouration (0.0%, 0.0%, 0.0%, 5.7% and 0.0%, respectively). Majority of AEs were mild to moderate with no

severe events. There were no deaths and only 8 SAEs[29] and none of them were related to study drug according to the investigator. Overall 17 subjects discontinued study or treatment due to 21 AEs and the GI AEs were most common (diarrhoea and constipation). While there were some trends suggesting increase in ferritin, TSAT and hemoglobin in the PA21 groups, no clinically significant changes were noted with other laboratory markers. Vital signs and 12-lead ECG showed no clinically significant changes or abnormal findings for any treatment group.

> **Comments**: There were no specific safety concerns in this study in 183 Japanese patients compared to those of other racial origin evaluated in studies PA-CL-03A and PA-CL-05A/05B.

8.8.1.4. Renal/Hepatic impairment

PA21 is indicated in patients with ESRD on dialysis and hence it has not been evaluated in patients with mild/ moderate renal impairment. An analysis of TEAEs by dialysis modality is presented below.

An analysis of TEAEs by hepatic impairment was not conducted and the clinical studies excluded subjects with abnormal liver function tests. Almost all subjects had normal or low liver transaminases at BL. Iron from PA21 is minimally absorbed systemically, and the liver is not involved in the metabolism or excretion of PA21. Subjects with haemochromatosis or any other condition associated with iron overload, even before the stage of showing clinical hepatic impairment, were excluded from both the Phase 2 and 3 studies.

8.8.1.5. AEs by dialysis modality

In the PA21-treated group, there were 650 subjects who were undergoing HD compared to 57 undergoing PD. In terms of age, and as typically observed in clinical practice, the HD group was slightly older (mean: 56.6 years) than the PD group (52.6 years), and the maximum age in the HD group was higher than the PD group (89 years compared to 79 years, respectively). The distribution of females and males within the two groups was similar. Although the PD population is considerably smaller, the nature and frequency of TEAEs were generally comparable between the PD (PA21 vs sevelamer: 86% vs 93%) and HD (89% vs 88%) groups. Some TEAEs were less frequent in the PD group (PA21vs sevelamer: diarrhoea: 14% vs 7%; nausea: 4% vs 20.7%; hyperphosphataemia: 9% vs 7%) compared with the HD group (diarrhoea: 24% vs 12%; , nausea: 10% vs 14%; hyperphosphataemia: 16.6% vs 13%)[30].

8.8.1.6. AEs by geographic region

In Studies PA-CL-05A/05B combined, the overall incidence of TEAEs in the PA21 group was highest in the US (93.9%), intermediate in EU (89.9%) and lowest in the ROW region (79.5%). In the sevelamer group, the incidence of TEAEs in the ROW region was also the lowest (80.2%), and there was little difference between the rate in the EU (93.5%) and the US (91.2%). The incidence of related TEAEs, serious TEAEs and severe TEAEs was higher in the US than in the other regions; however, the incidence in the 2 treatment groups in any region was similar, with the exception of related TEAEs which were more common with PA21 compared to sevelamer in all regions. There were more withdrawals due to TEAEs in the PA21 group compared to the sevelamer group in all regions: for US (PA21 vs sevelamer: 21.3% vs 8.2%), for the EU (27.7% vs 16.9%) and for the ROW (15.1% vs 8.9%). Death rates were similar between treatment groups in the US (2.6% vs4.1%) and ROW (2.9% vs 2.0%). The EU had the highest death rates overall, and a higher proportion of subjects in the sevelamer group died (6.5%) compared to the

[29] Cerebral infarction and Cardiac failure congestive (1 instance each in the PA21 3.75 g group), Liver abscess and Prostate cancer (1 instance each in the 7.5 g group), Brain stem infarction and Intracranial aneurysm (1 instance each in the 11.25 g group), Angina pectoris (1 instance in the 15 g group), and Arteriosclerosis obliterans (1 instance in the placebo group)

[30] TEAEs by dialysis modality for HD and PD patients were displayed in the sponsor's Integrated PA–CL-05A/05B CSR. Only important incidence of AEs have been discussed in report above.

PA21 group (3.8%). There are differences between the regions, but the distribution of TEAEs by SOC is similar; the TEAEs in the GI Disorders and the Metabolism and Nutrition Disorders SOCs are the first and second most frequently reported SOCs in all regions. The relatively high prior use of sevelamer in the US compared to EU and ROW territories, may have had an impact on the reporting of sevelamer TEAEs. The patterns observed in the PA21-treated groups, in relation to differences in regional reporting, are also seen in the sevelamer-treated groups. This indicates that, while there appear to be fewer TEAEs reported in ROW, the profile of TEAEs is the same, and the difference is most likely due to a different approach to reporting TEAEs, either due to cultural differences or differences in medical practice, rather than to any difference in individuals' susceptibility to TEAEs.

8.8.1.7. AEs by concomitant treatment:

A formal analysis of AEs by concomitant treatment was not carried out. PA21 has very low systemic bioavailability, and therefore it is unlikely there will be significant interaction between PA21 and systemically acting drugs. It is, however, possible that PA21 could interfere with the bioavailability of other orally administered drugs, but no such interaction has been identified in the DDI or clinical studies to date. Almost all subjects received at least 1 concomitant medication; Anti-hypertensive medication was very frequent, with beta-blockers, calcium channel blockers and angiotensin II antagonists commonly used. Anti-anaemic and anti-thrombotic agents were used by three quarters or more of the studied population. Approximately 40% of subjects received HMG-CoA reductase inhibitors to reduce lipids (Integrated PA-CL-05A/05B CSR); however, PA21 does not appear to interact with the lipid-lowering effects of these drugs (refer section 8.8.2 below). Approximately one-third of subjects used anti-diabetic drugs and over 40% took medication for acid related disorders. Just under a quarter of subjects in both treatment groups received systemic anti-bacterial agents. The widespread use and nature of the concomitant medications is as expected for subjects with ESRD, and provides the therapeutic background against which the efficacy and safety profile of PA21, in comparison with sevelamer, has been demonstrated.

8.8.2. Safety related to drug-drug interactions and other interactions

8.8.2.1. Pooled phase 1 DDI studies

Healthy volunteer studies showed no interaction in terms of bioavailability between PA21 and losartan (PA-DDI-001), furosemide (PA-DDI-002), digoxin (PA-DDI-004), warfarin (PA-DDI-005), or omeprazole (PA-DDI-003). In vitro studies have suggested the potential for interactions between PA21 and alendronate, doxycycline, levothyroxine, atorvastatin, paricalcitol, cephalexin and doxercalciferol, but not with ciprofloxacin, enalapril, hydrothiazide, metformin, metoprolol, nifedipine, quinidine, clopidogrel or simvastatin.

Five DDI studies were included in the Phase 1 Pooled Studies. TEAEs were described for 3 separate treatment combinations in these cross-over studies:

- Subjects receiving reference drug alone
- Subjects receiving PA21 and reference drug simultaneously
- Subjects receiving PA21 and reference drug administered 2 hours later.

PA21 was administered as 5.0 g three times daily with meals (15.0 g/day). Safety results for the individual DDI studies were provided.

There was a slight increase in the incidence of TEAEs in the PA21 and reference drug delayed (receiving PA21 followed by reference drug 2 hours later) group (82 subjects, 41.0%) compared to the PA21 and reference drug simultaneously group (76 subjects, 37.1%). The reference drug group had the lowest number of events (35 subjects, 17.6%). The TEAE profiles of the two PA21 groups (PA21 and reference drug simultaneously and PA21 and reference drug delayed) were very similar, with TEAEs reported in the GI Disorders SOC being the most common, reported by

47 subjects (22.9%) and 47 subjects (23.5%), respectively. The next most common events were in the Nervous System Disorders SOC with 32 subjects (15.6%) and 31 subjects (15.5%) in the PA21 and reference drug simultaneously and PA21 and reference drug delayed groups, respectively. TEAEs for the reference drug only group were most frequent in the Nervous System Disorders SOC, with a total of 15 subjects (7.5%), reporting events. The most common GI TEAEs were discoloured faeces, nausea, constipation, and diarrhoea, and the most common Nervous System Disorders TEAE was headache. There were no deaths. One subject in PA-DDI-005 (an interaction study with warfarin) experienced a serious and severe TEAE of rhabdomyolysis which led to study withdrawal. The event was not considered to be related to treatment and resolved without sequelae.

Administration of a single day's dosing of 15.0 g of PA21 (5.0 g 3 times per day) followed by a further 5.0 g dose the next morning had no demonstrable effect on any clinical chemistry parameters, haematological parameters, urinalysis parameters, physical examination, or ECGs evaluated in the 5 pooled DDI studies, whether given alone or in combination with single doses of losartan potassium, furosemide, omeprazole, digoxin, or warfarin.

Subjects taking aluminium, calcium or magnesium-containing antacids as well, as oral iron preparations, were excluded from the clinical trials due to the potential for interference with phosphate binding. Subjects taking medication for treatment of moderate to severe arrhythmic and seizure disorders, as judged by the Investigator, were also excluded from the Phase 2 study as per the sevelamer SmPC, although these were permitted in the Phase 3 trial. However, since the comparator medication was sevelamer, investigators may have been cautious about subjects with these medical conditions who were taking such medication being randomised to the study. No obvious interaction between PA21 use and typical medications taken by subjects with ESRD has been identified from the clinical trial programme to date, but the prescribing physician must always be aware of such possibilities.

8.8.2.2. Effect of PA21 on statins

In the post-hoc analysis (refer to section 5.2.6 above) of lipid levels (LDL-C, Total-C, and triglycerides) 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.

8.8.3. Safety in pregnancy/lactation

There are no available clinical data from the use of PA21 in human pregnancies and pregnant females, and pregnancy/lactation was an exclusion criteria in the clinical trials. Reproductive and developmental toxicity studies in animals revealed no adverse effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development. The benefit/risk needs to be considered when assessing the use of PA21 during pregnancy. There are no available clinical data from the use of PA21 in lactating women. Since absorption of iron from PA21 is minimal, excretion of iron from PA21 in breast milk is unlikely. A decision on whether to continue breast feeding or to continue therapy with PA21 should be made taking into account the benefit of breast feeding to the child and the benefit of PA21 therapy to the mother.

8.8.4. Overdose, drug abuse, withdrawal/rebound, effects on ability to drive or operate machinery or impairment of mental ability

No case of overdose has been reported. Some subjects reported compliance in excess of 120% (as measured by pill counting); however, this did not result in excessive dosing and was generally the result of dispensing and tablet return recording anomalies. Since the absorption of iron from PA21 is minimal, the risk of systemic iron toxicity is negligible. Any instances of hypophosphataemia due to phosphate binder overdose should be treated by standard clinical practice.

Drug abuse information is not available for PA21.

Study PA-CL-05A included a withdrawal study design in which a subgroup (n=49) of subjects was transferred to a low (non-effective) dose of PA21 (1.25 g/day) for 3 weeks. These subjects showed marked increases in serum phosphorus, within 1 week of transitioning to the LD of PA21 (PA-CL-05A). Subjects and healthy volunteers did not report any signs or symptoms indicative of being related to withdrawal or rebound on stopping this medication.

No studies on the effects on ability to drive and use machines have been performed.

8.9. 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 2 and 3 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 (BL) 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 3 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 International Conference on Harmonisation E1 guidance. 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 GI and Metabolism and Nutritional Disorders system organ classes (SOC). 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 3 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 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 2 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 3 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 2 and 3 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 GI 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 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 hydrochloride) 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 ESAs. 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 aPTT 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 HD 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 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 BL 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.

9. First round benefit-risk assessment

9.1. 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 LD) 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 HD and PD 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, HD or PD), 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 (e.g., changes in serum phosphorus levels) or to its physicochemical composition (e.g., 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.

9.2. First round assessment of risks

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

- Increased incidence of gastrointestinal adverse events.
- Higher incidence of TEAEs and withdrawals due to AEs, but these were mainly related to gastrointestinal 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.

9.3. 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 (HD and PD). PA21 and sevelamer treatment groups in Stage 1 and the PA21 MD and LD 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 ESAs. 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 LD) 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, HD or PD), and was not affected by other BL or disease characteristics.

Although the proposed starting dose of 1500mg/day was not used in the pivotal Phase 3 study (which used 1000mg/day), there was adequate data to support the proposed starting dose of 3tablets /day (1500mg/day) as discussed in section 7.2 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 (e.g., changes in serum phosphorus levels) or to its physicochemical composition (e.g., 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 this 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.

10. 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[31] and adequate response to the clinical questions in section 11.

11. Clinical questions

11.1. Pharmacokinetics

None.

[31] The section discussing recommended revisions to Product Information is not included in the Extract from the Clinical Evaluation Report

11.2. Pharmacodynamics

None.

11.3. Efficacy

1. The sponsors have provided the following justification for selecting the non-inferiority margin of 0.19mmol (0.6mg/dl) in the pivotal Phase 3 study PA-CL-05A:

   The number of randomised clinical trials comparing sevelamer (sevelamer carbonate or sevelamer hydrochloride) against placebo is very limited (Tonelli M, 2007[32]; Navaneethan SD[33], 2009). 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 SD of around 2.2 mg/dL (range from 2.1 mg/dL to 2.4 mg/dL) (Bleyer AJ, 1999; Braun J, 2004; Chertow GM, 1999) . 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 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 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 MD group versus the non-effective LD control group which essentially functions as a placebo control group. It is conventional, however, to state confidence intervals with 95%, not 97.5% 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.

2. The following statement appears in the CSR for study PA-CL-05A: 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 and an SD of 2.3 mg/dL [29], indicating a possible lower bound of the 95% CI of around 1.5 mg/dL.

[32] 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.

[33] 40 trials (6,406 patients) were included. There was no significant decrease in all-cause mortality (10 randomized controlled trials; 3,079 patients; relative risk [RR], 0.73; 95% confidence interval [CI], 0.46 to 1.16), hospitalization, 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 (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.

However, the reference to nos 29 seems to be inaccurate as the sevelamer PI is actually reference nos. 27. Could the sponsors confirm that this was just a typographical error?

11.4. Safety

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

11.5. Product Information

11.5.1. 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 (ESRD) includes patients treated by dialysis or transplantation, irrespective of the level of GFR. The pivotal Phase 3 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."

11.5.2. 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 same precautions have not been added to the proposed Australian PI.

[**Note**: other questions regarding the Product Information have not been included in this Extract from the Clinical Evaluation Report]

12. Second round evaluation of clinical data submitted in response to questions

In this section, an evaluation of the Supplementary report of analyses to assess pharmacodynamic interaction of Velphoro with oral Vitamin D analogues (included in the sponsor's response to the TGA request for information) is presented first and this is followed by evaluation of sponsor's response to each of the clinical questions raised in section 11 of the first round report (above).

12.1. Evaluation of the supplementary report of analyses to assess pharmacodynamic interaction of velphoro with oral vitamin D analogues

12.1.1. Objectives

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 (hereafter referred to as PA-CL-05A/05B) were conducted to further investigate any possible pharmacodynamic (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 to remove the restriction in the PI on the prescribing of oral Vitamin D analogues with Velphoro and evaluates the possible impact of Velphoro and sevelamer, given concomitantly with stable doses of oral Vitamin D analogues, on the levels of serum iPTH.

12.1.2. Methodology

As part of both the efficacy and the clinical chemistry safety analyses in PA-CL-05A/05B, the levels of serum iPTH were determined at baseline (BL) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 and at end of study/termination. For purposes of the analyses detailed in this report, an analysis population termed the "Oral Vitamin D Population" was derived from the safety set in PA-CL-05A/05B The Oral Vitamin D Population comprised subjects taking stable doses of concomitant oral Vitamin D analogues (ATC4 "Vitamin D and analogues" and "Other antiparathyroid agents" which includes colecalciferol, ergocalciferol, alfacalcidol, calcitriol, doxercalciferol or paricalcitol, excluding cinacalcet/cinacalcet hydrochloride).

A subject will only be considered for the Oral Vitamin D Population if under a non-zero stable dose of oral Vitamin D analogue at BL and either at Week 12, Week 24, Week 52, or at overall endpoint in the absence of any of the exclusion medications (including cinacalcet/cinacalcet hydrochloride). A subject was on a stable dose if taking an oral Vitamin D analogue at BL and the same Vitamin D analogue to at least 1 post-BL time point of interest (i.e., based on serum iPTH assessment dates at Week 12, Week 24, Week 52 or overall endpoint), and if there was no change to the dose of the Vitamin D analogue, nor any addition or deletion of any other Vitamin D analogue, nor any addition of any of the exclusion medications noted above, identified by preferred term, within the ATC4 classes of interest.

Any change to the dose of the Vitamin D analogue, or any addition or deletion of any other Vitamin D analogue (or any of the medications identified by preferred term, within the ATC4 classes of interest), or any addition of the exclusion medications, led to the end of the stable dose period and exclusion from the Oral Vitamin D Population from that time point onwards. Subjects receiving concomitant intravenous Vitamin D analogues during the stable dose period were excluded from the population.

> **Comments**: The assessment of iPTH levels was done at baseline and regular intervals over the duration of studies PA-CL-05A/05B and provided adequate data to evaluate effect of Velphoro on iPTH in patients receiving oral Vitamin D analogues. The population of patients on oral vitamin D analogues was well-defined and patients receiving intravenous Vitamin D analogues were excluded from this supplementary analysis as the drug interaction is not expected with IV Vitamin D analogues.

12.1.3. Endpoints and analysis

Results from the subjects were analysed based on the study drug treatment in PA-CL-05A/05B (i.e., Velphoro or sevelamer), and on the type of oral Vitamin D analogue co-administered: i.e., active (alfacalcidol, calcitriol, doxercalciferol, or paricalcitol), inactive (colecalciferol, ergocalciferol), or both active and inactive analogues. Changes from BL over time in serum iPTH were calculated, and the 95% confidence interval (CI) was derived at each time point. Only serum iPTH values during stable doses of the oral Vitamin D analogues at BL, Week 12, Week 24, Week 52 or overall endpoint were used.

The BL value for serum iPTH parameter was defined as the last non-missing evaluable value prior to or on the date of the first study drug intake. The overall endpoint serum iPTH value was defined as the latest post-BL evaluable value prior to the end of the study (PA-CL-05A/05B with last observation carried forward-rule) and prior to or at the end of the stable dose period, collected no later than 7 days after the last dose of Velphoro or sevelamer.

12.1.4. Results

Overall, there were 187 subjects (Velphoro, N=127; sevelamer, N=60) included in the Oral Vitamin D Population. The analysis population was further subdivided according to the type of concomitant oral Vitamin D analogue (i.e., active, inactive, or both). The mean duration of study drug exposure was 272.4 days (1 to 394 days) and 297.2 days (13 to 372 days) in the Velphoro and sevelamer groups, respectively; the mean daily dose 1,740 mg Velphoro and 7.7 g sevelamer carbonate. Exposure in the subgroup taking active Vitamin D analogues was similar to the overall Oral Vitamin D Population.

The duration of exposure to oral Vitamin D analogues was similar between treatment groups and duration was longer for the Active subgroup in both treatment groups (Table 14). The 2 most common oral Vitamin D analogues co-administered (as a stable dose) were the active Vitamin D analogues, alfacalcidol and calcitriol.

Table 14: Duration of exposure to stable doses of oral vitamin D analogues in the Oral Vitamin D Population and Vitamin D Subgroups (Active, Inactive, Both)

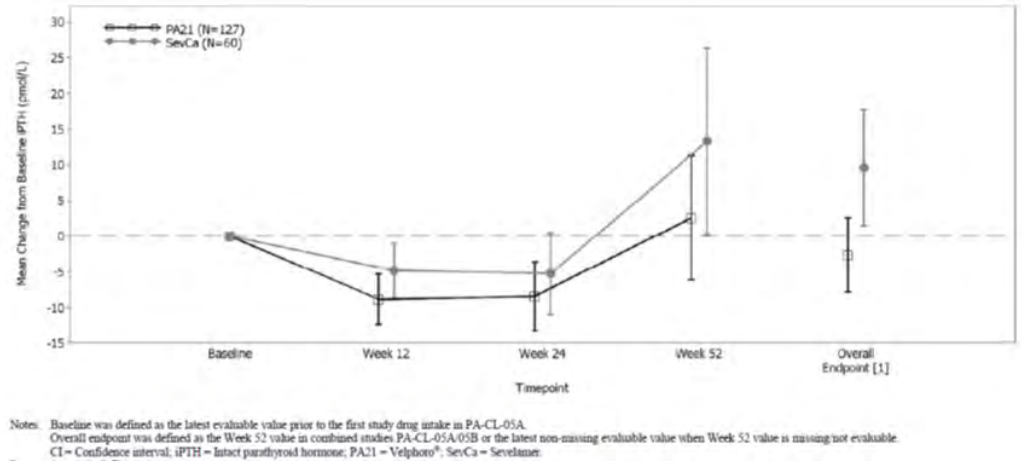
Parameter	Velphoro®				Sevelamer			
	Active (N=98)	Inactive (N=19)	Both (N=10)	Total (N=127)	Active (N=49)	Inactive (N=7)	Both (N=4)	Total (N=60)
Duration of stable oral Vitamin D dose (days)								
n	98	19	10	127	49	7	4	60
Mean (SD)	754.1 (721.46)	489.7 (267.51)	501.5 (548.24)	694.6 (666.67)	778.7 (652.36)	579.7 (487.42)	413.8 (261.94)	731.2 (620.73)
Median	536.0	431.0	296.0	501.0	609.0	452.0	350.0	547.0
Min/max	34.0/3,885.0	46.0/945.0	194.0/2,007.0	34.0/3,885.0	121.0/3,627.0	176.0/1,526.0	184.0/771.0	121.0/3,627.0
Number of subjects on stable oral Vitamin D dose, n (%)								
Week 12	88 (89.8%)	14 (73.7%)	8 (80.0%)	110 (86.6%)	47 (95.9%)	6 (85.7%)	4 (100.0%)	57 (95.0%)
Week 24	76 (77.6%)	9 (47.4%)	5 (50.0%)	90 (70.9%)	40 (81.6%)	2 (28.6%)	2 (50.0%)	44 (73.3%)
Week 52	46 (46.9%)	4 (21.1%)	1 (10.0%)	51 (40.2%)	23 (46.9%)	0 (0.0%)	2 (50.0%)	25 (41.7%)
Overall endpoint	85 (86.7%)	14 (73.7%)	6 (60.0%)	105 (82.7%)	38 (77.6%)	4 (57.1%)	2 (50.0%)	44 (73.3%)

Notes: Max = Maximum; Min = Minimum; SD = Standard deviation.

Within the active subgroup, i.e., subjects exclusively taking concomitant active Vitamin D analogues, 58 Velphoro-treated subjects and 29 sevelamer-treated subjects were taking alfacalcidol; 33 Velphoro-treated subjects and 20 sevelamer-treated subjects were taking calcitriol.

For Velphoro-treated subjects on stable doses of oral Vitamin D, a statistically significant mean (±SD) decrease in serum iPTH was seen at Week 12 (-8.8 ± 18.49 pmol/L; 95% CI: -12.4, -5.3) and Week 24 (-8.5 ± 22.20 pmol/L; 95% CI: -13.2, -3.7). There was no statistically significant change from BL in serum iPTH at Week 52 (2.6 ± 31.06 pmol/L; 95% CI: -6.2, 11.3) or at overall endpoint (-2.6 ± 26.78 pmol/L; 95% CI: -7.8, 2.5). For sevelamer-treated subjects on stable doses of oral Vitamin D, a small statistically significant decrease in mean serum iPTH from BL was seen at Week 12 (-4.9 ± 14.50 pmol/L; 95% CI: -8.8, -1.0), with no statistically significant change at Week 24 (-5.3 ± 17.97 pmol/L; 95% CI: -11.0, 0.5). Statistically significant increases were seen at Week 52 (13.3 ± 31.45 pmol/L; 95% CI: 0.3, 26.2) and overall endpoint (9.6 ± 26.73 pmol/L; 95% CI: 1.4, 17.7) Figure 6).

Figure 6: Change in baseline in mean (95% CI) serum iPTH (pmol/L) in the Oral Vitamin D population



Notes: Baseline was defined as the latest evaluable value prior to the first study drug intake in PA-CL-05A.
Overall endpoint was defined as the Week 52 value in combined studies PA-CL-05A/05B or the latest non-missing evaluable value when Week 52 value is missing/not evaluable.
CI = Confidence interval; iPTH = Intact parathyroid hormone; PA21 = Velphoro®; SevCa = Sevelamer.

Results for Velphoro and sevelamer-treated subjects on stable doses of active Vitamin D analogues (active subgroup) were similar to those for the whole Oral Vitamin D Population. However, the numbers of Velphoro- and sevelamer-treated subjects in in the inactive and both subgroups were too few to provide meaningful analysis.

> **Comments**: According to the KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease[34], patients treated with hemodialysis or peritoneal dialysis with serum levels of intact PTH levels >300 pg/mL (33.0 pmol/L) should receive an active vitamin D sterol (such as calcitriol, alfacalcidol, paricalcitol, or doxercalciferol to reduce the serum levels of PTH to a target range of 150 to 300 pg/mL (16.5 to 33.0 pmol/L).

Results from this post-hoc analysis suggest that the reduction in iPTH in the Velphoro-treated patients was statistically significant only at weeks 12 and 24 (not at week 52). However, it is difficult to interpret if the statistically significant reduction was clinically relevant as the mean values at weeks 12, 24 and 52 were still above the recommended target range of 150 to 300pg/ml (16.5 to 33,opmol/L). The proportion of Velphoro-treated patients who achieved the target iPTH values or a 50% reduction in iPTH from baseline following treatment with Vit D analogues would have been more relevant, but this information was not provided in the supplementary analysis.

The sponsors indicate that serum iPTH levels remained relatively stable over time in both treatment groups, suggesting that concomitant dosing of Velphoro does not result in loss of control of serum iPTH levels. However, the mean values at weeks 12, 24 and 52 were still above the recommended target range of 150 to 300pg/ml (16.5 to 33,opmol/L) and data on the proportion of Velphoro-treated patients who achieved the target iPTH values or even a 50% reduction from baseline following treatment with Vit D analogues was not provided. Hence, it is difficult to conclude that Velphoro does not affect the serum iPTH lowering efficacy of concomitant oral Vitamin D analogues administered to CKD patients on dialysis.

The DDI studies with Velphoro showed a reduction of 60% to 80% of paricalcitol in the supernatant at pH 3.0 and 5.5 (in the presence of phosphate (400 mg P/L)) (INO-11-050 and STU-PA21DDI-B200830-001). However, the sponsors state that when the same studies were done with placebo, containing only the sucrose and starches from Velphoro and no iron (III)-oxyhydroxide, a reduction of 40% to 70% of paricalcitol was observed in the supernatant at pH 3.0 and 5. These data indicate that a substantial part of the adsorption has to be attributed to

34 <https://www.kidney.org/professionals/kdoqi/guidelines_bone/guide8b.htm>

the carbohydrate component of Velphoro. Since the pharmacokinetics of paricalcitol is not affected by food (Studies 20000007 and M02-437), the observed in vitro adsorption of paricalcitol by Velphoro is not expected to be clinically meaningful, especially when considering that the carbohydrate content of a single tablet of Velphoro is only approximately 1.5 g, considerably less than the carbohydrate content in a meal.

> **Comments**: The statement by sponsors that the extensive adsorption in vitro by Velphoro of Vitamin D analogues, paricalcitol was attributed to the carbohydrate component of Velphoro cannot be justified by the clinical evaluators and this should be clarified with the non-clinical evaluators.

Overall, the evidence provided in the S31 response by the sponsors is not adequate to justify removal of the labelling restriction in the PI on the prescribing of oral Vitamin D analogues with Velphoro.

12.2. Evaluation of sponsor's response the clinical questions

The sponsor's response to the questions raised by the TGA in section 11 (above) is shown below followed by the evaluator's comments on the sponsor's response.

12.2.1. Pharmacokinetics

None.

12.2.2. Pharmacodynamics

None.

12.2.3. Efficacy

12.2.3.1. Sponsor's response to Question 1

The point estimate of the difference between PA21 and sevelamer treatments was 0.08 mmol/L, and the upper bound of the 97.5% 1-sided CI of this difference was at 0.14 mmol/L (05A/05B CSR). Thus, this upper bound represents less than 50% of the magnitude of the "clinically relevant" change of 0.3 mmol/L as estimated by Kalantar-Zadeh et al, 2006 [Kalanter-Z-K, et al, 2006]. In the absence of data from randomised controlled trials, the applicant believes that the point difference of 0.08 mmol/L and the 0.14 mmol/L upper bound of the 97.5% 1-sided CI between PA21 and sevelamer is not clinically relevant. This point difference and its upper bound is well within the diurnal variation of serum phosphorus concentrations seen in healthy human subjects and in patients on HD.

In published studies, diurnal variations of serum phosphorus up to approximately 0.25 mmol/L have been seen in healthy subjects and patients undergoing HD [Ring T et al, 1995; Portale AA, et al, 1987; Jubiz W, et al, 1972]. Therefore, as the upper bound of the 97.5% 1-sided CI is within the daily physiological fluctuation of serum phosphorus, the applicant believes that PA21 is also clinically non-inferior to sevelamer.

As described in International Conference on Harmonisation guidelines (E9, section 3.3.2), for non-inferiority trials a 1-sided interval should be used. In a non-inferiority trial, 1 only defines an upper bound, say, ΔNI, and when the 97.5% 1-sided CI for the treatment difference (Δ) lies to the left of ΔNI, the test drug (PA21 in this case) will be called non-inferior to the comparator (sevelamer in this case). In a non-inferiority trial, only 1 boundary of the classical 2-sided 95% CI is considered. This corresponds to a 1-sided 97.5% CI that is bounded at 1 side. This 1-sided CI also corresponds to a 1-sided Type 1 error level of 0.025, in contrast to the 2-sided 0.05 level when testing for superiority. Therefore the choice of a 1-sided CI of 97.5% for a non-inferiority analysis corresponds to a control of a 2-sided Type 1 error of 0.05, which is commonly accepted as the standard by the regulators.

Evaluator's comments on sponsor's response: The above response by the sponsor is acceptable.

12.2.3.2. Sponsor's response to question 2

The applicant confirms that this reference on page 232 of the PA-CL-05A CSR should actually be No. 27 and is a typographical error

Evaluator's comments on sponsor's response: The above response by the sponsor is acceptable.

12.2.4. Safety

12.2.4.1. Sponsor's response to question 1

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 and this information has been included in the round 1 evaluation report (section 8.5.9.1).

12.2.5. Product Information

12.2.5.1. Sponsor's response to question on indications

The proposed PI was modified to address the evaluator's comments and the indications were changed 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.

12.2.5.2. Sponsor's response to question on interactions with other medicines

[The original draft PI included the following text on DDIs: *In vitro studies with the following drugs showed an interaction: alendronate, cephalexin, doxycycline, levothyroxine, atorvastatin, doxercalciferol and paricalcitol*.]

The applicant proposes to delete simvastatin, atorvastatin, doxercalciferol and paricalcitol from the list of drugs in the in vitro DDI section since there is clinical data available for the these drugs. In vitro data is considered superseded in the presence of clinical data. In case of atorvastatin, doxercalciferol and paricalcitol the applicant believes that mentioning the presence of in vitro DDI effects may be confusing and misleading if clinical data demonstrates the absence of DDI effects.

An analysis on pooled Phase 3 PA-CL-05A/05B studies was already part of the submitted marketing authorisation application dossier in Australia determining if there were any pharmacodynamics interaction between PA21 and either atorvastatin, simvastatin, or other statins (i.e., HMG-CoA reductase inhibitors) administered concomitantly in CKD patients. Specifically, the potential of PA21 to affect the lipid-lowering effects of these drugs was investigated (Module 5, Supplementary post-hoc report to the PA-CL-05A/05B CSR).

[In relation to the question under section 11.5.2, above]: The applicant does not believe that it is necessary to include the statement from the US PI that Velphoro should not be prescribed with oral levothyroxine. The modified statement is consistent with the levothyoroxine SPC which

states that administration of iron salts and levothyroxine should be separated by at least 2 hours (see Section 4.5 of levothyroxine SPC).

Similarly, the applicant considers it unnecessary to restrict the concomitant administration of Vitamin D analogues. Further analyses from the Velphoro clinical development programme have now been submitted to FDA to support a labelling supplement to remove this restriction in the USPI on the prescribing of oral Vitamin D analogues with Velphoro. These analyses are presented below.

As the use of Vitamin D and its analogues is standard clinical practice for patients on dialysis, the protocol for in the Phase 3 studies PA-CL-05A and PA-CL-05B (hereafter referred to as PA-CL-05A/05B) allowed for the use of these drugs during the study. The proportions of subjects taking Vitamin D and its analogues, ATC Level 4 category "Vitamin D and analogues" (PA21: 31.1%; sevelamer: 36.8%), and calcimimetics (PA21: 21.7%; sevelamer: 24.5%) were similar between the 2 treatment groups. The concomitant use of Vitamin D analogues under the ATC Level 4 category "Other anti-parathyroid agents" was also similar between treatment groups. For example, the use of the potent Vitamin D analogues such as paricalcitol and doxercalciferol were 33.0% and 12.6%, respectively in the PA21 group, compared to 35.3% and 15.2%, respectively in the sevelamer group (see PA-CL-05A/05B Clinical Study Report (CSR). Serum phosphorus levels during the studies were very similar between the subjects who were taking concomitant Vitamin D analogue drugs compared to those subjects who were not taking these drugs; and importantly, these levels and changes from baseline (BL) were also very similar between the PA21 and sevelamer groups (see Table 15 below).

Table 15: Mean serum phosphorous levels (mmol/L), actual change from baseline, by Vitamin D analogue use in Studies PA CL 05A/05B, FAS (N = 1,041)

Time Point		PA21 (N=707)				Sevelamer (N=348)			
		With Vit D[1] (N=444)		No Vit D[1] (N=250)		With Vit D[1] (N=220)		No Vit D[1] (N=127)	
	Parameter	Actual	Change from Baseline	Actual	Change from Baseline	Actual	Change from Baseline	Actual	Change from Baseline
Baseline	Mean (SD)	2.5 (0.55)	–	2.5 (0.64)	–	2.4 (0.50)	–	2.4 (0.68)	–
	Median	2.4	–	2.5	–	2.4	–	2.4	–
	Min/Max	0.4/4.6	–	0.8/5.6	–	1.4/4.2	–	0.4/4.7	–
Week 12	Mean (SD)	1.8 (0.43)	- 0.7 (0.60)	1.8 (0.51)	- 0.7 (0.66)	1.7 (0.41)	- 0.7 (0.58)	1.7 (0.49)	- 0.7 (0.74)
	Median	1.8	- 0.7	1.8	- 0.7	1.7	- 0.7	1.6	- 0.6
	Min/Max	0.7/3.1	- 2.9/0.9	0.5/4.0	- 2.3/1.2	0.9/3.1	- 3.0/1.0	0.7/3.6	- 2.6/1.6
Week 24	Mean (SD)	1.7 (0.45)	- 0.7 (0.63)	1.8 (0.51)	- 0.8 (0.67)	1.7 (0.44)	- 0.7 (0.57)	1.6 (0.46)	- 0.7 (0.74)
	Median	1.7	- 0.7	1.7	- 0.8	1.7	- 0.7	1.6	- 0.7
	Min/Max	0.6/3.4	- 2.9/1.2	0.8/3.7	- 2.6/1.7	0.6/2.9	- 2.4/1.0	0.3/2.9	- 2.7/1.0
Week 52	Mean (SD)	1.7 (0.47)	- 0.7 (0.66)	1.9 (0.58)	- 0.6 (0.71)	1.7 (0.48)	- 0.7 (0.67)	1.7 (0.36)	- 0.6 (0.71)
	Median	1.7	- 0.7	1.8	- 0.6	1.6	- 0.7	1.7	- 0.6
	Min/Max	0.7/3.1	- 2.7/1.4	1.0/3.7	- 2.2/1.6	0.6/4.1	- 2.3/2.0	0.9/2.4	- 2.8/1.0
Endpoint[2]	Mean (SD)	1.7 (0.50)	- 0.7 (0.64)	1.9 (0.62)	- 0.6 (0.73)	1.7 (0.50)	- 0.7 (0.67)	1.9 (0.56)	- 0.5 (0.83)
	Median	1.7	- 0.8	1.8	- 0.6	1.7	- 0.7	1.8	- 0.5
	Min/Max	0.4/3.2	- 3.0/1.4	0.9/3.7	- 2.2/1.6	0.6/4.1	- 2.3/2.0	0.9/3.7	- 2.8/1.8

1 Use of Vitamin D includes Vitamin D and analogues, as well as other anti-parathyroid agents (excluding cinacalcet and cinacalcet hydrochloride) any time from study start, up to and including the time point in question. Medications in this category initiated after the time point in question are not considered. Use at Baseline includes all such medications taken prior treatment and within 4 weeks of study medication start.
2 Endpoint is Week 52 (05B Week 28) results or latest available results after Week 24 if Week 52 missing.
Notes: "–" Indicates not applicable.
FAS = Full analysis set; Max = Maximum; Min = Minimum; SD = Standard deviation; Vit = Vitamin.
Source: Appendix Y, Tables E.68.3.1 and E.68.3.2.

Similarly, concomitant Vitamin D analogue use was not a significant factor in the analysis model and did not have a significant interaction with study treatments.(see Table 16 below).

Table 16: MMRM-MAR analysis of change in serum phosphorous from baseline in subjects treated with Vitamin D analogues, PPS (N=685)

Statistic	N	p-value	LS Mean Difference	SE	95% CI
MMRM-MAR Model[1]					
Number of subjects in the model	685				
Treatment		0.005			
Week		0.010			
Baseline serum phosphorus		<0.001			
Dialysis status		0.896			
Region		0.072			
Vit D use		0.643			
Treatment*Vit D use		0.372			
Treatment*week		0.649			
Serum phosphorus (mmol/L): PA21 vs. sevelamer[2]					
At Week 12		0.029	0.08	0.04	(0.01, 0.15)
At Week 24		0.012	0.10	0.04	(0.02, 0.17)

1 MMRM-MAR: Mixed Model for Repeated Measures assuming the Missing at Random mechanism is used. The model includes subject as a random effect, fixed effects of week, treatment, baseline serum phosphorus, region (US/EU/ROW), Vitamin D analogues used (Yes/No), and treatment*week and treatment*Vitamin D use interaction. Type III analysis p-values are presented. Covariance structure = Unstructured.

2 Difference in change from baseline between PA21 and sevelamer treatment groups.

Notes: CI = Confidence interval; EU = European Union; LS Mean = Least-square mean; MMRM-MAR = Mixed Model for Repeated Measures-Missing at Random; PPS = Per-protocol; ROW = Rest of world; SE = Standard error; US = United States.

As shown in Table 16 above, concomitant Vitamin D analogue use was not a significant factor in the analysis model and did not have a significant interaction with study treatments. The applicant therefore believes it is unlikely for the concomitant use of any of these drugs to have any significant impact on the efficacy of PA21 compared to sevelamer.

In vitro drug-drug interaction (DDI) studies (INO-11-050 and STU-PA21DDI-B200830-001) have shown adsorption of the Vitamin D analogue, paricalcitol, by Velphoro. Based on this observation, and despite the fact that no loss of control of serum intact parathyroid hormone (iPTH) levels was seen in clinical studies PA-CL-05A and PA-CL-05B, where several hundred subjects were treated concomitantly with oral Vitamin D analogues, the approved USPI states that Velphoro should not be prescribed with oral Vitamin D analogues. The applicant has subsequently conducted post-hoc analyses of pooled data from PA-CL-05A/05B to further investigate any possible pharmacodynamic (PD) interaction between Velphoro and oral Vitamin D analogues, with respect to their effects in controlling serum iPTH levels. These analyses assess the possible impact of Velphoro and sevelamer, given concomitantly with stable doses of oral Vitamin D analogues, on the levels of serum iPTH (see Supplementary Report of Analyses to Assess for Pharmacodynamic Interaction of Velphoro (PA21) with Oral Vitamin D Analogues above) and were conducted to support a labelling supplement to remove the restriction in the USPI on the prescribing of oral Vitamin D analogues with Velphoro.

For Velphoro subjects on stable doses of oral Vitamin D analogues, statistically significant decreases from BL in mean serum iPTH were seen at Weeks 12 and 24, and no statistically significant changes from BL were observed at Week 52 or overall endpoint. In contrast, for sevelamer subjects on stable doses of oral Vitamin D, no statistically significant change in BL was seen at Week 24 (compared with a statistically significant decrease in the Velphoro subjects) and statistically significant increases from BL were seen at Week 52 and overall endpoint (compared with no statistically significant change in the Velphoro subjects). Results for the subgroup on oral active Vitamin D analogues were consistent with the results for the total oral Vitamin D population.

Thus, the results of the present analyses demonstrate that despite extensive adsorption in vitro by Velphoro for the Vitamin D analogue, paricalcitol (DDI studies INO-11-050 and STU-PA21DDI-B200830-001), Velphoro does not affect the serum iPTH lowering efficacy of concomitant oral Vitamin D analogues administered to CKD patients on dialysis.

The DDI studies with Velphoro showed a reduction of 60% to 80% of paricalcitol in the supernatant at pH 3.0 and 5.5 (in the presence of phosphate (400 mg P/L)) (INO-11-050 and STU-PA21DDI-B200830-001). However, when the same studies were done with placebo, containing only the sucrose and starches from Velphoro and no iron(III)-oxyhydroxide, a reduction of 40% to 70% of paricalcitol was observed in the supernatant at pH 3.0 and 5.5. These data indicate that a substantial part of the adsorption has to be attributed to the carbohydrate component of Velphoro. Since the pharmacokinetics of paricalcitol is not affected by food (see Studies 20000007 and M02-437), the observed in vitro adsorption of paricalcitol by Velphoro is not expected to be clinically meaningful, especially when considering that the carbohydrate content of a single tablet of Velphoro is only approximately 1.5 g, considerably less than the carbohydrate content in a meal. This conclusion is consistent with the lack of any PD interaction between Velphoro and Vitamin D analogues observed in the present supplementary analyses of clinical studies PA-CL-05A/05B. Given that other active Vitamin D analogues (calcitriol, alfacalcidol and doxercalciferol) share a similar molecular structure and physicochemical properties with paricalcitol, it is likely that these other Vitamin D analogues may also be adsorbed in vitro by the carbohydrate component of Velphoro but that these in vitro effects would not be clinically meaningful. Based on the PD parameters assessed in these analyses, Velphoro does not affect the serum iPTH lowering efficacy of concomitant oral Vitamin D analogues.

Hence, the applicant believes that the concomitant administration of Vitamin D analogues do not affect the efficacy of Velphoro and Velphoro does not affect the efficacy of Vitamin D analogues. Therefore, there is no reason to prohibit the prescribing of Velphoro and Vitamin D analogues.

The applicant proposes to include the following sentence into the product information: “In addition, clinical studies demonstrated no impact of Velphoro on iPTH lowering effect of oral Vitamin D analogues.” and to delete doxercalciferol and paricalcitol from the listed compounds in the in vitro DDI section to avoid confusion. The sponsor has made the following changes (bold and strikethrough font) to 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~~’

> **Evaluator’s comments on sponsor’s response**: The sponsors indicate that serum iPTH levels remained relatively stable over time in both treatment groups in the post-hoc supplementary analysis (refer section 12.1), suggesting that concomitant dosing of Velphoro does not result in loss of control of serum iPTH levels. However, the mean values at weeks 12, 24 and 52 were still above the recommended target range of 150 to 300pg/ml (16.5 to 33,opmol/L) and data on the proportion of Velphoro-treated patients who achieved the target iPTH values or even a 50% reduction from baseline following treatment with Vit D analogues was not provided. Hence, it is difficult to conclude that Velphoro does not affect the serum iPTH lowering efficacy of concomitant oral Vitamin D analogues administered to CKD patients on dialysis.
>
> Overall the evidence is not adequate to support the change proposed by the sponsors (above).

Furthermore, it is suggested that the labelling restriction on the prescribing of oral Vitamin D analogues with Velphoro should be added to the Australian PI as well.

13. Second round benefit-risk assessment

13.1. 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 Section 9.1.

13.2. 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 Section 9.2.

13.3. Second round assessment of benefit-risk balance

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

14. 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 section 12.2.5[35]).

15. References

Alfrey AC, LeGendre GR, Kaehny WD. The dialysis encephalopathy syndrome. Possible aluminum intoxication. N Engl J Med. 1976 Jan 22;294(4):184-8.

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.

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.

Block GA. Control of serum phosphorus: implications for coronary artery calcification and calcific uremic arteriolopathy (calciphylaxis). Curr Opin Nephrol Hypertens. 2001;10(6):741-7.

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):104-15.

[35] Other recommended revisions to the PI are not included in the Extract from the Clinical Evaluation Report.

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):1640-4.

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;14:2907-14.

Chertow GM, Burke SK, Lazarus JM, Stenzel KH, Wombolt D, Goldberg D, 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.

Damment SJP, Pennick M. Clinical pharmacokinetics of the phosphate binder lanthanum carbonate. Clin Pharmacokinet. 2008;47(9):553-63.

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.

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.

Hergesell O, Ritz E. Phosphate binders on iron basis: a new perspective? Kidney Int. 1999; Suppl 73:S42-5.

Hergesell O, Ritz E. Stabilized polynuclear iron hydroxide is an efficient oral phosphate binder in uraemic patients. Nephrol Dial Transplant. 1999;14(4):863-7.

ICH Harmonised Tripartite Guideline: E6(R1): Guideline for good clinical practice. 1996 Jun 10.

Jono S, McKee MD, Murry CE, Shioi A, Nishizawa Y, Mori K, et al. Phosphate regulation of vascular smooth muscle cell calcification. Circ Res. 2000;87(7):e10-7.

Jubiz W, Canterbury JM, Reiss E, Tyler FH. Circadian rhythm in serum parathyroid hormone concentration in human subjects: correlation with serum calcium, phosphate, albumin, and growth hormone levels. J Clin Invest. 1972 Aug;51(8):2040-6.

Kalantar-Zadeh K, Kuwae N, Regidor DL, Kovesdy CP, Kilpatrick RD, Shinaberger CS, et al. Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. Kidney Int. 2006 Aug;70(4):771- 80. Epub 2006 Jul 5.

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.

Kestenbaum B, Sampson JN, Rudser KD, Patterson DJ, Seliger SL, Young B, et al. Serum phosphate levels and mortality risk among people with chronic kidney disease. J Am Soc Nephrol. 2005;16(2):520-8.

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

Kidney Disease: Improving Global Outcomes (KDIGO). 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.

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

Meric F, Yap P, Bia MJ. Etiology of hypercalcemia in hemodialysis patients on calcium carbonate therapy. Am J Kidney Dis. 1990 Nov;16(5):459-64.

Moe SM, Chertow GM. The case against calcium-based phosphate binders. Clin J Am Soc Nephrol. 2006;1(4):697-703.

Mohammed IA, Hutchison AJ. Phosphate binding therapy in dialysis patients: focus on lanthanum carbonate. Ther Clin Risk Manag. 2008;4(5):887-93.

Navaneethan SD, Palmer SC, Craig, JC, Elder GJ, Strippoli GFM. Benefits and harms of phosphate binders in CKD: a systematic review of randomized controlled trials. Am J Kidney Dis. 2009;54(4):619-37.

Ossareh S. Vascular calcification in chronic kidney disease: mechanisms and clinical implications. Iran J Kidney Dis. 2011 Sep;5(5):285-99.

Palmer SC, Hayen A, Macaskill P, Pellegrini F, Craig JC, Elder GJ, 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.

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.

Pisoni RL, Fuller DF, Bieber BA, Gillespie BW, Robinson BM. The DOPPS practice monitor for US dialysis care: trends through August 2011. Am J Kidney Dis. 2012;60(1):160-5.

Port FK, Pisoni RL, Bommer J, Locatelli F, Jadoul M, Eknoyan G, 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.

Portale AA, Halloran BP, Morris RC Jr. Dietary intake of phosphorus modulates the circadian rhythm in serum concentration of phosphorus. Implications for the renal production of 1,25-dihydroxyvitamin D. J Clin Invest. 1987 Oct;80(4):1147-54.

Renagel Tablet (sevelamer hydrochloride) 400 & 800mg. Prescribing Information. Genzyme Corporation, Cambridge, MA, US. 2011.

Renvela (sevelamer carbonate). Prescribing Information. Genzyme Corporation, Cambridge, MA, US. 2011.

Renvela (sevelamer carbonate). Prescribing Information. Genzyme Corporation, Cambridge, MA, US. 2010. Available from: <http://www.renvela.com/docs/renvela_PI.pdf>.

Ring T, Sanden AK, Hansen HHT, Halkier P, Nielsen C, Fog L. Ultradian variation in serum phosphate concentration in patients on haemodialysis. Nephrol Dial Transplant. 1995;10(1):59-63.

Tentori F, Blayney MJ, Albert JM, Gillespie BW, Kerr PG, Bommer J. 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.

Tonelli M, Wiebe N, Culleton B, Lee H, Klarenbach S, Shrive F, et al. Systematic review of the clinical efficacy and safety of sevelamer in dialysis patients. Nephrol Dial Transplant. 2007;22:2856-66.

Wills MR, Savory J. Aluminium poisoning: dialysis encephalopathy, osteomalacia, and anaemia. Lancet. 1983 Jul 2:29-34.

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