



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 June 2014
EMA/567960/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Velphoro

Common name: mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches

Procedure No. EMEA/H/C/002705/0000

Note

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



Table of contents

Note	1
1. Background information on the procedure	7
1.1. Submission of the dossier	7
1.2. Manufacturers	8
1.3. Steps taken for the assessment of the product	8
2. Scientific discussion	9
2.1. Introduction	9
2.2. Quality aspects	11
2.2.1. Introduction	11
2.2.2. Active Substance	11
2.2.3. Finished Medicinal Product	14
2.2.4. Discussion on chemical, pharmaceutical and biological aspects	16
2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects	16
2.2.6. Recommendations for future quality development	16
2.1. Non-clinical aspects	17
2.1.1. Introduction	17
2.1.2. Pharmacology	17
2.1.3. Pharmacokinetics	23
2.1.4. Toxicology	25
2.1.5. Ecotoxicity/environmental risk assessment	32
2.1.6. Discussion on non-clinical aspects	32
2.1.7. Conclusion on the non-clinical aspects	33
2.2. Clinical aspects	33
2.2.1. Introduction	33
Tabular overview of clinical studies	34
2.2.2. Pharmacokinetics	36
2.2.3. Pharmacodynamics	42
2.2.4. Discussion on clinical pharmacology	42
2.2.5. Conclusions on clinical pharmacology	43
Clinical efficacy	43
2.2.6. Dose response study	43
2.2.7. Main studies	54
Methods	54
Clinical studies in special populations	79
Analysis performed across trials (pooled analyses AND meta-analysis)	79
Supportive study	79
2.2.8. Discussion on clinical efficacy	79
2.2.9. Conclusions on the clinical efficacy	83
2.3. Clinical safety	83
Patient exposure	83
Adverse events	84
Serious adverse events and deaths	87

Long-term safety / Integrated analysis	88
Laboratory findings	91
Immunological events	94
Safety related to drug-drug interactions and other interactions.....	94
Discontinuation due to AES	94
2.3.1. Discussion on clinical safety	95
2.3.2. Conclusions on the clinical safety.....	98
2.4. Pharmacovigilance.....	100
2.5. Risk Management Plan	100
Important identified risks.....	101
Important potential risks	101
Missing information	101
2.6. User consultation	105
3. Benefit-Risk Balance.....	105
<i>Benefits</i>	105
<i>Beneficial effects</i>	105
<i>Uncertainty in the knowledge about the beneficial effects</i>	106
<i>Risks</i>	106
<i>Unfavourable effects</i>	106
<i>Uncertainty in the knowledge about the unfavourable effects</i>	107
<i>Benefit-Risk balance</i>	108
<i>Importance of favourable and unfavourable effects</i>	108
<i>Benefit-risk balance</i>	109
<i>Discussion on the benefit-risk balance</i>	110
4. Recommendations	111

List of abbreviations

ACE	Angiotensin converting enzyme
ADME	Absorption, distribution, metabolism and excretion
ADR	Adverse drug reaction
AE	Adverse event
Alb	Albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	Analysis of covariance
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC0-24	Area under the plasma concentration-time curve from time 0 to 24
AUC0-infinity	Area under the concentration-time curve from time 0 extrapolated to infinite time
AV	Arteriovenous
BL	Baseline
BMI	Body mass index
BP	Blood pressure
BW	body weight
Ca × P	Calcium-phosphorus product
Chol	Cholesterol
CI	Confidence interval
CKD	Chronic kidney disease
CKD-MBD	Chronic kidney disease-metabolic bone disorder
C _{max}	Peak plasma concentration
C _{max}	Peak serum concentration
CPK	Creatine phosphokinase
Crea	Creatinine
CRF	Chronic renal failure
CSR	Clinical study report
CYP	Cytochrome P450
DDI	Drug-drug interaction
DPD	Deoxyprodinoline
ECG	Electrocardiogram
EMA	European Medicines Agency (previously EMEA)
Epi	Epithelium
ESA	Erythropoiesis stimulating agent
ESRD	End stage renal disease
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FGF-23	Fibroblast growth factor 23
FUP2	Follow-Up 2
GCP	Good Clinical Practice

GI	Gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GRAS	Generally regarded as safe
Hb	Haemoglobin
Hct	Haematocrit
HD	Haemodialysis
HDL	High density lipoprotein
hERG	Human ether-a-go-go related gene
HR	Heart rate
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 = Patient's
LD	Low dose
LDL	Low density lipoprotein
LFT	Liver function test
LN	lymph node
LO	Last observation
LOCF	Last observation carried forward
m/m	Mass per mass
Macroph	Macrophage
MCH	mean cell haemoglobin
MCHC	mean cell haemoglobin concentration
MCV	mean cell volume
MD	Maintenance dose
MedDRA	Medical Dictionary for Regulatory Activities
Mesen	Mesenteric
MIXED SAS	Mixed model procedure
MMRM-MAR	Mixed-effects model for repeated measures/missing at random
NOAEL	No observed adverse effect level
NOEL	No observed effect level
OC	Observed cases
OR	Odds ratio
PD	Peritoneal dialysis
PDE	Permitted daily exposure
PEPPS	Primary efficacy per-protocol set
PES	Primary efficacy set
Ph. Eur.	European Pharmacopoeia
Phos	Phosphate
PK	Pharmacokinetics
PPS	Per-protocol set
PT	prothrombin time
PTH	Parathyroid hormone

QoL	Quality of Life
QTcB	Corrected QT interval according to Bazett
QTcF	Corrected QT interval according to Fridericia
RBC	red blood cell
RES	Reticulo-endothelial system
Retic	Reticulocyte
ROW	Rest of the World
SAE	Serious adverse event
SAP	Statistical analysis plan
SCFA	Short-chain fatty acids
SD	Standard deviation
SF-36	Short Form 36
SG	specific gravity
SmPC	Summary of product characteristics
SOC	System organ class
SS	Safety set
SS2	Safety set for Stage 2
t _{1/2}	Terminal half-life
TEAE	Treatment-emergent adverse event
TG	Triglyceride
TIBC	total iron binding capacity
TIM TNO	gastrointestinal model of stomach and small intestine (TIM-1) and large intestine (TIM-2)
T _{max}	Time to C _{max}
TSAT	Transferrin saturation
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopoeia
Vol	Volume

1. Background information on the procedure

1.1. *Submission of the dossier*

The applicant Vifor Fresenius Medical Care Renal Pharma France submitted on 19 December 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Velphoro, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 March 2012. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant technical innovation.

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

Velphoro should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxy vitamin D3 or one of its analogues, or calcimimetics to control the development of renal bone disease.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/284/2011 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

New active Substance status

The applicant requested the active substance (mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches) contained in the above medicinal product to be considered as a new active substance in comparison to the known iron (III)- oxyhydroxide complexes previously authorised in the Union such as Ferrum Hausmann drops 50 mg/ml, and claimed that the mixture of polynuclear iron(III)-

oxyhydroxide, sucrose and starches differs significantly in properties with regard to safety and efficacy from the already authorised substances.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 23 July 2009. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

Vifor France SA
7-13 Boulevard Paul Emile Victor
92200 Neuilly-sur-Seine
France

1.3. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was Johann Lodewijk Hillege.

The Co-Rapporteur appointed by the CHMP was Romaldas Mačiulaitis.

- The application was received by the EMA on 19 December 2012.
- The procedure started on 30 January 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 April 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 19 April 2013.
- During the meeting on 30 May 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 30 May 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 14 August 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 September 2013.
- During the CHMP meeting on 24 October 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The summary report of the inspection carried out at the two Sponsor sites in the UK and Switzerland and two Clinical investigators sites in Russia and Ukraine between 13th January 2014 and 7th February 2014 and it was issued on 31st March 2014.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 14 April 2014.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 02 May 2014.
- During the CHMP meeting on 22 May 2014, the CHMP agreed on the second list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 29 May 2014.
- During the meeting on 26 June 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Velphoro.

2. Scientific discussion

2.1. Introduction

Velphoro (PA-21) is a new iron-based phosphate binder for oral administration.

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 polynuclear iron(III)-oxyhydroxide contained in PA21 maintains phosphate adsorption capacity but is practically insoluble with a low iron release.

Serum phosphate concentration is primarily determined by the ability of the kidneys to excrete dietary phosphate. In patients with chronic kidney disease (CKD), hyperphosphataemia occurs as a consequence of diminished phosphorus filtration and excretion. The key physiological components involved in the development of hyperphosphataemia and its adverse sequelae are phosphorus, calcium (Ca), calcitriol (1,25 dihydroxyvitamin D, principally synthesized in the kidney), parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF-23).

Decreased phosphorus excretion can initially be compensated by increased secretion of FGF-23 and PTH. With increasing phosphate levels, elevations in FGF-23 levels stimulate the renal excretion of phosphate and inhibit the synthesis of 1,25-dihydroxyvitamin D. PTH increases in response to reductions in 1,25(OH)2D. By increasing bone turnover and calcium phosphate release from bone and enhancing urinary phosphate excretion (via a decrease in proximal reabsorption), PTH can correct both the hypocalcaemia and the hyperphosphataemia. In more advanced stages of CKD, renal excretion of phosphorus is no longer sufficient to maintain normal serum phosphorus levels resulting in hyperphosphataemia. At this stage, dietary phosphate restriction may still reduce the serum concentration of phosphate, FGF-23, and PTH, although not usually to normal. This problem is exacerbated once maintenance dialysis is required; in this setting, there is essentially no phosphate excretion and oral phosphate binders must be given to limit phosphate absorption. In addition, levels of FGF-23 become extremely elevated, and the secondary hyperparathyroidism may contribute to the hyperphosphataemia by continuing to enhance the release of calcium phosphate from bone.

Elevated phosphorus levels may lead to metastatic calcification, a condition where calcium and phosphate precipitate into soft tissues, often in association with a high calcium-phosphorus product ($\text{Ca} \times \text{P} > 4.4 \text{ mmol}^2/\text{l}^2$). Soft tissue calcifications are especially common in CKD patients if the calcium-phosphorus product is chronically $> 5.8 \text{ mmol}^2/\text{l}^2$. Elevated serum phosphorus and calcium-phosphorus product are associated with increased risk of death in dialysis patients (Block 1998, Young

2005, Slinin 2005), although more data is needed. The higher mortality may be due to the adverse effects of metastatic calcification in soft tissues such as arteries, myocardium, and lung.

High circulating levels of PTH play an important role in the development of renal osteodystrophy and elevated circulating FGF-23 concentrations are strongly associated with increased cardiovascular mortality and renal failure. Therefore, treatment of hyperphosphataemic patients not only focuses on normal serum phosphorus levels but also on calcium, calcium-phosphorus product and PTH levels.

KDOQI guidelines:

The 2003 KDOQI practice guidelines recommend that the target serum phosphate should be between 1.13 and 1.78 mmol/L for patients with stage 5 CKD. A phosphate level of 1.78 mmol/L is considered a reasonable inflection point at which increased mortality has been observed (National Kidney Foundation, 2003a, Am J Kidney Dis). The normal phosphorus level in blood is 0.87 to 1.49 mmol/L. In addition, the calcium-phosphorus product should be below 4.4 mmol²/L². These US guidelines also form the basis for the EU guidelines.

Medical treatment of hyperphosphataemia

Phosphate binders:

Various phosphate binders are currently authorised and can be roughly divided into two groups, namely calcium-containing phosphate binders and non-calcium phosphate binders. Calcium salts (e.g. calcium carbonate and calcium acetate) are one of the preferred agents to bind intestinal phosphate. The two principal options in the latter group authorised more recently are sevelamer and lanthanum carbonate. Sevelamers (hydrochloride or carbonate) are non-absorbable agents that contain neither calcium nor aluminium. These drugs are cationic polymers that bind phosphate through ion exchange.

The most common adverse events with phosphate binders are GI events, in line with their local mode of action. Hypercalcaemia is a common complication of calcium salts and careful monitoring of serum calcium concentration is essential. The long-term safety of lanthanum, particularly its possible effect on bone and other organs, remains unclear.

Phosphate binders like aluminium hydroxide, magnesium-containing antacids and calcium citrate are not generally used as primary therapy because of their association with neurological, skeletal and haematological toxicity. Because of the limited phosphorus binding capacity of all phosphate binders, they are only effective if the dietary restrictions for phosphorus are continued simultaneously.

Which phosphate binder should be used, depends on many factors including comorbidity, side-effects, additional beneficial effects, patient preference and compliance. All phosphate binders have been shown effective in controlling serum phosphorus levels, which is the surrogate endpoint. There are some data indicating that calcium salts were superior to sevelamer in reducing phosphorus levels. No clear data are available on clinical endpoints like all-cause or cardiovascular mortality and the effect on the surrogate outcomes of bone mineral density or histomorphometry and vascular calcification are unclear. Compared with calcium salts, sevelamer and lanthanum carbonate were associated with significantly lower rates of treatment-related hypercalcaemia. The DCOR study (Suki W., et al. Effects of sevelamer and calcium-based phosphate binders on mortality in haemodialysis patients. *Kidney Int* 2007; 72: 1130-1137) did not report a difference in risk of all-cause mortality between sevelamer and calcium salts and more data are needed on the influence of calcium-based binders on progression of vascular calcification and the impact of decreasing vascular calcification on survival outcomes. The choice of phosphate binder in clinical practice will ultimately be an individual approach.

Other treatments:

Patients may receive calcium supplements to restore calcium levels. In addition, patients are usually treated with vitamin D or its analogues to reduce PTH levels. Calcimimetics may also be used to increase the sensitivity of the calcium-sensing receptor in the parathyroid gland to calcium.

However, calcitriol and other vitamin D analogues also increase intestinal phosphate absorption and can exacerbate the hyperphosphatemia unless bone remodelling is reduced due to inhibition of PTH secretion. High doses of vitamin D analogues also stimulate vascular calcification.

During the validation phase of the centralised procedure for Velphoro an anonymous letter was received from a third party by the EMA on 18th of January 2013. In this letter some concerns were raised concerning the percentage of the iron absorption in the target group, accumulation of the iron in the liver in non-clinical studies, side effects of iron, possible risks of accidents of poisoning with iron preparations, increase the risk of chronic diseases associated with high iron intake, risk of iron overload and inhibiting of absorption of zinc and copper and concerns regarding the chronic use of iron.

A second anonymous letter was received from a third party by the EMA on 3rd of October 2013. In this letter some concerns were raised concerning the daily (1,000 mg iron/day), claiming that it would induce oxidative stress in the stomach and intestine.

A third anonymous letters was received from a third party by the EMA on 5th November 2013 and fourth letter was received on 21th of November 2013. The issues raised are comparable to those raised in the initial two letters. A fifth letter was received from a third party by the EMA on the 20th June 2014 raising concerns on the potential cancerogenicity of the product.

The concerns raised by the anonymous letters were carefully assessed upon by the CHMP, and the relevant concerns raised were addressed in the questions to the Applicant during the evaluation procedure and were successfully addressed by the Applicant.

2.2. Quality aspects

2.2.1. Introduction

The finished product is available as chewable tablet containing 500 mg iron as polynuclear iron(III)-oxyhydroxide, sucrose, and starches, also known as sucroferic oxyhydroxide as active substance.

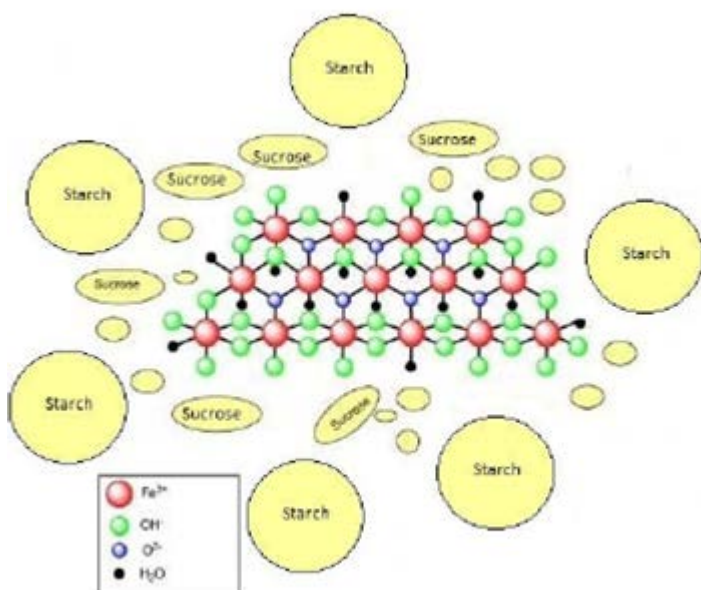
Other ingredients are woodberry flavour, neohesperidin-dihydrochalcone, magnesium stearate and colloidal anhydrous silica.

The product is available in primary packaging as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of the active substance is mixture of polynuclear iron(III)-oxyhydroxide, sucrose, and starches and has the following structure:



The polynuclear iron(III)-oxyhydroxide is the active moiety.

The hydrated polynuclear FeOOH core is “wrapped” by sucrose. The presence of sucrose is essential for the maintenance of the hydrated structure of the polynuclear FeOOH and maintains the high phosphate adsorption capacity. Starches, and the other carbohydrates, are used to improve process ability during the manufacturing process.

Neither sucrose nor the starches form direct covalent bonds to the active moiety. The interaction between the core surface and the sucrose occurs by hydrogen bonding of surface Fe(III)-OH groups with hydroxyl groups (OH) of sucrose.

It was sufficiently demonstrated that the active moiety polynuclear iron(III)-oxyhydroxide cannot be isolated and stored without the sucrose, and starch, which are also necessary for the processability of the active substance during the manufacturing process of the finished product.

The active substance is brown amorphous powder, odourless and slightly hygroscopic. This active substance is partly soluble in water.

Polymorphism was not been observed. In addition, the active substance has a non-chiral molecular structure.

Evidence of the physical-chemical structure was provided in the form of measurements by several analytical techniques, such as measurement of the mineralogical structure by X-ray diffraction (XRD) and edge structure spectroscopy (XANES), thermal gravimetric analysis (TGA), IR detection, mössbauer spectroscopy, microscopy, BET analysis and melting point.

Manufacture, characterisation and process controls

The active substance is synthesised in four steps: synthesis, desalination, addition of the carbohydrates and drying using commercially available well defined starting materials with acceptable specifications. A detailed description of the manufacturing process has been provided, including reaction conditions, quantities and starting materials and yields. The in-process controls are laid down.

The manufacturing process of the active substance is well controlled and consistently produces the amorphous form.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origins and characterised. The carry-over of impurities, reagents, solvents and catalysts from the starting material into the final active substance has been also discussed.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediates, starting materials and reagents have been presented. The active substance is packaged in low-density polyethylene (LDPE) foil (tube) or an LDPE cross-bottom bag. The primary packaging itself is stored in another LDPE cross-bottom bag containing a packed desiccant and is closed air-tight (secondary packaging). The materials in contact with the active substance comply with the EC directive 2002/72/EC and EC 10/2011.

Specification

The active substance specification includes tests for appearance, identification (IR and NIR), loss on drying (Ph. Eur.), particle size (Ph. Eur.), microbiological quality (Ph. Eur.), assay (complexometric titration, NIR, HPLC-RID) and in vitro phosphate adsorption (ICP-OES).

A detailed description for all analytical methods was provided. Full method validation data was also provided for the in-house analytical methods in accordance with the relevant ICH guidelines. The analytical methods proposed are suitable to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety.

Batch analysis data are provided on 5 production batches produced of the active substance. All the batches were manufactured according to the proposed synthetic route, and the batch analysis data show that the active substance can be manufactured reproducibly. All results are within the specifications and consistent from batch to batch.

Stability

Five production scale batches of the active substance packed in the intended commercial packaging from the proposed manufacturers were put on stability testing as per ICH conditions: under long term (25°C/60%RH), (30°C/60%RH) for up 48 months and accelerated (40°C/75%RH) for up 6 months. The active substance used in the primary stability studies was manufactured according to the commercial process.

Forced degradation studies were conducted by exposing the active substance to high temperature, aqueous hydrolysis, acid and base conditions. Based on these studies it is observed that the active substance is sensitive to acid conditions.

Photostability testing following ICH guidelines Q1B was performed on one batch of the active substance. The results showed that there are no significant changes for any of the evaluated parameters established for the stability studies.

The parameters tested are the same as for release. The analytical methods used were also the same as for release and were stability indicating.

The stability results indicate that the active substance is stable at controlled room temperature. The results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The aim of the pharmaceutical development was to develop a chewable tablet able to deliver the correct dose. Before starting the development the applicant studied important physical and chemical characteristics of the active substance such as solubility, stability, particle size, etc.

As already mentioned, the active substance is partly soluble in water. The sucrose present in the active substance dissolves in the aqueous medium of the gastrointestinal (GI) tract and is digested to glucose and fructose. Starch is digested to glucose and maltose. These compounds are absorbed. However, Polynuclear iron(III)-oxyhydroxide is practically insoluble and iron cannot be absorbed. Iron(III)-oxyhydroxides are microbiologically not stable as an aqueous suspension and are dehydrated when dried or stored, which results in a decrease of the phosphate binding capacity. Therefore, the iron(III)-oxyhydroxide alone cannot be isolated and stored as an active substance. Sucrose is added to the iron compound to stabilize the iron core and thus maintain the high phosphate adsorption capacity. Starches are added as processing aids to allow for isolation, characterisation and stability testing of the drug substance.

Considering that the iron component of the active substance is practically insoluble, the particle size of the active substance is not critical with regards to bioavailability as compared to drugs that need to be absorbed. The particle size distribution is narrow with low variability between batches due to the defined manufacturing process of the active substance by spray drying. Due to the high amount of active substance in the drug product (97%), the particle size distribution has no impact on the content uniformity.

The effect of the particle size distribution of the active substance on the phosphate adsorption was evaluated during formulation development. Differences found in phosphate adsorption of different particle sizes had no impact in the efficacy of active substance.

Compatibility studies of the active substance with a number of standard excipients used in chewable tablets were performed and the results did not show any significant interaction. The flavours and sweeteners were selected during the pharmaceutical development and evaluated by a taste sensor (electronic tongue, Astree e-tongue), which can detect taste in a manner similar to human gustatory sensation.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

During the drug development, the Applicant introduced some changes in the composition and in the manufacturing process in order to obtain the final formulation.

During the pharmaceutical development, the quality target product profile (QTPP) was defined according to the International Conference on Harmonisation Q8. The main objective of the applicant was to develop a pharmaceutical form that meets compendium and other relevant quality standards, and is packaged in child resistance packaging. The functional relationships linking material attributes and process parameters to the critical quality attributes (COAs) were determined by a design of experiments, in order to demonstrate that the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters provide assurance of quality. The pharmaceutical development and manufacturing process have been evaluated through the use of risk assessment and design of experiments to identify the critical product quality attributes and critical

process parameters. A risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies. The critical process parameters have been adequately identified. Based on the risk assessment and take in account that the manufacturing process is a standard process, the selections of the critical process parameters (CPPS) are considered justified. The DoE studies support the design space. The adequate process validation data further support the boundaries of the three parameters of the design space.

The active substance works by binding phosphate in the gastro-intestinal tract and is therefore not intended to be absorbed. Therefore, no bioequivalence studies between the clinical formulation and the proposed commercial formulation have been conducted. Nevertheless, the Applicant demonstrated that the different excipients ratio and active substance load used in the different formulations did not have any impact on product quality attributes. The discriminatory power of the dissolution method developed has been demonstrated.

The primary packaging is sufficiently described and is reflected in the SmPC. The material complies with Ph Eur and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the medicinal product.

Manufacture of the product and process controls

The manufacturing process consists of four main steps: blending, lubrication, compression and packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process pharmaceutical form.

The design space has been developed at commercial scale by using three different batches. It was also noted that the parameters of the DS are scale independent.

The validation of the manufacturing process has been evaluated on three consecutive production scale batches. The quality of the production batches was evaluated through the results of in process testing as well as the results of finished product testing. The process validation is supported by batch data on three production scale batches

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: characteristics (visual examination), identification (HPLC, NIRS), assay (HPLC), mass variation (Ph Eur), moisture, microbiological quality (Ph Eur), assay (complexometric titration, NIR, HPLC-RID), in vitro phosphate adsorption (ICP-OES), hardness (Ph Eur) and disintegration time (Ph. Eur.).

Batch analysis data of six scale batches of the finished product are provided. The results confirm the consistency of the process and its ability to manufacture a product complying with the product specification.

Stability of the product

Stability data of six scale batches for of finished product stored under long term conditions for 18 months at 25 °C / 60% RH, intermediate conditions for 18 months at 30 °C / 75% RH and for up to six months under accelerated conditions at 40 °C / 75% RH according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The parameters tested are the same as for release. The analytical methods used were also the same as for release and were stability indicating.

One batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. In addition stress stability studies were performed on one fully representative batch under various extreme conditions including high temperature, aqueous hydrolysis, acid and base conditions.

Based on the available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. This medicine contains a mixture of polynuclear iron(III)-oxyhydroxide, sucrose, and starches as an active substance. However, the polynuclear iron(III)-oxyhydroxide is considered the active moiety. The manufacturing flow-chart was provided with suitable in-process controls. The manufacturing process is adequately validated at full scale at the proposed manufacturing site and a validation protocol has been presented. The design space has been proposed and developed at commercial scale by using three different batches. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

None

2.1. Non-clinical aspects

2.1.1. Introduction

All pivotal toxicology studies were performed in accordance with GLP regulations.

2.1.2. Pharmacology

The intended pharmacological action of PA21 is to bind dietary phosphate in the gastrointestinal (GI) tract, resulting in phosphate excretion with the faeces and thereby preventing phosphate absorption. This is the intended mechanism of action for the control of serum phosphorus levels in patients with end stage renal disease (ESRD). In vitro studies demonstrated efficient phosphate binding by PA21 under simulated GI tract conditions (pH range of 1.2 to 8.5). Data from these in vitro studies showed at least equivalent phosphate binding capacity of PA21 compared to currently available phosphate binders. In vivo studies conducted in a rat model of chronic renal failure (CRF) showed that PA21 was as effective as calcium carbonate, sevelamer carbonate and lanthanum carbonate in correcting the hyperphosphataemia and associated secondary hyperparathyroidism observed in the model, and was more effective than calcium carbonate and, to some extent, lanthanum carbonate in preventing vascular calcification in the thoracic aorta.

Primary pharmacodynamic studies

In vitro

Data on the primary pharmacodynamic activity and mode of action of PA21 were largely provided by *in vitro* phosphate binding studies under simulated GI tract conditions.

Phosphate adsorption under gastrointestinal conditions

The phosphate binding capacity of PA21-2 was investigated over a pH range of 1.2 to 7.5, to cover the potential pH range that may be encountered in the GI tract ([Study SR-1330-01/E01](#)). An amount of PA21-2 corresponding to 50 mg iron was incubated with 10 mL of inorganic phosphate solution containing 11.14 mg phosphorus. At pH 1.2 (equivalent to that in an empty human stomach), PA21-2 bound 0.18 mg P/mg Fe, and there was some release of iron from PA21 at this very low pH (6.2% release; see pharmacokinetics section). At the pH which may be found in a full human stomach (about 2.5), phosphate binding was slightly higher (0.20-0.21 mg P/mg Fe) and similar binding values were observed at pH values of 4.5, 7.0 and 7.5, which may be encountered in the small and large intestines. There was no or little release of iron (0-1.3%) at pH 2.5 and above (see pharmacokinetics section). These data not only support the proposed dosing regimen of PA21 being taken with food, but they indicate that it is important that PA21 is taken with food. Iron release of 6.2% relates to 186 mg iron from a maximum dose of 3000 mg iron per day. This could lead to iron overload.

To further investigate phosphate binding capacity, and to compare PA21-2 to other marketed phosphate binders, a comparison was performed with sevelamer HCl, lanthanum carbonate, calcium acetate and calcium carbonate at pH values of 3.0, 5.5 and 8.0 ([Study TC-1118/E01](#)). 100 mg of each compound (corresponding to 21 mg iron for PA21-2) was incubated with 20 ml of a 20 mM phosphate solution, corresponding to 38 mg phosphate. The quantity of active substance needed to bind 1,000 mg of phosphate was calculated. The data showed that at the typical pH that may be encountered in the stomach after food (about pH 3.0), PA21-2 showed similar phosphate binding capacity as sevelamer HCl and lanthanum carbonate, the quantities of active substance required to bind 1,000 mg phosphate being 8.6 g (corresponding to 1.7 g Fe) for PA21-2, 7.1 g for sevelamer HCl and 6.9 g for lanthanum carbonate. Calcium acetate and calcium carbonate showed no or only low phosphate

binding capacity at this pH, although improved binding capacity was observed for these calcium salts at pH 5.5. At pH 5.5, and 8.0, PA21-2 showed lower phosphate binding capacity than at pH 3.0, but was superior to lanthanum carbonate at these higher pH values.

Further *in vitro* studies examined the phosphate adsorption capacity and iron release from PA21 under simulated GI tract conditions (Study REPO00122TC-EN01v.1). Two different pH cycles were examined, so as to reproduce the range and sequence of pH values that PA21 would encounter during a passage through the GI tract. These experiments showed high phosphate binding at low pH values (1.5 or 2.6), and robust binding up to a slightly alkaline conditions (pH 8.1). Iron release (6.3%) was only observed at the lowest pH tested (1.5), representative of the fasting state of the stomach. Iron release at higher pH values was low.

Mode of action

It is well known that iron oxides adsorb phosphates. The manner in which this is achieved was examined in older experiments with hydrated goethite (α -FeOOH) (Parfitt and Russell, 1977; Sigg and Stumm, 1981). It was shown that each phosphate can replace two OH groups in the α -FeOOH complex to form the binuclear, bidentate FeOPO(OH)OFe complex.

Experiments performed to assess the phosphate binding capacity of PA21 showed molar ratios phosphate to iron of up to 0.7 in the slightly acidic pH range (Geisser and Philipp, 2001), which could not be explained by the simple adsorption mechanism as described above. Such a ratio is only achievable if a major amount of iron phosphate is formed. Whether such a formation of a new phase would actually take place taking into consideration different pH conditions, was aimed to be clarified in [study REPO00128TC-EN03v.1](#). The approaches used included thermodynamic calculations, molar iron/phosphorus ratios, colour analysis and spectroscopy techniques, including inductively coupled plasma optical emission spectroscopy (ICP-OES), attenuated total reflectance Fourier transform infrared spectroscopy and X-ray photoelectron spectroscopy (XPS). One gram of PA21 API was incubated with 40 mL of phosphate buffer (57 g phosphorus/L) of different pH values (1.2, 3.0, 5.6, 8.2) for 2 hours at 37°C.

Results indicate that under acidic conditions, mainly iron phosphate is formed, whereas under slightly alkaline conditions, iron(III)-oxyhydroxide is the favoured chemical species.

The data above suggest there are two separate mechanisms by which phosphate is bound by PA21. The first mechanism is simple adsorption of phosphate to the iron complex. The older studies in which this was examined used hydrated goethite, which is a α -form of FeOOH, while the β -form (Akaganeite) is present in PA21. It is assumed that adsorption of phosphate occurs in a similar manner.

The second mechanism is the formation of iron phosphate, FePO₄, which seems to be the predominant mechanism at low pH (e.g. in the stomach), with decreasing quantities being formed at higher pH. In fact according to [study REPO00128TC-EN03v.1](#), FeOOH is indicated to be mainly converted to FePO₄ at low pH, when in the presence of phosphate.

It must be assumed that both mechanisms play a role, and that some FePO₄ is formed in the stomach, and further adsorption of phosphate to the FeOOH moiety will take place in the remainder of the GIT, where it is excreted in the faeces.

Phosphate binding in gastrointestinal transit (TIM) model

Studies were performed with an *in vitro* gastrointestinal transit model (TIM), to evaluate phosphate binding to PA21, iron release and uptake, fermentation of Fe³⁺ to Fe²⁺, and potential for bile sequestering.

Since Velphoro is intended to bind phosphorous from the diet, the fed state is most relevant for the evaluation of efficacy. In study V8091, two experiments were performed in the fed and fasted state, respectively, one with an actual meal, and one with a replacement meal which contained only a phosphate solution so as to imitate the same amount of phosphate intake as the "normal" meal. There are large differences in the outcome of the two experiments. Phosphorous binding is very low in the first experiment, with only a 17% reduction in absorption as compared to control (0.07 mg P/ mg Fe), whereas the second experiment showed a reduction of absorption of 37%. The amount of P per mg Fe could not be retrieved from the data of the second experiment. The authors of the report mention that the low binding efficacy of PA21 (and of the other products). A second study (V9209) was performed to investigate the low binding efficacy seen in the previous study. It is mentioned that different experimental conditions were used in this study, but it is not clear what the difference exactly is. The meal matrix is the same. Somewhat higher binding is observed, up to 0.13 mg P/ mg Fe.

Overall, the TIM studies are of limited value for the determination of efficacy of PA21 due to the low phosphate binding in the studies. The TIM studies also do not add information about the mechanism of action, as only the amount of Fe is measured and it is therefore not known whether the phosphate is bound in the FePO_4 form, or whether it is adsorbed to the FeOOH moiety.

However, in line with the *in vitro* data on iron absorption through the gut, the TIM experiment underscores the need for co-administration of PA21 with food, as in the fasted state 40 mg (10%) of the Fe ingested as PA21 was absorbed. This would amount to 300 mg Fe for the maximum dose of 3000 mg Fe in PA21. This is more than 16x the recommended daily dose of 18 mg Fe.

Up to 16% of bile acids were bound to PA21. Although this should not be considered as negligible, there are no signs, either from non-clinical studies or from the clinical trials that this is of any consequence.

Reduction of Fe^{3+} to Fe^{2+} does not seem to be an important factor in this simulation model as no Fe^{2+} was measured in the dialysate, and only a very minor amount was measured in the lumen.

In vivo

Phan 2012a: Effects of PA21, a New Iron-Based Phosphate Binder on Vascular Calcification in Chronic Renal Failure Rats.

PA21-2 was tested in a rat model of chronic renal failure. Serum phosphorous levels in CRF rats pre-treatment were elevated as compared to controls (5.39 ± 0.16 vs. 2.68 ± 0.18 mmol/L). The applicant states that after 4 weeks of treatment, there is a dose related decrease in phosphorus serum levels. However, it appears that the phosphorus levels are also reduced in untreated CRF rats (2.91 ± 0.24 for untreated vs. 2.21 ± 0.09 for treated with 5%). Other parameters, including phosphaturia, vascular calcification were reduced by PA21 treatment, while iPTH was somewhat reduced from 3261 pg/ml in de CRF control, to 1138 pg/ml in the PA21 5% group (control value of non-CRF rats: 105 pg/ml). Moreover, the dose which is used is expressed as percentage of the diet. Most effects are seen at 5%, but it is unclear how this dose relates to the clinical dose. Therefore, although it is clear treatment with PA21 in CRF rats has some effect, the effect on serum phosphorus is questionable in this model.

Phan 2012b: Effects of PA21 Compared to Lanthanum Carbonate and Sevelamer Carbonate on Phosphate Homeostasis and Vascular Calcifications in a Rat Model of Chronic Kidney Failure

In this second study using the CRF rat model, excretion of phosphorus in urine vs. faeces was measured. There is a large shift towards excretion via faeces after PA21 treatment (44% vs. 70%), indicating that phosphorus is bound to the complex and not absorbed from the GI tract. Other

parameters, including urine phosphorus and calcium, are very variable and therefore difficult to interpret. Arterial calcification was reduced due to treatment with PA21 and other products.

Secondary pharmacodynamic studies

Malluche 2010: Effects of Various Phosphate Binders on Mineral and Bone Metabolism.

In this secondary pharmacology study, the main focus was the effect of phosphate binders including PA21-2, on bone turnover, since this is one of the adverse effects seen in patients with ESRD, which is associated with disturbances in phosphorus homeostasis. To examine this, a rat model of induced renal failure was used. However, the only difference between rats with renal failure and those without, is a reduced creatinine clearance. Groups of 8 male Sprague Dawley rats were maintained on a high phosphate diet (0.73% phosphorus) and renal failure was induced in all groups (apart from a control group fed high phosphate diet only) by incorporation of adenine (0.75% in the first week, 0.50% thereafter) into the diet. Phosphate binders (PA21-2, aluminium hydroxide, calcium acetate, lanthanum carbonate and sevelamer carbonate) were administered at dosages of 600 mg/kg/day in the diet to rats for a period of 4 weeks (period when adenine was fed). Rats were investigated for renal function and calcium/phosphate metabolism markers (serum and urinary creatinine, calcium and phosphorus levels) as well as markers of bone metabolism (serum parathyroid hormone (PTH), calcitriol and fibroblast growth factor 23 (FGF-23) levels). Detailed histology and histomorphometry of femur samples, including static and dynamic parameters of bone structure, formation and resorption were measured by semi-automatic methods at standardised sites below the growth plate. Other parameters including serum or urine phosphorous and calcium, serum calcitriol and parathyroid hormone, are not affected, indicating that this might not be an appropriate model to study change in bone turnover. Some of the bone parameters measured (number of osteoblasts and osteoclasts/bone parameter) do seem to be affected due to induction of renal failure. Moreover, results are very variable, with large standard deviations. In conclusion, this study is of limited value for the evaluation of the impact of PA21-2 on bone turnover in ESRD patients.

Malluche 2012: Effects of PA21 Compared to Lanthanum Carbonate and Sevelamer Carbonate on Bone Abnormalities in a Rat Model of Chronic Renal Failure.

This study comprised a histopathological and histomorphometric examination of femur samples obtained from the rat CRF model study of Phan 2012b. The effects on bone turnover and formation were examined in this study. Unlike the previous study, this rat model does indeed show the symptoms of renal failure, including changes in serum and urine phosphorus and calcium, and serum iPTH. Bone samples were processed for mineralised bone histology, and stained with modified Masson-Goldner trichrome and Gomori stain (for iron). Static and dynamic parameters of trabecular bone structure, formation and resorption were measured at a standardised site below the growth plate using a semi-automated method. Cortical thickness was measured using the same methodology.

There were no changes in bone structure in CRF rats, but this might be an effect that will be seen later in time, as changes in bone formation are evident.

Treatment with PA21-2 caused a reversal of some of the effects seen on bone formation. The increased number of osteoblasts/bone perimeter, increased osteoblast surface and bone formation rate were reduced back to the value of normal rats. This indicates that higher bone turnover as seen in CRF rats can be normalized by PA21-2 treatment. However, treatment with PA21-2 had no effect on changes in the osteoid (increased thickness, surface and volume), and likewise mineralization lag time and osteoid maturation time remained as high as in untreated CRF rats. This indicates that, at least in this rat model, PA21-2 did not reduce osteomalacia as seen in CRF rats and ESRD patients.

Safety pharmacology programme

A standard battery of safety pharmacology studies was performed with PA21-2. The compound had no significant effects on respiratory, central nervous system or gastro-intestinal motility parameters in rats up to 5000 mg/kg. Also in dogs up to 1000 mg/kg, no effects on the cardiovascular system were observed. An *in vitro* hERG channel assay was not performed. This is agreed, considering the nature of the product.

Respiratory system

Study VFR081/052332 (GLP): Evaluation of Respiratory Parameters in the Conscious Rat Using Whole Body Bias Flow Plethysmography

A single oral dose of PA21 at 1,250, 2,500 or 5,000 mg/kg given to groups of 8 male CD rats produced no significant changes in respiration rate, tidal volume and minute volume. Morphine sulphate at an oral dose of 200 mg/kg produced statistically significant decreases in respiration rate and minute volume at 30 minutes post-dose and a significant decrease in respiration rate at 90 minutes post-dose, thus confirming the validity of the test system.

Central nervous system

Study VFR082/052395 (GLP): Irwin Dose Range in Rats, Including Body Temperature and Locomotor Assessment

A single oral dose of PA21 at 1,250, 2,500 or 5,000 mg/kg given to groups of 4 male CD rats produced no changes in the behavioural or physiological state during detailed observation performed up to 24 hours after dosing. No marked or statistically significant effects on locomotor activity or body temperature were observed.

Gastro-intestinal system

Study VFR085/052415 (GLP): Charcoal Propulsion Test in Rats

Single oral PA21 dosages of 1,250, 2,500 or 5,000 mg/kg were administered to groups of 10 male CD rats, 45 minutes prior to oral administration of a charcoal suspension. Rats were killed 30 minutes after charcoal administration and the distance the charcoal meal had travelled from the pyloric sphincter was determined, as a measure of GI motility. PA21 at 1,250 mg/kg had no effect on intestinal motility. At 2,500 and 5,000 mg/kg, slight increases in distance travelled by the charcoal meal were observed, but the increases were not dosage-related. It was, therefore, concluded that these changes were unlikely to be treatment-related or of biological significance. A group of rats dosed orally with morphine sulphate at 50 mg/kg as a positive control showed the expected significant reduction in GI motility, thereby confirming the validity of the test system.

Cardiovascular system

Study VFR083/043639 (GLP): Evaluation of Cardiovascular Effects in Conscious Telemetered Beagle Dogs

A single oral dose of PA21 at 250, 500 or 1,000 mg/kg to 2 male and 2 female beagle dogs showed no adverse effects on arterial blood pressure or heart rate at any dose. There were no effects of treatment on electrocardiographic rhythm or waveform morphology, and waveform intervals (including QT interval) were unaffected. Clinical findings in the test animals were restricted to a dose-dependent increase in the incidence of dark coloured faeces the day after PA21 administration, attributable to the excretion of PA21 and/or its iron content, this finding not being considered adverse.

An *in vitro* study examining potential for PA21 to cause delayed ventricular repolarisation (QT interval prolongation), as outlined in the ICH S7B guideline, was not performed. Such *in vitro* test systems (e.g., hERG assay) are not relevant or appropriate for high molecular weight compounds or insoluble compounds such as PA21. A compound of the size of PA21 would be unlikely to interact with ion channels involved in ventricular repolarisation, and the components of PA21 (iron(III)-oxyhydroxide, sucrose, starch) are all innocuous substances that are unlikely to exert any effects on cardiac conduction. In addition, QT intervals were assessed *in vivo* as part of the cardiovascular safety study conducted by telemetry in dogs, with no effects of PA21 being observed. Therefore, the omission of an *in vitro* study examining potential for QT interval prolongation is considered justified and further safety pharmacology studies are not required.

Pharmacodynamic drug interactions

An *in vivo* study and several *in vitro* studies were performed to assess the potential for pharmacodynamic interaction of PA21 with co-administered drugs, vitamins, nutrients and bile acids. An *in vivo* drug interaction study showed that only minimal amounts of iron are absorbed from PA21 in the mouse (0.55%), and that this is not affected by the co-administration of any other drug except ascorbic acid, which caused an increase in absorption to 0.83% of the total ingested PA21.

Several drugs tested *in vitro* showed a potential to bind to and interact with PA21. These findings have led to a clinical interaction study, which showed no meaningful interactions.

There was no evidence of a biologically relevant adsorption or degradation of various water-soluble vitamins (folate, niacin, pantothenic acid, biotin, pyridoxine), amino acids (methionine and tryptophan) and anions (fluoride, oxalate and sulphate) or the macronutrient oxalate.

Binding of PA21 to the bile acids cholyglycine, chenodeoxycholyglycine and deoxycholytaurine was examined at pH 5.5 and 8.0. Up to 14.3% of chenodeoxycholyglycine was bound to PA21 in this *in vitro* test system. This is in line with what was found in the TIM-1 system (see primary pharmacodynamics).

In the study (SR-1039/E01), groups of 3 male NMRI mice were treated for 5 consecutive days with 1,140 mg/kg/day PA21 by oral gavage. The iron in the PA21 was radio-labelled with ⁵⁹Fe. In order to assess the potential interaction between PA21 and foodstuffs or other pharmaceutical products that may be administered to CKD patients, mice were treated either with PA21 only, or PA21 plus 1 of the following (all given by oral administration):

- Caffeine (66.7 mg/kg/day)
- Ascorbic acid (11.7 mg/kg/day)
- Calcium gluconate (200 mg/kg/day)
- Magnesium aspartate (66.7 mg/kg/day)
- Phytic acid (215.6 mg/kg/day)
- Furosemide/Lasix (250 mg/kg/day)
- Enalapril/Reniten (6.7 mg/kg/day)
- Captopril/Lopirin (25 mg/kg/day)

Mice were killed 16 days after the first dose of PA21 and/or foodstuff/pharmaceutical, and blood, liver, kidney, spleen, stomach, intestine and right femur were removed for radioactivity determinations. The percentage of the administered radioactivity dose recovered in the blood and other organs was calculated for each study group. In control animals, dosed only with labelled PA21, 0.55% ($\pm 0.10\%$) of

the administered dose was recovered in the blood and selected organs, this being consistent with previous mouse studies that showed 99.39% of administered PA21 was recovered in the faeces and urine in the first 10 days after administration. Of the various co-administered treatments, only ascorbic acid caused a slight increase in iron uptake and retention in the blood and tissues, 0.83% ($\pm 0.27\%$) of the administered radioactivity being recovered in mice co-administered PA21 and ascorbic acid. For all other co-treatments, recovery values were similar to those of the control animals, indicating that other foodstuffs and pharmaceutical products that may be administered to CKD patients are unlikely to interact with the iron component of PA21 in a way to induce dissociation of significant amounts of iron, and the various co-treatments are unlikely to increase the risk of iron uptake and accumulation during PA21 treatment.

The various *in vitro* DDI studies revealed no significant binding/interaction of PA21 with ciprofloxacin, enalapril, digoxin, metoprolol, nifedipine, warfarin, hydrochlorothiazide, metformin or quinidine. No adsorption was found for cinacalcet or glipizide either but results were inconclusive at some pH values. No conclusion could be drawn from the *in vitro* DDI study with candesartan cilexetil due to lack of tablet dissolution. Moderate adsorption to PA21 was noted for pioglitazone. Extensive binding or interactions were observed for furosemide, losartan, atorvastatin, doxycycline, alendronate, levothyroxine and paricalcitol. The observed adsorption of levothyroxine, paricalcitol and atorvastatin was less pronounced in the presence of phosphate, which will compete for binding to PA21.

These *in vitro* observations led to the conduct of human DDI studies for furosemide and losartan, and also 2 drugs where there were no clear *in vitro* interactions, but where a narrow therapeutic margin exists (i.e., warfarin and digoxin). A human DDI study has also been conducted for omeprazole where a marked increase in solubility was observed in the *in vitro* study. The human DDI studies showed no interactions between these drugs and PA21.

According to the applicant, no *in vitro* interaction of PA21 with bile acids was observed, consistent with the data from the TIM-1 study (V8091, see primary pharmacodynamics). Detailed interaction studies conducted with various water-soluble vitamins (folate, niacin, pantothenic acid, biotin, pyridoxine), amino acids (methionine and tryptophan) and anions (fluoride, oxalate and sulphate) showed no evidence of a biologically relevant adsorption or degradation of any of these dietary components under physiologically relevant conditions. Furthermore, the macronutrient oxalate was shown to have no detectable influence on the phosphate binding capacity of PA21 under simulated GI tract conditions. Therefore, presence of high concentrations of a competing anion in the diet such as oxalate will not influence the phosphate binding efficiency of PA21.

2.1.3. Pharmacokinetics

Kinetic studies were conducted in rats and dogs and in mice, with radiolabelled Velphoro, administered orally at clinically relevant or higher dosages. Humans are dosed three times a day, while the non-clinical species were dosed once daily in the kinetic studies. The exposure in the gastro-intestinal tract is therefore higher in the non-clinical species compared to humans, indicating that the local effects could be different due to differences in exposure. In addition, the human dose is provided as mg Fe while the dose administered to the pre-clinical species is provided as mg Velphoro per kg. The following calculation was used to convert from mg Velphoro to mg Fe: Velphoro consists of 33% polynuclear FeO(OH) and 0.63 of the weight of FeO(OH) is due to Fe. This conversion was applied in the interspecies comparison.

Absorption, distribution and excretion studies were conducted in rats and dogs, and to a lesser extent in mice, with radiolabelled Velphoro, administered orally at clinically relevant dosages.

Velphoro works by binding phosphate in the gastro-intestinal tract and is therefore not intended to be absorbed. The absorption of radioactivity was low, highest radioactivity levels in blood were 1.4% of the administered dose. The overall absorption could not be determined due to the lack of information, but appears to be low (<7%). The iron release under *in vitro* gastro-intestinal conditions indicated that the iron release was highest at low pH values, with a maximum of 6.3% at a pH of 1.2-1.5. The iron release was much lower at higher pH values (0.3%). However, the high iron release (67%) was observed in an experiment with artificial gastric juice without the presence of phosphate. In an experiment with simulated intestinal juices, the release was maximal 6.3%. Under physiological conditions phosphate is present, especially under fed conditions. It is therefore more realistic to expect a maximal worst-case iron release of 6.3% under human gastrointestinal conditions. Thus, a maximum amount of 31.5 mg Fe is released from Velphoro in the gastrointestinal fluids and is available for absorption.

Based on the *in vivo* distribution data, the blood-to-plasma ratio appears to be 1.3-1.9 indicating a distribution to blood cells. Distribution of radioactivity was observed to blood, liver, spleen, bone marrow and the gastro-intestinal tract wall. Radioactivity was present in rat after single dosing for 168 h after dosing in whole blood, blood cells and the liver. In addition, after repeated dosing for 5 days to mice radioactivity was present 11 days after the last dosing, but declined steadily. These data indicate that the small amount of systemically absorbed iron is present in a biodegradable form, rather than as a particle. In the large intestinal wall, where iron uptake is normally minimal due to lack of transporters, the presence of iron may indicate uptake of particles. There is no accumulation however, due to the high turnover of cells, and likewise there are no toxicological consequences. Distribution data from pigmented (Lister Hooded) rats were similar to those observed in albino (Sprague Dawley) rats, indicating a lack of binding of the radioactivity with melanin.

Excretion of radioactivity was only observed via faeces. Some gender differences in excretion rate were observed between male and female rats with a lower excretion rate in females compared to males. After 48 hours only trace amounts were detected in faeces. There was no excretion of radioactivity via urine or bile after oral administration of radiolabelled Velphoro.

Velphoro consist of polynuclear iron(III)oxyhydroxide, sucrose and starch. Enzymes present in the digestive juices digest sucrose and starch after oral administration into glucose, fructose and maltose. No differences in degradation were observed between the individual components sucrose and starch or present in Velphoro. The different *in vitro* experiments investigating the iron release under gastro-intestinal indicated differences in phosphate binding and iron release with a higher iron release in the presence of digestion enzymes. The presence of sucrose is essential for the maintenance of the hydrated structure of the polynuclear FeO(OH) and therefore of the high phosphate absorption capacity of Velphoro.

Drug interaction studies showed that a number of common foodstuffs or pharmaceutical products did not influence the radioactivity uptake from Velphoro. In addition, Velphoro did not induce CYP isozymes, indicating low potential for drug-drug interactions at the metabolic level. No information was provided regarding substrate or inhibition potential of Velphoro for CYP isozymes or transporters. However, based on the structure of Velphoro and its composition (polynuclear iron(III) oxyhydroxide, starch and sucrose), it is unlikely that Velphoro will be a substrate or inhibit CYP enzymes or drug transporters. If iron is released from Velphoro, than the iron will be absorbed by the iron transporters present in the duodenum.

2.1.4. Toxicology

Single dose toxicity

One single-dose toxicity study was performed by the oral route in rats. At a dosage of 1,000 mg Fe/kg, about 16 times the maximum likely human dose (60 mg Fe/kg for a 50 kg person), no deaths or signs of toxicity were observed. It was concluded that the lowest lethal dose of PA21 by the oral route in rats was greater than 1,000 mg Fe/kg. In accordance with the ICH M3 (R2) guideline, separate acute toxicity studies in 2 mammalian species for pharmaceuticals are not necessary where appropriate data are available from range finding studies, and studies providing information on acute toxicity by the clinical dose route alone are sufficient.

Repeat dose toxicity

Repeated dose toxicity studies were performed in rats and dogs (4, 13 and 26 or 39 weeks). Findings in rat studies can be divided into two groups. Firstly, a number of observed changes consist of an exaggerated pharmacological effect in healthy normophosphataemic animals, which are therefore not considered relevant for ESRD patients. These changes include serum phosphorus and calcium changes, a marked decrease in phosphorus excretion, with increased calcium excretion, accompanied by changes in pH, volume and specific gravity, increases in serum 1,25-dihydroxyvitamin D levels and 25-hydroxyvitamin D, and increases in markers of bone turnover (serum osteocalcin, urinary deoxypyridinoline). Other findings not of toxicological concern are dark/abnormal faeces and dark contents of the GI tract, which are both due to the nature of the medicinal product.

Second, effects related to the high iron content in PA21 are observed. This was most evident as increases in serum and tissue iron levels, principally in the liver and spleen, and sometimes in the kidney, and increased positive Perls staining which indicates an increase in iron deposition in the liver (periportal hepatocytes and Kupffer cells), spleen (red pulp macrophages), mesenteric lymph node macrophages, epithelial cells or lamina propria macrophages in the small and large intestine. Tissue iron content was generally increased by no more than 2-fold, as measured in liver, spleen and kidney. However, from the pharmacokinetic data, it is shown that the iron content is highest in the large intestinal wall, which indicates that iron content might be more than 2-fold increased in this organ. The extent of iron deposition in the large intestinal wall, and the form in which the iron is present, is cause for concern, since it could lead to local adverse reactions. This issue, including the epithelial hyperplasia in the large intestine, is further discussed in the section on carcinogenicity. With regard to increased iron content in systemic organs, the change is relatively small, and ESRD patients are generally anaemic and require the intake of additional iron, the risk of iron overload is considered small. Moreover, there were no signs of toxicity in these organs.

As with the rat studies, findings in dogs are generally related to the pharmacological effect of PA21, or to the high iron content, although effects are less extensive than in rats. Systemically increased tissue iron content was only seen after 39 weeks of treatment, at a dose of 60 mg /kg/b.i.d. However, increased iron deposition was seen at lower doses and at earlier time points, in the form of positive Perls staining in mesenteric and mandibular lymph nodes, surface epithelium of the colon and rectum, Kupffer cells, and several residential macrophages

Absorption of fat-soluble vitamins was not significantly affected by treatment with PA21.

The 4-week bridging study conducted in rats to test the new starch form in PA21-2, is considered adequate to conclude there are no significant differences between PA21 and PA21-2. Therefore, all non-clinical studies are appropriate for the evaluation of the drug intended to be marketed.

Genotoxicity

The *in vitro* studies were conducted with the highest dose of 5000 µg/plate or mg of PA21. Throughout the dossier however, doses have been calculated as mg Fe, since this is assumed the active moiety of the complex. This results in doses of up to 1000 µg Fe/plate or mg for the *in vitro* studies.

The *in vitro* assays (bacterial mutation or Ames test, chromosome aberration test) conducted with PA21 were negative and showed no mutagenic potential of PA21 up to 1000 µg/plate. In the chromosome aberration test, the highest concentration of 1000 µg/ml PA21-2 showed a positive result with an increased percentage of aberrant cells. The subsequent study with PA21-2 was negative with regard to chromosome aberrations, but showed an increased number of polyploid cells at all concentrations tested after 15 hours of exposure (and not after 3 hours). Polyploidy was not measured or reported on in the study with PA21. As part of the comparability or bridging exercise performed to support the change in starch source prior to Phase 3 clinical trials, the 2 *in vitro* assays were repeated with PA21-2 (i.e., PA21 manufactured using the potato and corn starch mixture), also with clear-cut negative results. The *in vitro* assays were conducted in accordance with the ICH S2 (R1) guideline, including the use of high concentrations of test material that caused some precipitation in the assay incubations.

There was concern regarding potential for *in vivo* genotoxic effects of PA21 due to the high iron content of PA21 (approximately 20% w/w), the high oral test material load (40 mg Fe/kg/day), and the lack of absorption of the iron from the compound, as demonstrated by the data from the rat and dog pharmacokinetic studies. It has been postulated that excessive dietary iron could increase radical generation in the GI tract, leading to mucosal injury, genotoxicity and even neoplasia. These concerns warranted a robust *in vivo* evaluation of the genotoxic potential of PA21. Conduct of conventional *in vivo* genotoxicity tests, such as the rodent bone marrow micronucleus test, was not appropriate or possible, due to lack of absorption/exposure of the bone marrow to PA21 or its components after oral administration. Parenteral (e.g., intravenous) administration of PA21, in order to ensure exposure of the bone marrow, was not possible due to the very low solubility of the compound in any vehicle that was suitable for injection. *In vivo* assessment of genotoxic potential of PA21 therefore involved conduct of 2 'site of contact' DNA damage tests (Comet assays), that examined potential for effects at the high local concentrations that may be encountered in the GI tract. These Comet assays were conducted in rats at dosages of PA21 up to 20 times the intended human dose (800 mg Fe/kg), and revealed no evidence of DNA damage in the stomach, duodenum or colon. An appropriate positive control (ethyl methanesulfonate) was included in these Comet assays, and induced significant increases in DNA damage in all tissues examined, thereby demonstrating validity of the assays. In addition, to supplement the Comet assay data, a peripheral blood reticulocyte micronucleus test was conducted as part of the chronic (26 week) oral toxicity study in rats (VFR096/072989). No increase in the proportion of peripheral blood reticulocytes that were micronucleated was observed after 4 or 24 weeks of treatment at oral PA21 dosages up to 500 mg Fe/kg/day, whereas a positive control group of rats treated with cyclophosphamide showed a clear increase in micronuclei in the blood reticulocytes. Flow cytometric analysis of micronuclei in peripheral blood reticulocytes has been demonstrated to be as effective as conventional bone marrow analysis for *in vivo* detection of genotoxic chemicals, and has the advantage of being less labour intensive, and repeat analysis in the same animals is possible (e.g., during the course of a repeated-dose toxicity study).

The *in vivo* genotoxicity tests were negative. Overall, it would have been more informative to have performed the *in vitro* tests with the FeOOH part of the PA21 complex. It can be assumed that these inconsistent findings are due to the nature of the substance, and it is therefore not considered relevant. Overall, a valid battery of *in vitro* and *in vivo* genotoxicity assays, in accordance with the ICH S2 (R1) guideline has been conducted with PA21, including 'site of contact' assays in GI tissues. There was no evidence of genotoxic potential of PA21 (or PA21-2) in any of the assays conducted.

Carcinogenicity

No other studies were performed apart from the long-term studies.

Table 4.4.1.1: Long term carcinogenicity studies performed with PA21:

Study ID /GLP	Dose/Route	Species/No. of animals	Major non-neoplastic findings
VFR0115 GLP	250, 500, 1000 mg Fe/kg/day Oral (diet)	CD-1 mouse 60/sex/dose	<p>≥250: ↓ Hct, Hb, RBC (all M), ↑ retic, ↓ alb, a1 glob, A/G ratio (all M), ↓ total prot, beta glob (all F), enlarged mes LN (M), dilated/cystic sinuses in mes LN (M), epithelial hyperplasia in colon (M), mucosal diverticulum in caecum (M)</p> <p>≥500: ↓ plasma crea and CI (M), ↓ plasma Na (F), ↑ urine pH, enlarged mand and mes LN (F), pigmented macrophages in spleen</p> <p>=1000: ↑ MCV, ↑ WBC (F), ↓ plasma TG, Na (M), ↓ plasma Phos, ↑ plasma glu and Fe (F), ↓ urine CI (F), ↑ urine SG (M), Ca, ↓ urine Phos, ↑ iron content in kidney (M) and liver, calculus in urinary bladder (M), roughened forestomach, transitional epithelial hyperplasia in bladder (M), extramedullary haemopoiesis (M), hyperkeratosis in stomach (M), epithelial hyperplasia in colon (F), inflammation in oesophagus, epithelial hyperplasia in caecum, mucosal diverticulum in caecum (F)</p> <p><u>Perls staining:</u></p> <p>≥250: liver, mes and mandib LN, duodenum (F), rectum (F)</p> <p>≥500: colon (F), rectum (M)</p> <p>=1000: colon (M), jejunum (F), caecum</p>
VFR0104 GLP	40, 150, 500 mg Fe/kg/day Oral (diet)	CD rat 65/sex/dose	<p>≥40: ↑ retic (F), ↑ urine CI (M), ↓ urine Phos, pigmented macroph in colon</p> <p>≥150: ↑ MCH, MCHC, ↑ PT (M), ↓ ALT, AST (M), ↑ total prot (M), ↑ urine pH (F), ↑ urine CI (F), ↑ bone turnover (wk 52), ↑ kidney (F) liver and spleen Fe content, abscessation in prostate, pigmented macroph in liver, adrenals and mesen/mandib LN</p> <p>=500: ↓ BW (M), ↑ Hct, Hb, MCV (M), ↓ retic (M), ↑ neutro, eos, ↑ APTT (F), ↓ ALP (M), ↓ plasma K (M), ↑ plasma Fe, ↑ gamma glob (M), ↑ plasma urea and phos (F), ↓ vit A and 25-hydroxy vit D (M), ↑↑ 1,25-dihydroxy vit D, ↑ urine SG (M), Na, Ca, ↓ urine prot (M), ↓ urine K (F), ↑ bone turnover (wk 100/103), cysts in mesen LN, thickened caecum and colon, dark prostate, tail scabs/inflammation (M), cortical pigment in kidney, epithelial hyperplasia in duodenum (F), colon and caecum, pigmented macroph in ileum (F), duodenum, caecum, rectum, and jejunum, submucosal inflammation in colon and caecum</p> <p><u>Perls staining:</u></p> <p>≥40: liver, mesen LN, mandib LN (M), duodenum, colon</p> <p>≥150: kidney (F), mandib LN (F), jejunum (F), caecum, rectum</p> <p>=500: kidney (M), ileum, jejunum (M)</p>

Mouse study

In the mouse carcinogenicity study, treatment at all dosages was tolerated with no significant effect on survival. Termination of males after 101 weeks of treatment, and females after 104 weeks of

treatment ensured that sufficient numbers of mice were available (more than 20/sex in most study groups) at termination for a meaningful assessment of tumour incidence to be carried out. The expected pharmacodynamics effects of PA21 were observed at urinalysis investigations (markedly reduced phosphorus and increased calcium at all dosage levels). In the initial assessment by the study pathologist, terminal investigations revealed treatment-related hyperplastic and neoplastic changes in the caecum and colon. Hyperplastic changes were also seen in the non-glandular region of the stomach and in the transitional epithelium of the urinary bladder at the high dosage level of 1,000 mg Fe/kg/day. A treatment-related increase in adenocarcinoma of the colon was observed at all dosages in males, and at the highest dose level (1,000 mg Fe/kg/day) in females. When a trend test was applied across all male study groups, the incidence of colon adenocarcinoma was significant at all dosage levels. An increased incidence of epithelial hyperplasia and mucosal diverticulum/cysts/hyperplasia was seen at the dosage levels at which treatment-related adenocarcinoma were observed. In the caecum, epithelial hyperplasia and diverticulum/cysts/hyperplasia were observed in mice of both sexes at 1,000 mg Fe/kg/day, and the incidence of adenocarcinoma and/or adenoma was considered above historical background range (0% for adenoma, 0-1.7% for adenocarcinoma) for males at 500 and 1,000 mg Fe/kg/day.

On this basis, a 'no-effect' dosage for induction of neoplastic changes in the large intestine was not established in the mouse carcinogenicity study, in view of the increased incidence of colon adenocarcinoma in males at 250 mg Fe/kg/day. There was a correlation between the PA21-induced hyperplasia and the presence of tumours in both the colon and caecum, suggesting that the neoplastic changes were part of a continuum that originated from chronic irritation, and subsequent proliferative response of the GI tract at the high oral dosages of PA21 administered. There was also evidence of local irritation in the non-glandular forestomach, with increased epithelial hyperplasia and hyperkeratosis in mice at 1,000 mg Fe/kg/day, but there was no effect of treatment on neoplastic findings in the stomach. As documented in the study report, an external peer review of the caecum and colon slides was performed, which confirmed the diagnoses and incidence of hyperplastic and neoplastic lesions reported by the testing laboratory.

The role of the iron content of PA21 in the induction of the caecum and colon tumours in mice needs to be considered. Huang X, 2003 reviewed the evidence for dietary iron and iron overload having a role in cancer. With respect to colorectal cancer in humans, there seems to be conflicting evidence. Some studies have shown a positive correlation between dietary iron and body iron stores with colorectal cancer risk. Individuals with haemochromatosis, an iron storage disease, also showed increased relative risk of colorectal cancer. Other studies have shown no association between body iron levels, iron intake or serum ferritin levels and colorectal cancer risk. Studies in rodents show that dietary iron can cause oxidative stress and cell proliferation in the intestinal tissues, but in the absence of colon carcinogens, iron does not appear to induce colorectal cancer in its own right.

Therefore, a role for the iron component of PA21 in the observed caecal and colonic tumours in mice remained equivocal. However, similar tumours were not induced in the rat carcinogenicity study, and chronic treatment of dogs at high PA21 dosages (up to 400 mg Fe/kg/day) showed no evidence of irritation, hyperplasia or neoplasia in the GI tract. Furthermore, given the lack of correlation between positive Perl's staining and sites of hyperplasia or diverticula, this causal relationship is no longer likely.

The applicant has performed a review of the histopathology slides of the adenocarcinoma samples of mice treated with PA21 by an expert in rodent toxicologic pathology and experimental carcinogenesis. It is stated that most of the tissue samples previously classed as adenocarcinomas, have been misclassified and should actually be termed "diverticula". In fact after re-classification, there are 3 instances of adenocarcinoma at the mid dose, and 1 at the high dose.

The re-classification and cellular/tissue characteristics on which this is based, are described by the expert pathologist recruited by the applicant. The four reconfirmed cases of adenocarcinoma comprised of proliferating cells with the affected mucosa extending into the gut lumen. In these adenocarcinomas there was increased mitosis, crowding of cells, loss of cellular polarity, anisokaryosis, hyperbasophilia, stromal invasion and cellular atypia. In contrast, diverticula are generally characterized by prominent mucus-filled cysts, with some localized distortion of tubular contour of the large intestine. The morphological features of the lesions classed as adenocarcinoma by the study pathologist but not reconfirmed by the expert, are identical to the diagnostic features of the diverticula, with the exception that the submucosal cystic glands herniated through the outer muscular tunic of the large intestine. These lesions did not have any other features commonly ascribed to malignancies, and should therefore not be classed as such. The reasoning laid out by the expert could be followed by the assessor, and it was agreed that there are actually 4 adenocarcinomas as described above.

Regarding the relevancy of diverticula for humans, the expert states that this is likely due the high dietary burden of PA21, which is a bulky substance. Cysts develop and expand, producing mucus which displaced the crypt epithelium. With time and continued expansion together with intraluminal pressure due the continued treatment, some of the cysts penetrate the tunica muscularis. This phenomenon is unlikely to be relevant for humans, since the dose and therefore the intraluminal pressure is smaller in humans. Moreover, mice are known to be susceptible to the formation of diverticula due to irritation to the gut wall, or even spontaneously.

A formal Pathology Working Group (PWG), comprising a PWG chairperson, the study pathologist, the reviewing expert, and 3 independent expert histopathologists, was held in order to determine the definitive diagnoses and incidence of the mouse GI tract tumours. As a result of the PWG review, 2 of the adenocarcinomas previously reported in the colon were reclassified as diverticula and one as an adenoma. The adenoma as well as the single adenocarcinoma were considered unlikely to be test article-related by the PWG. The PWG concluded that the dietary administration of PA21 to CD-1 mice resulted in a dosage-related increase in mucosal epithelial hyperplasia and development of diverticula with cysts. There was no clear evidence of a tumourigenic response in male mice and no evidence of a tumourigenic response in female mice in this study. The pattern of low grade mucosal proliferation in the large intestine of male and female mice is consistent with persistent low grade epithelial damage and repair due to the physical disruption by large amounts of material in the lower intestinal tract that was not absorbed after oral administration. Considering the anatomical and physiological differences in the large intestine in humans as compared to mice, the absence of proliferative changes in the large intestine of dogs, and the paucity of similar findings in the rat carcinogenicity study, the low grade proliferative changes in the caecum and colon of mice are species specific and not relevant to human risk. Overall, the conclusions of the PWG are endorsed; there is no tumorigenic response in mice related to the test substance PA21.

Rat study

Treatment at 40, 150 and 500 mg Fe/kg/day in the rat carcinogenicity study was tolerated, with 16 and 9% reductions in weight gain at 500 mg Fe/kg/day in males and females, respectively. There was no adverse effect of treatment on survival, and termination of treatment after 103 weeks for males and 99 weeks for females ensured sufficient surviving animals were available at termination for a meaningful assessment of tumour incidence to be carried out. The expected pharmacodynamics effects of PA21 were observed at urinalysis investigations (markedly reduced phosphorus at the 150 and 500 mg Fe/kg/day dosage levels).

Terminal investigations in the rat carcinogenicity study revealed a statistically significant increase in the incidence of thyroid c-cell adenoma in males at 500 mg Fe/kg/day, the trend test across treated male groups also being positive for the incidence of this tumour.

The incidence of c-cell adenoma in males at 500 mg Fe/kg/day (21.9%) was greater than the historical background range for contemporary rat studies run at the test laboratory (range = 3.3-18.5%, n=757 control rats). The historical ranges for c-cell adenoma quoted by Charles River Laboratories for control CD rats in carcinogenicity studies are 1.4-14.8% (mean – 7.9%) in males and 2.9-16.7% (mean – 7.2%) in females. Therefore, the incidence of c-cell adenoma in all the treated male groups in the PA21 study was above the Charles River historical control range. Intergroup differences in the incidence of hyperplasia of the thyroid c-cells and hyperplasia of the parathyroid were also observed in this study. There was a slightly increased incidence/severity of c-cell hyperplasia amongst treated male groups, whilst in the parathyroid, there was a trend towards reduced hyperplasia in the high dose treatment groups. The interpretation of the trends observed for thyroid c-cell and parathyroid changes in the rat carcinogenicity study needs to take into account the observed changes in clinical pathology parameters that relate to alterations in calcium and phosphate homeostasis induced by PA21, as well as an understanding of the mechanisms involved in calcium and phosphate homeostasis in the body. As discussed previously, as a result of PA21 reducing the uptake of phosphate by the GI tract, the body will activate or up-regulate various compensatory mechanisms so as to maintain blood and tissue phosphate at physiological levels. The lack of dietary phosphate uptake in the PA21-treated animals ultimately results in mobilisation of phosphate, and associated calcium ions, from the skeleton. This is clearly apparent from the clinical pathology and bone turnover marker data from the rat toxicity studies, as well as the data collected as part of the rat carcinogenicity study. Urinary and, to some extent, serum calcium were increased at dosages of 150 and 500 mg Fe/kg/day, whilst bone markers (serum osteocalcin and urinary DPD) and serum 1,25-dihydroxyvitamin D levels were increased, clearly indicating that phosphate and calcium were being mobilised from the bone in order to maintain physiological phosphate levels. Apart from 1,25-dihydroxyvitamin D₃, serum calcium levels are closely controlled by PTH from the parathyroid gland, and calcitonin secreted by the c-cells of the thyroid. Calcitonin secretion increases in response to elevated serum calcium levels in order to maintain serum calcium levels within fairly tight limits and avoid hypercalcaemia, while the secretion of PTH is suppressed, slowing calcium release and bone resorption. Therefore, the non-neoplastic changes observed in the thyroid and parathyroid glands in the rat carcinogenicity study probably reflect the expected physiological response to phosphate depletion and consequent mobilisation of phosphate (and associated calcium ions) from the bone, namely increased 1,25-dihydroxyvitamin D₃ concentration, decreased PTH secretion and increased calcitonin secretion.

On this basis, the slightly increased incidence of c-cell adenoma in males treated at the highest dose of PA21 in the rat carcinogenicity study is considered to be pharmacological in origin, and related to the compensatory physiological responses to phosphate depletion in healthy rats. The findings are not considered to be of relevance to the target patient population, as the response to PA21 in hyperphosphataemic renal failure patients will be different than in healthy, normophosphataemic, rats. In addition, PA21 did not affect the incidence of c-cell carcinoma, while the increased incidence of adenomata in male rats was only significant at a multiple (12.5-fold) of the maximum likely human therapeutic dose, and only slightly exceeded the historical control incidence of this tumour. No effect of PA21 on c-cell tumours was observed in female rats. Proliferation of c-cells is a common spontaneous finding in rats, but not in mice, which may explain why PA21 exerted no effect on c-cells in the mouse carcinogenicity study. Rat carcinogenicity studies conducted with calcitriol (1,25-dihydroxyvitamin D₃) showed hyperplasia and adenomata in the c-cells of the thyroid, consistent with the calcaemic effect of the vitamin (leading to increased calcitonin secretion), and the changes were considered to be rat-specific. A possible direct effect of vitamin D or its metabolites on the growth of c-cells has been proposed, and rats fed a vitamin D-deficient diet show lower spontaneous incidence of c-cell tumours than control rats. These observations further support the concept that the c-cell findings in the PA21 rat carcinogenicity study are pharmacological in origin, species-specific and are unlikely to be relevant to patients given PA21 at the proposed doses.

Treatment-related increases in the incidence of epithelial hyperplasia were observed in the duodenum, caecum, colon and rectum in animals treated at 500 mg Fe/kg/day in the rat carcinogenicity study, with submucosal inflammation also being present in the caecum, colon and rectum at this dosage. However, in contrast to the mouse study, no increase in neoplastic lesions was observed in the GI tract tissues of rats.

Tumour findings in the long term rat study are limited to a small increase in C-cell adenomas in males at the highest dose of 500 mg Fe/kg/day. The applicant argues that this effect is pharmacologically related. The decrease in uptake of phosphate from the diet will lead to mobilization of phosphate and calcium from bone, to normalize the blood concentration of phosphate. Hypercalcaemia will lead to increased secretion of calcitonin from c-cells in the thyroid, which in leads to hyperplasia which could develop into neoplasia. This explanation can be followed, and relevance for ESRD patients is therefore considered unlikely.

Reproduction Toxicity

There was no effect on male or female fertility or early embryonic development from treatment with PA21. The slight increase in post-implantation losses was due to an abnormal litter with high late resorption. This was not considered treatment-related.

In the rat embryo-foetal development study, the only effects observed were a decrease in plasma phosphorous levels which is pharmacologically-related, and increased Fe levels in the liver of both dams and foetuses. Raised Fe levels in dams are not surprising, as similar findings were seen in the repeated dose studies. Increased liver Fe content in the foetuses however, raises some concern. However, there were no other signs of toxicity, and no increased Fe content in rabbit foetuses or in rat offspring in the peri- & postnatal development study.

In the rabbit embryo-foetal development study, there was an increased incidence of some skeletal variations, namely cranial fissures/extra sutures and incompletely ossified metacarpals/phalanges, at the highest dose. A decrease in foetal body weight was also seen at this dose. These adverse effects coincided with the pharmacologically-related effect of decreased plasma phosphorous levels in the pregnant females, which is most likely the cause of the foetal effects.

In the pre- and postnatal study in rats, no effects were observed in any of the parameters for development or reproduction function of the offspring of rats treated with PA21. A slight decrease in body weight in the F1 males is likely not treatment-related, as no such effect was seen in females, and this effect was only seen at later stages of development and not during the lactation period. Decreased plasma phosphorous of the F0 females is not considered adverse effects, and therefore, no adverse effects were seen in this study.

Toxicokinetic data

Only radioactivity was measured after oral administration of radiolabelled Velporo. Data from rat and dog indicate a low absorption, but distribution of radioactivity was observed to some organs (liver, spleen and the walls of the gastro-intestinal tract). Since the applicant only measured the radioactivity, it is unclear what was measured (Fe, FeO(OH) or (nano) particle). See kinetic section. The chemical structure of the radioactivity absorbed will influence the interpretation of the toxicity and kinetic studies.

Local Tolerance

Local tolerance effects are discussed in detail in the carcinogenicity section of this report. No specific local tolerance studies have been performed. Local tolerability in the GI tract was assessed as part of the repeated-dose toxicity studies in rats and dogs and in a GI tract transit time study in rats (Study

VFR085/052415).

Other toxicity studies

No other additional non-clinical safety studies have been performed on PA21, this is agreed with the CHMP.

2.1.5. Ecotoxicity/environmental risk assessment

Carbohydrates like sucrose and starches are exempted because they are unlikely to result in significant risk to the environment (EMA 2006). Therefore, only the polynuclear iron(III)-oxyhydroxide (pn-FeOOH) needs further consideration. Since Fe is an (essential) metal, the PBT assessment is not needed. The PEC in the influent of the STP is estimated at 0.024 mg/L. Against a background concentration of phosphate (P) of 8 mg/L in STP influent in the Netherlands (CBS 2007), an environmental risk assessment is deemed not necessary, given the nature of the active ingredient that binds to phosphate. It is also considered that in sewage treatment plants where chemical phosphate binding is required, iron salts are added to the influent water in an Fe/P ratio of 3:2. At 8 mg P/L iron would be added at a concentration of approximately 22 mg/L.

Therefore, the use of Velphoro is not expected to pose a risk to the environment.

2.1.6. Discussion on non-clinical aspects

Iron absorption through release of iron from the PA21 substance was a point of concern. It was shown in *in vitro* studies that up to 10% of iron can be released and absorbed, which corresponds to 300 mg Fe/day. This is far in excess of the recommended daily dose of 18 mg Fe. Although iron accumulation (2-fold) was seen in systemic organs in the non-clinical species, no toxicity was evident. During the assessment it has been shown that no more than 0.04% of the iron will be absorbed systemically by patients. As this is very low, there is no longer a concern regarding iron accumulation in patients, however the applicant will perform a post-authorisation study in patients will monitor the long term safety study longer than 1 year and the iron accumulation.

Also relevant in this respect is the form in which the Fe is absorbed. Since the radiolabel was attached to the Fe component in the substance and only radioactivity was measured, there is no information available in which form the radioactivity is present in the distribution studies, and this could be elemental Fe, Fe(O)OH, Fe(O)OH (nano)particle or even PA21. However, the iron, measured as radioactivity shows a distribution pattern essentially similar to normal iron, where most of radioactivity is present in organs of the RES, i.e. red blood cells and spleen. Moreover, radioactivity levels decline over time, indicating normal metabolism, rather than trapping and storage of particles. Further, additional *in vitro* data not be needed as the applicant provided long term *in vivo* data, which provide evidence not only of a pharmacokinetic profile similar to iron, but also of a lack of systemic toxicity as a result of chronic administration of PA21. It is therefore considered that the risk of systemic iron accumulation due to uncontrolled uptake of nanoparticles is very low. Monitoring of this potential risk was proposed by the applicant to be included in the RMP; this was agreed by the CHMP.

Further considerations by the Applicant presented explanation of performed *in vitro* DDI studies of selected medicines and their bounding classification while adding relevant statements in the SmPC concerning interactions with iron. The proposed information in the section 4.5 in the SmPC was considered acceptable by the CHMP.

There was concern regarding adenocarcinomas in the colon of mice. A re-examination of these lesions was performed by the applicant, resulting in a re-classification of a large part of the adenocarcinomas to diverticula lesions and hyperplasia. A further re-evaluation was performed by a pathology working

group (PWG) with 6 independent experts through the Applicant. In general, the re-classification by the PWG in which only a single adenocarcinoma was identified in group 3, was considered acceptable by the CHMP.

Overall, the conclusions of the PWG are endorsed by the CHMP; i.e. that there is no tumorigenic response in mice related to the test substance PA21. To further assess whether the colon and caecum hyperplasia and diverticula are test article related and/or relevant for humans, it is shown that there is no correlation between positive Perls' staining and intestinal lesions. It is also shown that Perls' staining is capable of detecting iron present as particles. Taken together, it is considered unlikely that the lesions are a result of absorbed iron and/or particles in the intestinal wall. A more likely explanation for the lesions is the bulky nature of the substance which was administered at high doses causing irritation of the intestinal wall. The relevance for humans is considered low due to the difference in anatomy between humans and mice. However, monitoring of this potential risk in humans is needed. A PASS performed by the applicant will provide relevant data to further characterise this potential risk.

Assessment of paediatric data on non-clinical aspects

No juvenile studies were conducted. Studies in juvenile "healthy" animals are unlikely to add any useful information with regard to potential extra risks for CKD patients. Omission of studies in juvenile animals is considered to be justified.

2.1.7. Conclusion on the non-clinical aspects

The non-clinical data provided support are acceptable to support the marketing authorisation for Velphoro.

2.2. Clinical aspects

2.2.1. Introduction

GCP

The applicant declared that the phase 2 and phase 3 clinical studies were conducted in accordance with the principles of the Declaration of Helsinki, including amendments in force up to and including the time the study was conducted. The applicant declared that the studies were conducted in compliance with the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), Committee for Proprietary Medicinal Products guideline (CPMP/ICH/135/95), and compliant with the EU Clinical Trial Directive (Directive 2001/20/EC) and the Code of Federal Regulations for informed consent and protection of patient rights (21 CFR, Parts 50 and 56).

In study PA-CL-05A, one study centre 701, located in Lithuania, was closed due to a GCP issue. Data from subjects enrolled at Centre 701 were included in the analyses as, following a GCP audit carried out by Vifor Pharma. A triggered GCP inspection in relation to the pivotal studies PA-CL-05A and PA-CL-05B was made. The inspection was scheduled at two investigator sites (Russia and Ukraine) and at the sponsor sites in Switzerland and in the UK. This was based on the outcome of the IR that concluded that the clinical data of Russian and Ukrainian sites are not acceptable for an assessment on the benefit/risk of Velphoro. An in-depth sensitivity analysis and reassessment of the benefit/risk of

the product, excluding all Russian and Ukrainian sites, were made by the Applicant as requested by the CHMP. The results of the analyses were reassuring and confirmed the validity of the data within the dossier for the benefit/risk discussion of the product.

Tabular overview of clinical studies

The clinical development program of Velphoro included 9 completed clinical studies which are relevant within the current application (Table 1). Long term safety data up to 28 weeks (PA-CL05B) were also submitted in support of the MAA; this study will provide relevant data on long-term safety over at least 1 year of follow-up. Two short-term clinical studies were performed in Japan (one phase 1 PK study for 7 days (n=30) and one phase 2 dose finding study for 6 weeks (n=146)) of which only a study synopsis and tables were included as supportive data. These studies were only briefly searched for additional safety events, and shortly mentioned where relevant.

Within the 9 clinical studies, a total of 1,112 healthy volunteers and patients received at least 1 dose of Velphoro. Of those, a total of 707 patients received up to 27 weeks of study medication in the single Phase 3 study.

Note on denotation:

- In the clinical studies, the strength of the tablets was expressed on the basis of the approximate total mass of the drug substance in the tablet – either as a 1.25 g/tablet, or as a 2.50 g/tablet. Within the report, the dose is expressed based on this total mass of drug substance. However, the fixed and defined value was always the iron content, and as it is the iron that binds phosphate, the iron content in the tablet is quantitatively assayed and controlled. Therefore, within the SmPC the iron content is mentioned which is more pharmacologically correct and is consistent with the dose presentation of the phosphate binder lanthanum carbonate.

Tablets used in various clinical studies, total mass and iron content

Study ID	Dose PA21 based on tablet strength (range investigated)	Dose PA21 based on iron content (range investigated)
Phase 1 VIT-CI-01/02	1.25 g tablet	250 mg iron per tablet (750 – 2500 iron per day)
Phase 1 Q-24120	⁵⁹ Fe-labeled powder	(2000 mg iron per day)
Phase 1 DDI studies	2.5 g tablet	500 mg iron per tablet (1000 – 3000 mg iron per day)
Phase 2 study PA-CL-03A	1.25 g tablet (1.25 g to 125 g PA21 per day)	250 mg iron per tablet (250 mg to 2,500 mg iron per day)
Phase 3 study PA-CL-05	2.5 g tablet (5 g to 15 g PA21 per day)	500 mg iron per tablet (1,000 mg to 3,000 mg iron per day)
	1.25 g tablet	250 mg iron per tablet (only withdrawal phase)

• **Table 1: Overview of all clinical studies.**

Study ID	Region	Study description	Dose range	No. subjects Age, gender	Healthy subjects or diagnosis in patients	Duration	Primary endpoint
Completed studies							
Phase 1							
VIT-CI-01/02	EU	Single-centre, randomised, double-blind, ascending, single-day and multiple-dose study.	PA21: 3.75 – 12.5 g/day	57 age: 18 – 60 years (32 male, 25 female)	healthy subjects	8 days	Evaluate the safety and tolerability of single-day and multiple ascending doses.
PA-DDI-001	US	Single-centre, randomised, open-label, 3-period crossover drug-drug interaction study.	PA21: 5.0 15.0 g/day	41 age: 20- 50 years (26 male, 15 female)	healthy subjects	3 treatment periods with 2 treatment days	losartan pharmacokinetics
PA-DDI-002	US	Single-centre, randomised, open-label, 3-period crossover drug-drug interaction study.	PA21: 5.0 15.0 g/day	41 age: 22 – 50 years (28 male, 13 female)	healthy subjects	3 treatment periods with 2 treatment days	furosemide pharmacokinetics
PA-DDI-003	US	Single-centre, randomised, open-label, 3-period crossover drug-drug interaction study.	PA21: 5.0 15.0 g/day	43 age: 20 – 49 years (22 male, 21 female)	healthy subjects	3 treatment periods with 2 treatment days	omeprazole pharmacokinetics
PA-DDI-004	US	Single-centre, randomised, open-label, 3-period crossover drug-drug interaction study.	PA21: 5.0 15.0 g/day	42 age: 20 -49 years (21 male, 21 female)	healthy subjects	3 treatment periods with 2 treatment days	digoxin pharmacokinetics
PA-DDI-005	US	Single-centre, randomised, open-label, 3-period crossover drug-drug interaction study.	PA21: 5.0 15.0 g/day	43 age: 20 – 50 years (26 male, 17 female)	healthy subjects	3 treatment periods with 2 treatment days	warfarin pharmacokinetics
Q-24120	EU	ADME, open-label, repeat single-dose study.	PA21: 10 g/day	24 (13 males and 11 females)	subjects with CKD (n=16) and healthy volunteers (n=8) with low iron stores.	7 days	Iron absorption as ⁵⁹ Fe labelled iron
Phase 2							
PA-CL-03A	US EU	Open-label, sevelamer controlled dose finding study to evaluate effect of PA21 on lowering of phosphate serum levels and tolerability in patients with CKD on haemodialysis	PA21, 5 arms: 1.25-12.5 g/day Sev. arm: 4.8 g/day Orally	PA21: 128 (82 male, 46 female) Mean age: 60.3 yrs Sev.: 26 (15 male, 11 female) Mean age: 61.1 yrs	Patients with CKD on maintenance haemodialysis is with HP (serum P>1.78 mmol/L)	6 weeks	Change in serum P from baseline
Phase 3							
PA-CL-05A	US EU ROW	Two stage open-label, confirmatory study to assess efficacy of PA21 on lowering of phosphate serum levels and safety in patients with CKD on dialysis. Stage 1: Sevelamer controlled study	Stage 1: PA21 start dose 5.0 g/day Sevelamer 4.8 g/day start dose Orally Stage 2: Low dose PA21	Stage 1: PA21: 707 (394 male, 313 female) Mean age: 56.3 yrs Sev.: 348 (219 male, 129 female) Mean age: 55.8	Stage 1: Patients with CKD on maintenance haemodialysis is or peritoneal dialysis with HP (serum P>1.94 mmol/L)	Stage 1: 24 weeks Stage 2:	Stage 1: Change in serum P from baseline, Non-inferiority vs Sev. Stage 2: Change in

		Stage 2: Low-dose PA21 controlled withdrawal phase versus maintenance PA21 dose	(1.25 g/day) Maintenance dose PA21	yrs Stage 2: Overall 94 (45 male, 49 female) Mean age: 58.2 yrs	Stage 2: Patients on haemodialysis with controlled serum P-levels (<1.78 mmol/L)	3 weeks	serum P from week 27 to week 24, superiority over LD (primary Analysis)
PA-CL-05B*		On-going extension study of PA-CL-05A to assess long-term safety and efficacy	Maintenance dose PA21 or sevelamer	PA21: 387 (219 male, 168 female) Mean age: 55.3 yrs Sev: 261 (162 male, 99 female) Mean age: 55.6 yrs	Patients with CKD maintenance haemodialysis or peritoneal dialyses completing PA-CL-05A (except stage 2 LD)	28 weeks	Long-term safety and tolerability of PA21

CKD=Chronic kidney disease; ROW=rest of world (Russia, Croatia, Serbia, Ukraine, South Africa);

HP=hyperphosphataemia; Sev.=sevelamer

* 28 week follow-up data were submitted during the evaluation of the MAA.

2.2.2. Pharmacokinetics

To support the pharmacokinetics of Velphoro, the following studies have been submitted:

Study Q-24120: An open label safety study with ⁵⁹Fe labelled PA21 in patients with chronic kidney disease and healthy volunteers.

PA-DDI-001: A single-centre, open-label, 3-period study of the pharmacokinetic effect of PA21 on losartan potassium in healthy male and female adults.

PA-DDI-002: A single-centre, open-label, 3-period study of the pharmacokinetic effect of PA21 on furosemide in healthy male and female adults.

PA-DDI-003: A single-centre, open-label, 3-period study of the pharmacokinetic effect of PA21 on omeprazole in healthy male and female adults.

PA-DDI-004: A single-centre, open-label, 3-period study of the pharmacokinetic effect of PA21 on digoxin in healthy male and female adults.

PA-DDI-005: A single-centre, open-label, 3-period study of the pharmacokinetic effect of PA21 on warfarin in healthy male and female adults.

Furthermore, adsorptions of several medicinal products to Velphoro have been studied *in vitro* in several studies. Pharmacokinetic variables, e.g. AUC_{0-t}, AUC_{inf}, C_{max}, t_{1/2}, if applicable, were calculated according to standard procedures. In case of comparability, standard 90% confidence intervals were applied.

Absorption

- Bioavailability**

The absorption of iron after administration of PA21 has been evaluated using ⁵⁹FE-PA21 in study Q-24120. In this study two groups were included, i.e. healthy volunteers and patients. The latter were patients with chronic kidney disease, i.e. 8 pre-dialysis patients (stage 3 or 4) with glomerular filtration rate <60 ml/min (as determined by the Cockcroft-Gault formula) and 8 haemodialysis patients (serum

ferritin levels 200 – 800 µg/l and/or having transferrin saturation in the range of 20 – 50%). Healthy volunteers were required to have serum ferritin <100 µg/l with no underlying disease.

Before drug administration, for patients on other phosphate-binding agents, a washout period of 7 days was applied.

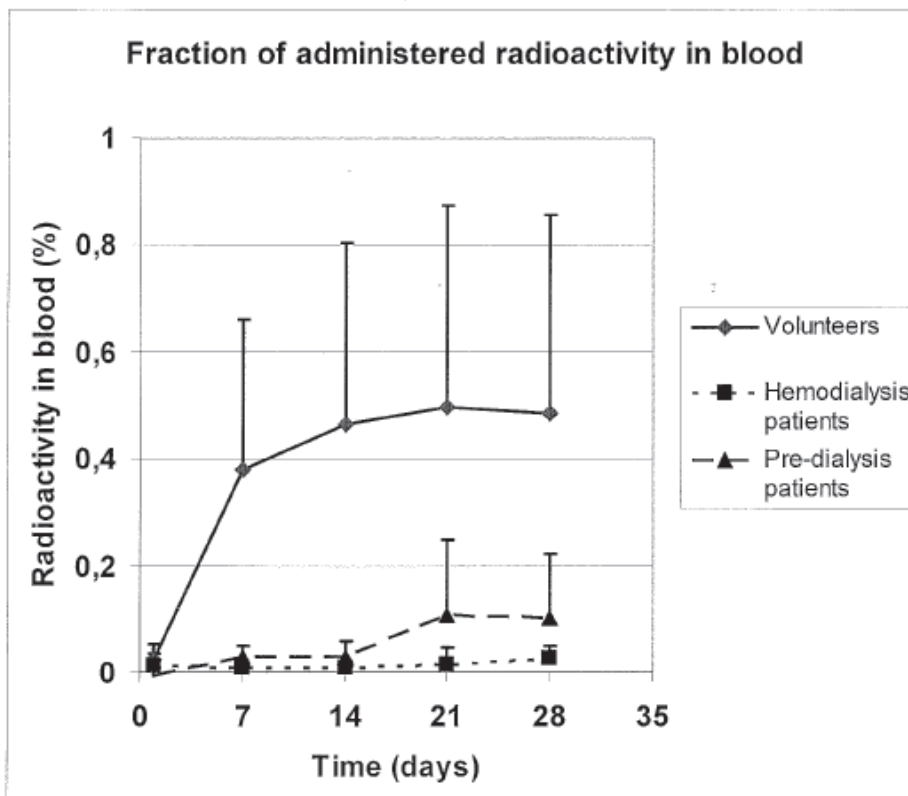
PA21 as suspension, was administered during 7 days at a dose of 10 g daily with meals (breakfast, lunch, diner) in 3 divided doses, i.e. 2.5 g, 5g and 2.5 g, corresponding to 500 mg, 1000 mg and 500 mg iron (total dose 2000 mg) per day. Healthy subject received at day 1 PA21 as ⁵⁹Fe labelled iron and the patients at day 7. One patient on haemodialysis did not take one dose at day 2.

Blood samples were taken at day 1, 7, 14, 21 and 28 after administration of the labelled dose. ⁵⁹Fe activity in plasma and blood was measured by a gamma counter.

The total amount of circulating ⁵⁹Fe was calculated based upon estimated blood volume, radioactivity in blood and amount of radioactivity administered.

The radioactivity in blood versus time is shown in figure PK 2.

Figure PK 2. Circulating radioactivity in blood in healthy volunteers, patients on haemodialysis and pre-dialysis patients as a function of time after administration (mean of 8 subjects per group; error bar=s.d.).



In healthy volunteers, after administration of ⁵⁹Fe labelled PA21, recovery of radioactivity in blood was low and ranged from 0.16 – 1.25% of the administered dose. After about 2 weeks, drug recovery did not increase. In patients absorption was much lower and ranged from 0 – 0.44% of the administered dose.

The difference in exposure may be explained by possible saturation of uptake at steady state but also due to the fact that iron absorption is related to iron stores and ferrin concentration, i.e. high ferrin

concentrations related to low absorption of iron, and the renal patients have higher ferrin concentrations.

Low levels of radioactivity in plasma were observed indicative for absorption of iron in erythrocytes. The multiple dose study in patients will reflect the clinical situation for patients. The administered dose is in line with the recommendations. In addition, possible non-linearity in uptake during multiple-dose is covered.

Based upon the maximal observed uptake in renally impaired patients, i.e. 0.44% of the administered dose, and taken into account that the maximum recommended dose is 3,000 mg (6 tablets) per day, a daily uptake of 13.2 mg can be expected. The applicant used a 0.1% uptake value translating into about 2 mg iron/day (using a 2000 mg dose). The applicant indicated that this is lower than the normal recommended intake of 5 mg/day. However, recommended maximal daily intake in females may be as high as 18 mg/day (see also assessment report module 4). Still, from these data it cannot be ruled out that due to treatment with PA21 recommended maximal intake of iron will be higher than normally recommended. The patients will be monitored for high iron accumulation.

Radio-activity was measured to evaluate the systemic absorption of iron. However, after 7 days and even after 14 days radioactivity levels increased in blood. As normally the transit time of a drug through the gastro-intestinal tract is less than 2 days, it is unclear how levels after 14 days can increase. This should be explained. Furthermore, excretion data (mass balance) is lacking. Systemic absorption was estimated based upon blood volume and the concentration of radioactivity in blood, however in this case it should be assumed that iron is not distributed. As this is not the case, absorption of iron may be higher than estimated in this study. The Applicant was asked to submit reports on main characteristics of radioanalytical methods employed in pharmacokinetic studies (both nonclinical and clinical) according to current guidelines, as well as validation reports of analytical methods of losartan, furosemide, omeprazole, digoxin and warfarin. Details of the sensitivity of gamma measurements of blood samples and estimation of administered radioactivity and effective dose in Study Q-24120 were provided. However, no requested validation reports of radioanalytical methods were included into Applicant's response.

As only the radioactivity of the labelled iron is measured, it is considered that this method cannot elucidate whether iron is absorbed as nanoparticles or not.

- **Comparison of trial formulations with finished product**

Two formulations were used during the development. The early formulation used in study Q-2120 and VIT-CI-01/02 contained PA21-1 as drug substance.

For the formulation used in the drug-drug interaction studies and the pivotal study PA-CL-05A, the manufacturing process of the drug substance was amended drug substance PA21-2).

Quality data indicated comparable iron release, structure, oxidative state, hydration state, particle size and stability for the formulations. A limited programme of non-clinical "bridging" studies showed that PA21-2 behaved in a similar manner to PA21-1 in terms of toxicity profile, genotoxic potential, and iron uptake/absorption.

Considering that iron absorption is very low and taking into account that the PA21 acts locally in the gastro-intestinal tract, and taken into account the submitted quality data (see module 3) and non-clinical data (see module 4) no difference in clinical activity is expected between the different formulations. In addition, in the pivotal phase III study the commercial tablet formulation PA21-2 has been used.

- **Influence of food**

In vitro data suggest that iron release predominantly occurs at low pH (similar to the gastric fasting state). Under fed conditions, absorption of iron is considered very low. At low pH there may be a possible higher iron release and thus absorption, however Velphoro should be administered with food this is reflected in section 4.2 of the SmPC. Furthermore, patients will be monitored for (too) high iron accumulation.

Distribution

Distribution studies in humans were not performed. Absorbed iron is expected to follow the normal iron distribution pathways.

Biotransformation

The therapeutic 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.

Elimination

- **Metabolism**

Polynuclear iron(III)-oxyhydroxide

Iron(III)-oxyhydroxides is microbiologically not stable as an aqueous suspension and is dehydrated when dried or stored, which results in a decrease of the phosphate binding capacity. Therefore, the iron(III)-oxyhydroxide alone cannot be isolated and stored as an active pharmaceutical ingredient (API). Sucrose is added to the iron compound to stabilize the iron core and thus maintain the high phosphate adsorption capacity. Starches are added as processing aids to allow for isolation, characterisation and stability testing of the drug substance. PA21 is partly soluble in water, release sucrose, starch and iron(III)-oxyhydroxide. Polynuclear iron(III)-oxyhydroxide is practically insoluble and therefore iron cannot be absorbed. The extent of iron release from an iron(III)-oxyhydroxide suspension was compared to that from Velphoro. Iron release from Velphoro *in vitro* was significantly lower than from iron(III)-oxyhydroxide under acidic conditions (pH 3.0); 1.2% versus 4.6% iron release.

Sucrose

Upon oral administration, sucrose is digested by sucrase or isomaltase glycoside hydrolase to glucose and fructose in the microvilli of the duodenum. Incubation of Velphoro with sucrase resulted in complete degradation of sucrose into glucose and fructose.

Starch

Upon oral administration, the starches are digested to maltose and glucose by amylase, which is present in the digestive juices (e.g. mouth). The degradation of starch was only partial, but did not differ between Velphoro-2 and starch alone.

Velphoro

Velphoro and various mixtures of iron(III)-oxyhydroxide, starch and/or sucrose were exposed to porcine pancreatin and rat intestinal mucosa, and analysed for glucose release (see assessment report module 3). The percentage of formed glucose from Velphoro concurred with the values expected from its individual components. In summary, the data indicate that Velphoro behaves like a mixture of its components and that the carbohydrates stabilise the iron(III)-oxyhydroxide core. As indicated before, iron is almost not absorbed from Velphoro. The major part is considered to be eliminated via faeces.

- **Inter-conversion**

Not applicable.

- **Pharmacokinetics of metabolites**

Not applicable.

- **Excretion**

Not studied Iron is almost not absorbed from Velphoro. The major part is considered to be eliminated via faeces.

Dose proportionality and time dependencies

This was agreed by the CHMP to not be applicable.

Intra-and inter-individual variability

Absorption is of iron minimal after multiple doses to patients. Absorption ranged from 0 – 0.4% (median 0.02%) in dialysis patients and from 0.008 – 0.44% (median 0.06%) in pre-dialysis patients.

Special populations

- **Impaired renal function**

Velphoro is indicated for the control of serum phosphorus levels in patients with end-stage renal disease (ESRD). Data for other renal subpopulations are not expected.

- **Impaired hepatic function**

Considering that iron is almost not absorbed from Velphoro, an impaired liver function is considered not to affect the pharmacokinetics and systemic exposure of iron. Furthermore, patients will be monitored for (too) high iron accumulation.

- **Gender, elderly/age, weight and race**

Iron is almost not absorbed from Velphoro. Gender, elderly/age, weight and race are considered co-variables not to affect the pharmacokinetics and systemic exposure of iron. Furthermore, patients will be monitored for (too) high iron accumulation.

The Applicant provided Table 41 which shows the age distribution of subjects receiving PA21 in the PA21 clinical programme.

- **Table 41 Age Distribution of Subjects Treated with PA21 in the PA21 Clinical Programme**

Trials Pooled	Age <65		Age 65-74		Age 75-84		Age ≥85	
	PA21	Overall	PA21	Overall	PA21	Overall	PA21	Overall
PK trials ⁽¹⁾	271/277		6/277	6/291	0	0	0	0
	285/291							
Controlled trials ⁽²⁾	587/835	845/1,209	175/835	252/1,209	68/835	104/1,209	5/835	8/1,209
Non-controlled trials	0	0	0	0	0	0	0	0

1 Includes studies VIT-CI-01/02, Q-24120, PA-DDI-001, PA-DDI-002, PA-DDI-003, PA-DDI-004, and PA-DDI-005.

2 Includes studies PA-CL-03A, PA-CL-05A, PA-CL-05B.

Note: PK = Pharmacokinetics.

Source: Module 5, Section 5.3.5.3, Table E.54.1.

The majority of the subjects (285/291) in the PK trials were <65 years. The Applicant marked that age distribution in the controlled trials was broadly representative of the dialysis patient population, with the majority (845/1,209) being aged <65 years and few (8/1,209) being ≥85 years. There was no upper age limit in the protocols for these studies, thus ensuring that the age distribution is appropriate to the population. The age group > 85 years is least represented (5/835) in controlled trials, as well as age group 75-84 (68/835).

- **Children**

The safety and efficacy of Velphoro in children below the age of 18 years has not yet been established (as described in the product information).

Pharmacokinetic interaction studies

The various *in vitro* drug-drug interaction studies, showed no significant adsorption/binding of ciprofloxacin, clopidogrel, enalapril, digoxin, metoprolol, nifedipine, omeprazole, simvastatin, warfarin, hydrochlorothiazide, metformin or quinidine to PA21. In addition, no adsorption was found for cinacalcet and glipizide, though results were inconclusive at some pH values. Moderate adsorption to PA21 was observed for pioglitazone. A strong binding was observed for furosemide, losartan, atorvastatin, doxycycline, alendronate, cephalexin, levothyroxine, doxercalciferol and paricalcitol. Adding phosphate to the solution reduced the interaction between PA21 and levothyroxine, paricalcitol and atorvastatin, possibly due to competing with binding sites.

The lack of a clinically relevant interaction was confirmed *in vivo* for digoxin, omeprazole and warfarin. Although an interaction *in vitro* was observed for furosemide and losartan, *in vivo* no interaction is observed.

2.2.3. Pharmacodynamics

Mechanism of action

The active substance in PA21 is a mixture of iron(III)-oxyhydroxide (pn-FeOOH), sucrose and starches. 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. This results in phosphate excretion with the faeces, thereby preventing phosphate absorption. In more detail, it appears that PA21 binds phosphate by two separate mechanisms. The first mechanism is simple adsorption of phosphate to the iron complex. The second mechanism is the formation of FePO₄. Which mechanism occurs depends on the pH.

Primary and Secondary pharmacology

Primary pharmacology was studied *in vitro* and *in vivo* in animal studies. In summary, *in vitro* studies demonstrated efficient phosphate binding by PA21 under simulated GI tract conditions (pH range of 1.2 to 8.5). The phosphate binding capacity appeared comparable to currently available phosphate binders. *In vivo* studies in a rat model of chronic renal failure showed that PA21 reduced urinary phosphorus excretion, increased faecal phosphorus excretion, and reduced arterial calcification. The effects on serum phosphorus levels were less obvious in this model.

2.2.4. Discussion on clinical pharmacology

PA21 is non-calcium, iron based phosphate binder, with a different mechanism of action compared to that of sevelamer. It includes both adsorption of phosphate to the iron complex and formation of FePO₄, dependent on pH. Phosphate binding by PA21 was demonstrated under simulated GI tract conditions (pH range of 1.2 to 8.5) and appeared comparable to currently available phosphate binders. Absorption from the gastrointestinal tract appears low. Preclinical absorption, distribution and excretion study results were reassuring and analysis showed absorption of radioactivity was low, highest radioactivity levels in blood were 1.4% of the administered dose this did not indicate significant iron (-particle) absorption.

No beneficial secondary pharmacological effects were demonstrated. *In vivo*, drug-drug interaction studies with losartan, furosemide, digoxin, warfarin and omeprazole, co-administered with PA21 showed no effect on absorption of losartan, furosemide, digoxin, warfarin and omeprazole. The interaction potential appears low based on *in vitro* and *in vivo* studies, although it is not clear to which extent interactions can be ruled out *in vivo*. Safety pharmacology studies did not show any significant effects on respiratory, central nervous system, or gastrointestinal motility parameters. Gastrointestinal effects are expected based on the local mechanism of action. The safety profile is further discussed in the safety section.

Although age group of ≥ 85 is clearly underrepresented and PK studies in age group >75 years are absent, these facts could be acceptable for the premarketing assessment but should be elaborated further post marketing through the PASS Long-term usage beyond 1 year.

The interaction potential seems low, but possible interactions cannot be completely ruled out, and this may be especially of concern with narrow therapeutic drugs. In SmPC section 4.5 this is covered. In addition, as a precaution, it is stated that Velphoro is almost not absorbed from the gastrointestinal tract. When administering any medicinal product that is known to interact with iron, the medicinal product should be administered at least one hour before or two hours after Velphoro.

2.2.5. Conclusions on clinical pharmacology

PA21 is non-calcium, iron based phosphate binder, with a different mechanism of action compared to that of sevelamer. It includes both adsorption of phosphate to the iron complex and formation of FePO₄, dependent on pH. Velphoro should be taken in conjunction with meals this is reflected in the section 4.2 of the SmPC. The interaction potential seems low, but it is not clear to which extent interactions can be ruled out in vivo. As a precaution, it is stated that Velphoro is not absorbed from the gastrointestinal tract. When administering any medicinal product that is known to interact with iron, the medicinal product should be administered at least one hour before or two hours after Velphoro. The interaction potential is discussed in SmPC section 4.5. In addition, it is stated that Velphoro is almost not absorbed from the gastrointestinal tract. When administering any medicinal product that is known to interact with iron, the medicinal product should be administered at least one hour before or two hours after Velphoro.

Clinical efficacy

2.2.6. Dose response study

Study PA-CL-03: An Open-label, Randomised, Active-controlled Multicentre Phase 2 Dose Finding Study to Evaluate the Ability of PA21 to Lower Serum Phosphate Levels and the Tolerability in Patients with Chronic Kidney Disease on Maintenance Haemodialysis.

Study participants: Adult (≥ 18 years) patients with ESRD on haemodialysis treatment 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 were eligible for this study after having provided signed and dated informed consent. Patients had to be on a stable dose of Vitamin D, Vitamin D metabolites or calcimimetics for at least 1 month. Patients had to be on restricted phosphate diet. If receiving therapy with erythropoietin, patients had to be on a stable dose ($\pm 25\%$ dose adjustments compared to dose at screening) for at least 1 month before screening and had to remain on a stable dose ($\pm 25\%$ dose adjustments, compared to dose at baseline) throughout the study.

Only patients with serum phosphorus levels > 1.78 mmol/L at the end of the washout phase (Week -1, second dialysis session (D2) or third dialysis session (D3) of the calendar week) were eligible for randomization.

Major exclusion criteria included uncontrolled hyperphosphataemia (> 2.5 mmol/L), hypercalcaemia (serum calcium > 2.5 mmol/L) or serum calcium below 1.9 mmol/L (7.6 mg/dL), severe hyperparathyroidism (intact parathyroid hormone (iPTH) levels > 600 ng/L) at screening, iron deficiency anaemia defined as haemoglobin < 10 g/dL and (ferritin < 100 ng/mL or transferrin saturation (TSAT) $< 20\%$) at screening, history of haemochromatosis, or history of other iron storage disorders. Further exclusion criteria were significant gastrointestinal disorders including motility

disorders, history of major gastrointestinal surgery in the past 5 years, active hepatitis B/C or other significant hepatic disorders (alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the upper limit of the normal range at screening), known seropositivity to human immunodeficiency virus, active infection or treatment with antibiotics at screening, serious medical conditions or planned major surgery that would interfere with the study, pregnancy, lactation or lack of effective contraception.

Use of antacids containing aluminium or magnesium within 1 month before screening, and use of oral iron preparations within 1 month before screening were not allowed as these could interfere with the assessment of phosphorus lowering efficacy. Subjects taking medication for treatment of moderate to severe arrhythmic and seizure disorders according to the Investigator's judgment were excluded, in line with the warnings and precautions section within the SmPC of Renagel and Renvela. Use of sevelamer (as Renagel or Renvela) within 3 months before screening and treatment with lanthanum carbonate (Fosrenol) at any time during the subject's life was not allowed.

Inclusion criteria were representative for the target population in need of phosphate binder treatment and in line with current KDOQI treatment guidelines. Patients with significant GI and liver co-morbidity or iron storage disorders were **excluded** from the trial. Further, patients using sevelamer and lanthanum carbonate and patients on PD were excluded from the study. Therefore, some selection of patients occurred of which the impact on the results is not known. However, these restrictions are assumed not to have a major impact on the results and can be considered acceptable for the dose-finding study. These patients were included in the pivotal phase 3 study. Iron infusion which is commonly seen within the target population, was also not allowed within this short-term phase 2 study. However, this was allowed within the phase 3 study, reflecting daily clinical practice.

Treatments: The study consisted of a screening phase (up to 1 week), a phosphate binder washout phase of 2 weeks, a 6-week treatment phase, and a 2-week run-out phase (Figure 1). The study visits took place on the day of the subject's dialysis sessions. During the treatment phase and the run-out phase, study visits took place on the day of the first dialysis session of the week.

Subjects eligible for treatment were randomized at Week 1, first dialysis session (D1) via an interactive voice response system (IVRS). Eligible subjects were randomized to either treatment with PA21 chewable tablets containing 1.25 g PA21 and 250 mg iron (five dosing groups) or sevelamer (HCl, Renagel) 800 mg tablets.

Subjects were withdrawn if their serum phosphorus levels exceeded the upper safety limit of 2.75 mmol/L at any time as of 2 weeks after the start of treatment, or decreased below the lower safety limit of 1.13 mmol/L at any time after the start of treatment. Subjects were also withdrawn if their serum calcium levels exceeded the upper safety limit of 2.5 mmol/L at any time after the washout period. The run-out phase was stopped prematurely if a subject's serum phosphorus level exceeded the upper safety limit of 2.75 mmol/L.

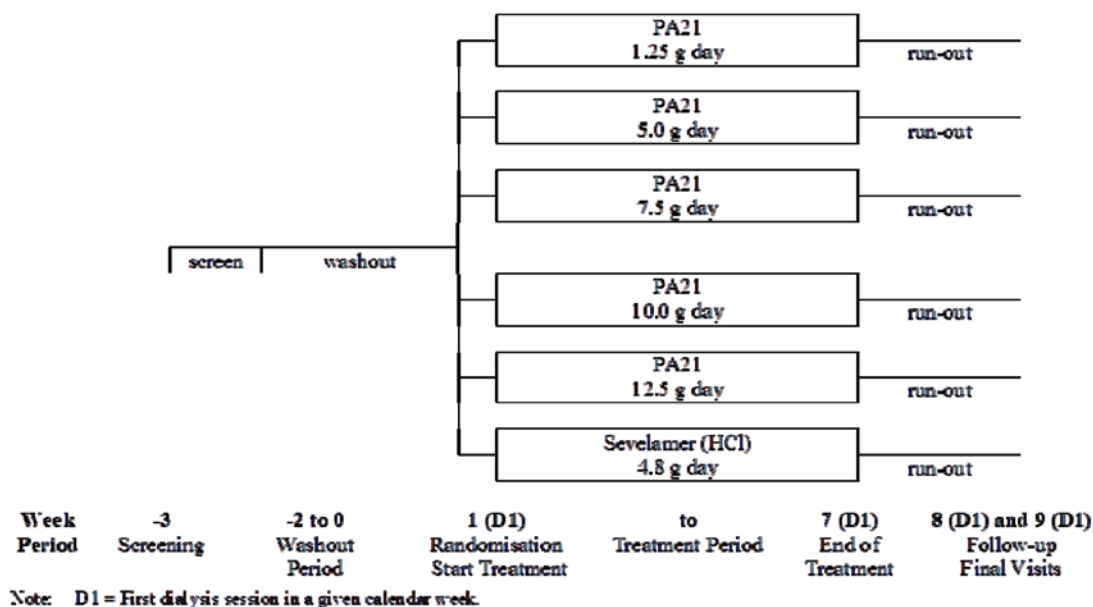


Figure 1: Schematic presentation of study design PA-CL-03A

Dosing: Patients were randomized to one of the 6 dosing groups as described in Figure 1. Dosing frequency was three times daily, except for the lowest dose of PA21 which was administered once daily. No dose adjustments were allowed.

The dose range of PA21 investigated covers a 2.5-fold range as the lowest dose is assumed to be ineffective. Sevelamer is widely used as phosphate binder and inclusion of this arm allows an exploratory comparison to a standard treatment. The dose of sevelamer is acceptable, although patients with baseline levels between 1.76-2.42 mmol/L are recommended a lower starting dose of 2.4 g/day. Safety limits were set for hypophosphatemia and the treatment period was relatively short.

The washout and treatment period are considered sufficient to observe changes in serum phosphorus levels.

Primary objective: To investigate the ability of different doses of PA21 to lower serum phosphorus levels in patients with chronic kidney disease (CKD) on maintenance haemodialysis.

Secondary objectives: To assess the efficacy/safety profiles of the different doses of PA21.

Primary efficacy endpoint:

The change from baseline in serum phosphorus levels at the end of treatment was defined as the primary efficacy endpoint. This endpoint was calculated by the change from baseline (week 1, first visit) to last value on treatment (week 7 first visit, or last-observation-carried-forward (LOCF) for missing values).

Secondary efficacy endpoints:

Secondary efficacy endpoints related to serum phosphorus level included:

- Change from baseline in serum phosphorus levels at each time point
- Proportion of subjects achieving controlled serum phosphorus levels (i.e., ≥ 1.13 to ≤ 1.78 mmol/L (≥ 3.5 to ≤ 5.5 mg/dL)) at each time point
- Time to reach the first controlled serum phosphorus level

Other secondary endpoints were:

- Serum total calcium levels; at each time point and change from baseline
- Serum calcium x phosphorus product; at each time point and change from baseline
- Serum iPTH levels; at each time point and change from baseline

Safety endpoints:

These included incidence of adverse events (AEs) and serious adverse events (SAEs), clinically relevant changes in vital signs and clinically relevant changes in laboratory evaluations. Adverse events that began or that worsened in severity after at least 1 dose of study treatment had been administered were considered treatment-emergent adverse events (TEAE).

The primary and secondary endpoints are the commonly used pharmacodynamic endpoints for the intended treatment.

Sample size:

A sample size of 19 subjects per group (total of 114 subjects), 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 0.65 mmol/L change in serum phosphorus, assuming an SD of 0.81 mmol/L using a 2-sided single sample t-test and testing treatment doses from the highest to lowest in an hierarchical manner. It was planned to randomize up to 132 subjects, based on the assumption that approximately 14% of subjects would drop out after randomization without having at least 1 post-baseline efficacy measurement.

Blinding: An open-label design was used because of challenges in maintaining blinding of study treatment. These were due to 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) and the expected discoloration of faeces with PA21 because of its iron content. The open-label design is not considered to bias the primary efficacy endpoint of serum phosphorus, because this is an objective laboratory measurement which was analyzed by a central laboratory.

Statistical methods:

Populations analysed:

The safety set (SS) consisted of all randomized subjects who received at least 1 dose of study treatment.

The Full analysis set (FAS) consisted of all randomized subjects who received at least 1 dose of study treatment and had at least 1 post-baseline efficacy evaluation (while on treatment).

The Per-protocol set (PPS) consisted of all FAS subjects, who were compliant with the study protocol, i.e., subjects without any major protocol deviations.

Primary analysis:

The **efficacy** analyses were performed on the FAS and on the PPS.

The absolute change from baseline in serum phosphorus levels at the end of treatment (i.e., value at Week 7, or last observation carried forward (LOCF) for missing values) was analysed within each of the 5 PA21 dose groups using a single sample paired t-test. To preserve the overall alpha, a hierarchical testing procedure was applied, testing from the highest PA21 dose (12.5 g/day) to the lowest dose (1.25 g/day). The same analysis was performed for the sevelamer group.

The **safety** analyses were performed on the SS. Summaries of safety data were provided per treatment group and also for the pooled PA21 group. Descriptive statistics were used to summarize treatment-emergent AEs (TEAEs), findings of physical examinations, vital signs and laboratory measurements (including shift tables with respect to normal ranges).

Secondary analyses:

The absolute change from baseline in serum phosphorus levels at the end of treatment (i.e., value at Week 7, D1, or LOCF for missing values) was also compared between the 5 PA21 dose groups by means of an analysis of covariance (ANCOVA) model with dose group as fixed effect and baseline serum phosphorus levels as covariates. Pair-wise comparisons of the 4 higher-dose groups versus the lowest dose group were performed by means of the Dunnett procedure using the lowest dose group as the control group. 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).

The proportion of subjects with controlled serum phosphorus levels (i.e., ≥ 1.13 to ≤ 1.78 mmol/L)

In the 5 PA21 groups was analyzed over time from baseline to week 9, for an increasing dose effect a 2-sided Cochran-Armitage test at a 5% significance level was used. Kaplan-Meier estimates were provided for the time to reach the first controlled serum phosphorus level. Log-rank tests were performed to pair-wise compare the different PA21 dose levels with the lowest dose level.

Changes in the planned analysis:

After finalisation of the SAP, dated 22 July 2009, the planned analyses were changed.

After database lock: During the mapping of the raw and derived legacy datasets into Clinical Data

Interchange Standards Consortium compliant datasets in 2012, inconsistencies between the original datasets and the final CSR, problems related to the programming and algorithm derivations due to lack of clarity, lack of documentation and insufficiently validated deliverables were discovered. These issues were considered to potentially impact the results of the final analysis that was described in the final PA-CL-03A CSR (15 June 2010). A list of the issues, and then the corrections to the analyses that have been affected by these issues are described below. The database was not re-opened and no data were altered during this re-analysis.

Issues identified:

- Visit windows: No visit windows were pre-defined for any of the efficacy parameters, which led to problems in the identification of subjects in the FAS. These were defined and applied for the re-analyses.
- Definition of the FAS was clarified.
- Compliance calculation: It was assumed that when the returned drug information was missing, all tablets were considered to have been taken which may overestimate compliance. A more conservative approach was applied for compliance calculation.
- Baseline clarification: For 1 subject the baseline was not correctly derived for the laboratory parameters, including the primary efficacy endpoint (serum phosphorus), as the value used for baseline was obtained after the treatment had started.
- Time from CKD: The calculation of the time from the start of CKD was not computed in accordance with the SAP when partial dates were filled.
- Concomitant medication: A failure of the SAS programming algorithm for assigning the prior and concomitant medications flags was discovered, resulting in omitted concomitant medications.
- Adverse events: For 2 subjects, the algorithm failed to classify 2 AEs as treatment-emergent, whereas the start date of the events were after the treatment start date for these 2 subjects.

The design of the study is considered adequate. The open-label design can be considered acceptable given the difficulties in blinding especially related to discoloring of faeces because of the iron content. Further, the primary endpoint and most other endpoints as well are based on serum phosphorus levels measured at a central laboratory which is considered an objective measurement not easily prone to bias. The statistical methods are considered adequate. Changes in planned analyses after database lock pertained to programming algorithms used. These are not considered to affect the study results as the database was not re-opened and no data were changed.

Results of study PA-CL-03A

Participant flow

A schematic presentation is shown in Figure 2. 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-fulfillment 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 (44.4% and 37.5%, respectively), and lowest in the PA21 7.5 g/day group (20.0%). Reasons for withdrawal are shown in Table 2.

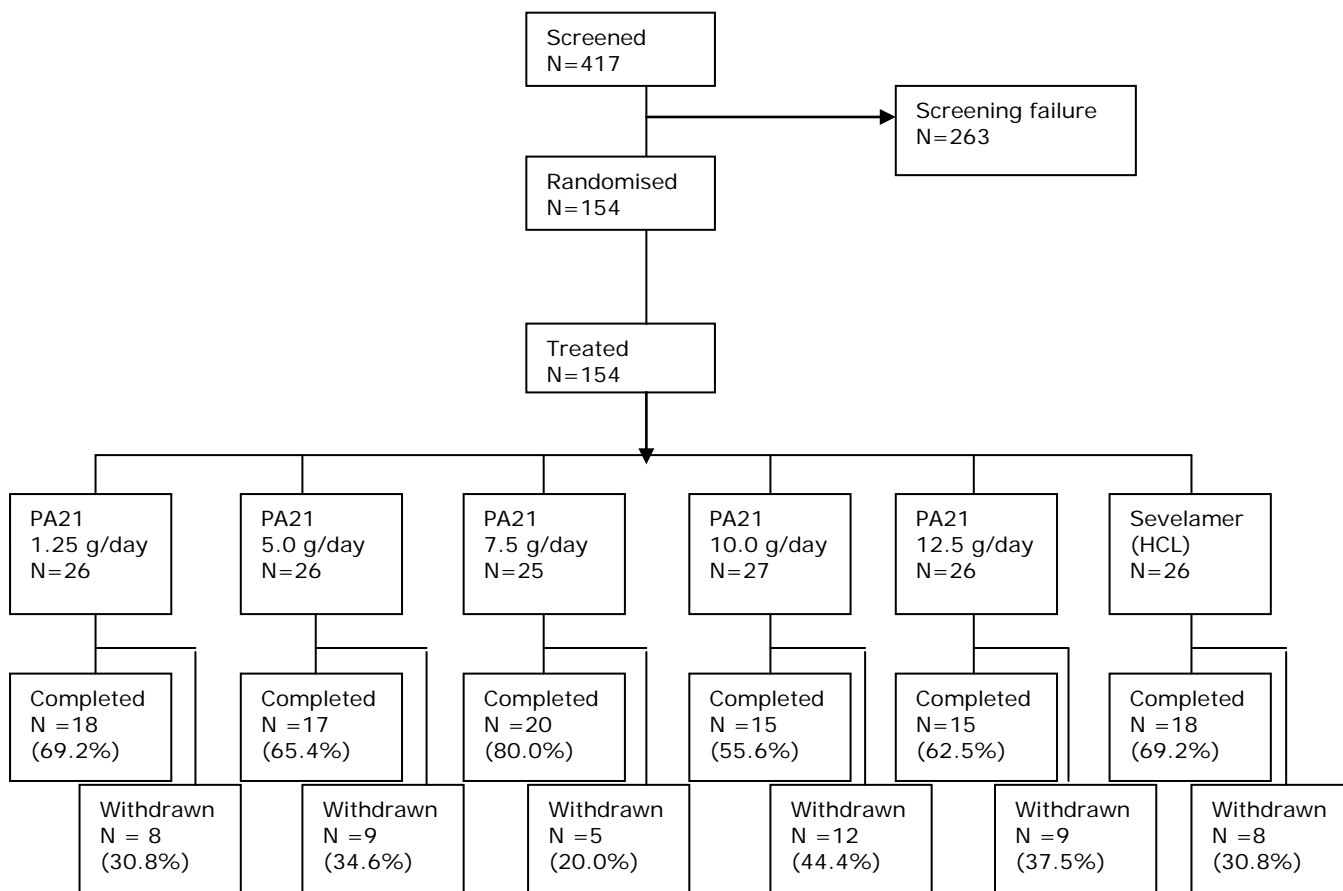


Figure 2: Subject disposition in study PA-CL-03A

Table 2: Summary of primary reasons for study discontinuation (all subjects randomized)

Reason	PA21						Sevelamer (HCl) (N=26) n (%)
	1.25 g/Day (N=26) n (%)	5.0 g/Day (N=26) n (%)	7.5 g/Day (N=25) n (%)	10.0 g/Day (N=27) n (%)	12.5 g/Day (N=24) n (%)	Total PA21 (N=128) n (%)	
Prohibited medication	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (7.7%)
Serum phosphorus below safety limit	1 (3.8%)	3 (11.5%)	3 (12.0%)	7 (25.9%)	6 (25.0%)	20 (15.6%)	1 (3.8%)
Serum phosphorus level above upper safety limit any time as of 2 weeks after start of treatment	4 (15.4%)	2 (7.7%)	0 (0.0%)	2 (7.4%)	0 (0.0%)	8 (6.3%)	2 (7.7%)
Serum calcium above safety limit	2 (7.7%)	2 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.1%)	0 (0.0%)
Protocol violation	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Adverse event	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (4.2%)	2 (1.6%)	2 (7.7%)
Withdrawal by subject	1 (3.8%)	0 (0.0%)	1 (4.0%)	2 (7.4%)	1 (4.2%)	5 (3.9%)	0 (0.0%)
Intercurrent illness, condition, or procedural complication	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Best interest of the subject (Investigator/study physician opinion)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	1 (4.2%)	2 (1.6%)	1 (3.8%)

Notes: Multiple reasons per subject are possible but only the primary reasons are summarised.

Withdrawal rates were high, between 20-45% overall. Most common reasons for withdrawal within the PA21 dose groups were low (high PA21 dose) or high (low PA21 dose) serum phosphorus levels related to the primary mechanism of action. These can be expected given the fixed dosing regimen, whereas doses are titrated in clinical practice. The single death was not related to treatment (see further section on Clinical Safety).

Recruitment

Subjects were randomized at 50 centres in 9 countries. The first subject first visit took place on 30 January 2009, and the last subject last visit took place on 13 October 2009. The majority of the patients were randomised in Eastern Europe (126/154), a minority within the US (21/154).

Conduct of the study

The study protocol was dated 7 August 2008 and there were 3 formal amendments to the study. One was implemented before the first study subject was randomized. The second amendment (17 March 2009) included several clarifications and modifications to in- and exclusion criteria. The third amendment (10 June 2009) pertained to a reduction of the sample size.

Baseline data

The most important baseline characteristics of the FAS are shown in Table 3. In general, demographic baseline characteristics were comparable between groups. The majority of patients were male (about 60%) and the mean age was around 60 years. The main primary cause of CKD was other followed by glomerulopathy. The median duration of ESRD was between 2 -3 years, whereas ranges were broad.

In the FAS, 145 subjects (96.7%) had relevant medical and/or surgical history in addition to CKD. Most commonly recorded illnesses were hypertension and diabetes. The most commonly used prior and concomitant medications were calcium supplements, followed by "other anti-anaemic preparations" (ESA) and heparin products. Proportions of concomitant medications were largely similar across all treatment groups. Concomitant use of vitamin D and analogues was seen in 37 (29.4%) and 11 (45.80%) patients on PA21 and sevelamer HCl, respectively. 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.

Table 3: Summary of baseline characteristics in study PA-CL-03A (FAS population)

Variable	1.25 g/Day (N=26) n (%)	5.0 g/Day (N=26) n (%)	7.5 g/Day (N=25) n (%)	10.0 g/Day (N=25) n (%)	12.5 g/Day (N=24) n (%)	Total PA21 (N=126) n (%)	Sevelamer (HCI) (N=24) N(%)
Demographics							
Gender, n (%)							
Male	17 (65.4)	19 (73.1)	16 (64.0)	15 (60.0)	13 (54.2)	80 (63.5)	14 (58.3)
Female	9 (34.6)	7 (26.9)	9 (36.0)	10 (40.0)	11 (45.8)	46 (36.5)	10 (41.7)
Age (years) at screening							
Mean (sd)	60.1 (12.29)	59.7 (13.80)	61.9 (13.71)	60.8 (13.21)	59.3 (12.32)	60.4 (12.91)	61.6 (11.22)
Median	63.0	57.5	63.0	62.0	62.0	62.0	63.0
Range	36-84	34-85	39-85	34-81	28-77	28-85	33-80
Ethnicity, n (%)							
White	24 (92.3)	26 (100)	24 (96.0)	22 (88.0)	24 (100)	120 (95.2)	23 (95.8)
Black	2 (7.7)	0 (0.0)	0 (0.0)	2 (8.0)	0 (0.0)	4 (3.2)	0 (0.0)
Asian	0 (0.0)	0 (0.0)	1 (4.0)	0 (0.0)	0 (0.0)	1 (0.8)	1 (4.2)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.0)	0 (0.0)	1 (0.8)	0 (0.0)
Renal history							
Primary cause of ESRD, n (%)							
Glomerulopathy	7 (26.9)	4 (15.4)	6 (24.0)	8 (32.0)	5 (20.8)	30 (23.8)	7 (29.2)
Vascular nephropathy	7 (26.9)	4 (15.4)	5 (20.0)	7 (28.0)	3 (12.5)	26 (20.6)	3 (12.5)
Interstitial nephropathy	2 (7.7)	2 (7.7)	4 (16.0)	3 (12.0)	4 (16.7)	15 (11.9)	3 (12.5)
Other	9 (34.6)	16 (61.5)	9 (36.0)	7 (28.0)	12 (50.0)	53 (42.1)	11 (45.8)
Missing	1 (3.8)	0 (0.0)	1 (4.0)	0 (0.0)	0 (0.0)	2 (1.6)	0 (0.0)
Duration* (month)							
n	25	26	24	24	24	123	24
Mean (sd)	59.1 (79.29)	64.6 (56.56)	87.2 (71.75)	90.7 (111.04)	85.2 (66.95)	77.0 (78.75)	118.3 (140.29)
Median	40.8	47.3	63.6	48.9	74.0	54.2	65.0
Range	1-408	6-239	5-239	6-455	10-263	1-455	4-599
Pre-study phosphate binder, n (%)							
Any	23 (88.5%)	23 (88.5%)	20 (80.0%)	24 (96.0%)	20 (83.3%)	110 (87.3%)	22 (91.7%)
Aluminium-based	3 (1.5%)	1 (3.8%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	5 (4.0%)	1 (4.2%)
Calcium-based	23 (88.5%)	23 (88.5%)	20 (80.0%)	24 (96.0%)	20 (83.3%)	110 (87.3%)	22 (91.7%)
Sevelamer	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Other	1 (3.8%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	2 (1.6%)	0 (0.0%)

* Duration is the time since the first diagnosis of CKD.

The majority of patients were male (about 60%) and the mean age was around 60 years. The main primary cause of CKD was other followed by glomerulopathy.

Baseline characteristics are representative of the elderly CKD population on dialysis with significant co-morbidity. Almost all patients used calcium-based phosphate binders due to the exclusion of sevelamer and lanthanum.

Numbers analysed

The data sets analysed are summarised in Table 4.

Table 4: Analyses populations (all subjects randomised) in study PA-CL-03A

	PA21					Sevelamer (HCI) (N=26) n (%)	Overall (N=154) n (%)
	1.25 g/Day (N=26) n (%)	5.0 g/Day (N=26) n (%)	7.5 g/Day (N=25) n (%)	10.0 g/Day (N=27) n (%)	12.5 g/Day (N=24) n (%)		
SS	26 (100%)	26 (100%)	25 (100%)	27 (100%)	24 (100%)	26 (100%)	154 (100%)
FAS	26 (100%)	26 (100%)	25 (100%)	25 (92.6%)	24 (100%)	24 (92.3%)	150 (97.4%)

PPS	18 (69.2%)	21 (80.8%)	22 (88.0%)	20 (74.1%)	19 (79.2%)	20 (76.9%)	120 (77.9%)
------------	------------	------------	------------	------------	------------	------------	-------------

Major protocol deviations were identified for 34 (22.1%) of the 154 randomised subjects, varying between 19.2% in patients receiving 5.0 g/day PA21 and 30.8% in patients on 1.25 g/day PA21. The most common major protocol deviation was “non-compliance to study treatment”, occurring in 23 subjects (14.9%) overall. The proportion of subjects who did not comply with treatment was highest in the PA21 10.0 g/day group (6 subjects, 22.2%). Overall, a total of 10 patients used prohibited medications and 7 patients had violation of inclusion/exclusion criteria.

Treatment compliance was considered to be a compliance of 80% to 120%. Subjects generally complied well with their assigned treatment. 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. In the sevelamer (HCl) group, mean treatment compliance was 92.0%.

Outcomes and estimation

Primary efficacy endpoint

Change from baseline to the end of treatment in serum phosphorus levels is summarised for the FAS and PPS in Table 5. Mean baseline serum phosphorus levels were comparable between treatment groups. Mean decreases from baseline to end of treatment were statistically significant for all PA21 doses above 1.25 g/day and were broadly dose-dependent. The largest mean changes from baseline were seen in the two highest dose groups of PA21. In the sevelamer (HCl) group, mean change from baseline to end of treatment in serum phosphorus level was also statistically significant ($p < 0.001$). Comparable results were obtained for the PPS.

Table 5: Serum phosphorus levels and change in serum phosphorus (mmol/L) from baseline to end of treatment (Study PA-CL-03A)

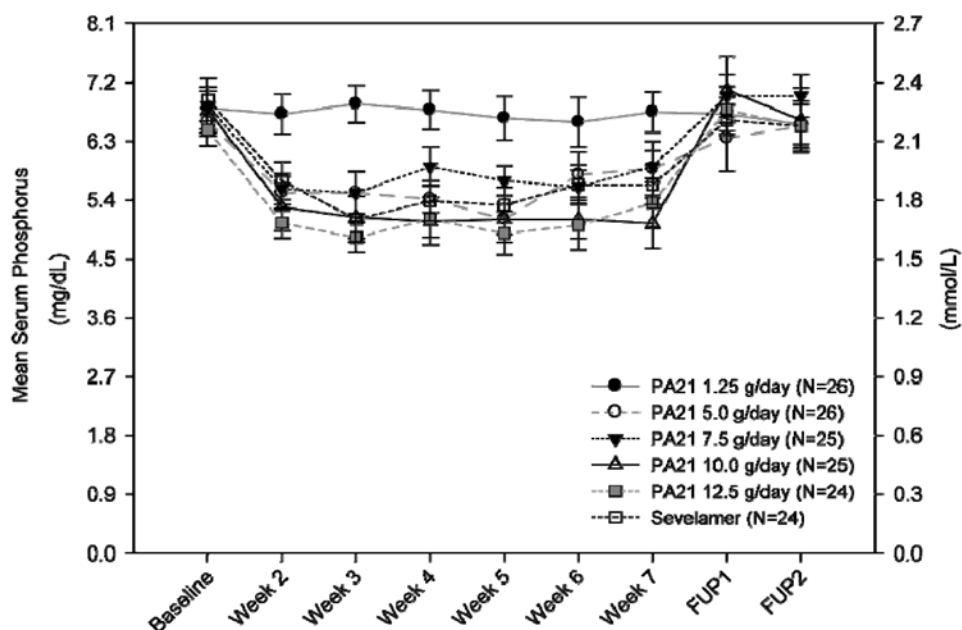
Variable	PA21					Sevelamer 48 g/day (N=24)
	1.25 g/Day (N=26)	5.0 g/Day (N=26)	7.5 g/Day (N=25)	10.0 g/Day (N=25)	12.5 g/Day (N=24)	
FAS						
Baseline						
Mean	2.203	2.135	2.212	2.186	2.089	2.242
(sd)	(0.531)	(0.348)	(0.372)	(0.565)	(0.383)	(0.519)
Min; max	1.11; 3.32	1.36; 2.68	1.46; 2.92	1.38; 2.99	1.34; 2.96	1.31; 3.89
End of treatment (LOCF)						
Mean	2.162	1.787	1.808	1.541	1.543	1.901
(sd)	(0.661)	(0.625)	(0.382)	(0.620)	(0.540)	(0.474)
Min; max	0.24; 3.40	0.38; 3.17	0.95; 2.37	0.23; 3.02	0.65; 2.58	1.23; 3.16
Change from baseline to end of treatment (LOCF)						
Mean	-0.042	-0.348	-0.404	-0.644	-0.547	-0.341
(sd)	(0.650)	(0.684)	(0.391)	(0.551)	(0.548)	(0.436)
p-value*	0.7448	0.0157	<0.001	<0.001	<0.001	<0.001

* Two-sided single sample t-test; p-values ≤ 0.05 according to the hierarchical procedure (descending dose) of PA21. End of treatment values based on value at Week 7 or last observation carried forward (LOCF) for missing data.

For the FAS, PA21 doses of 10.0 g/day and 12.5 g/day showed a statistically significantly greater reduction from baseline in serum phosphorus when compared to the PA21 1.25 g/day group. Within the PPS all PA21 doses of 5.0 g/day and above showed a statistically significantly greater reduction from baseline in serum phosphorus when compared to the PA21 1.25 g/day group.

When the study drug was stopped at Week 7 mean serum phosphorus levels returned towards baseline levels as subjects remaining in the study entered the 2-week run-out phase (FUP) (during which time

they did not receive treatment with a phosphate binder). This trend was noted earlier in the higher dose groups of hypophosphataemic subjects discontinuing treatment early (see Figure 3).



Notes: FAS = Full analysis set; FUP1 = Follow-up Visit 1; FUP2 = Follow up Visit 2.

Figure 3: Serum phosphorus levels at each time point in study PA-CL-03A (FAS).

All doses of PA21 between 5.0 g/day and 12.5 g/day were effective in lowering serum phosphorus levels; mean change from baseline varied between 0.348 mmol/L (5.0 g/day) and 0.644 mmol/L (10.0 g/day). The serum lowering effect was at least comparable to that of sevelamer (0.341 mmol/L). The effect appears dose-dependent, although interpretation is somewhat hampered by early withdrawal of patients in the highest dose groups.

Part of the population did not have serum phosphorus levels > 1.78 mmol/L at baseline as patients could have been included based on serum phosphorus levels in the week before. According to the applicant, this reflects natural changes in phosphorus levels commonly seen in these patients. This is further discussed below.

Secondary efficacy endpoints

Controlled serum phosphorus levels

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. Highest proportions were seen in the PA21 12.5 g/day group.

The proportions of subjects with controlled serum phosphorus levels (≥ 1.13 to ≤ 1.78 mmol/L) at week 7/end of treatment and at any time during treatment is shown in Table 6 based on the FAS.

Table 6: Proportion of patients with controlled serum phosphorus levels (≥ 1.13 to ≤ 1.78 mmol/L) in study PA-CL-03A (FAS).

Variable	PA21					Sevelamer (HCl) (N=24)
	1.25 g/Day (N=26)	5.0 g/Day (N=26)	7.5 g/Day (N=25)	10.0 g/Day (N=25)	12.5 g/Day (N=24)	
Baseline						
n/N (%)	5/26 (19.2%)	3/26 (11.5%)	3/25 (12.0%)	8/25 (32.0%)	6/24 (25.0%)	6/24 (25.0%)

Week 7						
n/N (%)	4/19 (21.1%)	7/17 (41.2%)	7/20 (35.0%)	6/14 (42.9%)	9/15 (60.0%)	8/19 (42.1%)
End of treatment						
n/N (%)	4/26 (15.4%)	12/26 (46.2%)	8/25 (32.0%)	9/25 (36.0%)	11/24 (45.8%)	11/24 (45.8%)
Any on treatment time point						
n/N (%)	14/26 (53.8%)	21/26 (80.8%)	17/25 (68.0%)	18/25 (72.0%)	21/24 (87.5%)	20/24 (83.3%)

Time to reach first controlled serum phosphorus level

In the FAS, median time to first controlled serum phosphorus level (≥ 1.13 to ≤ 1.78 mmol/L) 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 days in the PA21 1.25 g/day group, 14 days in the PA21 5.0 g/day group, 8 days in the PA21 7.5 g/day group, 14 days in the PA21 10.0 g/day group and 8 days in the PA21 12.5 g/day group. In the sevelamer (HCl) group median time to first controlled serum phosphorus level was 15 days.

For all doses of PA21 except the lowest dose, the proportions of patients with controlled serum phosphorus levels was increased at the end of treatment compared to baseline, which is a clinically relevant finding. No clear dose-response relationship was seen. Proportions on target with PA21 were largely comparable to that obtained with sevelamer (about 45%). A relatively high percentage of patients were already on treatment target at baseline (between 12% and 25%), suggesting that part of the population had serum phosphorus levels just above the target range. Serum phosphorus levels are known to fluctuate as a result of changes in diet, although patients were kept on a stable phosphorus diet within the study. Time to reach first controlled serum phosphorus level was between 8-14 days for PA21 doses between 5.0 g/day and 12.5 g/day and 15 days with sevelamer.

The efficacy data support the use of PA21 5.0 g/day as starting dose, although based on a limited number of patients of which some had phosphorus levels close by the target level. In clinical practice, doses will be up titrated based on regular monitoring of serum phosphorus levels.

Effects on serum total Ca, Ca X P and iPTH

In the FAS, baseline mean serum **calcium** levels were comparable in the 6 treatment groups (2.10 to 2.16 mmol/L). 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. In the sevelamer (HCl) group, mean changes from baseline were also small (0.02 to 0.12 mmol/L) over the study period.

In the FAS, the baseline mean serum **calcium x phosphorus** products were comparable in the 6 treatment groups (between 4.44 to 4.79 mmol²/L²). Mean decreases in serum calcium x phosphorus product from baseline to the last value during treatment ranged from -0.19 mmol²/L² in the PA21 12.5 g/day group, to -1.38 mmol²/L² in the 10.0 g/day group. The comparable value for the sevelamer (HCl) group was -0.78 mmol²/L². These changes were statistically significant for all groups except the PA21 1.25 g/day group.

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. Mean decreases from baseline in serum iPTH levels varied between 0.08 ng/L (PA21 7.5 g/day) and 60.65 ng/L (PA21 12.5 g/day) at end of treatment with PA21. The comparable value for sevelamer was -38.80 ng/L.

Serum calcium levels remained rather stable whereas decreases in serum calcium x phosphorus product were consistent with the decreases seen in serum phosphorus levels. Mean serum iPTH levels

were variable and tended to decrease especially in the highest dose group of PA21 and also for sevelamer.

2.2.7. Main studies

This application is based on one phase 3 confirmatory trial to demonstrate efficacy and safety of PA21 in patients with CKD.

Study PA-CL-05A: 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 Dialysis Patients with Hyperphosphataemia.

Methods

- **Study participants**

Adult (≥ 18 years) patients receiving maintenance HD 3 times/week with a Kt/V of ≥ 1.2 or peritoneal dialysis (PD) with a Kt/V of $\geq 1.7 \geq 3$ months, receiving stable doses of phosphate binder (1 or 2 allowed) for at least 1 month before screening were eligible for this study after having provided signed and dated informed consent. Only patients with serum phosphorus levels > 1.94 mmol/L during the washout phase (minimum of 2 weeks washout was obligatory) were eligible for randomization.

Main exclusion criteria included serum calcium below 1.9 mmol/L, hypercalcaemia (serum total calcium > 2.60 mmol/L) in subjects on non-calcium based phosphate binders, iPTH levels > 800 ng/L at screening. Subjects with iPTH > 600 ng/L at screening must be considered stable whereas patients with planned or expected parathyroidectomy within the next 12 months were excluded.

Further exclusion criteria were serum ferritin $> 2,000$ $\mu\text{g/L}$, history of haemochromatosis, or history of other iron storage disorders, history of major gastrointestinal surgery or significant GI or hepatic disorders in the past 3 years, active hepatitis B or active hepatitis C, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 times the upper limit of the normal range at screening, known seropositivity to human immunodeficiency virus, serious medical conditions or planned major surgery that would interfere with the study, unstable angina, unstable hypertension, uncontrolled diabetes, pregnancy, lactation or lack of effective contraception.

Subjects on PD with a history of peritonitis in the last 3 months or ≥ 3 episodes in the last 12 months were excluded. Use of antacids containing aluminium or magnesium and use of oral iron preparations within 1 month before screening was not allowed.

Inclusion criteria stage 2: 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 at Week 20.

Inclusion criteria were representative for the target population in need of phosphate binder treatment and in line with current KDOQI treatment guidelines. In- and exclusion criteria largely resembles that of the dose-finding study. Most important differences were the higher cut-off value for serum phosphorus level before inclusion (≥ 1.94 mmol/L), patients on PD were allowed, all patients should have been on prior phosphate binder therapy including sevelamer, and parenteral iron infusions were allowed during the study.

Again, patients with significant GI and liver co-morbidity or iron storage disorders were excluded from the trial. Further, patients with a history of peritonitis were excluded.

- **Treatments**

The study is a 2-stage re-randomization study (see

Figure 4).

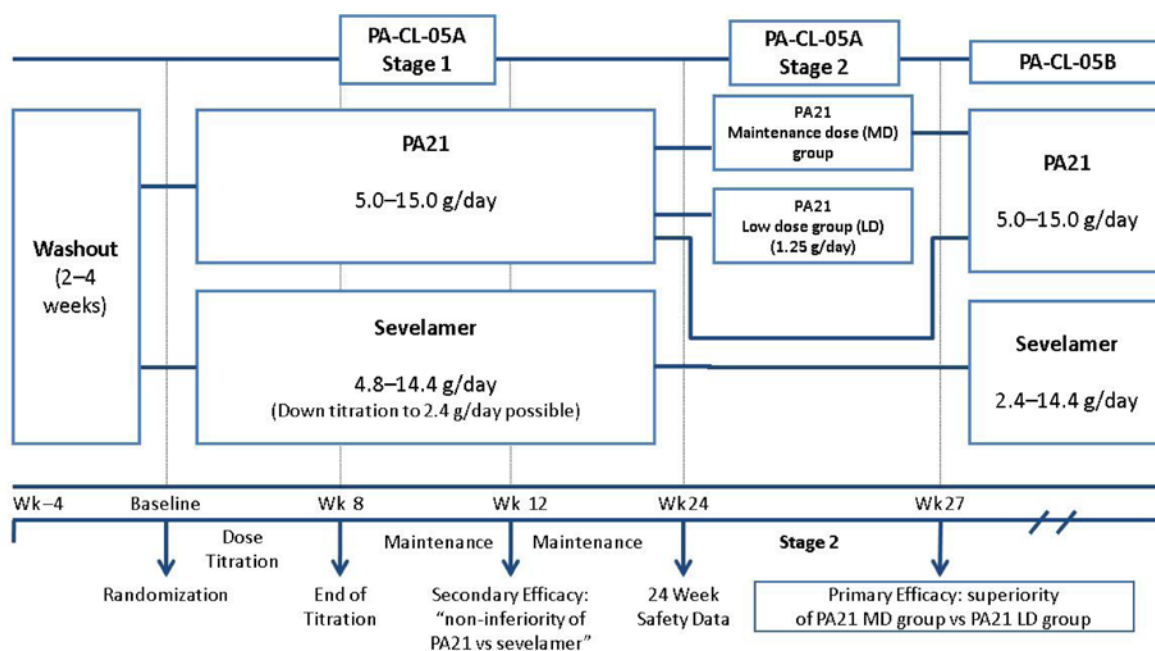


Figure 4: Schematic design of study PA-CL-05A

Stage 1:

Subjects who met all inclusion and exclusion criteria completed a washout from their previous phosphate binders for at least 2 weeks and a maximum of 4 weeks. Eligible subjects were randomised via IVRS in a 2:1 ratio to either PA21 or sevelamer, respectively, and entered the treatment period. During the **titration period of 8 weeks**, dose changes were allowed every 2 weeks. Dose changes indicated by the Week 8 blood sample were the final changes for the titration period. For analysis purposes, the Stage 1 titration period was defined as the baseline visit (Day 1) to Week 12 (Day 85). After the final dose titration, the subjects continued on a stable dose of either PA21 or sevelamer until the Week 12 assessment. Dose titrations for tolerability reasons throughout this 4-week period were allowed, however. The Stage 1 **maintenance period** was defined as the Week 12 visit (Day 85) to Week 24 visit (Day 169) for analysis purposes. During this period dose modifications were allowed for both tolerability and efficacy reasons (every 4 weeks).

PA21: PA21 chewable tablets containing 2.5 g PA21 and 500 mg iron.

The starting dose was 5.0 g/day, which was also the minimum dose. The maximum dose of PA21 was 15.0 g/day (6 tablets/day). Dosing frequency was three times daily except for the lowest dose of 5.0 g/day which was administered twice daily with meals.

Sevelamer: The active control was sevelamer carbonate, Renvela tablets containing 800 mg of sevelamer carbonate.

The starting dose was 4.8 g/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). Dosing frequency was three times daily with meals.

Stage 2:

In Stage 2, the first 100 subjects on HD (no PD allowed) who completed Stage 1 PA21 treatment group, and who had a controlled serum phosphorus level of <1.78 mmol/L at Week 20, were randomised via IVRS in a 1:1 ratio to the PA21 maintenance dose (MD) group or the PA21 low dose (LD) group for the next 3 weeks. No dose adjustments were allowed until Stage 2 was complete.

PA21 maintenance dose (MD): PA21 chewable tablets containing 2.5 g PA21 and 500 mg iron.

Patients continued with the same dose they had been receiving at the end of Stage 1 (Week 24).

PA21 low dose (LD): PA21 chewable tablets containing 1.25 g PA21 and 250 mg iron.

Patients were switched to a dose of 1.25 g/day, one tablet to be taken with the largest meal.

The design of the study including an active controlled treatment phase and a re-randomised withdrawal phase allows assessment of both efficacy in relation to current treatment and maintenance of effect or tolerability. Treatment duration is considered sufficient and dose of PA21 is supported by the dose-finding study. The exact reason for the maximum dose of PA21 of 15.0 g/day is not clear, but most likely based on the safety profile. The dose of sevelamer carbonate is in line with the highest recommended starting dose within the SPC (for serum phosphorus levels >2.42 mmol/L), which is acceptable.

Within the withdrawal phase, a PA21 low dose was used which appeared ineffective based on the phase 2 study. A real placebo could have been chosen to avoid discussions on potential efficacy of this dose, albeit limited.

• **Objectives**

Primary objective

- 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.
- To assess the long-term safety and tolerability of PA21 in patients on dialysis.

Secondary objectives

- Establish the non-inferiority 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.

• **Outcomes/endpoints**

Primary efficacy endpoint:

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 primary efficacy set (PES) (Stage 2).

Secondary efficacy endpoints:

The main secondary endpoint was the 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) Stage 1). If non-inferiority was shown, superiority testing was performed.

Other secondary efficacy endpoints related to serum phosphorus level included:

- Proportion of subjects achieving serum phosphorus control (Stage 1) based on:
 - within the KDOQI guideline target range of 1.13 to 1.78 mmol/L at a given time point
 - within the KDIGO normal range of 0.81 to 1.45 mmol/L at a given time point
- Duration of serum phosphorus control based on KDIGO normal or KDOQI guideline target range.
- The time for the phosphorus level to fall within KDIGO normal or KDOQI target range (Stage 1) or to rise without these ranges (Stage 2).
- Serum total calcium levels, serum calcium x phosphorus product and serum iPTH levels.

Other assessments included the assessment of pill burden, quality of life (SF-36 questionnaire), patient preference and patient satisfaction, changes in dietary habits, and changes in dialysis parameters.

Safety endpoints:

The primary safety assessments were the incidence of AEs and routine haematological and biochemical (including liver function) laboratory tests. Adverse events that began or that worsened in severity after at least 1 dose of study treatment had been administered were considered treatment-emergent adverse events (TEAE). Specific secondary safety endpoints included the proportion of subjects that developed hypo/hyperphosphataemia (<0.81 mmol/L / >2.75 mmol/L); hypo/hypercalcaemia (<1.9 mmol/L / >2.75 mmol/L) and hyperparathyroidism (iPTH value >600 ng/L). Other safety measurements were physical examination parameters, vital signs, standard 12-lead electrocardiogram (ECG) parameters, vitamin status (A, D, E, and K), iron status (iron, ferritin, transferrin and transferrin saturation), serum calcium and iPTH levels, biochemical markers of bone resorption and formation (carboxyterminal cross-linking telopeptide of bone collagen, tartrate-resistant acid phosphatase 5b, bone-specific alkaline phosphatase, and osteocalcin), and fibroblast growth factor 23 (FGF-23).

Overall, the endpoints are considered adequate and commonly used within clinical trials with phosphate binders. The primary endpoint assessed within the withdrawal phase mainly provides information on the maintenance of effect/absence of tolerability with PA21 in a selected population of responders. The main secondary endpoint is considered of equal importance as it provides information on the absolute effect size in the target population and efficacy relative to currently available treatment. In this respect, the proportion of responders according to the KDOQI target range reflects clinical treatment practice and is considered an important clinically relevant endpoint. Proportion of patients reaching phosphorus levels within the normal range are less relevant and not discussed separately discussed within this assessment report.

- **Sample size**

- Stage 2 (Primary Efficacy Analyses)

The sample size for Stage 2 of the study was based on the primary efficacy endpoint. The number of subjects needed for this analysis was 50 per group, assuming a difference between the groups of 0.42 mmol/L, an SD of 0.63 mmol/L, a power of 90% and a 2-sided significance value of 0.05. Therefore, it was planned to randomise a total of 100 subjects for Stage 2 of the study.

Stage 1 (Key Secondary Efficacy Analyses)

The sample size for Stage 1 of the study was based on the non-inferiority comparison between PA21 and sevelamer at week 12. Assuming a mean decrease in serum phosphorus levels of 0.65 mmol/L in both treatment groups with an SD of 0.63 mmol/L, a power of 90%, a non-inferiority margin of 0.19 mmol/L, and a randomisation ratio of 2:1 (PA21:sevelamer), a total of 507 per-protocol subjects were required (338 subjects in the PA21 group and 169 subjects in the sevelamer group). Assuming a 20% rate of subjects not being in the PPS, and to ensure that a sufficient number of subjects were exposed to PA21 after 6 months of treatment for the safety evaluation, enrolment was planned up to a maximum of 940 subjects. This resulted in an increase power to at least 95% for demonstrating non-inferiority of PA21 against sevelamer, under similar assumptions.

It was anticipated that approximately 100 subjects on PD would be recruited and randomised in a 2:1 ratio to PA21 or sevelamer (67 in the PA21 treatment group and 33 in the sevelamer group).

- **Randomisation**

At Stage 1, the randomisation ratio was 2:1 for PA21:sevelamer, and the randomisation were stratified by HD/PD status and country. At Stage 2, eligible subjects were randomised 1:1 to either PA21 MD or PA21 LD. Subjects were assigned to their treatment group by central randomisation via IVRS.

- **Blinding**

An open-label design was employed 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, 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. Moreover, the open-label design did not bias the primary efficacy endpoint of serum phosphorus, which is an objective laboratory measurement analysed by 1 of 2 central laboratories.

- **Statistical methods**

The final SAP dated 1 June 2012.

Populations analysed

The safety set (SS) included all randomised subjects who took at least 1 dose of study medication.

The Full analysis population (FAS) included all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline evaluable efficacy assessment.

The Per-protocol set (PPS) included all subjects in the FAS who completed the dose titration period and had ≥ 1 evaluable serum phosphorus result \geq Week 12, without major protocol deviations.

The safety set 2 (SS2) included all subjects who received at least 1 dose of study medication in Stage 2.

The primary efficacy set (PES) included all subjects randomised to Stage 2 who received ≥ 1 dose of study medication during Stage 2 and had ≥ 1 evaluable post-baseline efficacy assessment in Stage 2.

The primary efficacy per-protocol set (PEPPS) included all patients in the PES without major protocol deviations.

Major protocol violations included serum phosphorus <1.94 mmol/L prior to randomisation, concomitant phosphate binder use, compliance with study medication <70% or >120%, subject not taking treatment to which they were randomized, and use of prohibited medications.

Primary efficacy analysis

The primary efficacy analysis evaluated the change in serum phosphorus levels from Week 24 to Week 27 between the PA21 MD and LD control group. This analysis was conducted using an ANCOVA with the LOCF approach for missing data imputation, and baseline (Week 24) serum phosphorus level and region (US/EU/ROW) as covariates for the PES. Sensitivity analyses were conducted using the primary ANCOVA model on the observed cases (OC) and the mixed model for repeated measures missing at random (MMRM-MAR) model. This method relies on less stringent assumptions than the LOCF method.

The main primary efficacy analysis was repeated on the PEPPS.

Main secondary analysis:

The non-inferiority analysis to compare the change from baseline in serum phosphorus levels at Week 12 in the PA21 group to the sevelamer group on the PPS, was performed using ANCOVA-LOCF analysis. Treatment, baseline serum phosphorus level, dialysis status and region (US, EU, ROW) were treated as fixed effects in the model. If the upper bound of the 97.5% 1-sided CI fell below 0.19 mmol/L, then the non-inferiority of PA21 against sevelamer was concluded. If non-inferiority was achieved, testing of the superiority of PA21 against sevelamer group was planned using a similar model. The analysis was repeated on the FAS.

Non-inferiority margin: The non-inferiority margin was based on the absolute change in serum phosphorus from baseline reported for sevelamer in published clinical trials, which was about 0.64 mmol/L. Given the consistency of the published results, the choice of a margin of 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 (about 0.47 mmol/L). The concern 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) should be allayed 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.

Other secondary analyses:

The percentage of subjects who achieved control at Week 12 and Week 24 was summarised for the FAS. Similar analyses were included for subjects in Stage 2 at Weeks 24, 25, 26 and 27 for the PES. Logistic models were used to derive the odds ratios using treatment and baseline serum phosphorus value as covariates for the FAS and PES.

At Stage 1, the time for the serum phosphorus level to fall within the KDIGO normal or KDOQI target range was analysed using Kaplan-Meier on the FAS and the comparison between the 2 treatment groups was assessed using the log-rank test.

All efficacy analyses of laboratory values were based on results from the central laboratories.

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.

Quality of life was assessed using the standard SF-36 (Version 2.0) quality of life questionnaire. The SF-36 scale was analysed using the standard algorithms for Version 2.0. A traditional Likert scale was used for the patient preference and patient satisfaction assessments.

Safety analyses

The primary safety assessments were the AE profile and significant changes in routine biochemical/haematological laboratory tests. All AE summaries were done for all of the subjects in a treatment group combined and by the maximum dose received during the trial. In addition, AEs were evaluated for subgroups or subjects on HD and PD. Laboratory values, vital signs, physical examinations results, and ECG parameters were also summarised by treatment group using descriptive statistics and/or shift tables.

Modifications to the SAP:

There were few modifications to the statistical analyses as outlined in the final protocol. The main changes concerned inclusion of the PES, PEPPS, and SS2 analysis sets to define the appropriate subject groups for the primary efficacy analysis and safety and tolerability assessments for Stage 2, comparing PA21 MD and PA21 LD.

A Post-hoc Analysis Plan (Final Version 1.0, 7 October 2012) was developed for additional exploratory analyses following the review of the initial results. These included amongst others summaries of TEAEs by maximum dose during the titration and maintenance periods, adjusted using the number of subjects present at the beginning of the period, treatment-related TEAEs leading to withdrawal, overall and by maximum dose separately for stage 1 and 2, and the duration and outcome of diarrhoea events in the various stages.

Commonly applied statistical methods were used. The clinical relevance of the proposed non-inferiority margin was not discussed, and non-inferiority needs to be supported by the totality of data. A definition of a non-inferiority margin for the proportion of patients on target levels would have been helpful to interpret the clinical relevance of the results based on serum phosphorus levels only.

LOCF method was used for missing data for the analyses based on serum phosphorus levels in stage 1 and stage 2. This is considered a partial conservative approach. Performed sensitivity analyses are less conservative. Responders were only analyzed based on observed cases only. A sensitivity analysis was performed as well.

No major changes were made to the SAP after study completion.

Results

Participant flow

Overall, 1,840 subjects were screened, 781 subjects were not eligible for the study and 1,059 subjects were randomized. The most common reason for screening failure for stage 1 were serum phosphate levels that did not meet the entry criteria (34.3% of patients screened), other entry criteria not met (39.1%), subject withdrew consent (6.4%) and Investigator decision (1.8%).

Subject disposition and reasons for withdrawal are presented in Figure 5 and Table 7, respectively.

Stage 1

Of the 1,059 subjects randomised, 1,055 (99.6%) were treated, and 808 (76.3% overall; 72.5% of PA21-treated subjects and 84% of sevelamer-treated subjects) completed Stage 1. During Stage 1, 251 subjects (23.7%) prematurely discontinued the study: 195 subjects (27.5%) treated with PA21 and 56 (16.0%) treated with sevelamer.

The most common reasons for withdrawal in Stage 1 were non-fatal AEs other than phosphorus or calcium level related events (48.2% in PA21 group and 37.5% in sevelamer group of all withdrawals). Next commonly reported reasons were withdrawal of consent, renal transplant, hyperphosphataemia, and death (not reported to treatment, see further safety assessment). Investigator decision was related to non-compliance. The sponsor decision was due to closure of one site (701).

Stage 2

A total of 99 subjects on HD enrolled in Stage 2. Eight subjects were withdrawn from the PA21 MD dose due to protocol deviations; 5 subjects because they were dispensed PA-CL-05B drug in error and three because of non-compliance. Withdrawal rates with PA21 LD were low.

Table 7: Subject disposition and reasons for withdrawal in study PA-CL-05A

Parameter	Stage 1, N=1,059		Stage 2, N=99	
	PA21 (N=710)	Sevelamer (N=349)	PA21 MD (N=50)	PA21 LD (N=49)
Randomised	710 (100%)	349 (100%)	50 (100%)	49 (100%)
Randomised but not treated	3 (0.4%)	1 (0.3%)	5 (10.0%)	0 (0.0%)
Treated	707 (99.6%)	348 (99.7%)	45 (90.0%)	49 (100%)
Completed	515 (72.7%)	293 (84.0%)	42 (84.0%)	46 (93.9%)
Enrolled in PA-CL-05B extension study	392 (55.2%)	267 (76.5%)	41 (82.0%)	0 (0.0%)
Withdrawn ¹	195 (27.5%)	56 (16.0%)	8 (16.0%)	3 (6.1%)
Reasons for withdrawal²				
AE (other than P or Ca level events)	94 (48.2%)	21 (37.5%)	0 (0.0%)	0 (0.0%)
Consent withdrawn	32 (16.4%)	15 (26.8%)	0 (0.0%)	0 (0.0%)
Renal transplant	16 (8.2%)	7 (12.5%)	0 (0.0%)	0 (0.0%)
Phosphorus > 2.75 mmol/L	12 (6.2%)	0 (0.0%)	0 (0.0%)	1 (33.3%)
Death	9 (4.6%)	5 (8.9%)	0 (0.0%)	1 (33.3%)
Protocol violation	7 (3.6%)	0 (0.0%)	8 (100%)	0 (0.0%)
Investigator decision	5 (2.6%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
Sponsor decision	5 (2.6%)	4 (7.1%)	0 (0.0%)	0 (0.0%)
Calcium > 2.75 mmol/L	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Phosphorus < 0.81 mmol/L	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (33.3%)
Prohibited concomitant medication	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	10 (5.1%)	3 (5.4%)	0 (0.0%)	0 (0.0%)

¹ Includes subjects that were randomized but not treated; ² Percentages calculated on the total number of discontinuations.

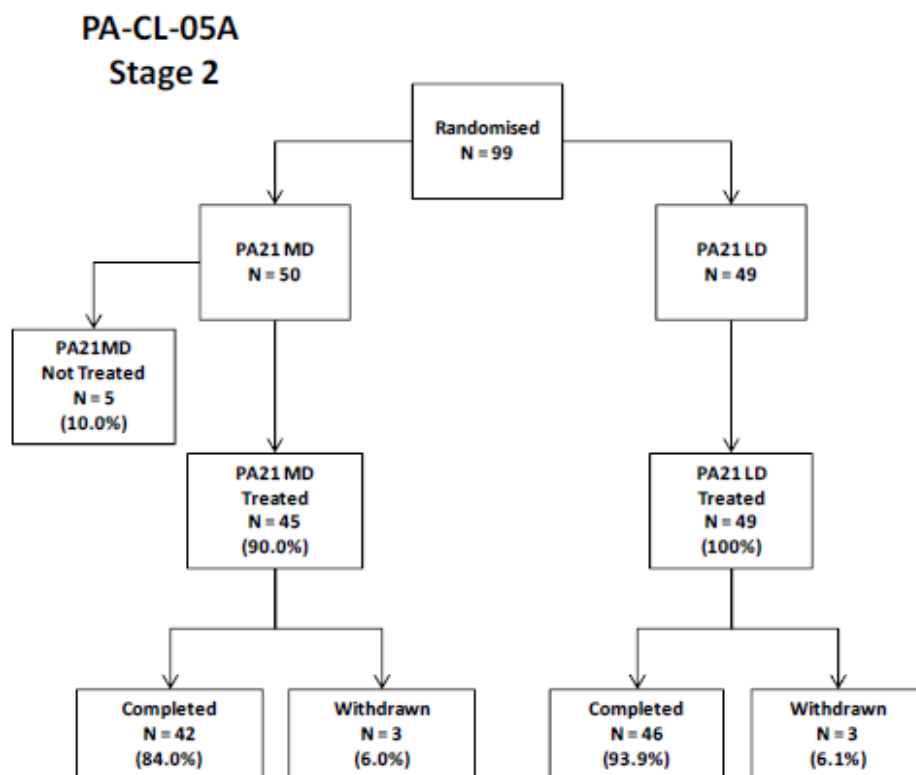
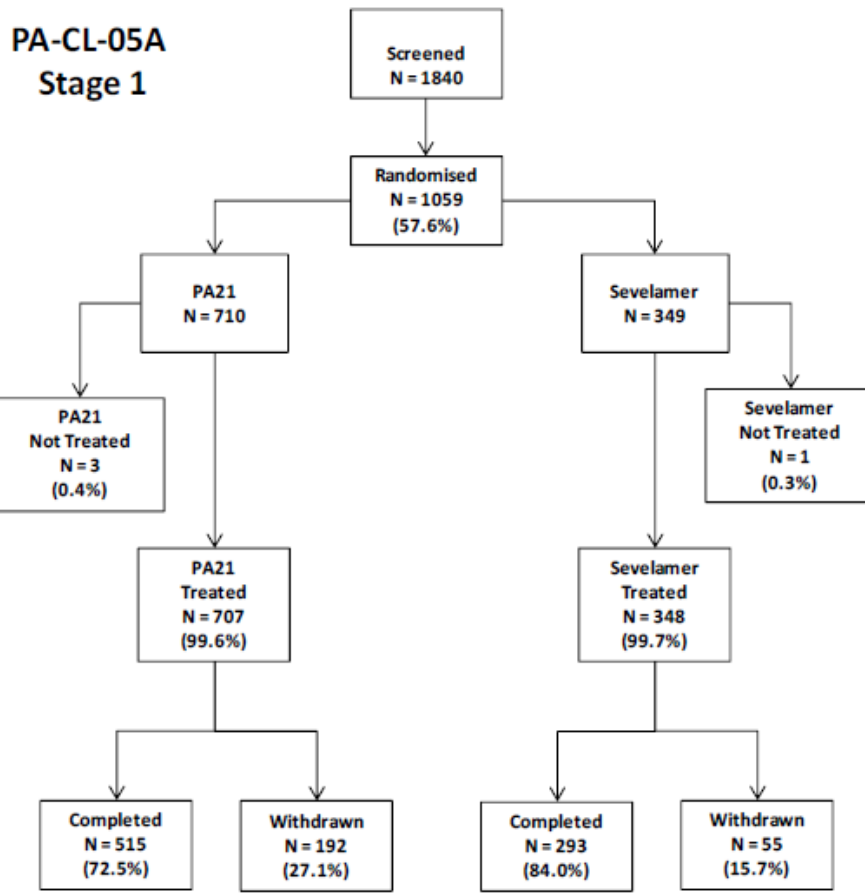


Figure 5: Subjects disposition in study PA-CL-05A.

Recruitment

Subjects were screened at 174 centres and randomized at 161 centres in the US, EU and ROW. The first subject first visit took place on 9 March 2011, and the last subject last visit took place on 9 April 2012. The majority of the patients were randomised in the US (516/1,059), followed by the ROW region (307/1,059 of which 151 in Russia) and the EU (236/1,059 of which 62 in Czech Republic).

In Stage 2, there was a single randomisation error by the site and only 99 subjects were actually enrolled in Stage 2. In the Stage 2 PES, 70 subjects (75.3%) came from the US, 15 (16.1%) from the EU, and 8 (8.6%) from the ROW region.

Conduct of the study

There were 3 formal amendments to the study protocol of which two were implemented prior to screening and enrolment of subjects. These included several clarifications to the wording in the protocol/eCRF (first amendment) and clarifications related to inclusion criteria, study visits, collection of safety data and a DSBM was added. Amendment 3, implemented during the conduct of Stage 1, introduced the following changes that impacted the conduct of the study: new upper limit of serum ferritin (>2,000 µg/L), increased sample size as the loss of evaluable subjects between randomized set and PPS was underestimated, calcium-based antacids were prohibited, frequency of Kt/V calculation was changed and parameters corrected for the Kt/V calculation.

About 1.5-2 times more patients on PA21 compared to sevelamer were withdrawn during the first stage of the study (27.5% versus 16.0%). Most common reasons were adverse events and withdrawal of consent in both groups. Based on the randomised population, 13.2% (94/710) of patients randomised on PA21 withdrew due to AEs other than phosphorus or calcium levels related events compared to 5.7% (20/349) of patients randomised to sevelamer, which is 2-3 times higher. Withdrawals due to fatalities and AEs, including hyperphosphataemia, are further discussed in the safety assessment.

Discontinuations rates were in general low during the withdrawal phase.

Baseline data

Stage 1

Within the FAS, 504 subjects (48.4%) came from the US, 232 (22.3%) from the EU and 305 (29.3%) from the ROW region. The mean age of subjects was 56.1 years, the majority were male (57.8%) and white (76.8%). The majority of patients were on HD (91.8%) (**Table 8**).

The Stage 1 treatment groups were generally comparable with minor differences between PA21 and sevelamer treatments groups. There was, however, an imbalance in the sex groups with a greater proportion of female subjects in the PA21 group (44.8%) than in the sevelamer group (36.9%). Descriptive summary statistics for demographic characteristics in the PPS and SS were similar to the FAS.

Table 8: Demographic baseline characteristics of patients in study PA-CL-05A.

Variable	Stage 1, FAS			Stage 2, PES		
	PA21 (N=694) n (%)	Sevelamer (N=327) n (%)	Total (N=1,041) n (%)	PA21 MD (N=44) n (%)	PA21 LD (N=49) n (%)	Total PA21 (N=93) n (%)
Demographics						
Gender, n (%)						
Male	383 (55.2%)	219 (63.1%)	602 (57.8%)	20 (45.5%)	24 (49.0%)	44 (47.3%)
Female	311 (44.8%)	128 (36.9%)	439 (42.2%)	24 (54.5%)	25 (51.0%)	49 (52.7%)

Race, n (%)							
	White	536 (77.2%)	236 (75.8%)	799 (76.8%)	28 (63.6%)	30 (61.2%)	58 (62.4%)
	Black / African American	127 (18.3%)	75 (21.6%)	202 (19.4%)	14 (31.8%)	18 (36.7%)	32 (34.4%)
	Asian	9 (1.3%)	6 (1.7%)	15 (1.4%)	0 (0.0%)	1 (2.0%)	1 (1.1%)
	Other	22 (3.2%)	3 (0.9%)	24 (2.3%)	2 (4.6%)	0 (0.0%)	2 (2.2%)
Ethnicity, n (%)							
	Hispanic or Latino	88 (12.7%)	38 (11.0%)	126 (12.1%)	9 (25.0%)	10 (20.4%)	19 (20.4%)
	Non-hispanic or Latino	606 (87.3%)	309 (89.0%)	915 (87.9%)	35 (79.5%)	39 (79.6%)	74 (79.6%)
Age (years)							
	Mean (sd)	56.3 (13.40)	55.8 (14.60)	56.1 (13.81)	59.3 (13.60)	57.2 (11.40)	58.2 (12.46)
	Median (Range)	57.0 (21-89)	56.0 (21-88)	57.0 (21-89)	58.0 (23-83)	58.0 (27-83)	58.0 (23-83)
Weight (kg)							
	Mean (sd)	83.1 (20.91)	84.0 (20.79)	83.4 (20.87)	84.1 (17.19)	85.1 (22.47)	84.6 (20.02)
Dialysis status, n (%)							
	Haemodialysis	638 (91.9%)	318 (91.6%)	956 (91.8%)	44 (100%)	49 (100%)	93 (100%)
	Peritoneal dialysis	56 (8.1%)	29 (8.4%)	85 (8.2%)	0 (0%)	0 (0%)	0 (0%)

The most common reasons for ESRD were diabetes mellitus, hypertension and glomerulonephritis. There were no notable differences between treatment groups relative to reason for ESRD, time to start of ESRD or first dialysis, baseline Kt/V value, or prior phosphate binder treatment. Also, no significant differences in subjects' ESRD were observed in the PES and SS relative to the FAS (Table 9). A total of 8% of patients had a previous renal transplant and 4.5% had a previous parathyroidectomy.

Most commonly used phosphate binders were calcium-based. About 38% of patients had ever used sevelamer in the year prior to screening.

Stage 2

Within the PES, 70 subjects (75.3%) came from the 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 or disease related differences between the PA21 MD and PA21 LD treatment groups. Similar results were obtained in the PEPPS and SS2.

Concomitant medication in Stage 1 and 2: Subjects had a broad range of disease histories and concomitant medication use typical for the patient population. Treatment groups were generally balanced. Within Stage 2, more subjects started concomitant medications in the LD group compared with the MD group (65.3% versus 15.6%), especially drugs used to treat hyperphosphataemia (e.g. anti-anaemic preparations and anti-parathyroid preparations). In Stage 1, more than 70% of subjects in both treatment groups were taking concomitant iron products; 70.6% in patients on PA21 and 74.1% in patients on sevelamer. Concomitant intravenous iron products were received by 66.3% of subjects on HD and 28.7% on PD.

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).

Table 9: Summary of ESRD of patients in study PA-CL-05A

Variable	Stage 1, FAS			Stage 2, PES		
	PA21 (N=694) n (%)	Sevelamer (N=327) n (%)	Total (N=1,041) n (%)	PA21 MD (N=44) n (%)	PA21 LD (N=49) n (%)	Total PA21 (N=93) n (%)

Primary cause of ESRD, n (%)							
Hypertension	158 (22.8%)	88 (25.4%)	246 (23.6%)	12 (27.3%)	16 (32.7%)	28 (30.1%)	
Glomerulonephritis	155 (22.3%)	87 (25.1%)	242 (23.2%)	7 (15.9%)	9 (18.4%)	16 (17.2%)	
Diabetes mellitus	196 (28.2%)	94 (27.1%)	290 (27.9%)	13 (29.5%)	20 (40.8%)	33 (35.5%)	
Pyelonephritis	27 (3.9%)	13 (3.7%)	40 (3.8%)	1 (2.3%)	0 (0%)	1 (1.1%)	
Polycystic kidney disease	66 (9.5%)	21 (6.1%)	87 (8.4%)	4 (9.1%)	0 (0%)	4 (4.3%)	
Interstitial nephritis	18 (2.6%)	10 (2.9%)	28 (2.7%)	1 (2.3%)	0 (0%)	1 (1.1%)	
Hydronephrosis	9 (1.3%)	4 (1.2%)	13 (1.2%)	2 (4.5%)	0 (0%)	2 (2.2%)	
Congenital	9 (1.3%)	5 (1.4%)	14 (1.3%)	1 (2.3%)	0 (0%)	1 (1.1%)	
Other	56 (8.1%)	25 (7.2%)	81 (7.8%)	3 (6.8%)	4 (8.2%)	7 (7.5%)	
Time from first dialysis (month)							
Mean (sd)	51.3 (48.77)	53.6 (55.04)	52.1 (50.93)	60.9 (63.66)	54.2 (40.40)	57.4 (52.51)	
Median (range)	35.9 (0.7-310.7)	38.3 (3.4-396.8)	37.0 (0.7-396.8)	37.8 (3.11-310.7)	47.2 (6.6-243.8)	43.3 (3.1-310.7)	
Baseline HD Kt/V value							
n	638	318	956	44	49	93	
Mean (sd)	1.6 (0.29)	1.6 (0.27)	1.6 (0.28)	1.6 (0.24)	1.7 (0.28)	1.7 (0.27)	
Baseline PD Kt/V value							
n	56	29	85				
Mean (sd)	2.3 (0.64)	2.2 (0.63)	2.3 (0.64)				
No. of pre-study phosphate binder, n (%)							<i>Not provided</i>
1	570 (82.1%)	291 (83.9%)	861 (82.7%)				
2 or more	105 (15.1%)	47 (13.%)	152 (14.6%)				
Pre-study phosphate binder, n (%)							<i>Not provided</i>
Aluminium based	21 (3.0%)	14 (4.0%)	35 (3.4%)				
Calcium based	455 (65.6%)	225 (64.8%)	680 (65.3%)				
Sevelamer	238 (34.3)	124 (35.7%)	362 (34.8%)				
Lanthanum	45 (6.5%)	14 (4.0%)	59 (5.7%)				
Other	9 (1.3%)	3 (0.9%)	12 (1.2%)				

At start of the study, the mean age of subjects was 56.1 years, the majority were male (57.8%) and white (76.8%). The most common reasons for CKD were glomerulonephritis, diabetes and pyelonephritis. Baseline and disease related characteristics were in general comparable. A somewhat higher rate of males in the sevelamer group is noted. About one third of the patients had used sevelamer before start of the study. The proportion of patients on PD (8%) is limited, but in line with what can be expected based on the assumed distribution in the overall ESRD population (about 10%). Treatment groups within the withdrawal phase were also in general comparable. Further, there appeared to be no important differences in baseline characteristics between patients entering the withdrawal phase compared to the overall population.

Compliance with study medication: The proportion of subjects compliant at 70 to 120% expected in Stage 1 was 82.6% for the PA21 group versus 77.2% for the sevelamer group (FAS). Low compliance (<70% expected) was more common in the sevelamer group compared with the PA21 group (21.3% versus 15.1%, respectively). 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 (PES). The PA21 LD group reported more patients with compliance rate >120% (18.4% vs. 2.3%). Non-compliance issues were most often related to improper recording of treatment rather than subjects actually not taking the amount of study medication as prescribed.

Numbers analysed

Numbers within the various analysis sets are summarised in **Table 10**.

Table 10: Number of patients in analysis sets in study PA-CL-05A.

Analysis set	Treatment group		
	PA21 (N=710) n (%)	Sevelamer (N=349) n (%)	Total (N=1,059) n (%)
SS	707 (99.6%)	347 (99.7%)	1,055 (99.6%)
FAS	694 (97.7%)	347 (99.4%)	1,041 (98.3%)
PPS	461 (64.9%)	224 (64.2%)	685 (64.7%)
Stage 2	PA21 MD (N=50) n (%)	PA21 LD (N=49) n (%)	Total (N=99) n (%)
SS2	45 (90.0%)	49 (100.0%)	94 (94.9%)
PES	44 (88.0%)	49 (100.0%)	93 (93.9%)
PEPPS	31 (62.0%)	27 (55.1%)	58 (58.6%)

Major protocol violations: Within Stage 1, 361 (34.1%) patients had at least one major protocol deviation (33.7% of PA21 and 35.0% of sevelamer treated patients). The most common major protocol deviations in Stage 1 were non-compliance (17.9% with PA21 and 22.6% with sevelamer), treatment duration <11 weeks (15.8% with PA21 and 8.0% for sevelamer), and prohibited use of phosphate binders before treatment or during titration (2.0% for PA21 and 2.9% for sevelamer).

In Stage 2, major protocol deviations were identified for 41 subjects (41.4%) of the randomised subjects (38.0% in PA21 MD and 44.9% in PA21 LD). The most common major protocol deviation was non-compliance with study medication (22.0% for PA21 HD and 34.7% for PA21 LD). Non-compliance issues were most often related to improper recording of treatment rather than subjects actually not taking the amount of study medication as prescribed.

Patients were mainly excluded from the per-protocol analysis sets due to non-compliance. Compliance rates are in general comparable to that known for patients with ESRD, although the applicant states that in part these rates can be explained by improper recording. Results are presented for different analysis populations and consistency between results is of importance.

Outcomes and estimation

Stage 2 - Primary efficacy endpoint

In the PES and PEPPS sets, mean serum phosphorus levels were maintained during Stage 2 in subjects that continued on their PA21 MD, while subjects in the PA21 LD showed marked increases as early as Week 25, one week after transitioning to the LD control (see

Figure 6 and Table 11). The primary efficacy analysis confirmed that the PA21 MD was superior to the PA21 LD. Results in the PEPPS were comparable to those in the PES. Sensitivity analyses based on observed cases only or the MMRM-RAM model resulted in similar results (mean difference PA21 LD vs MD: 0.50; 95% CI: 0.33, 0.68; PES).

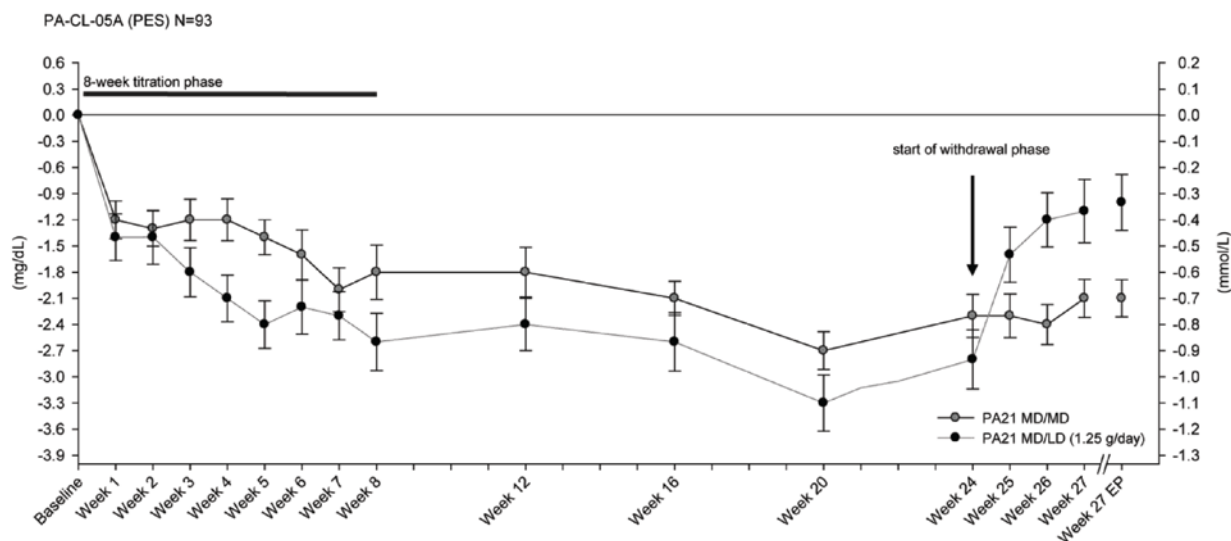


Figure 6: Mean (SEM) change in serum phosphorus levels for patients included in stage 2 primary efficacy set (PES, study PA-CL-05A).

Table 11: Analysis of serum phosphorus levels change from baseline (week 24) at week 27 ANCOVA-LOCF (study PA-CL-05A)

Serum Phosphorus (mmol/L)	PES (n=93)		PEPS (n=58)	
	PA21 MD (n=44)	PA21 LD (n=49)	PA21 MD (n=31)	PA21 LD (n=27)
Baseline, Week 24[#]				
Mean (sd)	1.5 (0.33)	1.6 (0.37)	1.5 (0.32)	1.6 (0.41)
Week 27, LOCF				
Mean (sd)	1.6 (0.35)	2.2 (6.8)	1.6 (0.33)	2.3 (0.61)
Change from baseline (LOCF)				
Mean (sd)	0.1 (0.40)	0.6 (0.47)	0.1 (0.36)	0.7 (0.50)
LS Means*	0.08	0.62	0.06	0.70
Difference LD vs MD (95% CI)	0.54 (0.37, 0.71)		0.64 (0.42, 0.85)	
p-value	<0.001		<0.001	

[#] Stage 2 baseline was Week 24 or latest value available before Week 24 when Week 24 result was missing. LOCF endpoint was Week 27 or includes the latest evaluable measurement after Week 24. LD = Low dose; LOCF = Last observation carried forward; MD = Maintenance dose; PES = Primary efficacy set; PEPPS = Primary efficacy per-protocol set. * ANCOVA-LOCF: ANCOVA analysis on endpoint results using a mixed model with the maximum likelihood estimation. The model includes treatment, baseline serum phosphorus levels, and region (US/EU/ROW) as fixed effects. ANCOVA = Analysis of covariance; CI = Confidence interval; LS = Least Square.

Within the withdrawal phase, superiority of the PA21 MD over PA21 LD was demonstrated. However, the mean serum phosphorus level on PA21 LD did not return to baseline levels prior to start of treatment. The applicant is requested to explain this observation and any impact on the interpretation of the data.

The mean PA21 dose in the MD group in Stage 2 was 7.4 g/day (range: 1.4 – 14.8 g/day) versus 1.3 g/day (range: 0.2 – 5.0 g/day) in the LD group (SS2). Subjects in the PA21 MD group were treated for a mean of 22.9 days (range: 15 – 43 days); subjects in the LD group were treated for a mean of 21.2 days (range: 9 – 33 days).

Stage 2 - Secondary efficacy endpoints

Proportions with controlled serum phosphorus levels

At stage 2 baseline (week 24), 72.7% of subjects in the MD group and 61.2% in the LD group were within the KDOQI target range (1.13 to 1.78 mmol/L). At week 27, 63.2% of patients in the MD were within the target range, versus only 15.2% in the LD group, confirming the efficacy of the MD.

Maintenance of effect was shown for PA21 MD based on proportions of patients remaining on target whereas the proportion of patients on target significantly decreased with PA21 LD. These results support the primary efficacy analysis.

Not all patients had controlled serum phosphorus level < 1.78 mmol/L at baseline (week 24) as the inclusion for stage 2 was based on week 20. It is acceptable that proportions may change due to the normal day-to-day fluctuations of serum phosphorus levels. However, percentages on target dropped with 30-40% in 4 weeks whereas patients were to be kept on a stable phosphorus diet. The applicant is requested to provide additional justification that all patients were indeed responders and no noticeable differences were observed between treatment groups.

The population included in Stage 2 is by definition a selected population as only responders were included. This can be accepted as Stage 1 will provide information on the absolute efficacy of PA21.

Effects on serum total Ca, Ca X P and iPTH

No changes over time in serum total calcium levels were observed in the PES. The calcium-phosphorus product was statistically significantly higher in the PA21 MD group compared with the LD group ($p < 0.001$). The iPTH levels increased in PA21 LD, although not statistically significant from PA21 MD.

The increases seen in serum calcium x phosphorus product and iPTH with the PA21 LD group reflect the changes in serum phosphorus levels.

Stage 1 – Secondary analyses comparing PA21 with sevelamer

The mean serum phosphorus level and mean change from baseline through week 24 are shown in Figure 7. The decrease in serum phosphorus from baseline to Week 12 was maintained through Week 24 for both treatment groups, demonstrating maintenance of efficacy. Serum phosphorus levels at Week 24 were on average 1.8 mmol/L (SD: 0.51) and 1.7 mmol/L (SD: 0.45) for PA21 and sevelamer, respectively (LOCF, FAS). Corresponding data for the PPS (LOCF) were 1.8 mmol/L (SD: 0.50) and 1.6 mmol/L (SD: 0.43) for PA21 and sevelamer, respectively.

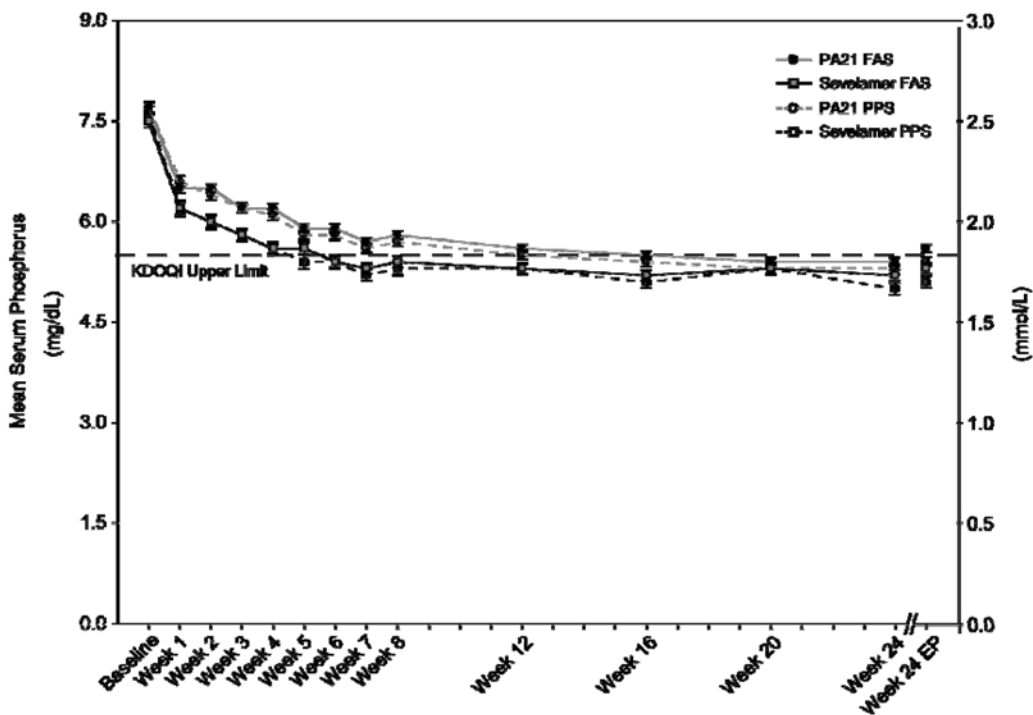


Figure 7: Mean (SEM) serum phosphorus levels during stage 1 PPS and FAS in study PA-CL-05A.

Key secondary efficacy analysis: Non-inferiority of PA21 v sevelamer

In Stage 1, the non-inferiority of PA21 versus sevelamer was demonstrated for efficacy in lowering serum phosphorus in ESRD patients (on HD or PD) after 12 weeks of treatment. The mean decrease from baseline to the Week 12 Endpoint (LOCF) was -0.7 mmol/L in the PA21 group compared to -0.8 mmol/L in the sevelamer group (PPS) (see Table 12). The least square mean estimate of the difference was 0.08 mmol/L with the upper bound of the 97.5% CI equal to 0.15 mmol/L, thus establishing non-inferiority based on a pre-defined non-inferiority margin of 0.19 mmol/L. Similar results were obtained for the FAS (N=1,041; mean difference: 0.10, 97.5% CI upper limit: 0.16).

Superiority analysis of PA21 against sevelamer indicated a significant difference in the change from baseline which was greater with sevelamer than PA21 (p=0.011). The corresponding point estimates for the difference between PA21 and sevelamer were 0.08 mmol/L (PPS) or 0.10 mmol/L (FAS).

Table 12: Week 12 non-inferiority analysis of PA21 vs sevelamer for efficacy in lowering serum phosphorus in stage 1 of study PA-CL-05A (PPS).

Mean Serum Phosphorus mmol/L (mg/dL)	Serum Phosphorus Change from BL to Week 12 (PPS)	
	PA21 (N=461)	Sevelamer (N=224)
BL ⁽¹⁾	2.5 (7.7)	2.4 (7.6)
SD	0.59 (1.82)	0.62 (1.92)
Week 12 EP ⁽²⁾	1.8 (5.5)	1.7 (5.2)
SD	0.43 (1.32)	0.42 (1.29)
Change from BL to Week 12 EP	-0.7 (-2.2)	-0.8 (-2.4)
SD	0.62 (1.91)	0.67 (2.07)
ANCOVA for PA21 vs. sevelamer, change from BL to Week 12 EP		
LS Means	-0.71 (-2.19)	-0.79 (-2.45)
Contrast [upper 97.5% CI ⁽³⁾], mmol/L (mg/dL)	0.08 (0.26) [0.15 (0.46)]	

1 BL is defined as measurement at Visit 4 (i.e., Week 0) or the last recorded value prior to randomisation, if Visit 4 is missing.

2 Missing data at Week 12 was replaced using the last post-BL measurement prior to Week 12.

3 Based on comparison of the upper limit of the CI with a non-inferiority margin of 0.19 mmol/L (0.6 mg/dL).

Notes: ANCOVA = Analysis of covariance; BL = Baseline; CI = Confidence interval; EP = Endpoint; LS = Least square; PPS = Per-protocol set; SD = Standard deviation.

Non-inferiority between PA21 and sevelamer was demonstrated at week 12 based on serum phosphorus levels and the predefined non-inferiority margin of 0.19 mmol/L. Within the FAS the mean difference was 0.10 mmol/L (97.5% CI upper limit: 0.16 mmol/L) and comparable results were obtained based on the PPS. Subsequently performed superiority analyses showed that in fact the change from baseline was statistically significantly higher with sevelamer. Although this difference is small and does not appear to be clinically relevant, the proportion of patients reaching target is considered an important parameter to assess clinical relevance of the effect. These analyses do raise concern on the non-inferiority of PA21 compared to sevelamer and are further discussed below.

Sensitivity analyses were performed for missing data. The number of patients with data is presented in the Table below.

Table 13: Number of patients with serum phosphorus measurements during the first 12 weeks in Study PA-CL-05A – FAS and PPS

FAS, Time (week)	PA 21 (N=694)	Sevelamer (N=347)
1	584 (84.1%)	302 (87.0%)
2	670 (96.5%)	335 (96.5%)
3	596 (85.9%)	308 (88.8%)
4	651 (93.8%)	334 (96.3%)
5	586 (84.4%)	303 (87.3%)
6	630 (90.8%)	331 (95.4%)
7	574 (82.7%)	289 (83.3%)
8	607 (87.5%)	318 (91.6%)
12	589 (84.8%)	318 (91.6%)
PPS, Time (week)	PA 21 (N=461)	Sevelamer (N=224)
1	382 (82.8%)	204 (91.1%)
2	452 (98.0%)	220 (98.2%)
3	404 (87.6%)	204 (91.1%)
4	453 (98.3%)	219 (97.8%)
5	411 (89.2%)	201 (89.7%)
6	452 (98.0%)	223 (99.6%)
7	411 (89.2%)	206 (92.0%)
8	448 (97.2%)	217 (96.9%)
12	457 (99.1%)	223 (99.5%)

The results of the sensitivity analyses are presented below.

Table 14: Change from baseline to week 12 serum phosphorus (mmol/L) for PA21 versus sevelamer using different models (summarised by assessor from tables in 14.2)

	FAS	PPS
Ancova- LOCF#	Mean difference: 0.10 mmol/L (+/- 0.03) N=1,041 97.5%-CI: (-infinity, 0.16)	Mean difference: 0.08 mmol/L (+/- 0.03) N=685 97.5%-CI: (-infinity, 0.15)
Ancova-OC#	Mean difference: 0.08 mmol/L (+/- 0.03) N=907 97.5%-CI: (-infinity, 0.14)	
MMRM-MAR##	Mean difference: 0.08 mmol/L (+/- 0.03) N=1,041 97.5%-CI: (-infinity, 0.14)	Mean difference: 0.07 mmol/L (+/-0.04) N=685 97.5%-CI: (-infinity, 0.14)

Covariates besides treatment in the models were: baseline, dialysis status, region (in the MMRM-MAR also week and treatment*week); # using besides covariates, only baseline and week 12 data
using besides covariates, data of all weeks from between baseline to week 12; non-inferiority margin is 0.19 (mmol/L).

The LOCF method was used for imputation of missing data. In the FAS, non-missing data from week 1 up to (not including) week 12 varied from 3.5% to 15.6% and from 3.5% to 13.0% in the PA21 and Sevelamer group respectively in stage 1. For the PPS, this was from 1.7% to 17.3% and from 0.4% to 10.3% respectively (the PPS by definition had fewer missing data). Therefore, the amount of missing data is reasonably comparable between groups, also at individual time points, but is not negligible. The reason for missings of data should be provided at different times to clarify whether these occurred randomly or could be related to efficacy. The applicant should further present the number of withdrawals at week 12 in both treatment groups and clarify whether these were handled as missings in the analyses.

Sensitivity analyses were performed with regard to missing values. The MAR model gives more or less the treatment effect if all patients had continued on treatment for the whole study duration. More precisely that given the covariates baseline dialysis status, region, week, the estimate for non-missing patients are unbiased estimate for all patients with that same covariates. The OC analysis is in essence a subset analysis, namely treatment effect in subset of patients that received treatment at baseline and week 12. The LOCF analysis gives the treatment effect in the scenario that after missing, patients do not further improve (nor worsen). This is partly conservative. This is because of the decreasing trend in both treatments, so that at a missing time point, LOCF for a patient will impute his/her worse condition of before. However, LOCF is influenced by differences in the percentage of missing data between groups and differences in timing of missing data within groups. E.g. if in the PA21 arm all patients are on treatment till week 8 and reach the target level, but are missing from week 8 onwards, then the LOCF estimate for PA21 will be the target level. However in reality, it is more sensible that patients off treatment will gradually return to baseline. Since in the PA21 arm there were more withdrawals this could be a critical issue. Therefore, additional sensitivity analyses are proposed.

The MAA performed an additional analysis based on KDOQI criterion, considering subjects having favoring P-lowering effect:

(1) patients were excluded from the FAS analysis (called Modified FAS, that construed 34% and 29% of Overall FAS population in PA21 and Sevelamer groups, respectively) if they were taking any prohibited medications (other P binders, oral iron, Ca and Mg compounds) or with overall compliance >120%, or with incomplete Kt/V assessments) and

(2) once subject did change dose it was treated as non-responder.

The proportion of responders were lower in Modified FAS as compared to Overall FAS populations (45.3% vs 36.5% in PA21 and 54.9 vs 45.6% in SEV groups at Week 12, i.e. **~9% lower**; 53.1% vs 41.1% in PA21 and 53.6 vs 45.2% in SEV groups at Week 24, i.e. **~8 to 12% lower**; and 51.9% vs 34.3% in PA21 and 55.2 vs 34.5% in SEV groups at Week 52, i.e. **~17 to 21% lower** in Modified FAS population. The number of analyzed at 3 time points are comparably lower than it was at baseline. Reaching only 20-30 % of the size that was at the baseline.

Further to this, MAA made odds ratios of responder rates PA21 vs SEV analysis using logistic regression model, adjusting for baseline serum P. At all three time points (Week 12, 24 and 52) the 95% CI for odds ratios included 1, indicating no statistically significant differences between PA21 and SEV groups. These analyses are reassuring that no differences are reasonable to expect.

Other secondary endpoints

Serum phosphorus levels over time

In the FAS, the mean serum phosphorus level had dropped below 1.78 mmol/L (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. In the PPS, the mean serum phosphorus level had dropped below 1.78 mmol/L by Week 5 in the sevelamer group and by Week 12 in the PA21 group.

MMRM-MAR analysis of trend over time showed that there were significant differences between treatment groups up to Week 12, with higher mean serum phosphorus levels for PA21 compared to sevelamer; 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.

Analyses of serum phosphorus levels over time showed that mean serum phosphorus levels tended to remain higher with PA21 than with sevelamer. Serum levels below the upper limit of the KDOQI target

range were reached earlier with sevelamer, which might be explained by starting with the optimal dose of sevelamer.

Responder analysis – controlled serum phosphorus

KDOQI target: A minority of patients had controlled serum phosphorus levels at baseline, 6.1% patients in the PA21 group and 8.4% in the sevelamer group (FAS, Table 15). 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). By week 24, there was only a slight difference between treatment groups (54.4% versus 52.6%). Based on logistic models, subjects in the sevelamer group were more likely to have controlled serum phosphorus at week 12 according to KDOQI (OR 0.69; 95% CI: 0.52, 0.91; p=0.010), whereas there was no statistical difference between groups at week 24 (OR 0.99; 95% CI: 0.73, 1.34; p=0.949).

Table 15: Proportion of subjects with serum phosphorus levels within the KDOQI target (1.13 to 1.78 mmol/L) at Stage 1 (FAS, N=1,041)

Time point	PA21 (N=694)	Sevelamer (N=347)	
Baseline subjects evaluated	694	347	
Baseline controlled: n (%)	42 (6.1%)	29 (8.4%)	
Week 12 subjects evaluated	589	318	
Week 12 controlled: n (%)	264 (44.8%)	174 (54.7%)	
Week 24 subjects evaluated	496	285	
Week 24 controlled: n (%)	261 (52.6%)	155 (54.4%)	
Analysis Statistic	Parameter estimate (SE)	p-value	Odds ratio (95% CI)
KDOQI target			
Logistic model at Week 12 (N1=907; N2=907)			
Intercept	1.9 (0.33)	<0.001	
Treatment*	-0.4 (0.14)	<0.001	0.69 (0.52; 0.91)
Baseline phosphorus	-0.7 (0.13)	<0.001	0.50 (0.39; 0.64)
Logistic model at Week 24 (N1=781; N2=781)			
Intercept	1.9 (0.35)	<0.001	
Treatment*	-0.0 (0.15)	0.949	0.99 (0.73; 1.34)
Baseline phosphorus	-0.7 (0.14)	<0.001	0.49 (0.38; 0.64)

* Odds ratio estimate for PA21 vs. sevelamer; CI: confidence interval; FAS: Full analysis set; KDOQI: Kidney Disease Improving Outcomes, N1/2: Number of subjects at week used in the model.

The median time for subjects to achieve control based on KDOQI was 23.0 days with PA21 and 18.6 days with sevelamer (Figure 8). The difference in time to control was statistically significant favoring sevelamer (p=0.004, Kaplan-Meier analysis). 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.

A similar trend was observed for patients reaching normal phosphorus levels (KDIGO range: 0.81 to 1.45 mol/l), but absolute numbers were much lower (data not shown).

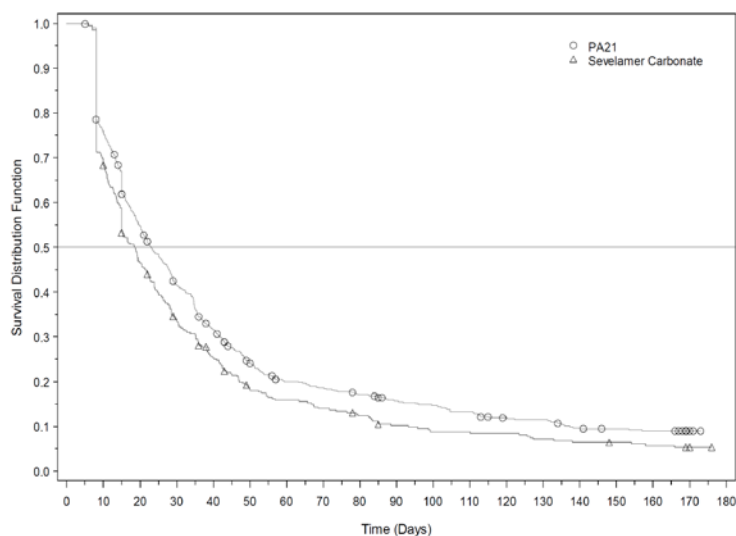


Figure 8: Time to first controlled serum phosphorus according to the KDOQI range Full Analysis Set. Stage 1

Dose

Dose distribution of PA21 over time in relation to KDOQI target is shown in Table 16. Most subjects (82.8%) were up-titrated to 7.5 g/day or above by Week 8. Of the PA21-treated subjects (292/620 (47.1%)) who had controlled serum phosphorus levels at Week 8 (according to the KDOQI target range), 73 (25.0%) subjects were taking 5.0 g/day and 88 (30.1%) subjects were taking 7.5 g/day. Of the sevelamer-treated subjects (160/325 (49.2%)) with controlled serum phosphorus, 53 (33.2%) subjects were taking the recommended starting dose of 2.4 or 4.8 g/day (data not shown).

Table 16: Dose distribution of PA21 in relation to KDOQI target for patients on PA21 in stage 1 of study PA-CL-05A (FAS)

Week	PA21 (FAS, N=694)						
	No per subgroup (% of all)	Mean dose (SD)	No. per subgroup (%) for each dose (g/day)				
			5.0 n (%)	7.5 n (%)	10 n (%)	12.5 n (%)	15 n (%)
Week 8							
All	620 (100%)	9.1 (2.65)	107 (17.3%)	164 (26.5%)	189 (30.5%)	155 (25.0%)	5 (0.8%)
Controlled*	292 (47.1%)	8.4 (2.55)	73 (25.0%)	88 (30.1%)	90 (30.8%)	39 (13.4%)	2 (0.7%)
Uncontrolled	328 (52.9%)	9.8 (2.54)	34 (10.4%)	76 (23.2%)	99 (30.2%)	116 (35.4%)	3 (0.9%)
Week 12							
All	583 (100.0%)	10.0 (3.21)	88 (15.1%)	124 (21.3%)	162 (27.8%)	117 (20.1%)	92 (15.8%)
Controlled	258 (44.5%)	9.2 (3.07)	53 (20.5%)	64 (24.8%)	74 (28.7%)	44 (17.1%)	23 (8.9%)
Uncontrolled	325 (55.7%)	10.6 (3.19)	35 (10.8%)	60 (18.5%)	88 (27.1%)	73 (22.5%)	69 (21.1%)
Week 24							
All	513 (100%)	11.0 (3.46)	61 (11.9%)	86 (16.8%)	115 (22.4%)	92 (17.9%)	159 (31.0%)
Controlled	261 (50.9%)	10.3 (3.40)	40 (15.3%)	51 (19.5%)	68 (26.1%)	45 (7.2%)	57 (21.8%)
Uncontrolled	252 (49.1%)	11.7 (3.36)	21 (8.3%)	35 (13.9%)	47 (18.7%)	47 (18.7%)	102 (40.5%)

* Subjects with controlled serum phosphorus levels according to KDOQI target range (1.13 to 1.78 mmol/L).

At week 12, 10% less patients on PA21 reach target levels compared to sevelamer (44.8% versus 54.7%), whereas the percentage of patients reaching target is comparable at week 24 (52.6% versus 54.4%). Dose distribution in relation to target shows that the majority of patients used doses of 7.5 g/day and higher at week 8 and above. Based on these data the applicant proposes a new starting dose of 7.5 g/day of PA21 which also allows three times daily dosing with meals. A reference is made to the publication by Fishbane S, et al. *A randomized, parallel, open-label study to compare once-daily sevelamer carbonate powder dosing with thrice-daily sevelamer hydrochloride tablet dosing in CKD patients on hemodialysis. Am J Kidney Dis. 2010 Feb;55(2):307-15.* This study showed that thrice daily dosing is more effective than once-daily dosing. According to the applicant, the higher dose is also supported by the safety data (see Clinical safety section).

Effects on serum total Ca, Ca X P and iPTH

The changes from baseline for serum total Ca, Ca x P, and iPTH are summarized in Table 17.

There were no clinically relevant changes in serum total calcium over time. The decreases in calcium-phosphorus product were consistent with changes seen in serum phosphorus. The calcium-phosphorus product was below the KDOQI target level (4.4 mmol²/L²) by Week 4 in both treatment groups. Mean serum iPTH levels decreased during Stage 1 in the FAS, although there was considerable variability among subjects.

Table 17: Change from L to week 12 and week 24 EP in serum total calcium, Ca x P, and iPTH in PA-CL-05A

	Serum Total Calcium mmol/L (mg/dL)		Serum Ca x P mmol ² /L ² (mg ² /dL ²)		Serum iPTH pmol/L (ng/L) ⁽¹⁾	
	PA21 (N=694)	Sevelamer (N=347)	PA21 (N=694)	Sevelamer (N=347)	PA21 (N=694)	Sevelamer (N=347)
BL ⁽²⁾	2.2 (8.8)	2.2 (8.8)	5.5 (67.9)	5.3 (65.4)	46.2 (435.0)	42.9 (403.9)
SD	0.19 (0.74)	0.20 (0.79)	1.35 (16.76)	1.31 (16.22)	31.87 (300.38)	28.89 (272.25)
Week 12	2.2 (9.0)	2.2 (9.0)	4.0 (50.1)	3.8 (47.5)	37.9 (357.3)	36.5 (343.7)
SD	0.18 (0.71)	0.18 (0.70)	1.07 (13.19)	1.02 (12.57)	26.90 (253.49)	25.69 (242.09)
Change from BL to Week 12	0.0 (0.2)	0.0 (0.2)	-1.4 (-17.4)	-1.5 (-18.3)	-8.7 (-81.7)	-6.0 (-57.0)
SD	0.18 (0.71)	0.17 (0.69)	1.38 (17.12)	1.41 (17.40)	25.20 (237.56)	23.56 (222.05)
Week 24 EP ⁽³⁾	2.2 (8.9)	2.2 (8.9)	4.1 (50.3)	3.9 (47.7)	39.8 (374.9)	39.2 (369.5)
SD	0.20 (0.81)	0.17 (0.70)	1.17 (14.54)	1.04 (12.85)	29.83 (281.11)	28.96 (272.92)
Change from BL to Week 24 EP	0.0 (0.2)	0.0 (0.2)	-1.4 (-17.7)	-1.4 (-17.7)	-6.6 (-62.7)	-3.2 (-30.1)
SD	0.21 (0.82)	0.20 (0.82)	1.50 (18.54)	1.37 (16.96)	29.22 (275.39)	25.49 (240.25)
ANCOVA for PA21 vs. Sevelamer for Change from BL to Week 24 EP						
Contrast for LS	0.00 [-0.02, 0.02]		0.15 [0.02, 0.29]		-1.62 [-4.78, 1.54]	
Mean [95% CI of the difference]	(0.01 [-0.08, 0.09])		(1.90 [0.19, 3.61])		(-15.30 [-45.08, 14.49])	
p-value	0.901		0.030		0.314	

1 1 ng/L is equivalent to 1 pg/mL.

2 BL is defined as measurement at Visit 4 (i.e., Week 0) or the last recorded value prior to randomisation, if Visit 4 is missing.

3 Week 24 value or the latest available value prior to Week 24, when Week 24 value was missing (LOCF).

Notes: ANCOVA = Analysis of covariance; BL = Baseline; Ca x P = Calcium-phosphorus product; CI = Confidence interval; EP = Endpoint; FAS = Full analysis set; iPTH = Intact parathyroid hormone; LOCF = Last observation carried forward; LS = Least square; SD = Standard deviation.

(FAS)

There were no changes in serum calcium levels, whereas changes in serum calcium x phosphorus product reflected the changes observed in serum phosphorus levels.

Quality of Life/ Patient preference / Patient satisfaction

Changes from baseline in quality of life scores were generally small overall. There were no trends observed and there were no significant differences between treatment groups for any SF-36 components. 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. There were no relevant differences observed between the 2 groups over time.

Bone markers, Fibroblast Growth Factor 23, and vitamins

Changes in relevant bone markers and vitamins did not reveal clinically relevant changes from baseline or between treatment groups. These are further discussed within the section on Clinical Safety.

Dialysis status

Subjects' dietary habits (including calcium, fluids, lipid, phosphate, potassium, protein, or sodium chloride intake) remained generally unchanged throughout Stage 1 (Week 1 to 24) and Stage 2 (Weeks 25 to Week 27) and there were no differences observed between treatment groups.

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.

Ancillary analyses

Stage 1

A greater reduction in serum phosphorus levels was seen in patients with higher baseline serum phosphorus levels. The interaction analyses using the ANCOVA-LOCF model to test the possible interaction between treatment with covariates of sex, age (<65, ≥65 years), race (White, Black, Other), ethnicity (Hispanic, Non-Hispanic), type of dialysis (HD or PD), time from first dialysis, reason for ESRD (hypertension, diabetes, other), number of prior phosphate binders (1, 2 or more) and prior use of sevelamer (yes, no) showed no remarkable differences in treatment effects on change from baseline in serum phosphorus across subgroups and no statistically significant interactions for any of these covariates.

Stage 2

There were no remarkable differences in treatment effects on the change from baseline in serum phosphorus across sub-groups (sex, age, race, ethnicity, and geographic region) and no significant p-values for any of these covariates.

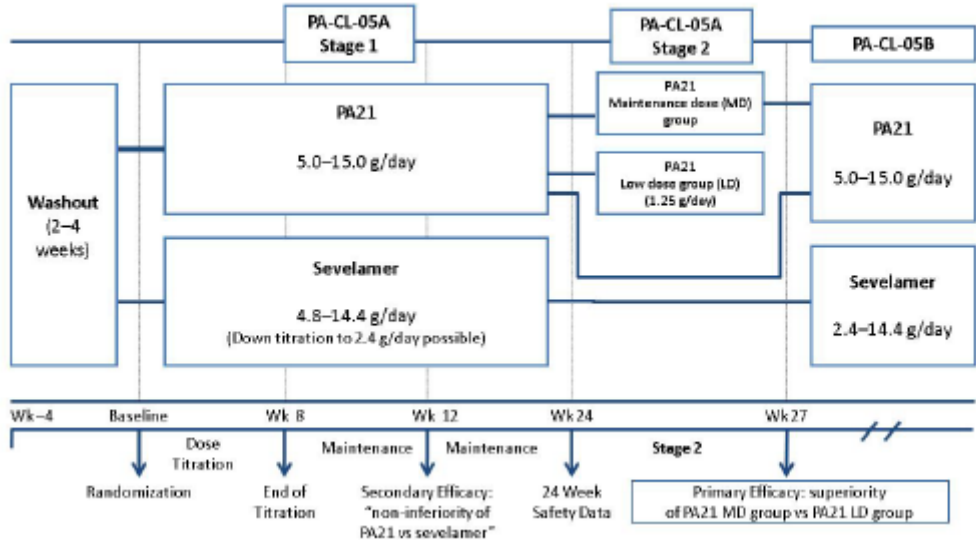
Summary of main studies

The following tables summarise the efficacy results from the main studies.

Phase 3 confirmatory trial PA-CL-05A

Table 18: Summary of efficacy for trial PA-CL-05A

Title: 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 Dialysis Patients with Hyperphosphataemia

Study identifier	PA-CL-05A		
Design	<p>This was a 2-stage re-randomisation study:</p> <p>After a 2-4 week washout period, eligible subjects were randomised and entered Stage 1 (serum P level >1.94 mmol/L). 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 in patients on HD or PD.</p> <p>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). The first 100 patients on HD with controlled serum P level at week 20 (<1.78 mmol/L) entered stage 2. 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.</p> <p>Patients were randomized 2:1 to PA21 or sevelamer.</p> 		
	Duration of main phase: Stage 1 Stage 2 Duration of Run-in phase: Duration of Extension phase:	24 weeks 3 weeks 2-4 weeks 26 weeks	
Hypothesis	<p>Primary analysis, stage 2: Superiority of PA21 maintenance dose (MD) versus PA21 low dose (LD) control in maintaining the phosphorus lowering effect in patients undergoing haemodialysis</p> <p>Primary secondary analysis, stage 1: Non-inferiority of PA21 (with possible assessment of superiority) versus sevelamer in lowering serum phosphorus in patients on dialysis after 12 weeks of treatment.</p>		
Treatments groups	PA21 MD (stage 2)	Week 24 maintenance PA21 dose for three weeks, n=50	
	PA21 LD (stage 2)	Fixed dose PA21 1.25 g/day for three weeks, n=49	
	PA21 (stage 1)	PA21 for 24 weeks, start dose of 5.0 g/day plus up-titration 8 weeks, n=710	
	Sevelamer (stage 1)	Sevelamer carbonate for 24 weeks, start dose of 4.8 g/day plus up-titration 8 weeks, n=349	
Endpoints and definitions	Primary endpoint	Serum P wk 24-27	Change in serum phosphorus levels from week 27 to week 24; PA21 MD versus PA21 LD (superiority, FAS)
	Secondary endpoint, primary	Serum P wk 12	Change in serum phosphorus level at week 12 from baseline; PA21 versus sevelamer (non-inferiority, PPS)

	Secondary endpoint, other	Controlled P	Proportion of subjects achieving phosphorus control (KDOQI target 1.13 to 1.78 mmol/L) at each time point	
Database lock	<date>			
<u>Results and Analysis</u>				
Analysis description		Primary Analysis – Superiority over low dose PA21		
Analysis population and time point description		Primary efficacy set (PES); First 100 patients on HD with controlled serum phosphorus at week 20 (<1.78 mmol/L) were randomised 1:1 into stage 2. PES consisted of patients with at least one dose of study medication in stage 2 and one evaluable efficacy assessment thereafter in stage 2.		
		Change at end of treatment week 27 from week 24 (LOCF)		
Descriptive statistics and estimate variability	Treatment group	PA21 MD	PA21 LD	
	Number of subjects	N=44	N=49	
	Serum P wk 24-27, LS Mean (mmol/L)	0.08	0.62	
	95% CI	-0.07; 0.23	0.47; 0.77	
Effect estimate per comparison	Primary endpoint	Comparison groups	PA21 LD versus PA21 MD	
		Difference LS means	0.54	
		95% CI	0.37; 0.71	
		P-value*	<0.001	
Notes	<p>* ANCOVA analysis on endpoint results using a mixed model with the maximum likelihood estimation. The model includes treatment, baseline serum phosphorus levels, and region (US/EU/ROW) as fixed effects. Endpoint results were calculated with Week 27 results or the latest evaluable measurement after Week 24 when Week 27 was missing (LOCF).</p> <p>All subjects randomized to PA21 LD and 44 of 50 (88%) of subjects randomized to PA21 MD were included in the PES. Of the 6 subjects in the MD group who were excluded from the PES, 3 were excluded because of errors in dispensing study drug and 3 because of non-compliance with the protocol.</p>			
Analysis description		Secondary analysis – Non-inferiority to sevelamer in lowering serum phosphorus level		
Analysis population and time point description		Per-protocol set (PPS); Patients who received at least one dose of study medication, completed the analysis dose titration period (baseline to week 12) and had at least one evaluable serum phosphorus result at or after week 12 and no major protocol deviations.		
		Change at end of treatment week 12 from baseline (LOCF)		
Descriptive statistics and estimate variability	Treatment group	PA21	Sevelamer	
	Number of subjects	N=461 (n=41 PD)	N=224 (n=16 PD)	
	Serum P, baseline	2.5	2.4	
	SD	0.59	0.62	
	Serum P (LOCF), Week 12	1.8	1.7	
	SD	0.43	0.42	
	Serum P wk 12, LS Mean change (mmol/L)	-0.71	-0.79	
	SE	0.03	0.04	

Effect estimate per comparison	secondary endpoint	Comparison groups	PA21 versus Sevelamer																																												
		Difference LS means	0.08																																												
		97.5% upper CI	0.15																																												
		P-value*	<0.001																																												
Notes	<p>* ANCOVA analysis on endpoint results using a mixed model with the maximum likelihood estimation. The model includes treatment, dialysis status, region (US/EU/ROW) and baseline serum phosphorus levels as fixed effects. Missing data at week 12 was replaced using the last post-baseline measurement prior to week 12 (LOCF). The non-inferiority margin was defined as 0.19 mmol/L.</p> <p>Table: Reasons for withdrawal of all subjects randomized in study PA-CL-05A</p> <table border="1"> <thead> <tr> <th rowspan="2">Reason for withdrawal</th> <th colspan="2">Stage 1</th> </tr> <tr> <th>PA21 (N=710)</th> <th>Sevelamer (N=349)</th> </tr> </thead> <tbody> <tr> <td>Total withdrawn</td> <td>195 (27.5%)</td> <td>56 (16.0%)</td> </tr> <tr> <td>Total completed</td> <td>515 (72.%)</td> <td>293 (84.0%)</td> </tr> <tr> <td>AE (other than P or Ca level events)</td> <td>94 (13.2%)</td> <td>20 (5.7%)</td> </tr> <tr> <td>Consent withdrawn/withdrawal by subject</td> <td>29 (4.1%)</td> <td>13 (3.7%)</td> </tr> <tr> <td>Phosphorus > 2.75 mmol/L</td> <td>11 (1.5%)</td> <td>0 (0.0%)</td> </tr> <tr> <td>Death</td> <td>9 (1.3%)</td> <td>5 (1.4%)</td> </tr> <tr> <td>Investigator decision</td> <td>8 (1.1%)</td> <td>3 (0.9%)</td> </tr> <tr> <td>Protocol violation</td> <td>4 (0.6%)</td> <td>0 (0.0%)</td> </tr> <tr> <td>Sponsor decision</td> <td>4 (0.6%)</td> <td>4 (1.1%)</td> </tr> <tr> <td>Calcium > 2.75 mmol/L</td> <td>2 (0.3%)</td> <td>0 (0.0%)</td> </tr> <tr> <td>Phosphorus < 0.81 mmol/L</td> <td>1 (0.1%)</td> <td>0 (0.0%)</td> </tr> <tr> <td>Prohibited concomitant medication</td> <td>1 (0.1%)</td> <td>0 (0.0%)</td> </tr> <tr> <td>Other</td> <td>32 (4.5%)</td> <td>11 (3.2%)</td> </tr> </tbody> </table>			Reason for withdrawal	Stage 1		PA21 (N=710)	Sevelamer (N=349)	Total withdrawn	195 (27.5%)	56 (16.0%)	Total completed	515 (72.%)	293 (84.0%)	AE (other than P or Ca level events)	94 (13.2%)	20 (5.7%)	Consent withdrawn/withdrawal by subject	29 (4.1%)	13 (3.7%)	Phosphorus > 2.75 mmol/L	11 (1.5%)	0 (0.0%)	Death	9 (1.3%)	5 (1.4%)	Investigator decision	8 (1.1%)	3 (0.9%)	Protocol violation	4 (0.6%)	0 (0.0%)	Sponsor decision	4 (0.6%)	4 (1.1%)	Calcium > 2.75 mmol/L	2 (0.3%)	0 (0.0%)	Phosphorus < 0.81 mmol/L	1 (0.1%)	0 (0.0%)	Prohibited concomitant medication	1 (0.1%)	0 (0.0%)	Other	32 (4.5%)	11 (3.2%)
Reason for withdrawal	Stage 1																																														
	PA21 (N=710)	Sevelamer (N=349)																																													
Total withdrawn	195 (27.5%)	56 (16.0%)																																													
Total completed	515 (72.%)	293 (84.0%)																																													
AE (other than P or Ca level events)	94 (13.2%)	20 (5.7%)																																													
Consent withdrawn/withdrawal by subject	29 (4.1%)	13 (3.7%)																																													
Phosphorus > 2.75 mmol/L	11 (1.5%)	0 (0.0%)																																													
Death	9 (1.3%)	5 (1.4%)																																													
Investigator decision	8 (1.1%)	3 (0.9%)																																													
Protocol violation	4 (0.6%)	0 (0.0%)																																													
Sponsor decision	4 (0.6%)	4 (1.1%)																																													
Calcium > 2.75 mmol/L	2 (0.3%)	0 (0.0%)																																													
Phosphorus < 0.81 mmol/L	1 (0.1%)	0 (0.0%)																																													
Prohibited concomitant medication	1 (0.1%)	0 (0.0%)																																													
Other	32 (4.5%)	11 (3.2%)																																													
Analysis description	Secondary analysis – Proportion of patients with controlled serum P level																																														
Analysis population and time point description	<p>Full analysis set: Patients who received at least one dose of study medication and had at least one evaluable serum phosphorus result post-baseline.</p> <p>Proportion of patients with controlled serum levels (KDOQI target) was assessed at week 12 and week 24</p>																																														
Descriptive statistics and estimate variability	Treatment group	PA21	Sevelamer																																												
	Number of subjects	N=694	N=347																																												
	Controlled P																																														
	Baseline	42/694 (6.1%)	29/347 (8.4%)																																												
Week 12	264/589 (44.8%)	174/318 (54.7%)																																													
Week 24	261/496 (52.6%)	155/285 (54.4%)																																													
Effect estimate per comparison	secondary endpoint	Comparison groups	PA21 versus Sevelamer																																												
		Week 12																																													
		Odds ratio	0.69																																												
		95% CI	0.52; 0.91																																												
		P-value*	0.010																																												
		Comparison groups	PA21 versus Sevelamer																																												
		Week 24																																													
		Odds ratio	0.99																																												
		95% CI	0.73; 1.34																																												
		P-value*	0.49																																												

Notes	<p>* Logistic models were used to derive the odds ratios using treatment and baseline serum phosphorus value as covariates for the FAS and PES.</p> <p>Proportion of patients on target increased in PA21 between week 12 and week 24 to the same level as that seen for sevelamer. However, appears mostly due to a lower denominator whereas numerator does not change. Therefore, it is not clear whether more patients reach target. Additional analyses are required.</p>
-------	--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Clinical studies in special populations

The pivotal study and most other clinical studies were performed in adult patients with chronic kidney disease on maintenance dialysis. No studies were performed in children and adolescents. A deferral was granted for the paediatric study which will commence after the data from the long-term extension study PA-CL-05B are available.

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

N/A

Supportive study

Study PA1201 was a Phase 2, parallel-group, randomised, double-blind, placebo-controlled, multicentre, dose-ranging (fixed dose) study which enrolled 183 Japanese ESRD patients on stable, maintenance HD. Treated subjects received PA21 at 3.75 g/day (N=39), 7.5 g/day (N=35), 11.25 g/day (N=33), or 15 g/day (N=34), or placebo (N=37) for 6 weeks (FAS). All doses of PA21 demonstrated a statistically significant lowering of serum phosphorus from baseline to Week 6 when compared with placebo ($p < 0.001$). The mean change in serum phosphorus showed a dose-dependent decrease for the PA21 dose-groups. Mean change from baseline was 0.05 mmol/L, -0.59 mmol/L, -0.84 mmol/L, -1.02 mmol/L, and -1.22 mmol/L with placebo, 3.75 g/day, 7.5 g/day, 11.25 g/day, and 15.0 g/day, respectively.

2.2.8. Discussion on clinical efficacy

Design and conduct of clinical studies

Both studies PA-CL-03A (dose-finding) and PA-CL-05A (pivotal study) including the long-term extension phase (PA-CL-05B) were open-labelled studies. Difficulties in blinding due to difference in tablet intake (PA21 chewable tablet whereas sevelamer tablets needs to be swallowed as a whole) and the anticipated discolouring of faeces with PA21 because of its iron content, are acknowledged. PA21 LD was used as "placebo" treatment in the withdrawal phase of study PA-CL-05A to avoid immediate patient unblinding. The open-label nature of the study can be acceptable as the primary endpoint based on serum phosphorus level is an objective endpoint and analysed by a central laboratory.

The primary endpoint in both studies is based on serum phosphorus levels, which is the commonly used pharmacodynamic endpoint in clinical trials in this patient population. It is clinically relevant as serum phosphorus levels above a certain level correlate with increased morbidity and mortality. The proportion of patients within the KDOQI target range (secondary endpoint) is considered an important clinically relevant endpoint as it reflects the treatment goal in clinical practice. Other secondary endpoints were appropriate as well. The phosphate binder wash-out phase of 2-4 weeks is acceptable.

The in-and exclusion criteria of both studies were largely similar and were adequate for the target population in need of treatment according to current clinical practice. Most important difference

between the two studies was the more stringent threshold for hyperphosphataemia in phase 3 (serum phosphorus > 1.94 mmol/L compared to >1.78 mmol/L in phase 2). This resulted in more patients already on target at baseline within the phase 2 study. Patients previously using non-calcium based phosphate binders (sevelamer and lanthanum carbonate) and patients on PD were allowed to be included in the phase 3 study as well, making this population more representative for the target population. Further, intravenous iron treatment was allowed within the phase 3 study, which reflects clinical practice. Patients with significant gastrointestinal disorders or a history iron storage disorders were excluded for safety reasons in both studies. Patients need to be on a stable phosphorus diet as in clinical practice.

Both studies used an active comparator, either sevelamer hydrochloride or carbonate, which are widely used in clinical practice in patients on maintenance dialysis. The starting dose of sevelamer was in line with the highest recommended starting dose (serum P>2.42 mmol/L), which is acceptable.

Phase 2 dose-finding study PA-CL-03A

The design of the dose-finding study (parallel group, active controlled, open-label) is considered adequate. Five fixed doses of PA21 were investigated (range: 1.25 g/day to 12.5 g/day), with the lowest dose expected to be ineffective, enabling investigation of a dose-effect trend. The comparator arm (sevelamer hydrochloride) allows exploring efficacy of PA21 in relation to currently available general accepted phosphate binder treatment. The duration of 6 weeks is considered sufficient to establish treatment effect as serum phosphorus levels are known to drop rapidly (within one to two weeks). The sample size of 19 patients per treatment group was based on the primary analysis (change from baseline in serum phosphorus level). Withdrawal rates were high (20% - 45% for PA21 and 31% for sevelamer) mainly due to too low or high serum phosphorus levels resulting from the fixed dose regimen, which impacts interpretation of results.

Phase 3 pivotal study PA-CL-05A

The design of the pivotal study includes an active controlled treatment phase (stage 1) followed by a re-randomised withdrawal phase (stage 2) and is considered acceptable. Several aims are addressed within this study, i.e. superiority of PA21 over an ineffective treatment dose, non-inferiority to sevelamer and long-term treatment.

The primary endpoint (change in serum phosphorus level between maintenance PA21 dose versus low, ineffective dose of PA21), provides information on the maintenance of effect of PA21 in patients responding to PA21. Demographic characteristics of the patient population appeared comparable to the overall responder population. More Black/African American were included as a large proportion of subjects from the US entered stage 2, but race was not associated with the outcome. The main secondary endpoint (non-inferiority to sevelamer at week 12) is considered an important endpoint as well. The clinical relevance of the chosen non-inferiority margin of 0.19 mmol/L was not justified. The proportion of patients within the KDOQI target range is of clinical relevance as it reflects clinical practice.

The starting dose of 5 g/day is supported by the phase 2 study; the reason for the maximum dose of 15 g/day is not evident based on phase 2. PA21 LD as "surrogate placebo" is supported by phase 2 study.

About 1.5-2 times more patients on PA21 compared to sevelamer were withdrawn during the first stage of the study (27.5% versus 16.0%). Most common reasons were adverse events and withdrawal of consent in both groups. Withdrawal due to adverse events was higher in the PA21 treatment group.

One study site was closed as it was noticed by the CRO that study procedures had been performed at 2 non-approved satellite sites. This action is considered adequate. According to the Applicant, this was an isolated issue.

Phase long-term extension study PA-CL-05B

Subjects completing PA-CL-05A could enrol into the long-term extension study up to one year of follow-up. Exclusion criteria including high ferritin levels and elevated liver enzymes are considered acceptable /reflect clinical practice. Twice as many patients on PA21 (15.4% compared to 8.5% on sevelamer) did not enrol into the long-term extension study, the main reason being not willing to provide consent in both treatment groups. It cannot be excluded that some selection has occurred regarding tolerability of treatment, however reported baseline demographic and disease related characteristics were comparable between patients enrolling study PA-CL-05B and PA-CL-05A. Relatively more patients from the ROW were included in the long-term study (36% versus 29%) and less patients from the US.

A concern was raised on GCP compliance based on the database errors between PA-CL-05A and PA-CL-05B identified during the long-term extension study. Further, a concern was raised based on the change in dialysis adequacy frequency for inclusion (from "once weekly" to "during three months") and the observed missing dialysis adequacy data. Although the identified errors did not impact efficacy or safety a concern remains on the quality of auditing/monitoring of the studies especially taking into account the regional spread of the audits performed. This affects the validity of the data in general. Further, assurance was required that no additional treatments were performed that could affect the primary endpoint. Therefore the CHMP requested for a GCP inspection. The GCP inspection included two sponsor sites and two investigational sites (one each in Russia and Ukraine) for the pivotal phase 3 study PA-CL-05A and the long-term extension study PA-CL-05B. The outcome of the inspection confirmed data integrity and the data are therefore acceptable to be used for the discussion on the benefit/risk as concluded by the Inspectors. Given the major findings at the investigational sites, the CHMP requested additional sensitivity analyses for the main efficacy endpoints excluding all Russian and Ukrainian sites, before concluding on the benefit/risk of the product. The results of the analyses were reassuring and confirmed the validity of the all data within the dossier for the benefit/risk discussion of the product. Furthermore, additional sensitivity analyses in which patients with missing values or changes in concomitant medication potentially influencing serum P-values were counted as non-responders confirmed the robustness of the efficacy results.

Efficacy data and additional analyses

Within study PA-CL-3A, baseline characteristics were comparable between treatment groups. All PA21 dose groups except for the lowest dose, showed a statistically significant reduction in serum phosphorus level from baseline. The mean reduction of the 5.0 g/day and 7.5 g/day PA21 treatment groups were comparable to that seen with sevelamer (FAS, around 0.34 to 0.40 mmol/l reduction). Higher reductions were observed with the two highest doses and the effect appears dose-related. The results are likely influenced by the high number of withdrawals especially for the highest dose groups due to serum phosphorus levels below the safety limit. The results support the choice of 5 g/day as starting dose for the pivotal study in which doses are up titrated based on serum phosphorus levels.

Within study PA-CL-05A, baseline characteristics did not show marked differences between treatment groups at the start of study or the withdrawal phase, and between patients included in the withdrawal phase and the overall included population. About 8% of patients entering the study were on peritoneal dialysis, in line with the expected percentage (about 10%) in the general population on dialysis.

Although by definition all patients were responders at start of the withdrawal phase (assessed at week 20), about 30-40% were not on target at week 24, whereas patients were kept on a stable phosphorus diet. According to the Applicant, this can be explained by the natural high variability of serum phosphorus levels over time. Still, a variation of 30-40% is considered large given the variation seen in the overall population over time (roughly 10%). Also, serum phosphorus levels in the PA21 LD group did not return to the week 0 baseline value, suggesting that this dose shows some efficacy. This was also seen in individual cases in study PA-CL-03A. Despite the large variation observed and the placebo response which would result in a lowering of the effect, superiority of PA21 MD over PA21 LD in maintenance of effect was shown at the end of the withdrawal phase (mean difference of 0.54 mmol/L).

In the active controlled treatment phase, the serum phosphorus lowering effect of PA21 was non-inferior to sevelamer at week 12 based on mean change in serum phosphorus level. Mean change from baseline is in line with that known for sevelamer. A slightly larger change from baseline was observed for sevelamer (mean difference of 0.08 mmol/L for the PPS or 0.10 mmol/L for the FAS, statistically significant). Missing data were few when non-inferiority was analysed using the PPS population at week 12. Non-inferiority of PA21 to sevelamer based on mean change in serum phosphorus levels was confirmed by post-hoc sensitivity analyses using more conservative methods for handling of missing data. On the other hand, the greater portion of patients in the sevelamer group compared with the PA21 group on KDOQI target (54.7% versus 44.8%, OR=0.69, 95% CI: 0.52, 0.91) indicates a poorer performance of PA21. Although responder rates between treatment groups were comparable at week 24 based on observed cases (sevelamer: 54.4% versus PA21: 52.6%) this is not supported by an analysis based on the ITT population (sevelamer: 44% versus PA21: 37%). Long-term data up to one year show that efficacy is maintained and mean serum phosphorus levels are comparable between treatment groups, supporting clinical relevant efficacy of PA21. Proportion on KDOQI target was maintained over the period of 6 to 12 months. Although it appears that proportion responders are somewhat lower for PA21 than on sevelamer, this difference (estimated about 7% based on ITT analysis) is considered acceptable given the totality of data.

It remains unknown whether the proposed higher starting dose of 7.5 g/day PA21 will improve proportions on target and/or time to reach target. However, a thrice daily dosing is reasonable based on the number of meals/day and supported by the fact that most patients have their dose increased during follow-up (mean daily dose of PA21 at week 12 was 10.0 g/day and only 15% of patients were still on the starting dose of 5 g/day). It remains uncertain whether higher starting doses (>7.5 g PA21/day) would be beneficial for patients with higher baseline serum phosphorus levels (e.g. > 2.42 mmol/L as with sevelamer). However, it can be acceptable to start treatment at a starting dose of Velphoro is 1,500 mg iron (3 tablets) per day for tolerability reasons and the dose can be up titrated in a reasonable time period.

A post-hoc responder analysis stratified for baseline serum phosphorus levels (<2.42 mmol/L and \geq 2.42 mmol/L) showed comparable response rates between PA21 and sevelamer for both groups from week 24 onwards.

Although the majority of patients received the maximum daily dose at week 52 (about 40%), one quarter of patients on PA21 received a dose of \leq 7.5 g/day (1,500 mg/day iron), which supports the starting dose of 7.5 g/day.

Prior to stopping phosphate binder treatment for the washout period about 34% - 38% of patients had serum phosphorus levels within the KDOQI range. This rate is in the same order of magnitude as estimated based on the ITT analysis (37% - 44%) in the clinical trial at week 24.

Based on the mean daily doses of PA21 and sevelamer at week 12 and 24, the average number of pills to be taken is about 4 tablets per day with PA21 compared to 9-12 tablets per day with sevelamer. 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. This is assumed to be beneficial in terms of patient compliance.

Change from baseline at week 12 was comparable for patients below 65 years and older (n=115 ≥ 65 yrs) for PA21 and between treatment groups. Other subgroup analyses (age, geographic region, dialysis state, previous sevelamer treatment) did not show an effect of subgroup. Although the number of patients on PD was limited, based on current knowledge there are no indications that efficacy of phosphate binders depends on dialysis status.

2.2.9. Conclusions on the clinical efficacy

PA21 has demonstrated superiority in lowering serum phosphate levels at doses of 5-12.5 g/day over the PA21 ineffective dose of 1.25 g/day. The effect appeared dose-related and most patients required doses of 10-15 g/day, administered three times daily with meals. The final posology in section 4.2 of the SmPC has a recommended starting dose of Velphoro is 1,500 mg iron (3 tablets) per day, divided across the meals of the day. Velphoro is for oral administration only and must be taken with meals. Patients receiving Velphoro should adhere to their prescribed diets.

Maintenance of effect has been demonstrated after 24 weeks of treatment. The phosphorus lowering effect of PA21 was non-inferior to sevelamer after 12 weeks of treatment. In contrast, a lower proportion of patients on PA21 reached KDOQI target at week 12 which is the treatment aim in daily clinical practice. In addition, the duration to first time on KDOQI target was longer with PA21. The proportion of patients on KDOQI target appeared comparable at week 24 based on observed cases but remains lower based on the intention-to-treat analysis. No data are available with the proposed starting dose of PA21 7.5 g/day, but the majority of patients needed a dose increase. A thrice daily dosing is reasonable allowing dosing with each meal. Withdrawal rates were higher for PA21 than for sevelamer, mainly related to a difference in withdrawals because of adverse events (see safety section). Serum phosphorus levels appeared stable up to 24 weeks. Further, in patients tolerating PA21 at week 24, maintenance of effect was shown up to one year of treatment and mean serum phosphorus levels were comparable to that observed with sevelamer. A tendency was seen for a slightly lower responder rate with PA21 throughout the one-year follow-up.

The outcome of the inspection confirmed data integrity and the data are therefore acceptable to be used for the discussion on the benefit/risk, as concluded by the inspectors. Given the major findings at the investigational sites (one each in Russia and Ukraine), the CHMP requested additional sensitivity analyses for the main efficacy endpoints excluding all Russian and Ukrainian sites, before concluding on the benefit/risk of the product. The results of the analyses were reassuring and confirmed the validity of the all data within the dossier for the benefit/risk discussion of the product.

2.3. Clinical safety

Patient exposure

Safety data were available from 7 phase 1, 1 phase 2 and 1 phase 3 clinical study.

Within the phase I studies a total of 261 healthy volunteers and 16 CKD patients received PA21 in doses ranging from 3.75 g/day to 15.0 g/day of PA21 (750 to 3000 mg/day). The phase 2 study included 128 CKD patients and the phase 3 study included 707 CKD patients treated with PA21,

amounting to a total of 835 patients on dialysis treatment (778 HD and 57 PD) who received PA21 in doses ranging from 1.25 to 15 g PA21 /day. Within the phase 2 and 3 studies, a total of 374 patients received sevelamer, either as hydrochloride (n=26) or carbonate (n=348).

Safety analyses were performed for each clinical study. Pooled safety analyses were presented for the 5 DDI studies including 210 healthy volunteers in which each subject received a maximum of 8 doses of PA21 (Population 2) and for the phase 2 and phase 3 study combined (Population 1).

The mean duration of exposure in Population 1 was 129.1 days (SD=63.2; range: 1-253 days) for patients treated with PA21 and 147.1 days (SD=47.4; range: 1 -218 days) for sevelamer treated patients.

Duration of treatment by mean daily doses of PA21 is shown below. A total of 514 patients were treated for at least 24 weeks.

Safety data based on the long-term extension study submitted within the response to Day 120 LoQ are described separately further on.

Table 19: Number of subjects receiving PA21 by mean daily dose and duration of exposure in phase 2 and phase 3 clinical studies.

Actual Duration of Exposure (Days) ⁽¹⁾	PA21 Mean Daily Dose (g/day)						Total (Any Dose) n (%)
	1.25	>1.25-5.0	>5.0-7.5	>7.5-10.0	>10.0-12.5	>12.5-15.0	
1	0	3	0	0	0	0	3 (0.4%)
2-14 (0<weeks≤2)	3	24	4	0	2	1	34 (4.1%)
15-28 (2<weeks≤4)	4	13	9	2	1	1	30 (3.6%)
29-42 (4<weeks≤6)	11	26	19	11	8	2	77 (9.2%)
43-84 (6<weeks≤12)	9	18	42	21	8	1	99 (11.9%)
85-168 (12<weeks≤24)	0	34	41	49	46	14	184 (22.0%)
≥169 (weeks>24)	0	72	112	114	86	22	406 (48.6%)
Total (Any duration) n (%)	27 (3.2%)	190 (22.8%)	227 (27.2%)	197 (23.6%)	151 (18.1%)	41 (4.9%)	

1 The total duration of exposure in the study irrespective of dose(s) received.

Notes: Population 1 includes Studies PA-CL-03A and PA-CL-05A.

Each subject is represented once in the table.

Mean daily dose is derived as the sum of the total doses per day across the study divided by total duration of exposure.

Adverse events

The percentage of patients with TEAEs was 80% in PA21 treated patients of which 17% were serious and 11% severe. The majority of TEAEs was of mild severity (about 70%).

Table 20: Overview of Treatment-emergent adverse events: PA-CL-03A and PA-CL-05A (Population 1).

	PA21 (N=835) n (%)	Sevelamer (N=374) n (%)
Total adverse event count	2,771	1,130
Any TEAE	668 (80.0%)	280 (74.9%)
Deaths ⁽¹⁾	14 (1.7%)	7 (1.9%)
Any serious TEAE	141 (16.9%)	71 (19.0%)
Any severe TEAE	92 (11.0%)	39 (10.4%)
Discontinuation due to TEAE	141 (16.9%)	29 (7.8%)

1 Subject 838-908 who died during the follow-up period and the death was not recorded in the database prior to database lock and therefore does not appear in the Section 14 Summary Tables or Appendix 16 listing of deaths.

Notes: Population 1 includes Studies PA-CL-03A and PA-CL-05A.

For subject counts, subjects are included only once, even if they experienced multiple events in that category.

Percentages are based on the total number of subjects in the safety set for that treatment group.

TEAE = Treatment-emergent adverse event.

The study results did not demonstrate a clear dose-relationship for PA21, except for phosphorus levels.

Table 21: Treatment-emergent adverse events occurring in ≥ 5% of patients by system organ class and preferred term: PA-CL-03A and PA-CL-05A (Population 1).

System Organ Class Preferred Term	PA21 (N=835) N (%)	Sevelamer (N=374) N (%)
Subjects with at least 1 TEAE	668 (80.0%)	280 (74.9%)
Gastrointestinal Disorders	351 (42.0%)	124 (33.2%)
Diarrhoea	151 (18.1%)	29 (7.8%)
Faeces discoloured	124 (14.9%)	1 (0.3%)
Nausea	53 (6.3%)	40 (10.7%)
Vomiting	34 (4.1%)	20 (5.3%)
Constipation	31 (3.7%)	25 (6.7%)
Metabolism and Nutrition Disorders	243 (29.1%)	99 (26.5%)
Hyperphosphataemia	96 (11.5%)	29 (7.8%)
Hypophosphataemia	46 (5.5%)	20 (5.3%)
Vascular Disorders	98 (11.7%)	52 (13.9%)
Hypertension	51 (6.1%)	27 (7.2%)

Subjects experiencing more than 1 AE within each preferred term and system organ class were only counted once. Preferred terms reported by ≥5% of subjects were included. SOCs with no preferred terms reported by ≥5% of subjects were not included.

Gastrointestinal TEAEs were the most common AEs among both treatment groups; 42% for PA21 and 33.2% for sevelamer. Most commonly reported preferred terms with PA21 were diarrhoea (n=151, 18.1%) and faeces discolored (n=124, 14.9%) which occurred more frequently in the PA21 group.

Other GI TEAEs that were more frequent with PA21 treatment compared to sevelamer treatment included: upper abdominal pain (19 subjects, 2.3% versus 7 subjects, 1.9%); gastritis (14 subjects,

1.7% versus 4 subjects, 1.1%); and gastro-esophageal reflux (5 subjects, 0.6% versus no subjects). In addition, patients on PA21 experienced tooth discolouration (1.1% PA21) and tongue discolouration (0.6% PA21) which was not seen on sevelamer.

GI TEAEs reported less frequently in the PA21 group compared to the sevelamer group included nausea (53 subjects, 6.3% in the PA21 group versus 40 subjects, 10.7% with sevelamer), and constipation (31 subjects, 3.7% versus 25 subjects, 6.7% respectively).

Of all GI TEAEs, 247 (29.6%) in the PA21 group and 59 (15.8%) in the sevelamer group were considered treatment-related. The most common treatment-related GI TEAEs for PA21 were diarrhoea (n=96 subjects (11.5%) for PA21 and n=11 (2.9%) for sevelamer), followed by discoloured faeces (n=120 subjects (14.4%) for PA21 and n=1 (0.3%) for sevelamer). All tooth discolourations reported for PA21 were treatment-related.

A total of 14 PA21-treated subjects (1.7%) reported severe TEAEs in the Gastrointestinal Disorders SOC compared with 8 subjects (2.1%) in the sevelamer group. In the PA21 group there were 2 reports of severe TEAEs (0.2%) for each of diarrhoea, peritonitis and GI haemorrhage. Other severe events were reported by single subjects.

TEAEs within the SOC Metabolic and Nutrition Disorders were reported in 243 patients (29.1%) with PA21, comparable to sevelamer (26.5%). The highest frequency was reported for hyperphosphataemia (11.5% with PA21 versus 7.8% with sevelamer). Other TEAEs with an incidence >1% in PA21-treated subjects were hypercalcaemia, hyperkalaemia, hypocalcaemia, decreased appetite, fluid overload and hypoglycaemia. The frequency of these events was generally similar to that in the sevelamer-treated subjects. Treatment-related TEAEs with PA21 were hypophosphataemia (n=34), hyperphosphataemia (n=22), hypercalcaemia (n=6), hypocalcaemia (n=4), decreased appetite (n=4 subjects), and hypoglycaemia (n=3).

TEAEs within the SOC Infections and Infestations were reported in 166 patients (19.9%) with PA21, comparable to sevelamer (19.8%). Common TEAEs in the PA21 included nasopharyngitis (n=22), upper respiratory tract infection (n=21), bronchitis (n=19) and frequencies were comparable to those reported within the sevelamer treated group. For 2 subjects (0.2%) in the PA21 group TEAEs were considered treatment-related, including diverticulitis and influenza, each reported once.

TEAEs within the SOC General Disorders and Administration Site Conditions were reported in 121 patients (14.5%) with PA21, comparable to sevelamer (14.4%). Most common events were pyrexia (n=27 with PA21) and chest pain (n=17 with PA21). Product taste abnormal was reported more frequently in the PA21 treatment group (n=23, 2.8%) than in the sevelamer group (n=2, 0.5%), and considered treatment-related.

TEAEs within the SOC Vascular Disorders were reported in 98 patients (11.7%) with PA21, comparable to sevelamer (13.9%). TEAEs reported by >1 subject included hypertension (n=51), hypotension (n=24) and peripheral vascular disorder (n=2) with PA21. Frequencies were comparable to that of sevelamer. Hypertensive crisis was more frequent in the PA21-treated group (n=5) versus no subjects in the sevelamer-treated group. Cases were not considered treatment-related.

TEAEs within the SOC Cardiac Disorders were reported in 76 patients (9.1%) with PA21, comparable to sevelamer (8.8%). TEAEs reported by >1 subject included myocardial infarction (n=9), atrial fibrillation (n=9), congestive cardiac failure (n=8), and tachycardia (n=6) with PA21. No cases of acute myocardial infarction were reported for sevelamer. For the combined preferred terms acute myocardial infarction and myocardial infarction, 12 TEAEs (1.4%) were reported for PA21 compared to 3 (0.8%) for sevelamer. No differences were seen with regard to TEAEs associated with disorders of cardiac rhythm. Two cases were considered treatment-related to PA21 including arrhythmia (n=1) and ventricular extra systole (n=1).

TEAEs within the SOC Skin and subcutaneous Disorders were reported in 66 patients (7.9%) with PA21, comparable to sevelamer (6.7%). Most commonly reported events were pruritus (n=27) and rash (n=9) with PA21.

Most commonly reported TEAEs within the DDI studies occurred within the Gastrointestinal Disorders, Nervous System Disorders and Infections and Infestations SOCs. The most commonly reported preferred term was discoloured faeces and headache.

Serious adverse events and deaths

No **deaths** occurred in the phase 1 studies. Within the phase 2 and phase 3 clinical study, 14/835 (1.7%) of patients on PA21 and 7/374 (1.9%) of patients on sevelamer died. One of these deaths occurred during the phase 2 study in the PA21 group.

The majority of deaths were related to Cardiac Disorders (n=7, 0.8% in the PA21 group and n=5, 1.3% in the sevelamer group), most commonly due to cardiac arrest (n=3 in the PA21 group, n=1 in the sevelamer group) and myocardial infarction or acute myocardial infarction (n=2 in the PA21 group, n=1 in the sevelamer group). Renal and Urinary Disorders accounted for 3 deaths in the PA21 group (2 renal failures, 1 renal tubular necrosis). One death in the PA21 group was attributed to GI haemorrhage. No deaths were considered by the Investigators to be related to study treatment.

Serious adverse events: One subject with CKD experienced a serious TEAE of myocardial infarction within a non-DDI phase 1 study, whereas one healthy subject had severe rhabdomyolysis. Both events were considered not-related to study drug and patients recover from the event.

Within the phase 2 and 3 clinical studies, a total of 141 (16.9%) patients on PA21 and 71 (19.0%) patients on sevelamer experienced a serious TEAE. Most commonly reported SAEs were in the SOC Cardiac disorders, with 34 subjects (4.1%) on PA21 and 14 subjects (3.7%) on sevelamer reporting a serious cardiac TEAE. Acute myocardial infarction was the only PT to be reported at a frequency of >1% for PA21 (1.1%). Within none of the other SOCs, a PT was reported at a frequency of >1% for PA21.

Serious TEAEs related to peritonitis were reported in 6 subjects (0.7 %) in the PA21 group and included the Preferred Terms peritonitis (n=4), peritoneal infection (n=1) and bacterial peritoneal infection (n=1). In comparison, serious TEAEs related to peritonitis were reported in 1 subject (0.3 %) in the sevelamer group (PT bacterial peritoneal infection). Most cases were subjects on PD, 2 were receiving HD.

Gastrointestinal haemorrhage was reported by 3 (0.4%) subjects in the PA21 group (none in the sevelamer group), and was a contributor to death in two subjects. Both subjects had other risk factors for GI bleeding and in neither case was PA21 thought to be related to the deaths or the preceding haemorrhage. One subject had a duodenal ulcer haemorrhage which might be related to PA21. Diarrhoea was reported as a serious TEAE in 2 (0.2%) subjects receiving PA21 and 1 (0.3%) subject in the sevelamer group. Pancreatitis or pancreatitis acute were reported as serious TEAEs by 2 (0.2%) of PA21 subjects and 1 (0.3%) of sevelamer subjects. Other serious GI disorders were infrequent across both treatments.

Two subjects had serious TEAEs considered by the Investigator to be related to study treatment, and both subjects were in the PA21-treated group (discoloured faeces and duodenal ulcer haemorrhage) in study PA-CL-05A. Both subjects recovered.

Long-term safety / Integrated analysis

A total of 391 patients on PA21 and 267 patients on sevelamer were treated within the long-term extension study PA-CL-05B.

In PA21-treated subjects, the overall duration of exposure for the combined PA-CL-05A/PA-CL-05B studies (SS) ranged from 1.0 to 420.0 days, with a mean of 243.1 days (SD=130.6). The overall duration of exposure during the PA-CL-05B study extension (SS5B) ranged from 3.0 to 225.0 days, with a mean of 176.4 days (SD=49.5).

In sevelamer-treated subjects, the overall duration of exposure for the combined PA-CL-05A/PA-CL-05B studies ranged from 13.0 to 413.0 days, with a mean of 294.1 days (SD=112.4). The overall duration of exposure during PA-CL-05B ranged from 5.0 to 215.0 days, with a mean of 181.5 days (SD=41.9). With continued treatment in PA-CL-05B, 319 subjects completed at least 52 weeks (approximately 12 months) of treatment with PA21.

The Table below illustrates the absolute numbers and percentage of subjects at each dose level at the start of Week 4, Week 8, Week 12, Week 24, and Week 52 treatment periods during studies 05A/5B.

Table 22: Number of subjects by PA21 dose over 52 weeks in PA-CL_05A/05B, SS

	Number of Subjects (%)				
	1,000 mg/day	1,500 mg/day	2,000 mg/day	2,500 mg/day	3,000 mg/day
Week 4 (N=656)	203 (30.9%)	444 (67.7%)	8 (1.2%)	1 (0.2%)	0 (0.0%)
Week 8 (N=620)	107 (17.3%)	164 (26.5%)	189 (30.5%)	155 (25.0%)	5 (0.8%)
Week 12 (N=583)	88 (15.1%)	124 (21.3%)	162 (27.8%)	117 (20.1%)	92 (15.8%)
Week 24 (N=513)	61 (11.9%)	86 (16.8%)	115 (22.4%)	92 (17.9%)	159 (31.0%)
Week 52 (N=319)	36 (11.3%)	52 (16.3%)	47 (14.7%)	47 (14.7%)	137 (42.9%)

Note: SS = Safety set.

Source: PA-CL-05A/05B Clinical Study Report, Section 14.3, Table 14.3.3.1.

In studies 05A/05B, mean (\pm SD) overall exposure to PA21 (all doses) was 243.1 \pm 130.6 days for 707 subjects (SS). The number of subjects who received 1,500 mg/day at some point in the trial was 609, and their average duration of exposure to the 1,500 mg/day dose was 57.6 \pm 82.7 days. A total of 610 subjects were exposed to at least 1,500 mg/day for an average duration of 223.7 days (median 226.5, range: 2-406).

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 (88.8% and 88.5%, respectively). The overall TEAE profiles for the 2 treatment groups were similar with the exception of higher incidence in PA21-treated subjects for treatment-related TEAEs (45.3% with PA21 versus 24.7% with sevelamer) and withdrawals for TEAEs (20.9% versus 10.3%). These differences were driven by GI TEAEs.

Table 23: Overall summary of TEAEs. SS (N=1,055) and SS5B (N=658)

	Pooled PA-CL-05A/05B		PA-CL-05B	
	PA21 (N=707)	Sevelamer (N=348)	PA21 (N=391)	Sevelamer (N=267)
Any TEAE	628 (88.8%)	308 (88.5%)	289 (73.9%)	205 (76.8%)

Any related TEAE	320 (45.3%)	86 (24.7%)	57 (14.6%)	24 (9.0%)
Any severe TEAE	113 (16.0%)	61 (17.5%)	40 (10.2%)	27 (10.1%)
Any serious TEAE	188 (26.6%)	103 (29.6%)	78 (19.9%)	52 (19.5%)
Any serious related TEAE	3 (0.4%)	1 (0.3%)	1 (0.3%)	1 (0.4%)
Death	21 (3.0%)	14 (4.0%)	7 (1.8%)	7 (2.6%)
Withdrawal due to TEAE	148 (20.9%)	36 (10.3%)	32 (8.2%)	13 (4.9%)

The most commonly reported TEAEs while on PA21 were in the SOCs Gastrointestinal Disorders (52.5%), Metabolism and Nutrition Disorders (37.8%), Infections and Infestations (29.7%), General Disorders and Administration Site Conditions (21.1%) and Vascular Disorders (21.1%). For sevelamer, corresponding frequencies were in the SOCs Gastrointestinal Disorders (42.8%), Metabolism and Nutrition Disorders (39.7%), Infections and Infestations (32.5%), General Disorders and Administration Site Conditions (25.0%) and Vascular Disorders (24.1%). Apart from the SOC Gastrointestinal Disorders there were no SOCs with an increased frequency for PA21.

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).

TEAEs reported by $\geq 5\%$ are summarized in the Table below.

Table 24: Treatment-emergent adverse events occurring in $\geq 5\%$ of patients by preferred term. SS (N=1,055) and SS5B (N=658).

System Organ Class Preferred Term	Integrated PA-CL-05A/05B (SS)		PA-CL-05B (SS5B)	
	PA21 (N=707)	Sevelamer (N=348)	PA21 (N=391)	Sevelamer (N=374)
	N (%)	N (%)	N (%)	N (%)
Subjects with at least 1 TEAE	628 (88.8%)	308 (88.5%)	289 (73.9%)	205 (76.8%)
Diarrhoea	167 (23.6%)	40 (11.5%)	32 (8.2%)	15 (5.6%)
Faeces discoloured	114 (16.1%)	1 (0.3%)	3 (0.8%)	1 (0.4%)
Hyperphosphataemia	113 (16.0%)	44 (12.6%)	47 (12.0%)	29 (10.9%)
Hypertension	79 (11.2%)	41 (11.8%)	38 (9.7%)	20 (7.5%)
Nausea	69 (9.8%)	50 (14.4%)	23 (9.7%)	11 (4.1%)
Muscle spasms	48 (6.8%)	27 (7.8%)	26 (6.6%)	16 (6.0%)
Headache	43 (6.1%)	20 (5.7%)	20 (5.1%)	8 (3.0%)
Vomiting	42 (5.9%)	32 (9.2%)	14 (3.6%)	12 (4.5%)
Hypotension	41 (5.8%)	31 (8.9%)	19 (4.9%)	21 (7.9%)
Hypophosphataemia	40 (5.7%)	29 (8.3%)	22 (5.6%)	14 (5.2%)
Hyperkalaemia	38 (5.4%)	25 (7.2%)	17 (4.3%)	16 (6.0%)
Constipation	36 (5.1%)	29 (8.3%)	10 (2.6%)	5 (1.9%)
Hypocalcaemia	33 (4.7%)	22 (6.3%)	14 (3.6%)	8 (3.0%)
AV fistula or graft complications	32 (4.5%)	26 (7.5%)	8 (2.0%)	13 (4.9%)
Pyrexia	32 (4.5%)	19 (5.5%)	8 (2.0%)	11 (4.1%)
Hyperparathyroidism, secondary	30 (4.2%)	31 (8.9%)	15 (3.8%)	23 (8.6%)
Nasopharyngitis	29 (4.1%)	20 (5.7%)	13 (3.3%)	8 (3.0%)
Dyspnoea	28 (4.0%)	19 (5.5%)	10 (2.6%)	7 (2.6%)
Anaemia	28 (4.0%)	29 (8.3%)	15 (3.8%)	15 (5.6%)
Upper respiratory tract infection	25 (3.5%)	18 (5.2%)	5 (1.3%)	11 (4.1%)
Chest pain	23 (3.3%)	20 (5.7%)	6 (1.5%)	8 (3.0%)

Subjects experiencing more than 1 AE within each preferred term and system organ class were only counted once. Preferred terms reported by $\geq 5\%$ of subjects were included. SOCs with no preferred terms reported by $\geq 5\%$ of subjects were not included.

The most common GI events (occurring in >5.0%) in patients on PA21 were diarrhoea (23.6%), discoloured faeces (16.1%), nausea (9.8%) and constipation (5.1%). In the sevelamer group, the most common GI events were nausea (14.4%), diarrhoea (11.5%), vomiting (9.2%), abdominal pain (9.2%) and constipation (8.3%). Only 3 cases of diarrhoea with PA21 (Subjects 404-913, 410-901 and 874-905) and 2 cases with sevelamer (Subject 866-922 and 873-909) were classified as serious during the combined studies.

In both treatment groups the highest incidence of GI TEAEs was during the first 4 weeks of treatment. Discoloured faeces, which were reported almost exclusively in the PA21 group, were almost all reported during the first 4 weeks of treatment. In the PA21 group, diarrhoea was also reported more frequently during the first 4 weeks of treatment, the incidence reduced over time to a level of around 4 to 5% from Week 24 onwards. Other common GI events, nausea, vomiting and constipation, occurred at a similar low incidence throughout the 52 weeks of treatment.

Within the integrated analysis, a total of 320 (45.3%) of patients on PA21 reported treatment-related TEAEs compared to 86 (24.7%) of patients on sevelamer. The most commonly reported treatment-related TEAEs ($\geq 2\%$) were faeces discoloured (110; 15.6%), diarrhoea (92, 13.0%), nausea (28; 4.0%), hypophosphatemia (28; 4.0%), product taste abnormal (27; 3.8%), hyperphosphataemia (24; 3.4%), constipation (21; 3.0%), vomiting (15; 2.1%), and dyspepsia (14; 2.0%). For patients on sevelamer, the most commonly reported treatment-related TEAEs were nausea (18; 5.2%), constipation (17; 4.9%), hypophosphataemia (13; 3.7%), and diarrhoea (8; 2.3%).

Death and serious adverse events

Thirty-five subjects experienced fatal TEAEs during the study (PA-CL-05A and PA-CL-05B combined) 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. The causes of death were generally consistent with the medical conditions of ESRD patients on dialysis. As expected in this patient population, a large proportion 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.

Serious adverse events occurred in 188 (26.6%) of PA21-treated subjects and 103 (29.6%) of sevelamer-treated subjects. In PA-CL-05B, serious TEAEs were reported in 19.9% and 19.5%, respectively. The largest proportions of serious TEAEs in the integrated PA-CL-05A/PA-CL-05B

analysis were associated with the SOCs of Infections and Infestations (n=63; 8.9% for PA21 and n=34; 9.8%) for sevelamer) and Cardiac Disorders (n=44; 6.2% for PA21 and n=23; 6.6% for sevelamer).

Serious TEAEs by preferred term and reported for $\geq 1\%$ of patient on PA21 were pneumonia (n=13, 1.8%), sepsis (n=7, 1.0%), acute myocardial infarction (n=10, 1.4%), congestive cardiac failure (n=9, 1.3%), fluid overload (n=8, 1.1%), and chest pain (n=11, 1.6%). Serious TEAEs by preferred term and reported for $\geq 1\%$ of patient on sevelamer were pneumonia (n=8, 2.3%), sepsis (n=4, 1.1%), atrial fibrillation (n=5, 1.4%), AV fistula thrombosis (n=4, 1.1%), dyspnoea (n=5, 1.4%), fluid overload (n=9, 2.6%), chest pain (n=6, 1.7%), anaemia (n=6, 1.7%).

Serious peritonitis (6 with PA21 and 1 with sevelamer) and serious diarrhoea (3 with PA21 and 2 with sevelamer) were the only serious GI disorders reported in >0.5% of subjects in either group. All serious peritonitis events occurred in subjects on PD.

Serious GI bleedings were reported in 4 patients on PA21, 1 duodenal ulcer haemorrhage, 1 gastrointestinal haemorrhage and 2 upper gastrointestinal haemorrhage. A total of 5 patients reported serious GI bleeding on sevelamer; 2 duodenal ulcer haemorrhage, 2 gastrointestinal haemorrhage and 2 upper gastrointestinal haemorrhage.

Treatment-related serious TEAEs occurred in 4 subjects. Three subjects on PA21 reported a total of 4 events, duodenal ulcer haemorrhage, faeces discoloured, gastric disorder and upper GI haemorrhage. One subject on sevelamer reported a GI haemorrhage which was considered treatment-related. All patients recovered without sequelae upon treatment.

Laboratory findings

Haematology parameters: The majority of patients had subnormal Hgb levels at baseline. The number of TEAEs in this group was limited and no differences were observed between treatment groups.

Coagulation parameters: There was no demonstrable effect of PA21 on coagulation parameters. TEAEs were reported in 13 (1.6%) of patients with PA21 and 3 (0.8%) patients with sevelamer.

Clinical chemistry parameters: There were no significant changes with PA21. HDL, LDL and triglycerides showed modest reductions with sevelamer.

Liver enzyme parameter: Alkaline phosphatase levels increased during treatment with a mean change of 8.59 IU/L (SD=30.12) with PA21 and 20.97 IU/L (SD=38.65) with sevelamer at last observation. Increases were about twice as high in females compared to males. No important changes were seen for other liver enzyme parameters.

Iron status parameters: Baseline serum ferritin levels were high. Serum iron, serum ferritin and serum TSAT levels increased during treatment with PA21 in study PA-CL-05A (Table 13). Data from the radiolabelled iron absorption study indicated that iron absorption was between 0-0.44% in ESRD patients.

Table 25: Summary of Iron Status parameters in Stage 1 of study PA-CL-05A.

Iron status parameter	Time point	PA21 (N=707) Mean (SD)	sevelamer (N=348) Mean (SD)
Ferritin (ng/ml)	Baseline	666.6 (439.6)	714.6 (521.9)
	Wk 24/endpoint	789.2 (508.0) ^{1,2}	752.8 (497.4) ¹⁾
Iron (micromole/L)	Baseline	11.6 (5.57)	12.0 (5.20)
	Wk 24/endpoint	13.5 (6.77) ¹⁾	12.8 (6.51) ¹⁾
Transferrin (g/L)	Baseline	22.9 (4.82)	22.7 (4.57)
	Wk 24/endpoint	22.4 (4.36) ^{1,2}	24.6 (4.93) ¹⁾
Transferrin Sat. (%)	baseline	26.6 (13.1)	27.8 (13.8)
	Wk 24/endpoint	31.3 (16.1) ^{1,2}	27.3 (15.3)

¹statistically significant change from baseline; ²statistically significant between treatment groups.

Vitamins: No clinically significant changes were seen in the circulating levels 1,25-hydroxy-vitamin D, vitamin A, E or K. Modes reductions were seen in 25-hydroxy-vitamin D levels in both treatment groups, which were not considered clinically relevant.

Calcium, phosphorus, parathyroid hormone and bone parameters: Serum phosphorus levels decreased over time, whereas calcium levels remained stable. Ca X P product decreases reflected the decreased in serum phosphorus. iPTH did not change substantially.

Significant changes in bone-specific alkaline phosphatase were seen for both treatment groups, similar as those observed for total alkaline phosphatase. Fibroblast growth factor-23 appeared to decrease slightly over time, but ranges were broad (-27.9 μ g/dl (SD= 234) for PA21 and -45.6 μ g/L (SD= 219) for sevelamer).

Vital signs and physical findings

There were no clinically relevant changes in the physical examination findings.

ECG recordings: Mean changes from BL to week 12, week 24, and endpoint in PQ, QRS, QT and RR intervals and the HR were not statistically or clinically relevant. Results between treatment groups were comparable.

Long-term data:

Laboratory values

Iron parameters:

In the pooled PA-CL-05A/PA-CL-05B studies (SS), TEAEs related to increased iron parameters were reported by a similar proportion of subjects in both treatment groups: 20 (2.8%) subjects treated with PA21 and 10 (2.9%) subjects treated with sevelamer. In PA-CL-05B (SS5B), TEAEs related to increased iron parameters were reported by a slightly larger proportion of subjects in the PA21 group: 10 (2.6%) subjects treated with PA21 versus 3 (1.1%) subjects treated with sevelamer.

None of these events was severe, considered serious or led to withdrawal. Most of the subjects were also receiving concomitant IV iron and/or ESA.

Iron overload was considered related to treatment in 2 patients on PA21. Both patients received the maximum dose of PA21 (12.5 g/day). One patient had elevated TSAT (80%) and iron (48.1 $\mu\text{mol/L}$) but no increased ferritin. The iron overload resolved without treatment and PA21 was continued. One patient reported increased ferritin levels (3.087 pmol/L). PA21 dose was maintained until the end of the study and the event was ongoing at that time.

Mean changes from baseline 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.

No clinically meaningful changes in haemoglobin levels were observed in either treatment group.

Other laboratory evaluations:

Serum calcium values remained relatively stable throughout the studies in both treatment groups over 52 weeks. There were no clinically meaningful changes in serum iPTH and no differences between treatment groups over 52 weeks.

Transitory Vitamin D decreases were observed in both treatment groups; these may be associated with seasonal factors.

Significant increases from baseline in bone-specific alkaline phosphatase were observed in both treatment groups. Increases were generally greater in the sevelamer group. Differences between groups were not statistically significant except at the combined endpoint. Mean values were greater for female subjects at baseline and mean changes during treatment were greater in females than males.

There were no other clinically relevant changes in laboratory parameters and no relevant differences observed between treatment groups over 52 weeks.

Vital signs and physical findings

There were no significant effects on vital signs, ECGs or physical examination findings and there were no differences observed between treatment groups over 52 weeks.

Safety in special populations

Subgroup analyses were presented for the intrinsic factors gender, age, and race. Further, subgroup analyses were performed for extrinsic factors like geographic region.

Gender: There were 476 males and 359 females treated with PA21. The incidence of TEAEs was 79.6% for males and 80.5% for females. Incidence and nature of TEAEs were in general comparable between males and females, without marked differences between sexes in severe and serious TEAEs, discontinuations due to a TEAE, or deaths.

Age: There were 462 patients below 65 years and 248 patients of 65 years and older that received treatment with PA21. Proportions of any TEAE and number of deaths were somewhat higher in patients ≥ 65 years. A higher proportion of patients ≥ 65 years discontinued treatment (21.8 % versus 14.8%). This was also seen for sevelamer (12.1% versus 5.8%). Incidence and nature of TEAEs did not show marked differences between age groups. A slight difference was seen for TEAEs in the SOC Gastrointestinal Disorders with higher frequencies of diarrhoea for patients ≥ 65 years (21.% versus 16.7%). The same trend was observed for treatment-related GI TEAEs and events leading to discontinuation in the SOC Gastrointestinal Disorders (5.6% versus 1.2% discontinued due to diarrhoea in patients ≥ 65 years and <65 years, respectively).

Race: The majority of patients treated with PA21 was white (n=668), followed by black (n=134). There was a slightly higher incidence of TEAEs in Black patients (88.8% versus 78.0%) and a higher incidence of serious TEAEs (21.6% versus 16.0%). For the SOC Gastrointestinal Disorders, incidence was slightly higher in the White group compared to the Black group (19.2% versus 12.7%).

Geographic region: In total, 360 patients were treated within the US, 215 in EU and 260 in ROW. For PA21, the incidence of TEAEs was highest in the US (n=325, 90.3%), followed by EU (n=175, 81.4%) and lowest in the ROW region (n=168, 64.6%). In all regions, the majority of TEAEs were in the SOC Gastrointestinal Disorders and included diarrhoea, nausea, and vomiting.

CKD patients on peritoneal dialysis:

In total, 57 patients on PD were treated with PA21 versus 30 with sevelamer. Forty subjects (70.2%) experienced any TEAE with PA21 treatment versus 24 patients with sevelamer treatment (80%).

In 5 of 57 PA21-treated subjects 6 episodes of peritonitis were registered (8.8%) versus 3 episodes in 30 sevelamer-treated subjects (6.7%) during a treatment period of maximal 6 months. No clinically relevant differences were observed between PA21 treated and sevelamer treated PD patients.

The proportions of subjects who had serious or severe TEAEs, who were withdrawn for TEAEs or died, were similar for HD and PD groups.

Immunological events

Four cases with hypersensitivity reaction on PA21 were reported within the first 6 months, which were not related to treatment.

Safety related to drug-drug interactions and other interactions

No obvious interactions between PA21 use and typical medications taken by subjects with ESRD have been identified from the clinical trial program to date. 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.

As absorption of PA21 is considered minimal and PA21 is not metabolised or excreted by the liver, potential interactions are considered to be restricted to the GI tract. Five DDI studies in healthy volunteers did not show interactions in terms of bioavailability for a wide variety of relevant drugs, i.e. losartan, furosemide, digoxin, warfarin and omeprazole. In vitro several drugs have been evaluated for the potential to adsorb to PA21. Although adsorption was shown in vitro, the in vivo interaction studies showed no interaction. However, it is unclear to which extent in vivo interactions, i.e. PA21 affecting absorption of co-administered drugs, can be ruled out based upon in vitro data or in general.

Discontinuation due to AES

Overall, a total of 141 PA21-treated subjects (16.9%) were discontinued from treatment due to an AE, compared with 29 (7.8%) sevelamer-treated subjects. The main SOCs, with events that led to discontinuation in both treatment groups, were Gastrointestinal Disorders: 61 (7.3%) PA21-treated subjects and 13 (3.5%) sevelamer-treated subjects; Metabolism and Nutrition Disorders: 40 (4.8%)

PA21-treated subjects and 4 (1.1%) sevelamer-treated subjects; and General Disorders and Administration Site Conditions: 17 (2.0%) PA21-treated subjects and 3 (0.8%) sevelamer-treated

subjects. The most frequent PTs causing discontinuation in PA21-treated subjects were diarrhoea (21 subjects, 2.5%), hyperphosphataemia (17 subjects, 2.0%), hypophosphataemia (14 subjects, 1.7%) and nausea (11 subjects, 1.3%); and in sevelamer-treated subjects were constipation (5 subjects, 1.3%), and diarrhoea (4 subjects, 1.1%).

Long term data:

During PA-CL-05B, a larger proportion of subjects were withdrawn for TEAEs in the PA21 group: 32 subjects (8.2%) in the PA21 group and 13 subjects (4.9%) in the sevelamer group. The most common reason for discontinuation in both treatment groups was hyperphosphataemia, which led to discontinuation in 11 subjects (2.8%) in the PA21 group and in 7 subjects (2.6%) in the sevelamer group. Seven subjects (1.8%) in the PA21 group withdrew from PA-CL-05B due to GI TEAEs compared to 1 (0.4%) in the sevelamer group.

In the integrated analysis, more subjects in the PA21 group compared with the sevelamer group were withdrawn from treatment for TEAEs (148; 20.9% versus 36; 10.3%, respectively). 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. The most frequent PTs ($\geq 1.0\%$) causing discontinuation in PA21-treated subjects were diarrhoea (25 subjects, 3.5%), hyperphosphataemia (23 subjects, 3.3%), hypophosphataemia (14 subjects, 1.7%), nausea (11 subjects, 1.6%), product taste abnormal (13 subjects, n=1.8%), constipation (7 subjects, 1.0%), and vomiting (7 subjects, 1.0%); and in sevelamer-treated subjects were hyperphosphataemia (7 subjects, 2.0%), and constipation (5 subjects, 1.4%).

Overall, a larger proportion of subjects in the PA21 treatment group were withdrawn as a result of treatment-related TEAEs: 12.7% (n=90) of PA21-treated subjects versus 2.9% (n=10) of sevelamer-treated subjects. Events in the GI Disorders SOC were the treatment-related TEAEs that most often led to withdrawal (n=61 and n=7 for the PA21 and sevelamer groups, respectively). The most common treatment-related TEAE leading to withdrawal were diarrhea (n=22), product taste abnormal (n=13) and nausea (n=10) for patients on PA21. The most common treatment-related TEAE leading to withdrawal for patients on sevelamer was constipation (n=4).

2.3.1. Discussion on clinical safety

The safety profile of Velphoro is based on a total of 778 patients on haemodialysis and 57 patients on peritoneal dialysis, who received Velphoro treatment of up to 55 weeks.

Based on the integrated data including the long-term extension study it is estimated that about 610 patients were treated with at least 7.5 g/day PA21 (1,500 mg/day) with a mean duration of 223.7 days and 335 received this dose for at least 6 months. This is considered sufficient to assess the common AEs.

The population included is representative of the target population on maintenance dialyses. A minority of patients (n=57, 6.8%) were on PD. Most patients were Caucasian and treated within the US. There are no indications of markedly qualitative differences in safety profile between geographic regions / races and data can be considered valid for the EU population. However, consistently lower TEAEs rates were reported in ROW versus US and EU, especially within study PA-CL-05A. Based on the observed differences, a concern was raised on the conduct of the study in general, and throughout regions. The outcome of the GCP inspection confirmed that the data are acceptable for a discussion on the benefit/risk of the product, which was confirmed by the additional analyses excluding Russian and

Ukrainian sites. The differences in frequencies of AE reporting throughout geographic regions might (partly) be explained by differences in patient population with regard to age, severity of underlying disease and culture in reporting of adverse events. This is acceptable to the CHMP also given that no issues on validity of data remained.

The percentage of patients with any TEAE was high, which is to be expected in this population with extensive co-morbidity. The most commonly reported TEAEs for PA21 were within the SOC of Gastrointestinal Disorders, which was also the SOC wherein TEAEs were most commonly reported as treatment-related AEs. This reflects the fact that the drug is hardly absorbed. Most commonly reported gastrointestinal TEAEs were diarrhoea (18.1% in study PA-CL-05A and 23.6% based on integrated study 5A/5B) and discoloured faeces (14.9% in study PA-CL-05A and 16.1% based on integrated study 5A/5B). Diarrhoea appeared dose-related based on phase 1 studies, but this was not confirmed by the phase 2 clinical study. Uncertainty remains on a dose relationship as the majority of patients started with a lower dose and were subsequently up titrated. Although it cannot be excluded that TEAEs might be higher at the proposed starting dose of 7.5 g/day PA21, there are no signals that this would lead to major changes in frequencies. This is based on the current data using uptitrated doses, which show no signs of increased risk of TEAEs or new safety signals including doses twice as high as the proposed starting dose. Further, the most commonly reported adverse events are considered manageable and once discontinued, the patient can be switched to other available safe and effective phosphate binders.

The frequency of adverse events (included in SmPC section 4.8) included all patients treated during the clinical trials including patients following the lower dose of PA21. Discoloured faeces because of the iron content of PA21 are expected, and most likely experienced by all patients. It has the potential to mask gastrointestinal blood loss; however, the Applicant has presented reassuring data that it does not interfere with the standard laboratory tests. Relevant information is included in SmPC section 4.5. A warning on masking and delaying diagnosis of potential GI bleeding is currently included in section 4.4 of the SmPC. Abnormal product taste but also tooth discolouring are expected findings due to the iron content of PA21 and are included in section 4.8 of the SmPC. Abnormal taste in combination with other GI events might have a negative effect on treatment compliance in daily practice, but the impact is not easily assessed from clinical studies.

Patients with a wide range of gastrointestinal disorders were excluded from the studies and a warning is included in SmPC section 4.4. The type of patients that might be considered more vulnerable patients with an increased risk of GI or other adverse events (e.g. patients with motility disturbances or damage to the intestinal wall) were limited within the studies. PA21 should be used carefully in these patients and use in these patients should be followed up post-registration as part of the PSURs/RMP.

Use in patient population with a history or evidence of significant GI disorders is included as missing information in the RMP. There are currently no safety signals (including preclinical) that warrant a contraindication.

The irritation seen in mice was considered related to the bulk substance and neoplasms were not likely related to PA21. The preclinical findings were assessed to be species-specific and not to have implications for human safety.

The second most commonly reported TEAEs were within the SOC Metabolism and Nutrition Disorders, with the most commonly reported event being hyperphosphataemia. This may partly reflect a suboptimal starting dose. Within the SOC Skin and Subcutaneous Tissue Disorders, pruritus and rash were considered treatment-related events which are also known for other phosphate binders. There were no signs of increased infection rates or interference with nutrient absorption, or absorption of copper ions. In addition, hypersensitivity reactions were rare.

Overall, TEAEs were reported more frequently on PA21 compared to sevelamer, which is largely

explained by the differences in gastrointestinal events and hyperphosphataemia. The majority of TEAEs reported within the other SOCs, did not show markedly differences between PA21 and sevelamer. As gastrointestinal TEAEs were in general mild and resolved during the study, this is not necessarily a matter of concern. The lower frequencies with sevelamer might partly be explained by the fact that one third of the population had already used sevelamer prior to the study, but is not likely to account for all differences observed. Gastrointestinal events more frequently experienced within the sevelamer group were nausea, vomiting and constipation. More patients discontinued on PA21 compared to sevelamer because of adverse events. Although the majority of patients discontinued early, 85/707 (12%) patients on PA21 discontinued during the maintenance phase of PA-CL-05A compared to 25/348 (7%) patients on sevelamer. The main reasons for withdrawal in this time period were again TEAEs other than those due to blood phosphorus or calcium levels (n=32) or withdrawal by subject (n=16). Discontinuation rates were markedly lower for patients in the long-term extension study on PA21 which can be expected, but still higher than for sevelamer.

The clinical relevance of the observed increase in serum ferritin level and also transferrin saturation levels with PA12 is not known. Absolute serum ferritin levels were in the same order of magnitude as with sevelamer, and TEAE suggestive of potential iron overload were observed in similar proportions between treatment groups (about 2%). Only 1 event was considered related to PA21. Taking into account the one year follow-up data, frequencies of TEAEs related to iron parameters were slightly increased but still reported by a similar proportion of subjects in both treatment groups: 20 (2.8%) subjects treated with PA21 and 10 (2.9%) subjects treated with sevelamer. None of these events was severe, considered serious or led to withdrawal. One additional event was considered treatment-related to PA21, mounting up to a total of 2 events.

The radiolabeled study showed that a very limited amount of iron is absorbed in ESRD patients (0-0.044%). In case of the maximum dose of 3000 mg iron/day (15 g PA21/day) and a maximal absorption of 0.04%, this would mean a maximal daily absorption of 1.2 mg iron/day or 36 mg/month. Therefore, absolute iron absorption is not negligible but low compared to the amount given to patients through IV infusions, mounting up to 190 mg/month.

Although serum ferritin and TSAT levels increased within the first 6 months and were higher for PA21 than for sevelamer, one-year data in patients tolerating PA21 did not show a further increase in iron status parameters. Iron status parameters of patients not entering the long-term extension study were comparable to those of patients entering the study. Post-hoc stratified analyses for patients with and without IV infusions showed that the increase was seen in patients receiving IV iron but not in patients receiving only PA21. Further, there were no signs of early toxicity or an increased risk of adverse events related to iron overload and absolute changes in iron parameters were small. Although the risk over longer periods of use is not known, the risk of iron accumulation could be manageable through routine monitoring of relevant iron status parameters. Prescribers should in that case be warned on the risk of additional iron absorption from PA21 and special attention should be paid to the long-term follow-up of potentially iron-related adverse events.

Preclinical data were reassuring based on additional data/analysis and did not indicate significant iron (-particle) absorption.

Patients with a history of haemochromatosis or other iron accumulation disorders were excluded from the clinical trials and PA21 is contraindicated in these patients. Deaths were reported at low and comparable rates between PA21 and sevelamer, mostly related to cardiac disorders. None were considered treatment-related. Also, most commonly reported serious TEAEs were reported within the SOC Infections and Infestations and the SOC Cardiac Disorders, in line with the underlying co-morbidity of ESRD patients. Serious GI bleedings were reported in few patients, 4 on PA21 and 5 on sevelamer. One case of serious duodenal ulcer haemorrhage and one case of upper GI haemorrhage

within the PA21 group was considered to be treatment-related. No effect was seen on coagulation parameters and preclinical findings are reassuring as these did not reveal an increased risk of bleeding and the irritation and neoplasms observed were considered species-specific and not relevant for humans. Based on the long-term data, there were eight cases of peritonitis in patients on PD with PA21 (14.0%) compared to three cases on sevelamer (10%), however this is an expected adverse event in this population and overall rates were low. This can be explained as patients with a history of peritonitis were excluded from the clinical studies. This is addressed in SmPC section 4.4 and the RMP. Gastrointestinal TEAEs remained the majority of TEAEs and nature of events was comparable to that in HD. The limited number of patients precludes a meaningful interpretation of observed differences with patient on HD. Some events more frequently reported in PD compared to HD can be explained by the dialysis procedure and there are at the moment no indications of a different safety profile. Given the limited number of patients on PD, use in patient population with a history or evidence of significant GI disorders is included as missing information in the RMP. Next to this use in patient population with CKD Stage 1-4 is included as important potential risk in the RMP. A sufficient number of patient's ≥ 65 years were included in the studies, including above 74 years of age. There were no signs of unexpected increases in AEs or new AEs.

In vitro several drugs have been evaluated for the potential to adsorb to PA21. Although adsorption was shown in vitro, the in vivo interaction studies showed no interaction. The interaction potential seems low, however, it is unclear to which extent in vivo interactions, i.e. PA21 affecting absorption of co-administered drugs, can be ruled out based upon in vitro data or in general. This may especially of concern with narrow therapeutic drugs. This has been included in section 4.5 of the SmPC as well as a precaution that Velphoro is almost not absorbed from the gastrointestinal tract. When administering any medicinal product that is known to interact with iron, the medicinal product should be administered at least one hour before or two hours after Velphoro.

From the safety database all the adverse reactions reported in clinical trials have been included in tabular form in section 4.8 of SmPC.

2.3.2. Conclusions on the clinical safety

The safety profile of PA21 is mainly characterised by gastrointestinal adverse events of mild nature, which reflects its local action and limited absorption. Most commonly observed events were diarrhoea and discoloured faeces. Gastrointestinal events were reported more frequently with PA21 compared to sevelamer and more often led to study discontinuation. This might render the product somewhat less favourable for long-term treatment. The extension period of 6-12 months did not indicate new safety signals and almost half of the patients continued treatment for one year. Preclinical findings on neoplasms were considered species-specific and not relevant for humans. Iron absorption was limited, but not negligible, and did not lead to clinically relevant changes in iron status parameters. Long-term treatment for one-year in patients tolerating PA21 did not indicate further iron accumulation. These data suggest that the risk of iron accumulation is low and can be managed by routine monitoring and further follow-up of iron-related adverse events post-approval. The planned PASS will provide relevant data to characterise and evaluate this potential risk. Preclinical data were reassuring based on additional data/analysis and did not indicate significant iron (-particle) absorption.

The outcome of the inspection confirmed data integrity and the data are therefore acceptable to be used for the discussion on the benefit/risk, as concluded by the inspectors. Given the major findings at the investigational sites (one each in Russia and Ukraine), the CHMP requested additional sensitivity analyses for the main efficacy endpoints excluding all Russian and Ukrainian sites, before concluding

on the benefit/risk of the product. The results of the analyses were reassuring and confirmed the validity of the all data within the dossier for the benefit/risk discussion of the product.

2.3.3 Third party interventions related to safety

During the validation phase of the centralised procedure for Velphoro an anonymous letter was received from a third party by the EMA d.d. 18th of January 2013. CHMP commented on the questions in this anonymous letter by referring to the questions raised to the Applicant during the evaluation procedure. The safety profile is assessed based on the data submitted within the dossier which is considered to be the most informative and the most relevant for the product in the target population. This cannot be replaced by literature data from other products and most likely in different settings as these references were published 10-30 years ago. Furthermore, the data cited in the anonymous letter on iron-related toxicity at doses mentioned in literature cannot be directly applied to the administered dose of iron in the form of PA21. The majority of the iron within the complex is not soluble and therefore not readily available for absorption. It is agreed that part of the patient population might be treated with PA21 for several years. Therefore at least one year data are needed to assess the long-term safety profile. Regular monitoring of serum iron status parameters might mitigate the risk of iron overload. Furthermore, the CHMP cannot comment on unpublished data cited in the anonymous letter, or on studies that have been stopped and presumably not submitted.

At Day 120 of the procedure, there was concern regarding adenocarcinomas in the colon of mice. An anonymous letter was received from a third party by the EMA dated October 3rd, 2013. In this letter some concerns are raised concerning the promotional materials and the dose to be administered per day. An explicit concern is raised on the administered dose of 1,000 mg iron/day because of the potential oxidative stress in the stomach and intestine. The iron (III)-oxyhydroxide active moiety of PA21 powder is insoluble with a low iron release (limit: $\leq 5.0\%$ m/m). Therefore, the safety profile of the proposed iron dose within PA21 cannot be directly related to other iron preparations used in clinical practice.

An anonymous letters was received from a third party by the EMA d.d. 5th November 2013 and a second one dated 21th of November 2013. The issues raised in the third and fourth anonymous letter were comparable to those raised in the initial two letters. The safety of the product with respect to iron-related toxicity, including long-term safety, has been addressed within the various assessment reports up till now. It is the conclusion of the CHMP that there is no aggravated risk for adenocarcinoma in rats that received PA21. Based on the assessment as laid down in the current reports, the uncertainties on the safety profile are resolved and the safety profile of the product is acceptable with adequate risk minimization measures as laid down in the RMP and reflected in the SmPC.

At Day 180, a re-examination of these lesions was performed, resulting in a re-classification of a large part of the adenocarcinomas to diverticula. The cellular/tissue characteristics on which this re-classification is based can be followed by the assessor. However, at Day 180 a concern remained on the re-evaluation of the carcinogenicity findings which was not performed according to agreed principles.

2.4. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.5. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 4.0 the PRAC considers by consensus that the risk management system for sucroferric oxyhydroxide (mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches (Velphoro) for the control of serum phosphorus levels in adult CKD on HD or PD within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxy Vitamin D3, calcimimetics or one of its analogues to control the development of renal bone disease could be acceptable provided an updated risk management plan and satisfactory responses to the List of Questions below are submitted:

1. Given the limited number of patients on PD in the clinical trials the Applicant's position that the safety from the larger HD group can be extrapolated to the smaller PD population cannot be supported. Patients on peritoneal dialysis should be listed as missing information in the RMP.
2. As Velphoro is a new product intended for long-term use potentially over many years, it is considered that the safety concerns with this product identified in the RMP cannot be adequately addressed through routine pharmacovigilance. The Applicant should propose an observational post-marketing safety study (PASS) to investigate the long-term safety of PA21 (over 1 year). In particular this study should collect information on long-term safety, iron accumulation, masking of potential GI bleeding, and use in patients with PD. The Applicant should also discuss the feasibility as to whether markers of GI irritation/inflammation as a possible mechanism for diarrhoea in patients exposed to PA21 could be measured in the PASS.

Following the PRAC meeting in June 2014, the Applicant submitted an updated Risk Management Plan, version 5.0 addressing these issues and therefore the Risk Management Plan is considered acceptable.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

Table 26: Summary of Safety concerns

Important identified risks	<ul style="list-style-type: none"> • Diarrhoea
Important potential risks	<ul style="list-style-type: none"> • Masking of potential GI bleeding due to Velphoro®-induced discoloured (black) faeces • Potential iron accumulation
Missing information	<ul style="list-style-type: none"> • Use in paediatric population <18 years • Use in pregnant and lactating women • Long-term usage beyond 1 year • Use in patient population with CKD Stage 1-4 • Use in patient population with HIV and HBV and/or HCV infections • Use in patient population with concurrent significant hepatic disorders • Use in patient population with a history or evidence of significant GI disorders • Use in patient population with history of haemochromatosis, or any other iron accumulation disorders • Use in patient population receiving Velphoro concomitantly with other PBs • Use in patient population receiving aluminium-, calcium- or magnesium containing antacids and/or oral iron preparations • Use in PD patients

The PRAC agreed.

- **Pharmacovigilance plans**

Table 27: Ongoing and planned studies in the PhV development plan

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
PA-CL-PED-01; Clinical Study; Category 3	Investigate the "Use in paediatric population <18 years" (as any use of Velphoro® in the paediatric population <18 years is considered off-label use	Missing information	Planned	Update will be provided in the next DSUR (data lockpoint: 15-Feb- 2015). This study is part of the PIP which is due in October 2016
PASS Category 3	Feasibility Phase: Feasibility Assessment Report to evaluate the assessment of possible mechanism of diarrhoea using markers of GI irritation/ inflammation in patients exposed to Velphoro. Submission of a Study Synopsis to conduct a PASS including the plan: To investigate the "Masking of potential GI bleeding due to Velphoro-induced discoloured (black) faeces"	Important identified risk Important potential risk	Planned	Within 3 months of the European Commission decision.

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
	<p>To investigate the "Potential iron accumulation"</p> <p>To investigate the "Long-term usage beyond 1 year"</p> <p>To investigate the "Use in PD patients"</p>	<p>Important potential risk</p> <p>Missing information</p> <p>Missing information</p>		

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

- **Risk minimisation measures**

Table 28: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Diarrhoea	Diarrhoea is listed in Velphoro® RSI in Section 4.8 Undesirable Effects. Based on the clinical trial data, the vast majority of the diarrhoeal events seen with Velphoro were mild or moderate in severity, occurred early in treatment, were transient, and resolved or improved with continued treatment. In general, adult CKD patients undergoing dialysis are under regular clinical monitoring and have access to clinical support, as required.	None
Important potential risks		
Masking of potential GI bleeding due to Velphoro- induced discoloured (black) faeces	Proposed text in Velphoro RSI in Section 4.4 Special Warnings and Precautions for Use. Velphoro can cause discoloured (black) stool. Discoloured (black) stool may visually mask GI bleeding (see Section 4.5). Proposed text in Velphoro RSI in Section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction: Velphoro does not affect guaiac based (Haemoccult) or immunological based (iColo Rectal, and Hexagon Obti) faecal occult blood tests. Discoloured faeces are listed in Section 4.8 Undesirable Effects.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	The planned PASS will provide relevant data to characterise and evaluate this potential risk. Adult CKD patients on HD or PD are under regular clinical monitoring, including evaluation of standard clinical laboratory parameters and having access to standard clinical therapy.	
Potential iron accumulation	Proposed text in Velphoro RSI in Section 4.3 Contraindications. The planned PASS will provide relevant data to characterise and evaluate this potential risk. Adult CKD patients on HD or PD are under regular clinical monitoring, including evaluation of standard clinical laboratory parameters and having access to standard clinical therapy. Prescription-only medicine.	None
Missing information		
Use in paediatric population <18 years	Proposed text in Velphoro RSI: Section 4.1 Therapeutic Indications, Section 4.2 Posology and Method of Administration, and Section 5.1 Pharmacodynamic Properties. Planned clinical trial PA-CL-PED-01. Prescription-only medicine.	None
Use in pregnant and lactating women	Proposed text in Velphoro RSI: Section 4.6 Fertility, Pregnancy and Lactation. Prescription-only medicine.	None
Long-term usage beyond 1 year	Velphoro safety data is based on 1 year treatment. More than 590 subjects have been exposed to Velphoro for up to 52 weeks. 240 subjects received 15.0 g/day (the maximum recommended dose) and their average duration of exposure was 172.6 days with this dosage. Overall, the frequency and severity of TEAEs did not increase during the 1 year long-term treatment. The planned PASS will provide relevant data on long-term usage beyond 1 year. Adult CKD patients on HD or PD are under regular clinical monitoring, including evaluation of standard clinical laboratory parameters. Prescription-only medicine.	None
Use in patient population with CKD Stage 1-4	Proposed text in Velphoro RSI: Section 4.1 Therapeutic Indications. Prescription-only medicine.	None
Use in patient population with HIV, HBV and/or HCV infections	Velphoro has not been studied in all specific patient populations (including the population with HIV, HBV and/or HCV infections) as the benefit/risk profile is not expected to be different from the populations under study. The decision regarding the use of Velphoro in specific patient populations should be taken by the physician based on	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	<p>clinical needs and the physician's experience. As Velphoro is a chewable drug and absorption of iron is minimal, the efficacy and safety is not expected to be altered in this specific patient population.</p> <p>Adult CKD patients on HD or PD are under regular standard clinical monitoring.</p> <p>Prescription-only medicine.</p>	
Use in patient population with significant hepatic disorders	<p>Proposed text in Velphoro RSI: Section 4.4 Special Warnings and Precautions for Use.</p> <p>Adult CKD patients on HD or PD are under regular standard clinical monitoring.</p> <p>Prescription-only medicine.</p>	None
Use in patient population with a history or evidence of significant GI disorders	<p>Proposed text in Velphoro RSI: Section 4.4 Special Warnings and Precautions for Use.</p> <p>Adult CKD patients on dialysis are under regular standard clinical monitoring.</p> <p>Prescription-only medicine.</p>	None
Use in patient population with history of haemochromatosis, or any other iron accumulation disorders	<p>Proposed text in Velphoro RSI: Section 4.3 Contraindications.</p> <p>Adult CKD patients on HD or PD are under regular clinical monitoring, including evaluation of standard clinical laboratory parameters</p> <p>Prescription-only medicine.</p>	None
Use in patient population receiving Velphoro concomitantly with other PBs	<p>Prescription-only medicine.</p> <p>Use restricted to physicians experienced in the treatment of hyperphosphataemia in adult CKD patients on HD or PD.</p> <p>Adult CKD patients on HD or PD are under regular standard clinical monitoring.</p>	None
Use in patient population receiving aluminium-, calcium- or magnesium-containing antacids and/or oral iron preparations	<p>Prescription-only medicine.</p> <p>Use restricted to physicians experienced in the treatment of hyperphosphataemia in adult ESRD patients on dialysis.</p> <p>Adult CKD patients on HD or PD are under regular standard clinical monitoring.</p>	None
Use in PD patients	<p>The indication for Velphoro is listed in the proposed RSI under Section 4.1 Therapeutic Indications.</p> <p>Velphoro safety data is based on experience of treating 57 PD subjects in clinical trials. Haemodialysis and PD patients were generally comparable in terms of demographics, disposition in the trials and safety profile over 12 months treatment with Velphoro.</p> <p>The planned PASS will provide additional relevant data to evaluate the benefit/risk in PD patients.</p> <p>Prescription-only medicine.</p>	None

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice without changes.

2.6. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

3. Benefit-Risk Balance

Benefits

Beneficial effects

PA21 has been shown to lower serum phosphorus levels in patients on dialysis with hyperphosphataemia. The absolute mean phosphorus lowering effect was -0.71 mmol/L after 12 weeks in the single pivotal study ($p < 0.001$) at a starting dose of 5 g/day. Serum phosphorus levels remained stable during 12-24 weeks. The proportion of patients on phosphorus levels within the target range (1.13 to 1.78 mmol/L) increased from 6.1% at baseline to 44.8% and 52.6% at week 12 and 24, respectively, supporting clinical relevant efficacy. Most patients needed doses between 10-15 g/day.

Maintenance of effect was shown during the 3 week withdrawal phase starting after 24 weeks of treatment (difference of 0.54 mmol/L compared to a low dose PA21, $p < 0.0001$). A trend for a dose-effect relationship was shown in the dose-finding study for doses between 5.0 -12.5 g/day.

The serum phosphorus lowering effect after 12 weeks was comparable to that obtained with sevelamer (mean difference 0.08 mmol/L; upper 97.5% CI: 0.15 mmol/L, non-inferiority margin: 0.19 mmol/L). The proportion of responders at week 12 was lower compared to sevelamer (44.8% PA21 versus 54.7% sevelamer; OR: 0.69; 95% CI: 0.52, 0.91) but comparable at week 24 (52.6% PA21 versus 54.4% sevelamer) based on observed cases.

Serum phosphorus lowering effects were comparable between relevant subgroups (HD and PD, patient's ≥ 65 years of age).

Within the long-term extension study, serum phosphorus levels and proportion of patients on KDOQI target were maintained between 6 and 12 months.

The average number of tablets to be taken daily for PA21 was approximately half the number of tablets to be taken with sevelamer (between 4-5 tablets/day for PA21 and 9-12 tablets/day for sevelamer based on week 24 data). This remained stable within the extension period.

For patients completing one year of follow-up, about 27% received a dose of ≤ 7.5 g/day (1,500 mg/day iron), whereas 43% received the maximum dose of 15 g/day PA21 (3,000 mg/day iron).

The outcome of the inspection confirmed that the data are acceptable to be used for the discussion on the benefit/risk. This was reassured by the results of additional sensitivity analyses on main efficacy endpoints excluding all Russian and Ukrainian sites.

Uncertainty in the knowledge about the beneficial effects

Assessment of the effect size during the 3 weeks withdrawal phase is hampered by inclusion of patients varying in KDOQI responder status and the use of a “placebo-dose” of PA21 which is still effective. This most likely results in an underestimation of the effect size, but the observed effect is still statistically significant supporting the serum phosphorus lowering effect of PA21. Further, the serum phosphorus lowering effect over time is considered of most important to demonstrate efficacy of PA21. Withdrawal rates during the active-controlled phase were higher for PA21 than for sevelamer, mainly due to a difference in withdrawals due to adverse events. As can be expected, discontinuations were lower and comparable between treatment groups during the extension phase of 6-12 months. Still, more patients discontinued on PA21 because of adverse events.

The clinical relevance of the chosen non-inferiority margin is not known, however, the 10% difference in proportion of patients on target at week 12 in favour of sevelamer can be considered clinically relevant. Although the proportion of responders appears comparable at week 24, this is not supported by an intention-to-treat analyses suggesting that the proportion of responders remain lower for PA21 than for sevelamer (about 7% at week 24). The long-term data are considered supportive for a comparable efficacy of PA21 to sevelamer based on mean serum phosphorus levels, although responder rates are somewhat lower. However, the difference as estimated based on the ITT analyses at week 24 is considered acceptable and almost half of the patients continued treatment on PA21 for one year which supports clinical relevant efficacy. In terms of efficacy, a concern was raised on the reason for change in dialysis adequacy frequency as inclusion criterion; the Applicant explained that the initial weekly frequency was an error writing in the protocol and not representing normal clinical practice. This is acceptable. Additional sensitivity analyses on concomitant treatment potentially affecting serum phosphorus levels using a conservative approach confirmed the robustness of the efficacy results.

The proposed starting dose of PA21 of 7.5 g/day was not studied in the phase 3 study. Phase 2 studies suggest a dose-response relationship. It can be anticipated that a higher starting dose of 7.5 g/day would at least result in similar efficacy and maybe somewhat higher efficacy or efficacy reached at an earlier time. In addition, there is a strong rationale for thrice daily dosing given that most patients will consume three meals/day and currently authorised phosphate binders are also given thrice daily. The rapid increase in dosing over time supports a higher starting dose.

It is not known whether patients with higher baseline serum phosphorus levels would benefit from higher starting doses of PA21, as for sevelamer. However, post-hoc analyses suggest comparable efficacy in the long-term between PA21 and sevelamer independent of baseline serum phosphorus level. Although the majority of patients received the maximum daily dose at week 52 (about 40%), one quarter of patients on PA21 received a dose of ≤ 7.5 g/day (1,500 mg/day iron), which can be considered supportive for the starting dose of 7.5 g/day. Moreover, patients will be uptitrated based on serum phosphorus levels and there would be no unacceptable delay in treatment effect.

Risks

Unfavourable effects

The most commonly reported TEAEs with PA21 were of gastrointestinal nature (42%) and of mild severity within the pooled phase 2/3 analysis up to 6 months. Most commonly reported treatment-related TEAEs were diarrhoea and discoloured faeces. Diarrhoea was mostly mild and resolved with

continued PA21. Gastrointestinal TEAEs were more common with PA21 compared with sevelamer (42% versus 33%). Serious TEAEs were reported at comparable frequencies between treatment groups (16.9% on PA21 and 19.0% on sevelamer) as were deaths (1.7% on PA21 and 1.9% on sevelamer).

Withdrawal rates were higher in the PA21 group compared with sevelamer (29.3% versus 16.8%, respectively for the pooled safety analysis) and more often due to adverse events (16.9% versus 7.8%, respectively for the pooled safety analysis).

Similar trends were seen based on the integrated P-CL-05A/05B long term data, with the following results: For PA21, gastrointestinal TEAEs were reported in 52.5% of patients (versus 42.8% on sevelamer); serious TEAEs were reported in 26.6% of patients (versus 29.6% on sevelamer) and deaths were reported in 3.0% of patients (versus 4.0% on sevelamer). A contraindication was added in section 4.3 SmPC with haemochromatosis and any other iron accumulation disorders.

Withdrawal rates were reported in 48.2% of patients (versus 35.0% on sevelamer) and 20.9% of withdrawals were due to adverse events (versus 10.3% on sevelamer).

Serum ferritin and TSAT levels more rapidly increased on PA21 compared to sevelamer. TEAEs related to iron status parameters were reported in comparable rates between both treatment groups (about 2% within the first 6 months and about 2.8% based on the integrated data up to one year).

Uncertainty in the knowledge about the unfavourable effects

No dose effect was observed but interpretation is difficult as only a minority of patients started treatment at different doses. Therefore it is uncertain whether the incidence of adverse events on the proposed starting dose of 7.5 g/day is currently underestimated.

The integrated data including the long-term extension study contains safety data from about 335 patients treated with at least 7.5 g/day PA21 (1,500 mg/day) for at least 6 months and 240 patients received the maximum dose of 15 g/day PA21 (3,000 mg/day) for a mean duration of 173 days. This is considered acceptable to establish the common safety profile for PA21. Although it cannot be excluded that TEAEs might be somewhat higher at the proposed starting dose of 7.5 g/day PA21, there are no signals that this would lead to major changes in frequencies. This is based on the current data using uptitrated doses, which show no signs of increased risk of TEAEs or new safety signals including doses twice as high as the proposed starting dose. Further, the most commonly reported adverse events are considered manageable. It was concluded that when the treatment is discontinued the patient can be switched to other available safe and effective phosphate binders.

The frequency of adverse event reporting was consistently lower in the ROW compared to the US and EU, affecting about one third of the patient population included in the studies. The differences were less pronounced based on the extension study. The impact on the safety profile of PA21 is not known. The outcome of the GCP inspection is considered reassuring in this aspect as it confirmed that the data are acceptable for a discussion on the B/R based on the current database, which was confirmed by the additional analyses excluding Russian and Ukrainian sites. The differences in frequencies, but not in type, might be (partly) explained by differences in age, underlying disease severity and differences in culture in reporting AEs. This is acceptable also given that no issues on validity of data remained.

Further, regarding the cause of the tumours/lesions, an association with particle uptake in the gut wall could not be excluded, as it was uncertain whether Perl's staining would be capable of detecting iron, present in the form of intact particles. A re-assessment of the carcinogenicity data from the mouse study was conducted by an ad-hoc Pathology Working Group. With their response to the CHMP Day 180 LoOI, the Applicant provided sufficient information to exclude a significant uptake of iron (-particle) and supports the absence of a tumorigenic response in mice or rats related to PA21. Sufficient

information was provided to show that Perls' staining is capable of detecting iron as a particle, and the lack of correlation between positive Perls' staining and presence of colon hyperplasia or lesions provide reassurance that effects in the colon of mice are not the result of iron (particle) accumulation in the intestinal wall.

It is unclear whether iron accumulation will increase over time and could eventually result in clinically relevant adverse events. Absolute iron absorption is not negligible and non-clinical and PK studies indicate that there is a potential for accumulation of absorbed iron or particle. Preclinical data are reassuring considering the initial concern on inert particle accumulation as it appears that iron absorption occurs most likely in biodegradable form. Clinical data up to one year do not indicate cumulative iron accumulation and the absolute amount absorbed is limited compared to the amount of iron that patients receive through iv treatment. This means that regular monitoring of iron storage parameters can suffice in combination with the follow-up post-approval of iron-related adverse events.

Few patients experienced serious gastrointestinal events (2.3% on PA21 compared to 1.6% on sevelamer) within 6 months of follow-up and were slightly higher based on the long-term integrated data (3.7% in both treatment groups). No serious events except one case of faeces discolouring and one case of duodenal ulcer bleeding was considered related to PA21 after 6 months of treatment an additional case of gastric disorder and upper GI haemorrhage were considered treatment-related. As patients with a wide variety of gastrointestinal disorders were excluded from the studies, it is not known whether certain patients might be more vulnerable to (serious) gastrointestinal events when treated with PA21. The B/R should be carefully assessed before treating these patients with PA21 and attention should be paid to AEs in these patients during follow-up post approval.

It is uncertain how the abnormal product taste experienced by part of the patients (about 3%) might affect patient's compliance with PA21 in daily clinical practice. Few patients reported lower compliance rates, however, compliance in daily clinical practice is difficult to predict from clinical trial data. Abnormal product taste is included in section 4.8 of the SmPC.

In vivo drug-drug interactions did not reveal significant interactions with losartan, furosemide, digoxin, warfarin, and omeprazole. The interaction potential seems low; however it remains questionable to which extent the *in vitro* interactions showing lack of interference can be extrapolated to *in vivo*. This may especially be of concern with narrow therapeutic drugs. The section 4.5 of the SmPC sufficiently addresses these aspects. The limited number of patients on PD precludes a meaningful interpretation of the safety profile and this needs to be followed-up post-approval (missing information RMP).

Benefit-Risk balance

Importance of favourable and unfavourable effects

PA21 has demonstrated clinically significant reductions in serum phosphorus levels in patients on maintenance dialysis. These levels were maintained throughout the treatment period of 6 months. In patients tolerating PA21, efficacy based on serum phosphorus levels was maintained in the period of 6 to 12 months and comparable to sevelamer. Almost half of the population continued on treatment for one year. Clinically relevant efficacy was shown in patients on HD and PD, although the latter formed a minority of the total population.

Almost half of the treated population reached target serum phosphorus levels in line with treatment guidelines. This is of clinical relevance as higher serum phosphorus levels are associated with increased morbidity and mortality. The proportions reaching target serum phosphorus levels with PA21 were lower compared to sevelamer at week 12, but appeared comparable at week 24 and responder rates

were maintained up to one year.

Withdrawal rates were also higher for PA21 compared to sevelamer, mainly due to adverse events and to a lower extent due to lack of efficacy.

Average daily tablet intake with PA21 was about half that of sevelamer, it can be assumed that this might favour treatment compliance.

The safety profile of PA21 is characterised by gastrointestinal events which were seen at higher rates than with sevelamer. More patients on PA21 also discontinued treatment due to adverse events compared to sevelamer, indicating a poorer tolerability of PA21, which might implicate lower compliance in clinical practice.

No signs of increased numbers of serious adverse events related to PA21 were seen in the clinical studies. Treatment up to one year did not raise new safety signals.

Absolute iron absorption is not negligible and non-clinical and PK studies indicate that there is a potential for accumulation of absorbed iron, most likely in the biodegradable form. Intestinal lesions observed in the non-clinical setting most likely relate to the bulky nature of the substance, the relevance for humans needs post-approval follow-up. Potential iron accumulation in predisposed patient population is included as important potential risk in the RMP. There are no indications of carcinogenicity related to PA21. Treatment up to one year in humans did not show signs of iron accumulation due to PA21 or an increase in iron-related adverse events. Potential iron absorption from PA21 is low compared to the amount of iron patients receive through iv iron infusion which is common with the population.

The outcome of the inspection confirmed that the data is acceptable to be used for the discussion on the benefit/risk. This was reassured by the results of additional sensitivity analyses on main efficacy endpoints excluding all Russian and Ukrainian sites.

The concerns raised by the four anonymous letters were carefully assessed and commented upon by the CHMP, some of the concerns were referred to in the questions raised during the evaluation procedure and successfully addressed by the Applicant.

Benefit-risk balance

PA21 shows a clear beneficial effect in terms of serum phosphorus lowering in patients on maintenance dialyses with an acceptable safety profile based on data up to one year. Although it cannot be excluded that the phosphorus lowering effect and the tolerability is somewhat less than the currently available phosphate binders (sevelamer), long-term efficacy appears comparable in patients tolerating PA21.

Patients with a recent history of peritonitis (within the last 3 months), significant gastric or hepatic disorders and patients with major gastrointestinal surgery have not been included in clinical studies with Velporo. Velporo should only be used in these patients following careful assessment of benefit/risk. Velporo contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. Velporo can cause discoloured (black) stool. Discoloured (black) stool may visually mask gastrointestinal bleeding.

The potential iron absorption appears limited and not associated with toxicity based on preclinical data and currently available human data up to one year, and does not preclude a positive B/R.

The benefit risk balance in the proposed indication is considered positive.

Discussion on the benefit-risk balance

All patients with CKD Stage 5 will (in the end) need phosphate binders to reduce their serum phosphorus levels.

One phase 3 clinical study has been performed in patients with CKD on dialysis to investigate the efficacy and safety of Velphoro in this population. This study was an open-label, randomised, active-controlled (sevelamer carbonate), parallel group study for up to 55 weeks. Adult patients with hyperphosphataemia (serum phosphorus levels ≥ 1.94 mmol/L) were treated with Velphoro at a starting dose of 1,000 mg iron/day followed by an 8-week dose titration period. Non-inferiority to sevelamer carbonate was determined at week 12. Subjects were continued on their study medication from week 12 to week 55. From week 12 to 24, dose titrations were allowed for both tolerability and efficacy reasons. Treatment of patient sub-populations from week 24 to week 27 with maintenance dose of Velphoro (1,000 to 3,000 mg iron/day) or low dose (250 mg iron/day) of Velphoro demonstrated superiority of the maintenance dose.

In Study-05A, 1,055 patients on hemodialysis (N=968) or peritoneal dialysis (N=87) with serum phosphorus ≥ 1.94 mmol/L following a 2-4 week phosphate binder washout period, were randomized and treated with either Velphoro, at a starting dose of 1,000 mg/day (N=707), or active-control (sevelamer carbonate, N=348) for 24 weeks. At the end of week 24, 93 patients on hemodialysis whose serum phosphorus levels were controlled (< 1.78 mmol/L) with Velphoro in the first part of the study, were re-randomized to continue treatment with either their week 24 maintenance dose (N=44) or a non-effective low dose control 250 mg/day, N=49) of Velphoro for a further 3 weeks.

Following completion of Study-05A, 658 patients (597 on hemodialysis and 61 on peritoneal dialysis) were treated in the 28-week extension study (Study-05B) with either Velphoro (N=391) or sevelamer carbonate (N=267) according to their original randomization.

Mean serum phosphorus levels were 2.5 mmol/L at baseline and 1.8 mmol/L at week 12 for Velphoro (reduction by 0.7 mmol/L). Corresponding levels for sevelamer carbonate at baseline were 2.4 mmol/L and 1.7 mmol/L at week 12 (reduction by 0.7 mmol/L), respectively.

The serum phosphorus reduction was maintained over 55 weeks. Serum phosphorus levels and calcium-phosphorus product levels were reduced as a consequence of the reduced dietary phosphate absorption. The response rates, defined as the proportion of subjects achieving serum phosphorus levels within the KDOQI recommended range were 45.3% and 59.1% at week 12 and 51.9% and 55.2% at week 52, for Velphoro and sevelamer carbonate, respectively.

The mean daily dose of Velphoro over 55 weeks of treatment was 1,650 mg iron and the mean daily dose of sevelamer carbonate was 6,960 mg.

The gastrointestinal safety profile largely resembles that of sevelamer, with diarrhoea being predominant with PA21 and constipation more often seen with sevelamer.

There is a strong rationale for a starting dose of 7.5 g/day, (three tablets per day) allowing treatment with each meal, as the tablet need to be taken with food. Other available phosphate binders are also administered thrice daily and most of the patients had their dose increased early during treatment within the clinical trial. It can be anticipated that efficacy will at least be similar to that seen with the current starting dose.

Tolerability of PA21 is less than for sevelamer and more often leads to withdrawal. Still, over half of patients on PA21 were included in the long-term extension study and almost half continued treatment for one year with doses up to 15.0 g/day. It cannot be excluded that comparison with sevelamer is partly biased by the fact that about one third of patients were on sevelamer prior to start of the study, which most likely are patients tolerating sevelamer. Moreover, adverse events most commonly

reported including diarrhoea were mostly mild and are considered manageable. Patients discontinuing treatment can be switched to other available phosphate binders.

One year data did not show an increased risk of iron accumulation or adverse events related to iron parameters. The amount of iron potentially absorbed from PA21 is low compared to the iron administered iv as part of the treatment regimen for CKD dialysis patients. As iron status parameters are monitored regularly, any potential increased would be noticed and considered manageable by stopping the drug or changes to the iv iron treatment. The risk of iron accumulation in a broader population should be followed up post approval in the PASS and as part of the RMP and PSURs.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Velphoro in the control of serum phosphorus levels in adult chronic kidney disease (CKD) patients on haemodialysis (HD) or peritoneal dialysis (PD), is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the non-clinical and clinical properties of the active substance, the CHMP considers that mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches which is a complex of iron (III)- oxyhydroxide is qualified as a new active substance. The physical properties *in vivo* of the iron active moieties in the registered iron parental products differ from the physical properties *in vivo* of the active substance, and as a consequence the efficacy/safety profile is different and therefore it is agreed the compound is a new active substance.