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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Review Completion Date	October 10, 2013
Established Name	(b) (4) (PA21)
(Proposed) Trade Name	Velphoro
Therapeutic Class	Phosphate binder
Applicant	Vifor Fresenius Medical Care Renal Pharma
Formulation(s)	Oral chewable tablet
Dosing Regimen	500 mg/tablet
Indication(s)	Control of serum phosphorus in patients with chronic kidney disease on dialysis
Intended Population(s)	Adult patients with chronic kidney disease on dialysis

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Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	10
1.1	Recommendation on Regulatory Action	10
1.2	Risk Benefit Assessments	11
1.3	Recommendations for Post market Risk Evaluation and Mitigation Strategies	11
1.4	Recommendations for Postmarket Requirements and Commitments	11
2	INTRODUCTION AND REGULATORY BACKGROUND	12
2.1	Product Information	12
2.2	Tables of Currently Available Treatments for Proposed Indications	12
2.3	Availability of Proposed Active Ingredient in the United States	12
2.4	Important Safety Issues with Consideration to Related Drugs.....	12
2.5	Summary of Presubmission Regulatory Activity Related to Submission	13
2.6	Other Relevant Background Information	13
3	ETHICS AND GOOD CLINICAL PRACTICES.....	13
3.1	Submission Quality and Integrity	13
3.2	Compliance with Good Clinical Practices	13
3.3	Financial Disclosures.....	14
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	14
4.1	Chemistry Manufacturing and Controls	14
4.2	Clinical Microbiology.....	15
4.3	Preclinical Pharmacology/Toxicology	15
4.4	Clinical Pharmacology	15
4.4.1	Mechanism of Action.....	15
4.4.2	Pharmacodynamics.....	16
4.4.3	Pharmacokinetics.....	16
5	SOURCES OF CLINICAL DATA.....	17
5.1	Tables of Studies/Clinical Trials	17
5.2	Review Strategy	18
5.3	Discussion of Individual Studies/Clinical Trials.....	18
5.3.1	Study PA-CL-03A.....	18
5.3.2	Study PA-CL-05A.....	20
5.3.3	Study PA-CL-05B.....	23
6	REVIEW OF EFFICACY.....	25
6.1	Indication	27
6.1.1	Methods	27
6.1.2	Demographics.....	27
6.1.3	Subject Disposition.....	32
6.1.4	Analysis of Primary Endpoint(s).....	34

Velphoro (b) (4)

6.1.5	Analysis of Secondary Endpoints(s).....	35
6.1.6	Other Endpoints:.....	41
6.1.7	Subpopulations	41
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations	44
6.1.9	Discussion of Persistence of Efficacy and/ Tolerance Effects.....	46
6.1.10	Additional Efficacy Issues/Analyses.....	47
7	REVIEW OF SAFETY.....	48
7.1	Methods.....	49
7.1.1	Studies/Clinical Trials Used to Evaluate Safety	49
7.1.2	Categorization of Adverse Events.....	50
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	51
7.2	Adequacy of Safety Assessments	51
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations.....	51
7.2.2	Explorations for Dose Response.....	53
7.2.3	Special Animal and/or In Vitro Testing	55
7.2.4	Routine Clinical Testing	55
7.2.5	Metabolic, Clearance, and Interaction Workup	55
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class ..	55
7.3	Major Safety Results	56
7.3.1	Deaths.....	56
7.3.2	Non-fatal Serious Adverse Events	57
7.3.3	Dropouts and/or Discontinuations	61
7.3.4	Significant Adverse Events.....	63
7.3.5	Submission Specific Primary Safety Concerns	63
7.4	Supportive Safety Results	64
7.4.1	Common Adverse Events	64
7.4.2	Laboratory Findings	71
7.4.3	Vital Signs.....	78
7.4.4	Electrocardiograms (ECGs).....	78
7.4.6	Immunogenicity.....	78
7.5	Other Safety Explorations.....	79
7.5.1	Dose Dependency for Adverse Events	79
7.5.2	Time Dependency for Adverse Events.....	80
7.5.3	Drug-Demographic Interactions	80
7.5.4	Drug-Disease Interactions.....	81
7.5.5	Drug-Drug Interactions.....	81
7.6	Additional Safety Evaluations	81
7.6.1	Human Carcinogenicity	81
7.6.2	Human Reproduction and Pregnancy Data.....	81
7.6.3	Pediatrics and Assessment of Effects on Growth	81
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	81
7.7	Additional Submissions / Safety Issues	81

8	POSTMARKET EXPERIENCE	82
9	APPENDICES	82
9.1	Literature Review/References	82
9.2	Labeling Recommendations	82
9.3	Advisory Committee Meeting	82
9.4	Additional clinical study information	82
9.4.1	Study PA-CL-03A: Demographic information and patient disposition	82
9.4.2	Study PA-CL-05B: Demographic information and patient disposition	85
9.4.3	Study PA1201: Summary of protocol, demographic information and patient disposition	87

Table of Tables

Table 1: Commonly used drugs for control of serum phosphorus level in chronic dialysis patients	12
Table 2: Summary table of efficacy and safety studies	17
Table 3: Summary of demography at stage 1 in Study PA-CL-05A	28
Table 4: Summary of ESRD for stage 1 in Study PA-CL-05A	29
Table 5: Summary of demography at stage 2 in Study PA-CL-05A	30
Table 6: Summary of concomitant medications in stage 2 in Study PA-CL-05A	31
Table 7: Subject disposition in stage 1 in Study PA-CL-05A	32
Table 8: Subject disposition in stage 2 in Study PA-CL-05A	33
Table 9: Primary end point: Comparison of change in serum phosphorus levels from baseline to end of treatment in Stage 2 of Study PA-CL-05A (ITT population)	34
Table 10: Comparison of change in serum phosphorus levels from baseline to end of treatment in Stage 2 of PA-CL-05A (PP population)	35
Table 11: Comparison of change in serum phosphorus level from baseline to end of treatment in stage 2 of PA-CL-05A (without Vitamin D analogues).....	35
Table 12: Analysis of serum phosphorus change from baseline at all time points in stage 2 of Study PA-CL-05A (ITT population)	36
Table 13: Proportions of subjects with serum phosphorus levels within KDOQI and KDIGO target ranges in stage 2 of Study PA-CL-05A (ITT population)	36
Table 14: Change from baseline in serum total calcium, Ca x P, and iPTH in stage 2 of Study PA-CL-05A (ITT population)	37
Table 15: Time (Days) to the first serum phosphorus level within the KDOQI and KDIGO ranges at stage 1 of Study PA-CL-05A	38
Table 16: Week 12 non-inferiority analysis of PA21 vs. sevelamer for efficacy in lowering serum phosphorus in stage 1 of Study PA-CL-05A	38
Table 17: Change from baseline to Week 12 and Week 24 in serum total calcium, Ca x P, and iPTH in stage 1 of Study PA-CL-05A.....	39
Table 18: Change in serum phosphorus from baseline in ESRD patients treated for 6 weeks in Study PA-CL-03A.....	40
Table 19: Mean change in serum phosphorus from baseline in ESRD patients treated for 6 weeks with PA21 or placebo in Study PA1201	40
Table 20: Subgroup analysis based on age and gender: Change in serum phosphorus in stage 2	42
Table 21: Subgroup analysis based on race and ethnicity: Change in serum phosphorus in stage 2	42
Table 22: Subgroup analysis based on geographic region and medical history: Change in serum phosphorus in stage 2	42
Table 23: Subgroup analysis based on gender and age: change in serum phosphorus in stage 1	43
Table 24: Subgroup analysis based on race and ethnicity: change in serum phosphorus in stage 1	43
Table 25: Subgroup analysis based on region and dialysis status: Change in serum phosphorus in stage 1	44

Velphoro (b) (4)

Table 26: Subgroup analysis based on medical history: change in serum phosphorus in stage 1	44
Table 27: Dose distribution of PA21 and sevelamer in stage 1 of Study PA-CL-05A....	46
Table 28: Summary of clinical pharmacology studies for safety evaluation.....	49
Table 29: Extent of exposure to PA21 or sevelamer in Study PA-CL-03A	51
Table 30: Demographics including age, height, sex, and ethnic origin in Study PA-CL-03A	52
Table 31: Extent of exposure in stage 2 in Study PA-CL-05A	52
Table 32: Summary of extent of exposure to study treatment in Studies PA-CL-05A/05B	52
Table 33: Duration of exposure by time intervals in Studies PA-CL-05A/05B	53
Table 34: Summary of demography in Study PA-CL-05A/05B.....	53
Table 35: Summary of dosing of PA21 in DDI studies	53
Table 36: Summary of treatment-related TEAEs with doses of PA21 and sevelamer in Study PA-CL-03A.....	54
Table 37: Summary of TEAEs with doses of PA21 and sevelamer in Study PA-CL-05A	54
Table 38: Listing of deaths in all studies.....	56
Table 39: Summary of SAEs in Studies PA-CL-05A/05B	59
Table 40: Summary of SAEs in Study PA-CL-03A.....	61
Table 41: Summary of AEs leading to withdrawal in Study PA-CL-05A/05B.....	62
Table 42: Summary of TEAEs in Studies PA-CL-05A/05B.....	64
Table 43: Summary of treatment-related AEs in Study PA-CL-05A/05B.....	66
Table 44: Treatment-related TEAEs in Study PA-CL-03A.....	67
Table 45: Summary of hyperphosphatemia and hypophosphatemia in Studies PA-CL-05A/05B	68
Table 46: Summary of hypercalcemia and hypocalcemia in Studies PA-CL-05A/05B ..	69
Table 47: Summary of TEAEs of hyperparathyroidism in Studies PA-CL-05A/05B	69
Table 48: Summary of GI disorders in Studies PA-CL-05A/05B	70
Table 49: Summary of time of onset of GI TEAEs in Studies PA-CL-05A/05B.....	70
Table 50: Summary of TEAEs of diarrhea Studies PA-CL-05A/05B	71
Table 51: Summary of change of hemoglobin from baseline in Studies PA-CL-05A/05B	72
Table 52: Summary of changes of serum total calcium from baseline in Studies PA-CL-05A/05B	74
Table 53: Summary of iron parameters in Studies PA-CL-05A/05B.....	76
Table 54: Summary of AEs leading to withdrawal in Study PA-CL-03A	79
Table 55: Demographic characteristics in Study PA-CL-03A	83
Table 56: Subject disposition in Study PA-CL-03A.....	83
Table 57: Summary of primary reasons for study discontinuation in Study PA-CL-03A ..	84
Table 58: Summary of demography in Study PA-CL-05B	85
Table 59: Summary of ESRD in Study PA-CL-05 B	86
Table 60: Subject disposition in Study PA-CL-05B.....	87
Table 61: Demographic information in Study PA1201	89
Table 62: Patient disposition and reason for discontinuation in Study PA1201.....	90

Table of Figures

Figure 1: Study PA-CL-03A flow chart.....	20
Figure 2: Study PA-CL-05A flow chart.....	23
Figure 3: Study PA-CL-05B flow chart.....	25
Figure 4: Change in serum phosphorus levels from baseline to end of treatment in stage 2 of Study PA-CL-05A.....	34
Figure 5: Proportion of subjects with controlled serum phosphorus in stage 2 of Study PA-CL-05A.....	36
Figure 6: Mean change of serum phosphorus levels from baseline during Stage 1	47
Figure 7: Mean change of serum phosphorus levels from baseline in stages 1 and 2	47
Figure 8: Mean serum total cholesterol change from baseline at each time point in Studies PA-CL-05A/05B	73
Figure 9: Changes in mean serum alkaline phosphatase from baseline at each time point in Studies PA-CL-05A/05B	75

Abbreviations

ACE	angiotensin converting enzyme
ACEI	angiotensin converting enzyme inhibitor
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase (SGPT)
ANCOVA	analysis of covariance
ARB	angiotensin receptor blocker
AST	aspartate aminotransferases (SGOT)
AUC	area under the curve
BID	twice a day
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CABG	coronary artery bypass graft
CK	creatinine kinase
CKD	chronic kidney disease
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CRF	case report form
DDI	drug-drug interaction
DS	drug substance
DBP	diastolic blood pressure
ECG	electrocardiogram
ESAs	Erythropoiesis-stimulating agents
ESRD	end stage renal disease
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GFR	glomerular filtration rate
GI	gastrointestinal
GLP	Good Laboratory Practices
HbA1c	hemoglobin A1c
HGB	hemoglobin
HD	hemodialysis
HF	heart failure
INR	international normalized ratio
ICH	International Conference on Harmonization
iPTH	intact parathyroid hormone
IRB	institutional review board
ISE	Integrated Summary (Review) of Efficacy
ISS	Integrated Summary (Review) of Safety
ITT	intention-to-treat
KDOQI	Kidney Disease Outcomes Quality Initiative
KDIGO	Kidney Disease Improving Global Outcomes

Velphoro (b) (4)

LD	low dose
LOCF	last observation carried forward
LSM	least squares mean
MCHC	mean corpuscular hemoglobin concentration
MD	maintenance dose
MI	myocardial infarction
MRI	magnetic resonance imaging
NDA	New Drug Application
NS	not significant
OSI	Office of Science Investigation
PD	Peritoneal dialysis
PEY	person-exposure-year
PK	pharmacokinetic
PTCA	percutaneous coronary angioplasty
QD	once a day
QoL	Quality of life
QTc	QT interval corrected (for heart rate)
RAAS	renin-angiotensin-aldosterone system
RBC	red blood cells
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SPA	special protocol assessment
TEAE	treatment-emergent adverse events
TSAT	transferrin saturation
TIA	transient ischemic attack
ULN	upper limit of normal
US	United States

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, I recommend that Velphoro™ (PA21) be approved for the control of serum phosphorus levels in patients with chronic kidney disease (CKD) on hemodialysis (HD) or peritoneal dialysis (PD) therapy.

Velphoro™ demonstrated clinically and statistically significant reductions in serum phosphorus levels at therapeutic doses compared to a non-effective low dose control in one pivotal study. Velphoro™ was also effective in lowering phosphorus levels in a dose ranging, active-controlled trial. Collectively, the pivotal study, its one year extension study, and the dose-ranging study provide evidence that Velphoro™ is effective in lowering serum phosphorus levels and that efficacy is maintained during chronic administration. In these trials, Velphoro's™ effect on serum phosphorus was also similar to that observed with the active control, sevelamer (37% and 40% reduction from baseline in the Velphoro™ and Sevelamer treatment arms, respectively, in the pivotal phase 3 trial).

As with other phosphate binders, adverse reactions were primarily limited to the GI tract. Diarrhea was the most common adverse event (AE) in the Velphoro™ treatment arm and was reported at a higher incidence on Velphoro™. Diarrhea was also the major reason for AE-related patient withdrawal on Velphoro™. The majority of these diarrhea AEs occurred early after starting treatment, were mild in severity, and resolved with continued treatment. The incidence of other common GI AEs, including nausea, vomiting and constipation, appeared to be lower in the Velphoro™ arm when compared to the active control. The incidence of these common GI events was substantially lower during continued treatment in the study extension. No new or significant safety signals were observed during long-term treatment of up to one year.

Because Velphoro™ is an iron-based phosphate binder, effects on iron-related parameters were studied. Though increases in serum ferritin and TSAT were observed during the first 6 months of treatment with Velphoro™, further increases were not observed with continued treatment up to one year. There was also no evidence of iron accumulation with increased cumulative exposure. The concomitant use of IV iron and ESAs in these studies and regional differences in their use should be considered when interpreting these findings. Nonetheless, the results are consistent with a Phase 1 clinical pharmacology study which demonstrated minimal iron absorption.

Several drug-drug interaction studies (both *in vitro* and *in vivo*) were conducted to investigate Velphoro's™ effect on the bioavailability of other drugs. In *in vivo* studies conducted in healthy subjects, concomitant administration of Velphoro™ did not affect the bioavailability (based on measured AUC) of drugs commonly used in ESRD patients including losartan, furosemide, digoxin, warfarin, and omeprazole. In *in vitro* drug-drug interaction studies, there was no effect of Velphoro™ on ciprofloxacin, enalapril, hydrochlorothiazide, metformin, metoprolol, nifedipine, and quinidine. However, Velphoro™ did affect alendronate, doxycycline,

Velphoro (b) (4)
levothyroxine, atorvastatin, and paricalcitol. (b) (4)

. As the Tmax of paricalcitol is more than 3 hours, bioavailability may still be affected if paricalcitol is administered 2 hours after Velphoro™. (b) (4)
. In the pivotal study, Velphoro did not appear to affect the lipid lowering effects of HMG-CoA reductase inhibitors.

Overall, the AE profile of Velphoro™ is considered to be acceptable for a product used to control serum phosphorus levels in patients with end stage renal disease who are being treated with hemodialysis or peritoneal dialysis. Velphoro™ may also have a lower pill burden compared to some other phosphate binders. In the clinical studies, the average patient required 3 to 4 tablets a day.

1.2 Risk Benefit Assessments

The efficacy of Velphoro™ for the control of serum phosphorus level in ESRD patients on dialysis was demonstrated in a pivotal study and a dose-ranging study. The development program also provides evidence of the product's long-term effectiveness in controlling serum phosphorus levels.

As with other non-absorbed medicines, safety findings were primarily limited to GI adverse events. Diarrhea was the most common adverse event on Velphoro™. The majority of these diarrhea AEs occurred early after starting treatment, were mild in severity, and resolved with continued use of Velphoro™. No new or significant safety signals have emerged with long-term treatment in the safety extension study, and the findings from this study suggest maintenance of efficacy with chronic administration and a favorable tolerability profile. No safety concerns were raised by a comprehensive assessment of laboratory tests which included hematology and chemistry tests and ECGs. No significant iron accumulation was observed during treatment for up to 52 weeks in a long term study. The effects of Velphoro™ on the bioavailability of other drugs commonly used in ESRD patients have also been sufficiently characterized for the purpose of labeling.

Overall, Velphoro™ has a favorable benefit/risk profile as a treatment for the control of serum phosphorus levels in patients with ESRD.

1.3 Recommendations for Post market Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

Pediatric studies under the Pediatric Research Equity Act (PREA) (21 CFR 314.55(b) and 601.27(b)) should be deferred until after approval. (b) (4)

2 Introduction and Regulatory Background

2.1 Product Information

Velphoro™ (b) (4) PA21) is an iron-based phosphate binder. The proposed indication is for the control of serum phosphorus levels in patients with CKD on chronic HD or PD therapy. The proposed dose of Velphoro™ is 3 tablets (1500 mg) per day administered as 1 tablet (500 mg) 3 times daily with meals. The dose is to be titrated based on phosphorus levels from 1000 mg/day (2 tablets/day) to maximal 3000 mg/day (6 tablets/day).

2.2 Tables of Currently Available Treatments for Proposed Indications

Several drugs are currently used for the control of serum phosphorus levels in patients with CKD on chronic dialysis. Table 1 provides a list of phosphate binders including both approved products and those that are used off-label.

Table 1: Commonly used drugs for control of serum phosphorus level in chronic dialysis patients

Drug category	Drug names	Comments
Aluminum salts	Aluminum hydroxide	Aluminum toxicity related to liver, bone and brain. Rarely used now. <u>Not approved for this indication.</u>
Calcium salts	Calcium carbonate	Hypercalcemia and exacerbating calcification in vascular, bone and other soft tissues. <u>Not approved for this indication.</u>
	Calcium acetate (Phoslo, Phoslyra, Eliphos, etc)	Same as above
Magnesium salts	Magnesium hydroxide or carbonate	GI effect and hypermagnesemia, very limited use. <u>Not approved for this indication.</u>
Lanthanum salts	Lanthanum carbonate (Fosrenol)	GI adverse events, potential accumulation in the bone and other tissues
Sevelamer	Sevelamer Hydrochloride (Renagel)	Anion-exchange resin, GI adverse events, metabolic acidosis.
	Sevelamer carbonate (Renvela)	Same as above

2.3 Availability of Proposed Active Ingredient in the United States

PA21 is not currently marketed in this country.

2.4 Important Safety Issues with Consideration to Related Drugs

Currently marketed phosphate binders adsorb dietary phosphate in the GI tract, thus preventing its uptake into the body. The major safety concern with these products has been complications in the GI tract including diarrhea, constipation and obstruction. Another concern is that these products may bind other administered drugs. There are also drug specific safety concerns (see comments in table 1). However, these safety issues may not be relevant to this application as PA21 is an iron based phosphate binder.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

An end of phase II meeting was held on March 31, 2010 to discuss the phase 3 study plan. At the meeting, the Sponsor agreed to conduct a phase 3 trial with an active comparator arm and a randomized withdraw phase. There would be 6 months of treatment. A 52 week open label study for safety would also be conducted. The Division would review the completed phase 2 study (Study PA-CL-03A) to determine if one pivotal phase 3 trial would be adequate.

PREA requirements were discussed at a meeting on August 13, 2010. At the meeting, the Division and the Office of Pediatrics and Maternal Health Staff (PMHS) agreed that pediatric studies could be deferred until adult studies were completed (b) (4). The Sponsor would not request a waiver.

A pre-NDA meeting was held on September 19, 2012 to discuss the adequacy of the clinical studies including the efficacy, safety and drug-drug interaction (DDI) studies, and datasets that would be submitted. The Division agreed that the pivotal phase 3 study (Study PA-CL05A) together with the phase 2 dose-range finding study (Study PA-CL03A), and one year open label safety study (Study PA-CL05B) should be adequate for safety and efficacy. The conducted DDI studies were also acceptable. In addition, the Division agreed that the Sponsor could submit part of the long-term safety data from Study PA-CL05B at the time of NDA submission and that a complete clinical dataset for Study PA-CL-05B could be submitted as a minor amendment at the 120-Day Safety update.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

From the provided datasets, I did not identify any problems or major discrepancies which might confound the efficacy and safety evaluation of this product. The quality and integrity of the data submission are acceptable.

3.2 Compliance with Good Clinical Practices

According to the applicant, all studies were conducted in full compliance with Good Clinical Practice and in accordance with the ethical principles of the Declaration of Helsinki, informed patient consent and Institutional Review Board approval.

Following discussions with the statistical reviewer, Dr. Cherry Liu, three clinical study sites from the phase 3 pivotal study (Study PA-CL-05A) were identified for audit. Three US sites were chosen because of high enrollment rates and a larger number of responders. According to the report from the Office of Science Investigation, these sites conducted the studies adequately. OSI

Clinical Review
Shen Xiao, M.D., Ph.D.
NDA 205-109; SN-000
Velphoro (b) (4)

did not identify any disqualifying problems at the sites and concluded that the data from these sites were acceptable.

3.3 Financial Disclosures

The sponsor provided a detailed list of all the clinical investigators participating in the phase 2 efficacy study (Study PA-CL-03A) and the phase 3 pivotal study (Study PA-CL-05A). As the long-term (52 weeks) safety study (Study PA-CL-05B) is an extension of Study PA-CL-05A, the investigators in this study are the same as in the phase 3 pivotal study, and therefore the names of the investigators in this study was not re-submitted. The sponsor claimed in the FDA Form 3454 that the listed clinical investigators did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in the product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2 (b)); and were not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2 (f)).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

PA21 drug substance is a mixture of polynuclear iron (III)-oxyhydroxide (pn-FeOOH), sucrose and starches. (b) (4)

The drug product consists of a red-brown, round, flat-faced chewable tablet embossed with “PA 500”. (b) (4) Its mass is standardized to contain 500 mg iron (as PA21 drug substance (DS)) with a total nominal mass of (b) (4). The drug product is intended to be taken orally by chewing. PA21 DS contains approximately (b) (4) iron (III)-oxyhydroxide, approximately (b) (4) sucrose, approximately (b) (4) starches (b) (4).

Both the CMC and Biopharmaceutical reviews have been completed. Based on the Chemistry reviewer, Dr. Wong Thomas, and Biopharmaceutical reviewer, Dr. Elsbeth Chikhale, there is a dissolution issue for this product. The change in drug substance formulation from PA21-1 to PA21-2 could not be supported by comparative dissolution profile data due to the fact that the drug products using PA21-1 drug substance are more than 5 years old and expired. However, since the Phase 3 clinical and drug-drug interaction studies were conducted with the proposed

Velphoro (b) (4)

PA 21-2 drug substance, the bridging between the drug products using PA21-1 and PA21-2 is not an issue. Therefore, this should not significantly affect the clinical interpretation of the safety or efficacy data.

The sponsor committed to address this issue on October 16, 2013. Please see the detailed information in Chemistry and Biopharmaceutical reviews.

4.2 Clinical Microbiology

The submission does not include microbiology data.

4.3 Preclinical Pharmacology/Toxicology

Notable non-clinical findings include the following:

- In vitro studies demonstrated efficient phosphate binding by PA21 under simulated GI tract conditions (pH range of 1.2 to 8.5), with a phosphate binding capacity at least equivalent to currently available phosphate binders.
- In rat models of chronic renal failure, PA21 was as effective as calcium carbonate, sevelamer carbonate and lanthanum carbonate in correcting the hyperphosphatemia and associated secondary hyperparathyroidism.
- The most concerning safety finding was an increase in the incidence of adenocarcinomas in the colon and cecum in males at all dose levels (1250, 2500, and 5000 mg/kg/day) and in females at 5000 mg/kg/day in the mouse carcinogenicity study. The lowest dose with adenocarcinomas in the colon and cecum was only 5X the maximal human dose. The correlation between drug-induced hyperplasia and the presence of adenocarcinomas in both the colon and cecum, and the presence of adenoma and local irritation in nonglandular forestomach suggested that the neoplastic changes were part of a continuum that originated from chronic irritation, and subsequent proliferative response of the GI tract to orally administered PA21. Similar chronic irritation and subsequent proliferative were also seen at 2500 mg/kg/day in the rat carcinogenicity study, and October 16, 2013. in the 4-week and 26-week repeat dose toxicity studies in rats. Therefore, although adenocarcinomas were seen only in mice, PA21-associated epithelial hyperplasia is not a species-specific finding.
- In vitro studies exploring potential binding/interactions with other drugs are discussed under clinical pharmacology studies.

Reviewer comments: The local irritation/carcinogenicity findings in the GI tract may be relevant to ESRD patients on long term treatment. Similar findings were also observed in other phosphate binders. For further details, see Dr. Yang Baichun's review.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

It is well known that iron compounds have phosphate adsorption properties. Please see the Section 4.1 of CMC for the mechanism of the PA21.

Velphoro (b) (4)

4.2.2 Pharmacodynamics

In vitro studies have demonstrated a strong phosphate binding capacity of PA21 over the entire physiologically relevant pH range of the GI tract (1.2-7.5). The phosphate binding capacity of PA21 peaked at pH 2.5, resulting in 96% of the available phosphate being adsorbed (phosphorus: iron concentration ratio 0.4:1).

In a study conducted in 16 CKD subjects (8 pre-dialysis and 8 HD), and 8 healthy subjects with low iron stores (ferritin <100 µg/L), the mean change from baseline in serum phosphorus was -1.05 mg/dL in the pre-dialysis patients, -1.86 mg/dL in the dialysis patients, and -0.25 mg/dL in healthy subjects. No trends were seen in serum intact parathyroid hormone (iPTH), or 1, 25-hydroxy-Vitamin D and 25-hydroxy-Vitamin D levels during treatment with PA21.

In studies conducted in healthy subjects, no remarkable differences in serum phosphorus concentrations were observed between active treatment groups and the placebo group. Urinary phosphorus concentrations tended to decrease over time in treated subjects, when compared with subjects in the placebo group. These findings indicate that PA21 may not have a significant effect on phosphorus levels when normal homeostatic mechanisms can be activated to prevent marked changes in serum or urinary phosphorus levels.

4.4.3 Pharmacokinetics

As PA21 is insoluble and exhibits minimal absorption, classical pharmacokinetic studies were not conducted. PK studies mainly focused on phosphate-binding capacity, iron release and absorption, and drug-drug interaction (DDIs). Although iron(III)-oxyhydroxide itself cannot be absorbed, its degradation product, mononuclear iron(III)-hydroxide, can be released from the surface of the polynuclear iron(III)-oxyhydroxide and absorbed.

Potential interaction between PA21 in aqueous solution and a range of drugs commonly used in ESRD patients were assessed in *in vitro* studies. No significant binding/interaction of PA21 was revealed with a number of drugs which may be co-administered with the compound including ciprofloxacin, digoxin, enalapril, metoprolol, nifedipine, warfarin, hydrochlorothiazide, metformin, and quinidine. In vitro interaction with PA21 was noted for pioglitazone. Extensive binding was observed for furosemide, losartan, atorvastatin, doxycycline, alendronate, levothyroxine, and paricalcitol.

Based on these findings, five *in vivo* drug interaction studies (N=40/study) were conducted with losartan, furosemide, digoxin, omeprazole and warfarin in healthy subjects receiving 1,000 mg PA21 three times a day with meals. PA21 did not alter the systemic exposure as measured by the area under the curve (AUC) of a single dose of any of the tested drugs when co-administered with PA21 or given 2 hours after. In vivo studies were not performed for levothyroxine and paricalcitol.

Reviewer comments: Considering that the Tmax of paricalcitol is more than 3 hours, bioavailability may still be affected if paricalcitol is administered 2 hours after PA21. (b) (4)
Please see the clinical

pharmacology review written by Dr. Ju-Ping Lai for further information.

5 Sources of Clinical Data

The initial NDA submission dated February 1, 2013 served as the primary source of clinical data for this review. At the pre-NDA meeting, the Division agreed that the final clinical study report for the long-term safety extension study PA-CL-05B could be submitted as a minor amendment with the 120-Day safety update. A clinical study report for an interim analysis including 58 patients treated for 12 months in Study PA-CL-05B was submitted with the initial NDA.

5.1 Tables of Studies/Clinical Trials

PA-21's clinical development program included biopharmaceutical studies, human pharmacokinetic and pharmacodynamic studies, drug-drug interaction studies, and efficacy and safety studies. Table 2 provides an overview of efficacy and safety studies. Please see the clinical pharmacology review for additional information on biopharmaceutical, pharmacokinetic, pharmacodynamic, and drug-drug interaction studies.

Table 2: Summary table of efficacy and safety studies

Study #	Design	N of patients	Control	Outcome	Other
PA-CL-03A	Randomized, parallel-group, open-label, active-control, dose-ranging study. Dose of PA21: 250, 1000, 1500, 2000 or 2500 mg/day vs. active control for 6 weeks	154 (97 M, 57 F) HD patients	Sevelamer 800mg	Serum phosphorus levels and safety	Dose-ranging
PA-CL-05A	Two-stage re-randomization study: Stage 1: prospective, randomized, parallel-group, dose-titration, open-label, active-controlled, 24-week study of PA21 compared with sevelamer carbonate. Stage 2: prospective, randomized, parallel-group, open-label, 3-week comparison of PA21 maintenance dose versus PA21 low dose control (primary efficacy analysis). Starting dose: 1000 mg/day titrated for efficacy and tolerability. Dose increases or decreases of 500mg/day permitted every 2 weeks up to Week 8. Maximum dose: 3000mg/day; minimum dose: 1000mg/day. PA21-low dose control group: 250 mg PA21.	Stage 1: 1059 HD and PD (616 M, 443 F) Stage 2: Maintain dose 45 HD (21 M, 24 F) Low dose 49 (24 M, 25 F)	Sevelamer 800mg	Serum phosphorus levels, and safety/tolerability	Phase 3 Pivotal study for safety and efficacy
PA-CL-05B	Parallel-group, randomized, open-label, active-controlled, multicentre, long-term extension study from PA-	659 HD (385 M, 274 F)	Sevelamer 800mg	Long term safety and tolerability	Long-term safety study

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	CL-05A. Subjects continued at the same dose as given at Week 24 during the maintenance period of PA-CL-05A.				
PA1201 (Japanese patients)	Randomized, double-blind, parallel-group, placebo-controlled, dose-ranging study. Subjects were randomized to either 1 of 4 PA21 treatment groups (750, 1500, 2250, or 3000 mg/day) or placebo for 6 weeks	183 Japanese HD (117M, 66 F)	Placebo tablets.	Serum phosphorus levels and safety	Dose-ranging

(Reviewer table)

5.2 Review Strategy

I reviewed the 4 studies shown in table 2. With regard to efficacy, I performed detailed reviews of the pivotal trial, PA-CL-05A, its extension study, PA-CL-05B, and the dose-ranging study, PA-CL-03A. I also reviewed the dose-ranging study conducted in Japanese hemodialysis patients, study PA 1201, for supportive evidence of efficacy.

Safety analyses were performed using data from all of the trials in table 2 as well as data from clinical pharmacology and drug-drug interaction studies. The long-term safety and tolerability of this product was mainly based on Study PA-CL-05B. I also compared this product with other approved phosphate binders regarding the safety assessments in ESRD patients on chronic dialysis.

5.3 Discussion of Individual Studies/Clinical Trials

The study designs and methodologies of the phase 2 dose-ranging study (PA-CL-03A), pivotal study (05A) and its extension (05B) are discussed in the following section. Efficacy and safety findings are discussed in Section 6 (Efficacy Review) and Section 7 (Safety Review), respectively. Other studies are described in the appendix.

5.3.1 Study PA-CL-03A

Study PA-CL-03A was an open-label, randomized, active-controlled multi-centre phase 2 dose finding study.

The primary objective was to investigate the ability of different fixed doses of PA21 to lower serum phosphorus levels in patients with chronic kidney disease (CKD) on maintenance hemodialysis. The major second objective was to assess the efficacy/safety profiles of the different doses of PA21 including the percentage of patients achieving controlled serum phosphorus levels (i.e., ≥ 3.5 to ≤ 5.5 mg/dL) after 1, 2, 3, 4, 5 and 6 weeks of treatment, separately; changes of serum levels of calcium, calcium x phosphorus products, and iPTH.

Major inclusion criteria included adult subjects whose serum phosphorus levels were >5.5 mg/dL, receiving maintenance hemodialysis 3 times a week for ≥ 3 months, receiving stable doses of phosphate binder (with or without Vitamin D) at least 1 month during the screening.

Major exclusion criteria included the following:

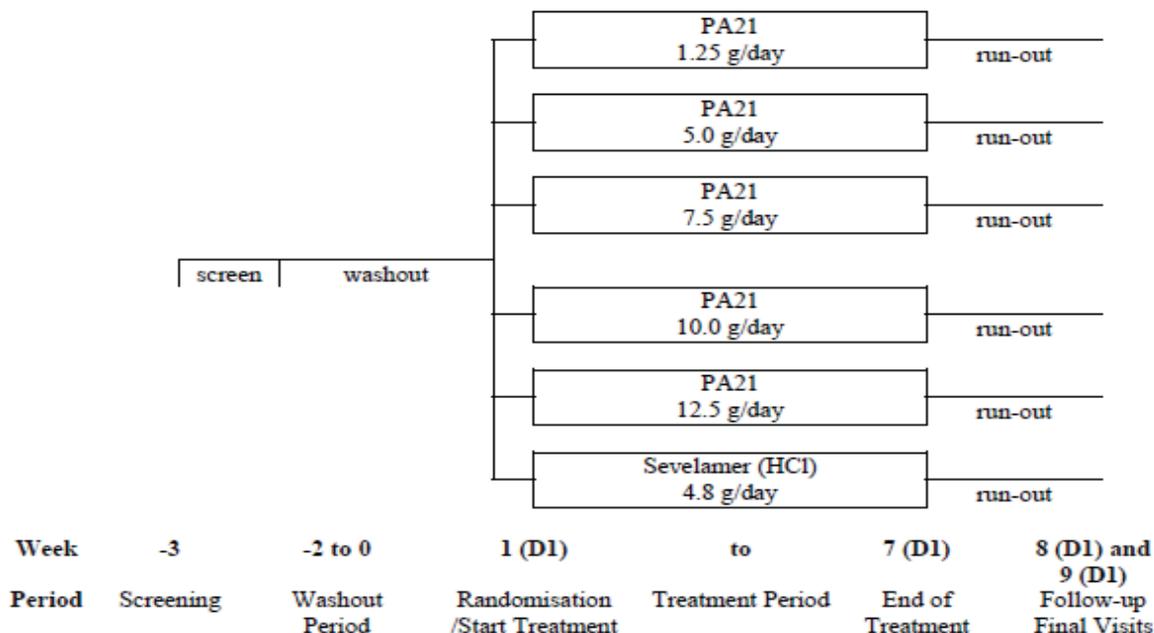
1. Uncontrolled hyperphosphatemia (>7.75 mg/dL) while subject was on conventional phosphate binders.
2. Hypercalcemia (serum calcium >10.0 mg/dL).
3. Hypocalcemia (serum calcium <7.6 mg/dL).
4. Severe hyperparathyroidism with iPTH levels >600 ng/L at screening.
5. Intention to initiate therapy with Vitamin D, Vitamin D metabolites or calcimimetics during the study or receiving non-stable therapy with these agents.
6. Known history of non-response to phosphate binders.
7. Iron deficiency anemia at screening (hemoglobin <10 g/dL and ferritin <100 ng/mL) or history of hemochromatosis (or ferritin >800 g/L) or other iron storage disorders.
8. Significant (based on Investigator's judgment) disorders/medical conditions (e.g., gastrointestinal or hepatic disorders, history of major gastrointestinal surgery within 5 years before screening, planned major surgery, active hepatitis, known seropositivity to human immunodeficiency virus, active infection, history of drug or alcohol abuse within 2 years of screening).
9. Pregnancy or lactation.

Study Design: This is a parallel group, randomized, open-label, active-controlled, multi-center dose ranging study. The study compared 5 fixed dosage regimens of PA21 with a single dosage regimen of sevelamer hydrochloride (HCl) and consisted of a screening phase (up to 1 week), a washout phase of 2 weeks, a 6-week treatment phase, and a 2-week run-out phase. The study visits took place on the day of the subject's dialysis sessions. Enrolled subjects underwent a washout of their previous phosphate binders for 2 weeks. At the end of the washout phase (Week -1, second dialysis session (D2) or third dialysis session (D3) of the calendar week), subjects had to have serum phosphorus levels >5.5 mg/dL to be eligible for treatment.

Subjects received PA21 at 250 mg/day (N=26), 1000mg/day (N=26), 1500 mg/day (N=25), 2000 mg/day (N=27), or 2500 mg/day (N=24), or sevelamer hydrochloride (Renagel®) at 4.8 g/day (N=26) for 6 weeks (42 days). No dose titration was allowed. Subjects were withdrawn if their serum phosphorus levels exceeded the upper safety limit of 8.5 mg/dL at any time as of 2 weeks after the start of treatment, or decreased below the lower safety limit of 3.5 mg/dL at any time after the start of treatment. Subjects were also withdrawn if their serum calcium levels exceeded the upper safety limit of 10 mg/dL at any time after the washout period. All study-related procedures took place before the initiation of the dialysis session of the visit day.

After the last dose of study treatment, patients underwent a 2-week run-out phase, during which they did not receive treatment with a phosphate binder. The run-out phase was stopped prematurely if a subject's serum phosphorus level exceeded the upper safety limit of 8.5 mg/dL. Follow-up assessments were done at 1 and 2 weeks following the final administration of study treatment. PA21 was administered with food and the daily dose was divided across 1 to 4 meals. Treatment with conventional phosphate binders could be resumed at the discretion of the Investigator after the second follow-up. The design is described in the following figure.

Figure 1: Study PA-CL-03A flow chart



Note: the list doses in above figure were in the total mass. Its tablet is standardized to contain 500 mg iron (as PA21 drug substance (DS)) with a total nominal mass of 2.5g. Doses of 1.25, 5.0, 7.5, 10 and 12.5g represent 250, 1000, 1500, 2000, and 2500 mg iron of PA21. D1: first dialysis session in a given calendar week. (Sponsor figure from PA-CL-03A study report)

5.3.2 Study PA-CL-05A

Study PA-CL-05A was an open-label, randomized, dose-titration, active-controlled, parallel group, multicentre, phase 3 study to investigate the safety and efficacy of PA21 compared with Sevelamer Carbonate followed by a randomized comparison of PA21 maintenance dose versus PA21 low dose in dialysis patients with hyperphosphatemia.

The primary objective was to establish the superiority of PA21 maintenance dose (MD) versus PA21 low dose (LD) control in maintaining the phosphorus lowering effect in patients undergoing hemodialysis (HD), by comparing the change in serum phosphorus levels during a 3-week period (Stage 2) that follows 24 weeks of PA21 treatment. Major secondary objectives including establish the non-inferiority (with possible assessment of superiority) of PA21 versus sevelamer carbonate (sevelamer) in lowering serum phosphorus in patients on dialysis after 12 weeks of treatment; and compare safety and tolerability of PA21 versus sevelamer. The primary endpoint is the change of serum phosphorus levels from the first dialysis session of Week 24 to the Week 27 – a superiority comparison between the PA21 MD group and the PA21 LD control group (fixed dose of 250 mg/day) in stage 2. The major secondary endpoints included the change from baseline in serum phosphorus levels at Week 12 – a non-inferiority comparison between PA21 and sevelamer and achievement of response (serum phosphorus control) at Week 12 and Week 24, defined as: 1) Percentage of subjects with serum phosphorus within the KDOQI guideline target range of 3.5 to 5.5 mg/dL and 2) Percentage of subjects with serum phosphorus within the KDIGO guideline normal range of 2.5 to 4.5 mg/dL

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Major inclusion criteria included adult subjects with serum phosphorus levels ≥ 6.0 mg/dL during the washout period (a minimum of 2 weeks washout period was obligatory), receiving maintenance HD 3 times/week with a Kt/V of ≥ 1.2 or peritoneal dialysis (PD) with a Kt/V of ≥ 1.7 within the last 3 months, a history of hyperphosphatemia and receiving stable doses of a phosphate binder(s) for at least 1 month prior to screening. Subjects were permitted to be on stable doses of 1 or 2 phosphate binders. For Stage 2: subjects entering Stage 2 must be on HD, complete Stage 1 with PA21 and have a controlled serum phosphorus level of < 5.5 mg/dL at Week 20.

Major exclusion criteria included the following:

1. Subjects with intact parathyroid hormone (iPTH) levels > 800 ng/L at screening. Subjects with iPTH > 600 ng/L at screening must be considered stable in the Investigator's opinion
2. Subjects with history (within 3 years of screening) of major gastrointestinal (GI) surgery likely to influence the outcome of treatment with phosphate binders or significant GI or hepatic disorders
3. Subjects with a history of hemochromatosis or other iron accumulation disturbances that might lead to iron overload or serum ferritin $> 2,000$ $\mu\text{g/L}$ at screening
4. Subjects on PD with a history of peritonitis in the last 3 months or ≥ 3 episodes in the last 12 months
5. Subjects on non-calcium based phosphate binders with hypercalcemia (serum total calcium > 10.50 mg/dL) at screening
6. Subjects with hypocalcaemia (serum total calcium < 7.6 mg/dL) at screening
7. Subjects taking any prohibited medications including antacids containing aluminum, calcium or magnesium phosphate binders, oral iron therapies and iron supplements (intravenous iron treatment during the course of the study is allowed, and must be recorded in the CRF). Concomitant medications that have a direct influence on serum phosphorus levels (e.g., Vitamin D, Vitamin D analogues and calcimimetics), dietary restrictions (e.g., phosphorus and calcium intake) and dialysis regimens remained unchanged. However, changes were allowed if indicated for safety and tolerability reasons.
8. Subjects taking more than 2 phosphate binders concomitantly prior to screening or subjects who are phosphate binder naïve prior to screening.
9. Pregnancy or lactation

Study design: This was a 2-stage re-randomization study. After a 2-4 week washout period, eligible subjects were randomized and entered Stage 1. Stage 1 was a prospective, randomized, parallel group, open-label, active controlled, 24-week study of PA21 compared with sevelamer carbonate. In this stage, treatment of PA21 chewable tablets containing 500 mg PA21 (2.5 g in total mass) was administered to 1,055 subjects (707 treated with PA21 and 348 treated with sevelamer). The starting dose was 1000 mg/day and the dose was titrated for efficacy and tolerability reasons. Dose increases or decreases of 500 mg/day every 2 weeks were permitted. The maximum dose of PA21 was 3000 mg/day (6 tablets/day) and the minimum dose was 1000 mg (2 tablets/day). PA21 was administered with food, and the daily dose was divided across the 2 to 3 largest meals of the day. Renvela® tablets containing 800 mg of sevelamer carbonate as an active control with a starting dose was 4.8 g/day and the dose was titrated for efficacy and tolerability reasons. Dose increases or decreases of 2.4 g/day (3 tablets/day) (1 tablet per meal) every 2 weeks were permitted. The maximum dose of sevelamer carbonate was 14.4 g/day (18

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tablets/day) and the minimum dose was 2.4 g/day (3 tablets/day). Sevelamer was administered with food, and the daily dose was divided across the 3 largest meals of the day.

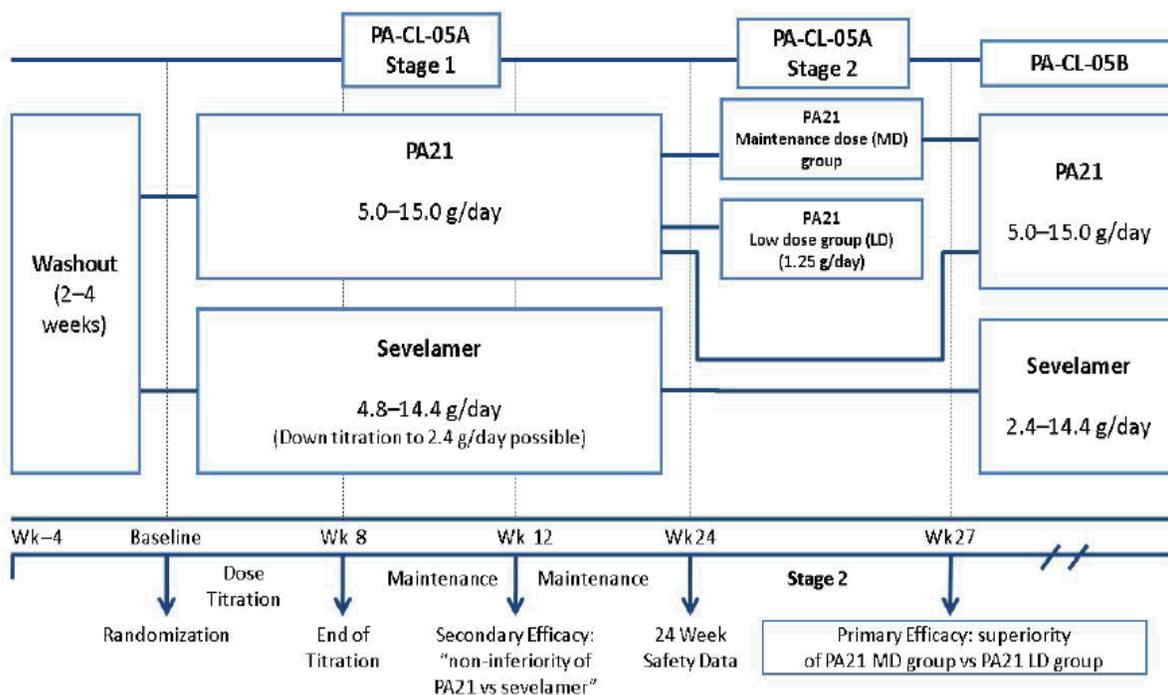
Subjects received an individualized maintenance dose (MD) of PA21 or sevelamer after an 8-week titration period. At the end of 12 weeks, the non-inferiority efficacy comparison with respect to change from baseline in serum phosphorus levels was performed for PA21 versus sevelamer. Subjects were continued on their study medication from Week 12 to Week 24.

For subjects on HD, serum phosphorus was measured at weekly study visits for the first 8 weeks of treatment, then every 4 weeks until Week 24. For subjects on PD, serum phosphorus was measured every second week for the first 8 weeks of treatment, and then every 4 weeks until Week 24. The Week 12 non-inferiority efficacy analysis used an analysis of covariance (ANCOVA) with baseline serum phosphorus level, dialysis status (HD/PD), and region as fixed effects. The baseline value was defined as the measurement at Visit 4 (i.e., Week 0) before first study drug dose or the last recorded value prior to randomization if measurement at Visit 4 was missing. The upper bound of the 97.5% 1-sided CI for mean change differences between treatment groups was compared to a non-inferiority margin of 0.6 mg/dL. The non-inferiority margin was chosen based on clinical considerations and the effects observed for sevelamer in the published literatures provided by the sponsor in which sevelamer was compared against active comparators.

Stage 2, starting at Week 24, was a prospective, randomized, parallel group, open-label, 3-week comparison of PA21 maintenance dose (MD) (dose previously titrated for efficacy) versus PA21 low dose (LD) control (fixed dose of 250 mg/day). It is a withdrawal design comparing 3 weeks of additional treatment with PA21, continuing at the dose titrated for efficacy in Stage 1 versus treatment withdrawal with 250 mg/day PA21, the dose previously shown to be ineffective in the phase 2 dose finding study (Study PA-CL-03A). In the LD, the drug product was PA21 chewable tablets containing 250 mg PA21 rather than 500mg PA21.

Subjects on HD from the Stage 1 PA21 treatment group were randomized 1:1 to either the PA21 MD group (N=50) or LD control group (N=49). Randomization was stratified by country. The option for entry into Stage 2 was presented as subjects completed Stage 1 (up to a maximum of 100 eligible subjects). For inclusion in this stage of the study, subjects were required to have a controlled serum phosphorus level at Week 20 (according to the upper limit of the KDOQI target range <5.5 mg/dL). Limits were introduced to prevent any single site contributing more than 8% of the subjects for the primary analysis (i.e., maximum of 8 subjects per US site and 8 subjects per non-US country). A superiority analysis of the change in serum phosphorus from Week 24 as a baseline to Week 27 was conducted. Endpoint for the PA21 MD versus LD (primary efficacy analysis) was analyzed by ANCOVA for the primary efficacy set (PES) with a 95% CI. No dose adjustments were permitted during Weeks 24 to 27. Serum phosphorus was measured weekly. The overall study design including both stages is described in the following figure.

Figure 2: Study PA-CL-05A flow chart.



Note: the list doses in above figure were in the total mass. Its tablet is standardized to contain 500 mg iron (as PA21 drug substance (DS)) with a total nominal mass of 2.5g. 5.0-15.0g/day means 2 to 6 tablets containing 1000 to 3000 mg PA 21. Low dose of 1.25g represents 250 mg PA21. ((Sponsor figure from PA-CL-05A study report)

5.3.3 Study PA-CL-05B

PA-CL-05B was an open-label, randomized, active-controlled, parallel group, multicentre, phase 3 study to investigate the long-term safety, tolerability and efficacy of PA21 compared with sevelamer carbonate in dialysis patients with hyperphosphatemia. This study was an extension of Study PA-CL-05A and was conducted in 143 centers in 3 regions including 43 centers in the EU, 56 centers in the US, and 44 centers in ROW.

The primary endpoint was a comparison of the adverse event (AE) profiles of PA21 and sevelamer including the incidence and number of treatment-emergent adverse events (TEAEs); incidence and number of treatment-related TEAEs; incidence and number of deaths, serious TEAEs, and TEAEs leading to withdrawal; biochemical and hematological laboratory tests by-visit values and changes from baseline. The major secondary endpoints included the number and proportion of subjects that develop hypercalcemia (total serum calcium >11.0 mg/dL), hyperphosphatemia (serum phosphorus >8.5 mg/dL) or hypophosphatemia (serum phosphorus <2.5 mg/dL) during study participation (confirmed by repeat sample 1 week later), despite “rescue” interventions; serum iPTH levels at each time point and change from entry into Protocol PA-CL-05B; iron status: iron, ferritin, transferrin and transferrin saturation; Vitamin status (A, D, E and K); discontinuations from treatment; concomitant medications; and serum phosphorus levels at each time point and change from entry into Protocol PA-CL-05B.

Subjects who had completed treatment in Protocol PA-CL-05A (Stage 1 or Stage 2) (except subjects randomized to the PA21 low dose group of the Stage 2 for primary efficacy assessment) were enrolled in this study. The major exclusion criteria included the following:

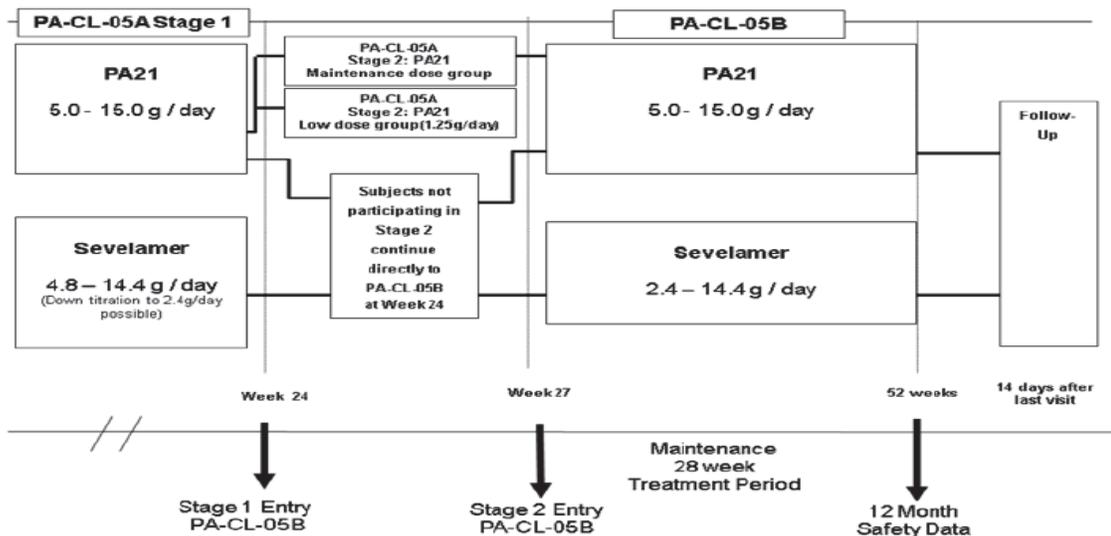
1. Subjects randomized to the PA21 low dose group of the Stage 2
2. Subjects with hypercalcemia (total serum calcium >11.00 mg/dL at the previous study visit in Protocol PA-CL-05A (Week 20 for Stage 1, Week 26 for Stage 2)) (central laboratory values).
3. Subjects with hypocalcemia (total serum calcium <7.6 mg/dL at the previous study visit in Protocol PA-CL-05A (Week 20 for Stage 1, Week 26 for Stage 2)) (central laboratory values)
4. Subjects with serum ferritin >2,000 μ /L at the previous study visit in Protocol PA-CL-05A (Week 20 for Stage 1, Week 24 for Stage 2; based on central laboratory values)
5. Subjects taking any prohibited medications as described in the above pivotal study.
6. Pregnancy and lactation

Study design: This was a parallel group, randomized, open-label, active-controlled, multicenter, long-term safety study. Eligible subjects who had completed 24 weeks of treatment in Stage 1, and subjects who had completed an additional 3 weeks in the PA21 maintenance dose arm of Stage 2 in Study PA-CL-05A were enrolled in this study. A total of 659 subjects were enrolled in the study including 391 subjects in the PA21 group and 268 subjects in the sevelamer group.

Subjects were to continue at the same dose as given at the end of the maintenance period of Study PA-CL-05A for both PA21 and sevelamer. Dose modifications for both tolerability and efficacy reasons were allowed (target serum phosphorus levels were between 2.5 and 5.5 mg/dL). Dose adjustments for efficacy were based on central laboratory values taken at regular study visits (every 4 weeks). The maximum dose of PA21 was to be 3000 mg/day (6 tablets/day) and the minimum dose was to be 1000 mg/day (2 tablets/day). The maximum dose of sevelamer carbonate was to be 14.4 g/day (18 tablets/day) and the minimum dose was to be 2.4 g/day (3 tablets/day).

The treatment was continued for a further 28 weeks. Study visits were conducted at 4-week intervals. For subjects on hemodialysis, visits were planned to coincide with the first dialysis session of the week. Collection of laboratory samples and completion of all other procedures required by the protocol were completed before dialysis was initiated. For subjects on peritoneal dialysis, visits were planned to coincide with the week day for visits used in Study PA-CL-05A (\pm 1 day). Subjects were withdrawn if their serum phosphorus levels exceeded the upper safety limit of 8.5 mg/dL or decreased below the lower safety limit of 2.5 mg/dL at any time during the study (confirmed by repeat sample 1 week later) despite appropriate dose adjustments. Subjects were withdrawn if their total serum calcium levels exceeded 11.0 mg/dL at any time during the study (confirmed by repeat sample 1 week later), despite appropriate “rescue” interventions, i.e., reducing or stopping calcium supplement, reducing or stopping dose of active Vitamin D metabolite, increasing dose of calcimimetic, or reducing calcium content in dialysate. Subjects were withdrawn if it was necessary to add an additional phosphate binder to the treatment regimen. All subjects, whether completing the study or withdrawn prematurely, were followed up 14 days after their last study visit to collect any new AEs and concomitant medications. The design is shown in the following figure.

Figure 3: Study PA-CL-05B flow chart



Note: the list doses in above figure were in the total mass. Its tablet is standardized to contain 500 mg iron (as PA21 drug substance (DS)) with a total nominal mass of 2.5g. Doses of 5-15 g represent 1000 to 3000 mg PA21. (Sponsor figure from 120-day safety update report)

Reviewer comments: The primary efficacy endpoint defined as to compare the difference of changes in serum phosphorus level from Week 24 as a baseline to Week 27 between the PA21 maintenance dose versus the low non-effective dose in stage 2 are reasonable. However, in the stage 1, non-inferiority margin proposed by the sponsor was not validated. Please also see Dr. Cherry Liu's Statistical review regarding this issue.

Some concomitant medications which have a direct influence on serum phosphorus levels (e.g., Vitamin D, Vitamin D analogues and calcimimetics) were allowed if indicated for safety and tolerability reasons. The pivotal study was an open-label trial and changes in the use of these medications could impact efficacy findings. This issue is addressed in section 6.

6 Review of Efficacy

Two studies, Study PA-CL-05A and Study PA-CL-03A, provide the main support for efficacy. Study PA-CL-05A, the pivotal phase 3 trial, was a 27-week, 2-stage re-randomization, withdrawal study with a 24-week randomized, open-label, active-controlled first stage in which PA21 was compared to both baseline and sevelamer carbonate for lowering serum phosphorus in ESRD patients on HD or PD. Study PA-CL-03A was a phase 2, 6-week open-label, randomized, active-controlled, dose-ranging study (250 to 2500 mg/day PA21) in ESRD patients on HD. Study PA-CL-05B was a 28-week extension study to Study PA-CL-05A and mainly examined the safety and tolerability of PA21 compared to sevelamer carbonate in patients on either HD or PD. However, data from this study were also used to evaluate long-term efficacy (changes from baseline to 12 months in serum phosphorus levels on PA21 compared to sevelamer). An additional study, PA1201, conducted in Japanese patients, also provides some efficacy data.

Velphoro (b) (4)

In stage 2 of the pivotal study (randomized withdrawal phase), the mean serum phosphorus level in the low dose control group was significantly increased from baseline (36%) compared to an increase of 6% in the maintenance group (1.8 mg/dl vs. 0.3 mg/dl, $P < 0.001$). The Week 24 maintenance dose (MD) of PA21 (mean of 1480 mg/day) was superior ($p < 0.001$) to the non-effective low dose (LD) control (250 mg/day) in ESRD patients on HD in this 3-week withdrawal phase. In stage 1 of the pivotal study, there was a significant reduction from baseline in serum phosphorus levels in the PA21 arm and this effect was maintained through Week 24. Effects on serum phosphorus were also similar in the PA21 and sevelamer carbonate groups (37% vs. 40% reduction of serum phosphorus level from baseline in the PA21 and sevelamer arms, respectively).

In Study PA-CL-03A, a dose-ranging study that explored doses from 250 mg/day to 2500 mg/kg, PA21 doses of 1000 mg/day to 2500 mg/day were shown to significantly ($p \leq 0.016$) reduce serum phosphorus in a dose-dependent manner whereas the 250 mg/day low dose (LD) was shown to be ineffective as compared to the baseline. The 1000 mg/day and 1500 mg/day doses showed similar efficacy to 4.8 g/day of sevelamer hydrochloride. In Study PA-CL-05B, the 28-week extension study of the pivotal trial, there were minimal changes in serum phosphorus levels between the study baseline (end of the Week 24) and the end of the study, indicating maintenance of serum phosphorus control with PA21. In addition, the pill burden for PA21 (median 4.5 tablets/day) was lower compared to sevelamer (median 10.3 tablets/day). In the 6-week, phase 2 study conducted in Japanese patients, Study PA1201, PA 21 doses of 750 mg/day to 3000 mg/day were shown to significantly ($p < 0.001$) reduce serum phosphorus levels from baseline to Week 6 when compared with placebo and in a dose-dependent manner.

Responder analyses were also performed by determining the proportion of subjects with controlled serum phosphorus levels as defined by the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines (3.5 to 5.5 mg/dL) in both PA-CL-03A and PA-CL-05A studies, and the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (2.5 to 4.5 mg/dL) in PA-CL-05A only. The results of these analyses were consistent with the primary efficacy endpoint findings. In PA-CL-03A, the proportion of subjects with controlled serum phosphorus levels at Week 7 (i.e., after 6 weeks of treatment) in the PA21 2500 mg/day group (60.0%) was statistically significantly greater than in the 250 mg/day LD group (21.1%) ($p = 0.034$). The proportion in the sevelamer group (42.1%) was similar to the PA21 1000 to 2000 mg/day dose groups (ranging from 35.0% to 42.9%). At the stage 2 baseline (Week 24) in Study PA-CL-05A, 72.7% of subjects in the MD group and 61.2% in the LD were within the KDOQI target range. At the end of stage 2 (Week 27) in this pivotal study, control of serum phosphorus was well maintained in the MD group, with 63.2% of subjects in the target range. In the LD group, withdrawal of the effective dose led to loss of control, with only 15.2% in the target range, similar to the LD group in PA-CL-03A after 6 weeks of treatment with 250 mg/day PA21.

The effect of PA21 on the reduction of serum phosphorus levels was consistent across all subgroups and was not affected by other baseline or disease characteristics including region (Europe, US, and rest of the world), dialysis type (HD or PD), sex, age (< 65 years or ≥ 65 years), race (Black, White or Other), ethnicity (Hispanic or Non-Hispanic), reason for ESRD (hypertension, diabetes or other), time from first dialysis, number of prior phosphate binders (1 or 2 or more), or prior sevelamer use (yes or no). In the overall or any subgroup analyses, there

Velphoro (b) (4)

were no changes in serum total calcium over time and no differences between treatment groups. Decreases in serum calcium-phosphorus product generally reflected changes in serum phosphorus. Mean serum iPTH levels decreased, although there was considerable variability among subjects.

Overall, the efficacy of PA21 for controlling serum phosphorus levels has been demonstrated. There is evidence of a dose-dependent relationship and treatment effects appear to be maintained at 12 months. PA21 efficacy does not appear to be affected by age, gender, race, ethnicity, primary diseases of ESRD, time of dialysis, or history of previous phosphate binder use. A statistically significant difference in serum phosphorus levels between the maintenance dose and the low (non-effective) dose was observed as early as one week in the randomized withdrawal phase of the pivotal trial. Based on these findings, dose titration for controlling hyperphosphatemia can be started as early as 1 week after treatment initiation and adjusted at weekly intervals thereafter if necessary.

6.1 Indication

The proposed indication for PA 21 (Velphoro™) is for the control of serum phosphorus levels in patients with end stage renal disease.

6.1.1 Methods

Studies supporting efficacy were examined separately, Analyses focused on Study PA-CL-05A. Other supportive studies that were analyzed included studies PA-CL-03A, PA1201, and PA-CL-05B.

6.1.2 Demographics

Demographic information for the pivotal trial is provided in this section; demographic data for other studies are provided in the appendix. Demographic data for subjects in the pivotal study are summarized in table 3. There was a gender imbalance in the two groups with a greater proportion of female subjects in the PA21 group (44.8%) than in the sevelamer group (36.9%).

Table 3: Summary of demography at stage 1 in Study PA-CL-05A

Demographic Variable	PA21 (N=694)	Sevelamer (N=347)	Total (N=1,041)
Age (years)			
n	694	347	1,041
Mean (SD)	56.3 (13.40)	55.8 (14.60)	56.1 (13.81)
Median	57.0	56.0	57.0
Min/max	21.0/89.0	21.1/88.0	21.0/89.0
Sex (n (%))			
Female	311 (44.8%)	128 (36.9%)	439 (42.2%)
Male	383 (55.2%)	219 (63.1%)	602 (57.8%)
Race (n (%))			
White	536 (77.2%)	263 (75.8%)	799 (76.8%)
Black/African American	127 (18.3%)	75 (21.6%)	202 (19.4%)
Asian	9 (1.3%)	6 (1.7%)	15 (1.4%)
American Indian/Alaska Native	1 (0.1%)	0 (0.0%)	1 (0.1%)
Native Hawaiian/Other Pacific Islander	6 (0.9%)	1 (0.3%)	7 (0.7%)
Other	15 (2.2%)	2 (0.6%)	17 (1.6%)
Ethnicity (n (%))			
Hispanic or Latino	88 (12.7%)	38 (11.0%)	126 (12.1%)
Non-hispanic or Latino	606 (87.3%)	309 (89.0%)	915 (87.9%)
Weight (kg)			
n	694	347	1,041
Mean (SD)	83.1 (20.91)	84.0 (20.79)	83.4 (20.87)
Median	80.0	81.2	80.5
Min/max	38.9/168.0	45.3/163.9	38.9/168.0
Dialysis status (n (%))			
Haemodialysis	638 (91.9%)	318 (91.6%)	956 (91.8%)
Peritoneal dialysis	56 (8.1%)	29 (8.4%)	85 (8.2%)

(Sponsor table from Study PA-CL-05A study report)

There were no notable differences between treatment groups related to reason for ESRD, time to start of ESRD, time to first dialysis, baseline Kt/V value, previous renal transplant, previous parathyroidectomy or prior treatment with sevelamer during the 12 months before screening. These data are shown in the following table.

Table 4: Summary of ESRD for stage 1 in Study PA-CL-05A

Demographic Variable	PA21 (N=694)	Sevelamer (N=347)	Total (N=1,041)
Reason for ESRD (n (%))			
Hypertension	158 (22.8%)	88 (25.4%)	246 (23.6%)
Glomerulonephritis	155 (22.3%)	87 (25.1%)	242 (23.2%)
Diabetes mellitus	196 (28.2%)	94 (27.1%)	290 (27.9%)
Pyelonephritis	27 (3.9%)	13 (3.7%)	40 (3.8%)
Polycystic kidney disease	66 (9.5%)	21 (6.1%)	87 (8.4%)
Interstitial nephritis	18 (2.6%)	10 (2.9%)	28 (2.7%)
Hydronephrosis	9 (1.3%)	4 (1.2%)	13 (1.2%)
Congenital	9 (1.3%)	5 (1.4%)	14 (1.3%)
Other	56 (8.1%)	25 (7.2%)	81 (7.8%)
Time from start of ESRD (months)⁽¹⁾			
n	692	347	1,039
Mean (SD)	63.7 (61.78)	67.7 (69.43)	65.0 (64.44)
Median	44.4	45.5	45.3
Min/max	3.1/445.5	0.4/407.2	0.4/445.5
Time from the first dialysis (months)⁽²⁾			
n	694	347	1,041
Mean (SD)	51.3 (48.77)	53.6 (55.04)	52.1 (50.93)
Median	35.9	38.3	37.0
Min/max	0.7/310.7	3.4/396.8	0.7/396.8
Baseline HD Kt/V value			
n	638	318	956
Mean (SD)	1.6 (0.29)	1.6 (0.27)	1.6 (0.28)
Median	1.5	1.5	1.5
Min/max	1.2/3.4	1.2/2.9	1.2/3.4
Baseline PD Kt/V value			
n	56	29	85
Mean (SD)	2.3 (0.64)	2.2 (0.63)	2.3 (0.64)
Median	2.2	2.1	2.2
Min/max	1.7/6.3	1.7/5.2	1.7/6.3
Previous Renal Transplant (n (%))			
Yes	58 (8.4%)	28 (8.1%)	86 (8.3%)
No	636 (91.6%)	319 (91.9%)	955 (91.7%)
Previous parathyroidectomy (n (%))			
Yes	28 (4.0%)	19 (5.5%)	47 (4.5%)
No	666 (96.0%)	328 (94.5%)	994 (95.5%)

1: Time from start of ESRD was the difference between the date of screening and the date of end-stage renal disease diagnosis. 2: Time from start of first dialysis was the difference between the date of screening and the date of the first dialysis. (Sponsor table from Study PA-CL-05A study report)

Compared with Stage 1, there was a higher proportion of Black/African American subjects and Hispanic subjects in Stage 2, likely because a large proportion of subjects from the US participated in this stage. There were no notable demographic differences between the PA21 MD and PA21 LD treatment groups. These data are summarized in the flowing table 5. The medical history profile for the Stage 2 subset of subjects was similar to the Stage 1 subjects.

Velphoro (b) (4)

Table 5: Summary of demography at stage 2 in Study PA-CL-05A

Demographic Variable	PA21 MD (N=44)	PA21 LD (N=49)	Total (N=93)
Age (years)			
n	44	49	93
Mean (SD)	59.3 (13.60)	57.2 (11.40)	58.2 (12.46)
Median	58.0	58.0	58.0
Min/max	23.0/83.0	27.0/83.0	23.0/83.0
Sex (n (%))			
Female	24 (54.5%)	25 (51.0%)	49 (52.7%)
Male	20 (45.5%)	24 (49.0%)	44 (47.3%)
Race (n (%))			
White	28 (63.6%)	30 (61.2%)	58 (62.4%)
Black/African American	14 (31.8%)	18 (36.7%)	32 (34.4%)
Asian	0 (0.0%)	1 (2.0%)	1 (1.1%)
American Indian/Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)
Native Hawaiian/Other Pacific Islander	1 (2.3%)	0 (0.0%)	1 (1.1%)
Other	1 (2.3%)	0 (0.0%)	1 (1.1%)
Ethnicity (n (%))			
Hispanic or Latino	9 (20.5%)	10 (20.4%)	19 (20.4)
Non-hispanic or Latino	35 (79.5%)	39 (79.6%)	74 (79.6%)
Weight (kg)			
n	44	48	92
Mean (SD)	84.1 (17.19)	85.1 (22.47)	84.6 (20.02)
Median	81.0	78.0	79.8
Min/max	50.8/123.9	44.1/167.3	44.1/167.3

(Sponsor table from Study PA-CL-05A study report)

Other factors in both Stage 1 and Stage 2 that could be related to changes in serum phosphate levels were also analyzed. These factors included previous treatment with phosphate binders, other medical history, prior medications other than phosphate binders, and concomitant medications.

- Previous Treatment with Phosphate Binders: Overall, 82.7% of subjects in Stage 1 used 1 phosphate binder, and 14.6% used 2 or more phosphate binders prior to the study. The use of phosphate binders prior to the study was not notably different between PA21 and sevelamer groups.
- Other medical history: Medical history was similar to the general ESRD dialysis patients. No notable differences in major medical conditions were observed between the 2 treatment groups. The overall medical history profile for the subset of subjects that entered Stage 2 was similar to the medical history profile of the Stage 1 subjects.
- Prior medications: Prior medications excluding phosphate binders were similar for the PA21 and sevelamer treatment groups. Anti-anemic preparations including iron supplements and erythropoiesis stimulating agents (ESA) were taken previously by 91.8% of subjects overall. Prior medication use by subjects participating in Stage 2 was similar to Stage 1. There were no notable differences between the PA21 MD and PA21 LD groups.
- Concomitant medications: Medications were recorded during Stage 1 with a start date on or after the first study drug intake. Concomitant medication use was similar for the 2 treatment groups overall. There were notable differences in the concomitant medications that were started in Stage 2 between the 2 groups. More subjects started concomitant medications in the LD group compared with the MD group (65.3% versus 15.6%). Noticeably more subjects in

Velphoro (b) (4)

the LD group started drugs were on anti-anemic preparations (ESAs) and anti-parathyroid preparations. It appears that more subjects in the LD group either re-started or had dose increases in ESAs compared to the MD group. Data on concomitant medications in stage 2 are summarized in the following table.

Table 6: Summary of concomitant medications in stage 2 in Study PA-CL-05A

ATC Level 2/ATC Level 4/ Preferred Term	PA21 MD (N=45) n (%)	PA LD (N=49) n (%)	Total (N=94) n (%)
At least 1 concomitant medication	7 (15.6%)	32 (65.3%)	39 (41.5%)
All other therapeutic products	2 (4.4%)	6 (12.2%)	8 (8.5%)
Drugs for treatment of hyperkalaemia & hyper phosphate	2 (4.4%)	6 (12.2%)	8 (8.5%)
Calcium acetate	0 (0.0%)	2 (4.1%)	2 (2.1%)
Sevelamer carbonate	1 (2.2%)	4 (8.2%)	5 (5.3%)
Sevelamer hydrochloride	1 (2.2%)	1 (2.0%)	2 (2.1%)
Sodium polystyrene sulphonate	1 (2.2%)	0 (0.0%)	1 (1.1%)
Antianaemic preparations	4 (8.9%)	15 (30.6%)	19 (20.2%)
Other antianaemic preparations	4 (8.9%)	15 (30.6%)	19 (20.2%)
Darbepoetin alfa	1 (2.2%)	0 (0%)	1 (1.1%)
Epoetin alfa	2 (4.4%)	14 (28.6%)	16 (17.0%)
Erythropoietin	1 (2.2%)	1 (2.0%)	2 (2.1%)
Antibacterials for systemic use	2 (4.4%)	4 (8.2%)	6 (6.4%)
Antithrombotic agents	2 (4.4%)	3 (6.1%)	5 (5.3%)
Calcium homeostasis	2 (4.4%)	7 (14.3%)	9 (9.6%)
Other anti-parathyroid agents	2 (4.4%)	7 (14.3%)	9 (9.6%)
Calcitriol	0 (0.0%)	1 (2.0%)	1 (1.1%)
Cinacalcet	1 (2.2%)	0 (0.0%)	1 (1.1%)
Paricalcitol	1 (2.2%)	6 (12.2%)	7 (7.4%)
Mineral supplements	0 (0.0%)	6 (12.2%)	6 (6.4%)
Calcium	0 (0.0%)	6 (12.2%)	6 (6.4%)
Calcium acetate	0 (0.0%)	2 (4.1%)	2 (2.1%)
Calcium carbonate	0 (0.0%)	3 (6.1%)	3 (3.2%)
Calcium-sandoz	0 (0.0%)	1 (2.0%)	1 (1.1%)
Vaccines	0 (0.0%)	4 (8.2%)	4 (4.3%)
Influenza vaccines	0 (0.0%)	3 (6.1%)	3 (3.2%)

(Sponsor table from Study PA-CL-05A study report)

There were no substantial differences in the overall percentage of subjects who received concomitant iron medications in the PA21 group versus sevelamer group (70.6% versus 74.1%) nor for any specific iron medications. The most commonly used iron medications overall were saccharated iron oxide, ferric sodium gluconate complex and iron dextran (53.2%, 10.9% and 7.4% of subjects, respectively). 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). All subjects that required added iron preparations received saccharated iron oxide.

Reviewer comments: In general, demographics were similar between the maintenance group and low dose (control) group in stage 2, and between the PA21 group and the sevelamer group in stage 1.

There was a significant difference in the use of the Vitamin D analogue, paricalcitol, between the MD and LD groups in stage 2 (6 in LD group, only 1 in the MD group). An efficacy analysis in which these 7 patients were excluded was conducted by the Statistical Reviewer, Dr. Liu

Velphoro (b) (4)

Ququan, to confirm that the imbalance in paricalcitol use did not affect the efficacy outcome. According to Dr. Liu Ququan, analyses in which these subjects were excluded produced similar results as analysis that included these subjects (discussed in Section 6.1.4).

6.1.3 Subject Disposition

Information on patient disposition in the pivotal study is discussed in this section. For a discussion of patient disposition in other trials, see the appendix. In Study PA-CL-05A, a total of 1,840 subjects were screened and 1,059 subjects were randomized to treatment in Stage 1. There were 710 in PA21 and 349 in sevelamer. 1,055 (99.6%) were treated, and 808 (76.3%) completed Stage 1.

During Stage 1, 251 subjects (23.7%) prematurely discontinued the study: 195 subjects (27.5%) treated with PA21 and 56 (16.1%) treated with sevelamer, including subjects who were randomized but not treated. The primary reasons for withdrawal in Stage 1 (excluding deaths) were non-fatal AEs other than phosphorus or calcium levels (45.8% of all withdrawals), and withdrawal of consent (18.7%), renal transplant (9.2%), protocol deviation (2.8%), Investigator decision (2.4%, all for non-compliance), hyperphosphatemia (4.8%), and Sponsor decision (3.6%, all due to closure of site 701). Less frequent reasons were hypercalcemia (0.8%), prohibited medications (0.8%) and hypophosphatemia (0.4%). Overall, a larger proportion of subjects in the PA21 group were withdrawn prematurely compared with the sevelamer group (27.5% versus 16.1%, respectively). This difference was mainly due to AEs which are discussed in section 7 of this review. The disposition of all subjects that were randomized at Stage 1, including reasons for discontinuation of treatment, is displayed for the overall set and by treatment in table 7.

Table 7: Subject disposition in stage 1 in Study PA-CL-05A

Parameter	PA21 (N=710) n (%)	Sevelamer (N=349) n (%)	Total (N=1,059) n (%)
Randomised	710 (100%)	349 (100%)	1,059 (100%)
Randomised but not treated	3 (0.4%)	1 (0.3%)	4 (0.4%)
Treated	707 (99.6%)	348 (99.7%)	1,055 (99.6%)
Completed 24 weeks	515 (72.5%)	293 (84.0%)	808 (76.3%)
Enrolled in PA-CL-05B extension study	392 (55.2%)	267 (76.5%)	659 (62.2%)
Withdrawn ⁽¹⁾	195 (27.5%)	56 (16.0%)	251 (23.7%)
Reason for discontinuation of treatment (study withdrawal) ⁽²⁾			
Death	9 (4.6%)	5 (8.9%)	14 (5.6%)
AE other than phosphorus or calcium levels	94 (48.2%)	21 (37.5%)	115 (45.8%)
Hyperphosphataemia	12 (6.2%)	0 (0.0%)	12 (4.8%)
Hypophosphataemia	1 (0.5%)	0 (0.0%)	1 (0.4%)
Hypercalcaemia	2 (1.0%)	0 (0.0%)	2 (0.8%)
Withdrew consent	32 (16.4%)	15 (26.8%)	47 (18.7%)
Investigator decision	5 (2.6%)	1 (1.8%)	6 (2.4%)
Sponsor decision	5 (2.6%)	4 (7.1%)	9 (3.6%)
Prohibited medication	2 (1.0%)	0 (0.0%)	2 (0.8%)
Protocol deviation	7 (3.6%)	0 (0.0%)	7 (2.8%)
Renal transplant	16 (8.2%)	7 (12.5%)	23 (9.2%)
Other	10 (5.1%)	3 (5.4%)	13 (5.2%)

1. Includes subjects that were randomized but not treated.; 2. The percentages of reasons for discontinuations were computed based on the total number of discontinuations.

(Sponsor table from Study PA-CL-05A study report)

Velphoro (b) (4)

In Stage 2, the first 100 subjects on HD who completed Stage 1 in the PA21 treatment group and who had a controlled serum phosphorus level of <5.5 mg/dL at Week 20, were randomized in a 1:1 ratio to the PA21 MD group or the PA21 LD group. There was a single randomization error by the site and only 99 subjects were actually enrolled in Stage 2. In Stage 2, 70 subjects (75.3%) came from the US, 15 (16.1%) from the EU, and 8 (8.6%) from the ROW region. Of the 99 subjects correctly randomized to Stage 2, 94 were treated and 88 completed Stage 2.

Of the 11 subjects who prematurely discontinued from the study, there were 8 of 50 subjects or 16% in the PA21 MD group and 3 of 49 subjects or 6.1% in the PA21 LD group. The withdrawals during Stage 2 in the PA21 MD were not related to safety. The reason for withdrawal in all subjects in the PA21 MD group was protocol deviation. Of these 8 subjects, 5 were dispensed PA-CL-05B study drug in error and 3 were non-compliant with the protocol. There was 1 death in the PA21 LD group (Subject 406-904 due to complications from a renal transplant) which was not attributed to treatment. There were events of high serum phosphorus levels (1 subject) and low serum phosphorus levels (1 subject) despite dose adjustments which led to withdrawals in the PA21 LD group. The disposition of all subjects that were randomized in Stage 2, including reasons for discontinuation of treatment, is summarized for the overall set and by treatment in table 8.

Table 8: Subject disposition in stage 2 in Study PA-CL-05A

Parameter	PA21 MD (N=50) n (%)	PA21 LD (N=49) n (%)	Total (N=99) n (%)
Randomised but not treated	5 (10.0%)	0 (0.0%)	5 (5.1%)
Treated	45 (90.0%)	49 (100%)	94 (94.9%)
Completed	42 (84.0%)	46 (93.9%)	88 (88.9%)
Enrolled in PA-CL-05B extension study	41 (82.0%)	0 (0.0%)	41 (41.4%)
Withdrawn ⁽¹⁾	8 (16.0%)	3 (6.1%)	11 (11.1%)
Reason for discontinuation of treatment (study withdrawal) ⁽²⁾			
Death	0 (0.0%)	1 (33.3%)	1 (9.0%)
AE other than phosphorus or calcium levels	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pregnancy	0 (0.0%)	0 (0.0%)	0 (0.0%)
Withdrew consent	0 (0.0%)	0 (0.0%)	0 (0.0%)
Investigator decision	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hyperphosphataemia	0 (0.0%)	1 (33.3%)	1 (9.0%)
Hypophosphataemia	0 (0.0%)	1 (33.3%)	1 (9.0%)
Hypercalcaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subject required treatment with an additional phosphate binder	0 (0.0%)	0 (0.0%)	0 (0.0%)
Prohibited medication	0 (0.0%)	0 (0.0%)	0 (0.0%)
Protocol deviation	8 (100.0%)	0 (0.0%)	8 (72.7%)
Sponsor decision	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)

1: Includes the subjects in the MD group randomized but not treated. These subjects were dispensed PA-CL-05B drug in error.

2: The percentages of reasons for discontinuations were computed based on the total number of discontinuations.

(Sponsor table from Study PA-CL-05A study report)

Reviewer comments: In the pivotal trial, discontinuation rates were higher in the PA21 MD group (16%) compared to the LD group (6%) in Stage 2, and in the PA21 group (27.5%) compared to the sevelamer group (16.1%) in Stage 1. In Stage 2, discontinuations for protocol deviations occurred at a higher incidence in the MD compared to LD group. In stage 1, the

Velphoro (b) (4)

difference was mainly due to non-fatal adverse events other than serum phosphorus and calcium level.

In the other supportive studies, subject disposition was similar in the treatment and control groups. Overall, patient disposition in these studies is acceptable for evaluating clinical efficacy.

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint was the change in serum phosphorus levels from the first dialysis session of Week 24 to the Week 27 measurement – a superiority comparison between the PA21 MD group and the PA21 LD control group (fixed dose of 250 mg/day) in stage 2. As shown in Table 9, the increase in serum phosphorus from baseline (Week 24) to the end of the study (Week 27) was 1.8 mg/dL in the PA21 LD group compared to an increase of 0.3 mg/dL in the PA21 MD group ($p < 0.001$). As shown in both Table 12 and Figure 4 (ITT population), mean serum phosphorus levels showed little change over time in the PA21 MD group, indicating continued serum phosphorus control. However, in the PA21 LD group, serum phosphorus levels were markedly increased as early as Week 25, one week after transitioning to the LD control.

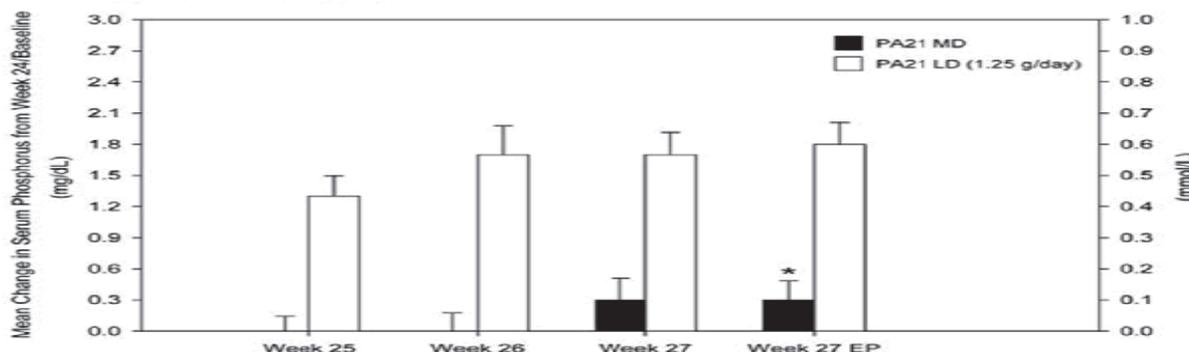
Similar results were observed in the PP population (see Table 10).

Table 9: Primary end point: Comparison of change in serum phosphorus levels from baseline to end of treatment in Stage 2 of Study PA-CL-05A (ITT population)

Time point	Serum phosphorus (mg/dl)		P value
	PA21 MD (n=44)	PA21 LD (n=49)	
Week 24 (baseline)	4.7±1.03	5.0±1.14	
Week 25	4.7±0.91	6.3±1.44	
Week 26	4.7±1.21	6.6±1.91	
Week 27	5.0±1.07	6.8±1.63	
Difference between baseline and Week 27	0.3±1.22	1.8±1.47	<0.001

(Reviewer table)

Figure 4: Change in serum phosphorus levels from baseline to end of treatment in stage 2 of Study PA-CL-05A



* $P < 0.001$ for the difference of change of serum phosphorus from baseline to end of week 27 between PA21 MD and LD (Sponsor figure from PA-CL-05A study report)

Velphoro (b) (4)

Table 10: Comparison of change in serum phosphorus levels from baseline to end of treatment in Stage 2 of PA-CL-05A (PP population)

Time point	Serum phosphorus (mg/dl)		P value
	PA21 MD (n=31)	PA21 LD (n=27)	
Week 24 (baseline)	4.6±0.99	5.0±1.27	
Week 25	4.7±0.95	6.5±1.62	
Week 26	4.7±1.23	6.8±2.31	
Week 27	5.0±0.94	6.9±1.82	
Difference between baseline and Week 27	0.4±1.17	1.9±1.53	<0.001

(Reviewer table)

Given the difference in use of Vitamin D analogues (calcitriol or paricalcitol) in the MD group (2 patients) and LD group (7 patients) in Stage 2 (see also discussion in Section 6.1.2), an analysis was conducted by the statistical reviewer, Dr. Cherry Liu, in which these patients were excluded. The analysis results were similar ($p < 0.0001$) to those obtained when these 9 patients were included. These data are summarized in table 11.

Table 11: Comparison of change in serum phosphorus level from baseline to end of treatment in stage 2 of PA-CL-05A (without Vitamin D analogues)

	PA21 MD	PA21 LD
N	42	42
LS Means (SE) (mg/dL)	0.23 (0.23)	2.02 (0.23)
Difference (95% CI)	1.79 (1.25, 2.33)	
P-value	<.0001	

(Reviewer table)

Reviewer comments: The primary endpoint was reached in this population based on the superiority of the maintenance dose over the low dose control for the reduction of serum phosphorus level.

6.1.5 Analysis of Secondary Endpoints(s)

Secondary endpoints in this pivotal study included the change from baseline in serum phosphorus levels at each time point (apart from end of treatment) in stage 2; the percentage of patients achieving controlled serum phosphorus levels in stage 2; the time to reach the first controlled serum phosphorus level in stage 1; and changes in serum levels of calcium, calcium x phosphorus, iPTH at each time point in both stage 2 and stage 1. There was no pre-defined ordering and none of these findings are described in the proposed labeling.

Change from baseline in serum phosphorus levels at each time point (apart from end of treatment) in stage 2: The comparison of the change from baseline in serum phosphorus levels at each time point between the MD and LD control is summarized in table 12. As shown in the table, the differences between the PA21 MD and LD groups were highly significant ($p < 0.001$) at all time points started from the first week (Week 25) in the Stage 2.

Velphoro (b) (4)

Table 12: Analysis of serum phosphorus change from baseline at all time points in stage 2 of Study PA-CL-05A (ITT population)

PA21 LD vs PA21 MD	Serum phosphorus (mg/dL) LS mean±SE	P value	95% CI
Contrasts at Week 25	1.37±0.22	<0.001	0.93; 1.82
Contrasts at Week 26	1.79±0.31	<0.001	1.17; 2.41
Contrasts at Week 27	1.56±0.27	<0.001	1.02; 2.10

(Reviewer table)

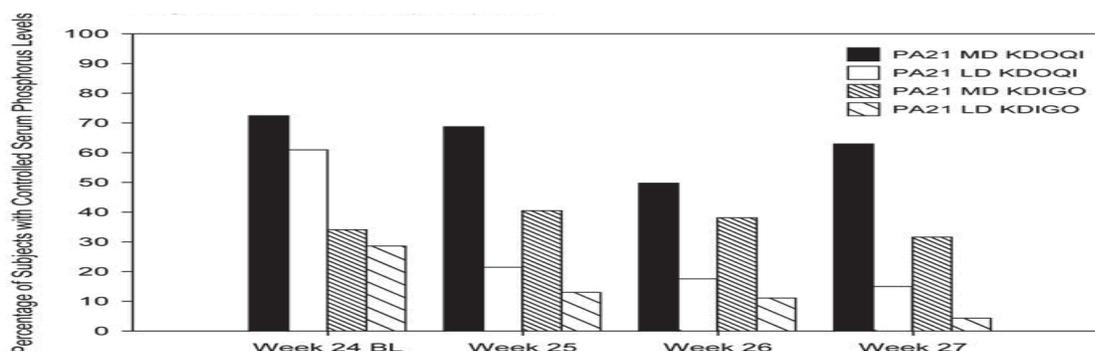
Percentage of patients achieving controlled serum phosphorus levels in stage 2: The control of serum phosphorus in Stage 2 was assessed using both the KDOQI target range (3.5 to 5.5 mg/dL) and the KDIGO range (2.5 to 4.5 mg/dL). At the Stage 2 baseline (Week 24), 72.7% of subjects in the MD group and 61.2% in the LD were within the KDOQI target range. At Week 27, 63.2% subjects in the MD group were within the target range, versus only 15.2% in the LD group. The differences between the MD and LD groups were highly statistically significant ($p \leq 0.004$) for both the KDOQI and KDIGO target ranges. Loss of control was rapid in the LD group; 1 week after withdrawal of the effective dose there was a substantial drop in the proportion of subjects with controlled serum phosphorus. Data are summarized in table 13 and described in the following figure 5.

Table 13: Proportions of subjects with serum phosphorus levels within KDOQI and KDIGO target ranges in stage 2 of Study PA-CL-05A (ITT population)

Time Point	Based on KDOQI Target Range ⁽¹⁾		Based on KDIGO Normal Range ⁽²⁾	
	PA21 MD (N=44)	PA21 LD (N=49)	PA21 MD (N=44)	PA21 LD (N=49)
Week 24: subjects evaluated	44	49	44	49
Week 24 controlled: n (%)	32 (72.7%)	30 (61.2%)	15 (34.1%)	14 (28.6%)
Week 25 subjects evaluated	42	46	42	46
Week 25 controlled: n (%)	29 (69.0%)	10 (21.7%)	17 (40.5%)	6 (13.0%)
Week 26 subjects evaluated	42	45	42	45
Week 26 controlled: n (%)	21 (50.0%)	8 (17.8%)	16 (38.1%)	5 (11.1%)
Week 27 subjects evaluated	38	46	38	46
Week 27 controlled: n (%)	24 (63.2%)	7 (15.2%)	12 (31.6%)	2 (4.3%)

(Sponsor table from PA-CL-05A study report)

Figure 5: Proportion of subjects with controlled serum phosphorus in stage 2 of Study PA-CL-05A



(Sponsor figure from PA-CL-05A study report)

Velphoro (b) (4)

Changes of Serum Total Calcium, Calcium-Phosphorus Product, iPTH in stage 2: No changes were observed over time in serum total calcium levels and no significant difference (p=0.075) was observed between MD and LD groups for the change from Week 24 baseline to Week 27. Consistent with the superiority of the PA21 MD over LD for control of serum phosphorus, the calcium-phosphorus product remained relatively constant over time in the MD group, but increased in the LD group with a statistically significantly higher change from Week 24 baseline to Week 27 endpoint as compared to the MD group (15.4 mg²/dL² versus 2.1 mg²/dL², respectively; p<0.001). Mean serum iPTH increased during Stage 2 in both the MD and LD treatment groups. At Week 27 endpoint, mean increases were greater in the LD group (105.4 ng/L) compared with the MD group (36.5 ng/L) without statistical significance (p=0.067). There was considerable variability among subjects. Data are summarized in table 14.

Table 14: Change from baseline in serum total calcium, Ca x P, and iPTH in stage 2 of Study PA-CL-05A (ITT population)

	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 MD (N=44)	PA21 LD (1.25 g/day) (N=49)	PA21 MD (N=44)	PA21 LD (1.25 g/day) (N=49)	PA21 MD (N=44)	PA21 LD (1.25 g/day) (N=49)
Week 24 BL⁽²⁾	2.3 (9.1)	2.3 (9.1)	3.5 (42.9)	3.6 (44.9)	37.3 (351.7)	34.5 (325.1)
SD	0.17 (0.68)	0.21 (0.84)	0.79 (9.79)	0.80 (9.97)	24.72 (232.95)	21.58 (203.35)
Week 27 EP⁽³⁾	2.3 (9.1)	2.2 (8.8)	3.6 (45.0)	4.9 (60.3)	42.0 (395.8)	46.1 (434.3)
SD	0.19 (0.77)	0.21 (0.86)	0.71 (8.78)	1.33 (16.53)	27.64 (260.50)	24.10 (227.14)
Change to Week 27 EP	0.0 (0.0)	-0.1 (-0.2)	0.2 (2.1)	1.2 (15.4)	3.9 (36.5)	11.2 (105.4)
SD	0.12 (0.48)	0.18 (0.71)	0.84 (10.38)	1.12 (13.93)	16.49 (155.44)	18.34 (172.83)
ANCOVA for PA21 MD vs. LD for Change from Week 24 BL to Week 27 EP						
Contrast for LS	-0.05 [-0.11, 0.01]		1.13 [0.74, 1.52]		6.69 [-0.49, 13.86]	
Mean [95% CI of the difference]	(-0.21 [-0.45, 0.02])		(13.99 [9.12, 18.85])		(63.03 [-4.58, 130.64])	
p-value	0.075		<0.001		0.067	

list doses were in the total mass which equal 250 mg/day in LD (1.25 g/day) (Sponsor table from PA-CL-05A study report)

Reviewer comments: Based on the data from stage 2, the clinically meaningful effect of PA21 on the reduction of serum level of phosphorus was demonstrated, and this effect would not significantly affect the serum level of calcium and iPTH in short-term.

Time to reach the first controlled serum phosphorus level in stage 1: The median time for subjects to achieve control based on KDOQI was 23.0 days with PA21 and 18.6 days with sevelamer. The difference in time to control was statistically significant favoring sevelamer (p=0.004). The time to control was notably longer with PA21 compared to sevelamer based on the KDIGO range. However, this may be because of the time to titration from the initial low dose to the optional dose. The time for subjects to achieve serum phosphorus control according to the KDOQI target and KDIGO normal ranges is summarized in table 15.

Velphoro (b) (4)

Table 15: Time (Days) to the first serum phosphorus level within the KDOQI and KDIGO ranges at stage 1 of Study PA-CL-05A

Statistic	PA21 (N=694)	Sevelamer (N=347)
Time (days) to first value within KDOQI target range ⁽¹⁾		
Number of subjects to achieve range	599 (86.3%)	320 (92.2%)
Number of censored	95 (13.7%)	27 (7.8%)
25% quartile (95% CI)	10.3 (8.1; 12.3)	8.0 (8.0; 9.4)
Median (95% CI)	23.0 (20.4; 26.9)	18.6 (15.0; 21.4)
75% quartile (95% CI)	48.6 (43.6; 53.8)	40.8 (35.2; 46.8)
Log-rank p-value	0.004	
Time (days) to first value within KDIGO normal range ⁽²⁾		
Number of subjects to achieve range	408 (58.8%)	237 (68.3%)
Number of censored	286 (41.2%)	110 (31.7%)
25% quartile (95% CI)	33.4 (28.2; 35.5)	23.0 (18.3; 27.1)
Median (95% CI)	81.8 (64.8; 103.8)	49.0 (42.6; 74.3)
75% quartile (95% CI)	NE (NE; NE)	172.0 (165.3; NE)
Log-rank p-value	0.005	

(Sponsor table from PA-CL-05A study report)

Efficacy Comparison of PA21 versus Sevelamer in stage 1: In Stage 1, using the applicant's pre-defined non-inferiority margin of 0.6mg/dl, 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 -2.2 mg/dL in the PA21 group compared to -2.4 mg/dL in the sevelamer. The least square mean estimate of the difference was 0.26 mg/dL with the upper bound of the 97.5% CI equal to 0.46 mg/dL. Data are summarized in table 16. The decrease in serum phosphorus from baseline to Week 12 was maintained through Week 24 for both treatment groups, demonstrating maintenance of efficacy.

Table 16: Week 12 non-inferiority analysis of PA21 vs. sevelamer for efficacy in lowering serum phosphorus in stage 1 of Study PA-CL-05A

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 versus 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 randomization, 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 0.6 mg/dL
- (Sponsor table from PA-CL-05A study report)

Reviewer comments: The proposed non-inferiority margin was not validated. Therefore, the analyses suggest similar efficacy at the doses used in this trial. It is hard to draw a conclusion beyond that.

Change from Baseline in Serum Total Calcium, Calcium–Phosphorus Product, and iPTH – Week 12 and Week 24 in stage 1: There were no changes in serum total calcium over time and no differences between treatment groups (p=0.901). Decreases in serum calcium-phosphorus product generally reflected the changes in serum phosphorus. Mean serum iPTH levels decreased during Stage 1, although there was considerable variability among subjects. Data are summarized in the following table 17.

Table 17: Change from baseline to Week 12 and Week 24 in serum total calcium, Ca x P, and iPTH in stage 1 of Study 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 ng/L is equivalent to 1 pg/mL.
 - BL is defined as measurement at Visit 4 (i.e., Week 0) or the last recorded value prior to randomization, if Visit 4 is missing.
 - Week 24 value or the latest available value prior to Week 24, when Week 24 value was missing (LOCF).
- (Sponsor table from PA-CL-05A study report)

Reviewer comments: The data from stage 1 suggest efficacy in lowering serum phosphorus levels in patients with ESRD undergoing PD or HD. The non-inferiority margin, however, was not validated. Therefore, the non-inferiority comparison between PA21 and sevelamer was inconclusive even though the results were similar. Similar to the findings in the stage 2, the serum level of calcium and iPTH in stage 1 were not be affected by PA21 and sevelamer.

Data from other studies supporting efficacy:

Study PA-CL-03A: In this phase 2 dose-ranging study, except for the PA21 low dose group (250 mg/day PA21), all PA21 treatment groups and the sevelamer 4.8 g/day group showed a highly significant decrease in serum phosphorus levels from baseline to end of treatment (primary endpoint). For the PA21 dose groups, the decrease in serum phosphorus levels was generally dose dependent. The decreases in mean serum phosphorus levels seen in the PA21 1000 mg/day and 1500 mg/day dose groups (-1.08 mg/dL from baseline) and (-1.25 mg/dL from

Velphoro (b) (4)

baseline) were comparable to the decrease seen in the sevelamer 4.8 g/day group (-1.06 mg/dL). Results were similar in both FAS the PPS. Data are summarized in the following table 18.

Table 18: Change in serum phosphorus from baseline in ESRD patients treated for 6 weeks in Study PA-CL-03A

Study Drug and Dose	Mean [SD] Serum Phosphorus, mmol/L (mg/dL)							
	FAS ⁽¹⁾				PPS ⁽²⁾			
	n	BL	Change From BL ⁽³⁾	p-value ⁽⁴⁾ (Change From BL)	n	BL	Change From BL ⁽³⁾	p-value ⁽⁴⁾ (Change From BL)
PA21 1.25 g/day	26	2.20 (6.82) [0.53 (1.64)]	-0.042 (-0.13) [0.65 (2.01)]	0.745	18	2.19 (6.77) [0.51 (1.57)]	0.07 (0.20) [0.65 (2.01)]	0.673
PA21 5.0 g/day	26	2.14 (6.61) [0.35 (1.08)]	-0.35 (-1.08) [0.68 (2.12)]	0.016	21	2.17 (6.72) [0.36 (1.10)]	-0.47 (-1.47) [0.65 (2.00)]	0.003
PA21 7.5 g/day	25	2.21 (6.85) [0.37 (1.15)]	-0.40 (-1.25) [0.39 (1.21)]	<0.001	22	2.20 (6.80) [0.39 (1.20)]	-0.41 (-1.26) [0.41 (1.27)]	<0.001
PA21 10.0 g/day	25	2.19 (6.77) [0.57 (1.75)]	-0.64 (-2.00) [0.55 (1.71)]	<0.001	20	2.17 (6.71) [0.58 (1.79)]	-0.64 (-1.97) [0.41 (1.28)]	<0.001
PA21 12.5 g/day	24	2.09 (6.47) [0.38 (1.19)]	-0.55 (-1.69) [0.58 (1.81)]	<0.001	19	2.07 (6.41) [0.34 (1.04)]	-0.57 (-1.77) [0.56 (1.74)]	<0.001
Sevelamer 4.8 g/day	24	2.24 (6.94) [0.52 (1.61)]	-0.34 (-1.06) [0.44 (1.35)]	<0.001	20	2.35 (7.28) [0.48 (1.49)]	-0.43 (-1.34) [0.40 (1.23)]	<0.001

1. All randomized subjects who received at least 1 dose of study treatment and had at least 1 post-BL efficacy evaluation (while on treatment – prior to follow-up evaluation) (N=150).
2. All randomized subjects that completed study per protocol (N=120).
3. Change from BL (Week 1, D1) to last value on treatment (Week 7, D1, or LOCF for missing values).
4. Single sample t-tests at 5% significance level, hierarchical procedure for PA21 dose groups (descending dose; no adjustment of alpha values).

Note: the list doses were in the total mass which equal 250 mg/day to 2500 mg/day PA 21(1.25 g/day to 12.5 g/day) (Sponsor table from PA-CL-03A study report)

Study PA1201: In this Phase 2, dose-ranging (fixed dose) study which enrolled 183 Japanese ESRD patients on stable, maintenance HD, 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 as shown in the following table 19.

Table 19: Mean change in serum phosphorus from baseline in ESRD patients treated for 6 weeks with PA21 or placebo in Study PA1201

Dose Group	N	LS Mean for Change from BL to EP, mmol/L (mg/dL)	95% CI, mmol/L (mg/dL)	ANCOVA		
				Difference Between LS Means (PA21-Placebo), mmol/L (mg/dL)	95% CI, mmol/L (mg/dL)	p-value
PA21 3.75 g/day	39	-0.59 (-1.84)	-0.72, -0.47 (-2.23, -1.44)	-0.64 (-1.98)	-0.82, -0.46 (-2.54, -1.41)	<0.001
PA21 7.5 g/day	35	-0.84 (-2.59)	-0.97, -0.70 (-3.01, -2.17)	-0.88 (-2.73)	-1.07, -0.69 (-3.31, -2.15)	<0.001
PA21 11.25 g/day	33	-1.02 (-3.17)	-1.16, -0.89 (-3.60, -2.74)	-1.07 (-3.31)	-1.26, -0.88 (-3.90, -2.72)	<0.001
PA21 15.0 g/day	34	-1.22 (-3.78)	-1.36, -1.09 (-4.20, -3.36)	-1.27 (-3.92)	-1.46, -1.08 (-4.51, -3.34)	<0.001
Placebo	37	0.05 (0.14)	-0.08, 0.18 (-0.26, 0.55)	N/A	N/A	N/A

Note: list doses of PA21 iron equal 750, 1500, 2250 and 3000 mg/day (Sponsor table from PA1201 study report summary)

6.1.6 Other Endpoints:

In Study PA-CL-05A, bone markers, fibroblast growth factor 23, and levels of some vitamins were assessed. Quality of life (SF-36) and patient preference/satisfaction were also studied.

Mean increases from baseline in carboxyterminal cross-linking telopeptide of bone collagen and osteocalcin and decreases in tartrate-resistant acid phosphatase 5b were small and not clinically relevant, and differences between the PA-21 and sevelamer treatment groups were not statistically significant. Alkaline phosphatase increased significantly from baseline in both treatment groups, but the increase in the sevelamer group was significantly greater than in the PA21 group.

Statistically significant decreases in fibroblast growth factor 23 were observed in both treatment groups, but differences between treatment groups were not statistically significant.

Mean Vitamin D levels decreased and Vitamin A, Vitamin E, and Vitamin K levels increased from baseline in both groups. The changes from baseline within treatment groups were statistically significant but not considered clinically meaningful.

Scores for patient preference, patient satisfaction, and Quality of Life (QoL) Short Form 36 (SF-36) were similar for subjects treated with PA21 and sevelamer. There were no significant changes from baseline in either group for any of the QoL (SF-36) scores. In the PA21 group, >77% of subjects found their treatment at Week 12 to be preferable or equal to their previous phosphate binder in terms of pill burden, ease of intake, side-effects and overall preference. Similarly, general satisfaction of PA21 subjects with their phosphate binder increased from 79% at the screening visit (reflecting the phosphate binder subjects were taking just prior to entering the study) to 91% at Week 24 (i.e., on PA21). Results were similar in the sevelamer group.

Reviewer comments: The clinical significance of these findings is unclear. These were exploratory analyses.

6.1.7 Subpopulations

Efficacy in Stage 2: Subgroup analyses of the primary endpoint evaluated factors including region (US, Europe, and ROW), gender, age (<65, ≥ 65 years), race (White, Black, Other), and ethnicity (Hispanic, Non-Hispanic). Overall, there were no significant differences in treatment effects on the change from baseline in serum phosphorus levels across sub-groups. However, because of the small sample sizes, interpretation is limited. Data are summarized in tables 20, 21, and 22.

Velphoro (b) (4)

Table 20: Subgroup analysis based on age and gender: Change in serum phosphorus in stage 2

	PA21 MD				PA21 LD (1.25 g/day)				p-value for Interaction with Treatment
	N	Mean [SD] Serum Phosphorus, mmol/L (mg/dL)			N	Mean [SD] Serum Phosphorus, mmol/L (mg/dL)			
		Week 24 BL	Week 27 EP	Change from Week 24-27 EP		Week 24 BL	Week 27 EP	Change from Week 24-27 EP	
All Subjects	44	1.5 (4.7) [0.33 (1.03)]	1.6 (5.0) [0.35 (1.07)]	0.1 (0.3) [0.40 (1.22)]	49	1.6 (5.0) [0.37 (1.14)]	2.2 (6.8) [0.53 (1.63)]	0.6 (1.8) [0.47 (1.47)]	N/A
Sex									0.893
Male	20	1.6 (4.9) [0.35 (1.08)]	1.7 (5.3) [0.27 (0.83)]	0.1 (0.3) [0.39 (1.19)]	24	1.6 (5.1) [0.31 (0.96)]	2.3 (7.0) [0.44 (1.36)]	0.6 (2.0) [0.35 (1.08)]	
Female	24	1.5 (4.5) [0.31 (0.96)]	1.5 (4.8) [0.39 (1.21)]	0.1 (0.3) [0.41 (1.27)]	25	1.6 (4.9) [0.42 (1.31)]	2.1 (6.6) [0.60 (1.87)]	0.5 (1.7) [0.57 (1.78)]	
Age									0.258
<65 years	28	1.5 (4.7) [0.36 (1.13)]	1.6 (5.0) [0.36 (1.12)]	0.1 (0.3) [0.44 (1.35)]	38	1.6 (5.0) [0.36 (1.13)]	2.3 (7.0) [0.57 (1.77)]	0.6 (1.9) [0.50 (1.55)]	
≥65 years	16	1.6 (4.8) [0.27 (0.84)]	1.6 (5.1) [0.33 (1.02)]	0.1 (0.2) [0.32 (0.99)]	11	1.5 (4.8) [0.39 (1.21)]	2.0 (6.2) [0.26 (0.80)]	0.5 (1.4) [0.36 (1.11)]	

(Sponsor table from PA-CL-05A study report)

Table 21: Subgroup analysis based on race and ethnicity: Change in serum phosphorus in stage 2

	PA21 MD				PA21 LD (1.25 g/day)				p-value for Interaction with Treatment
	N	Mean [SD] Serum Phosphorus, mmol/L (mg/dL)			N	Mean [SD] Serum Phosphorus, mmol/L (mg/dL)			
		Week 24 BL	Week 27 EP	Change from Week 24-27 EP		Week 24 BL	Week 27 EP	Change from Week 24-27 EP	
Race									0.915
Black	14	1.5 (4.7) [0.48 (1.49)]	1.5 (4.7) [0.31 (0.96)]	-0.0 (-0.0) [0.33 (1.02)]	18	1.5 (4.8) [0.35 (1.10)]	2.1 (6.4) [0.65 (2.03)]	0.5 (1.6) [0.54 (1.67)]	
White	28	1.5 (4.7) [0.25 (0.77)]	1.6 (5.1) [0.34 (1.04)]	0.1 (0.4) [0.40 (1.25)]	30	1.7 (5.2) [0.34 (1.04)]	2.3 (7.1) [0.43 (1.34)]	0.6 (1.9) [0.43 (1.32)]	
Other	2	1.6 (4.9) [0.18 (0.57)]	2.1 (6.5) [0.46 (1.41)]	0.5 (1.6) [0.64 (1.98)]	1	0.7 (2.1) N/A	2.0 (6.1) N/A	1.3 (4.0) N/A	
Ethnicity									0.353
Hispanic or Latino	9	1.5 (4.7) [0.31 (0.97)]	1.6 (5.1) [0.43 (1.33)]	0.1 (0.4) [0.47 (1.45)]	10	1.6 (4.9) [0.33 (1.03)]	2.4 (7.4) [0.38 (1.16)]	0.8 (2.4) [0.37 (1.15)]	
Not Hispanic or Latino	35	1.5 (4.7) [0.34 (1.05)]	1.6 (5.0) [0.33 (1.02)]	0.1 (0.3) [0.38 (1.18)]	39	1.6 (5.0) [0.38 (1.18)]	2.2 (6.7) [0.56 (1.72)]	0.5 (1.7) [0.49 (1.51)]	

(Sponsor table from PA-CL-05A study report)

Table 22: Subgroup analysis based on geographic region and medical history: Change in serum phosphorus in stage 2

	PA21 MD				PA21 LD (1.25 g/day)				p-value for Interaction with Treatment
	N	Mean [SD] Serum Phosphorus, mmol/L (mg/dL)			N	Mean [SD] Serum Phosphorus, mmol/L (mg/dL)			
		Week 24 BL	Week 27 EP	Change from Week 24-27 EP		Week 24 BL	Week 27 EP	Change from Week 24-27 EP	
Geographic region									0.800
US	33	1.5 (4.8) [0.35 (1.09)]	1.6 (5.0) [0.33 (1.03)]	0.1 (0.2) [0.38 (1.16)]	37	1.6 (4.9) [0.39 (1.20)]	2.2 (6.8) [0.53 (1.64)]	0.6 (1.9) [0.48 (1.50)]	
EU	7	1.6 (4.8) [0.27 (0.83)]	1.7 (5.3) [0.42 (1.30)]	0.1 (0.4) [0.44 (1.35)]	8	1.6 (4.9) [0.29 (0.89)]	2.1 (6.6) [0.25 (0.79)]	0.6 (1.7) [0.27 (0.84)]	
ROW	4	1.4 (4.3) [0.29 (0.89)]	1.6 (5.0) [0.40 (1.22)]	0.2 (0.7) [0.57 (1.77)]	4	1.9 (5.8) [0.29 (0.88)]	2.4 (7.3) [0.94 (2.91)]	0.5 (1.5) [0.77 (2.38)]	
Time from first dialysis⁽¹⁾	44	—	—	—	49	—	—	—	0.594
Reason for ESRD⁽²⁾	44	—	—	—	49	—	—	—	0.870
Number of prior phosphate binders⁽³⁾	44	—	—	—	49	—	—	—	0.863

(Sponsor table from PA-CL-05A study report)

No significant differences in treatment effects on the change from baseline were observed for serum total calcium, calcium-phosphorus product, or iPTH for any of the subgroups evaluated in stage 2.

Efficacy in Stage 1: Subgroup populations that were evaluated included gender, age (<65, ≥65 years), race (White, Black, Other), ethnicity (Hispanic, Non-Hispanic), previous sevelamer treatment (during the 12-month period preceding screening), region and dialysis status (PD versus HD). As in stage 2, time from first dialysis (as a continuous variable), reason for ESRD (Hypertension, Diabetes, Other), and number of prior phosphate binders (1, 2 or more) were also analyzed.

Overall, there were no significant differences in treatment effects on the change from baseline in serum phosphorus across sub-groups. No significant interactions with treatment were observed for 3 additional covariates: time from first dialysis (as a continuous variable), reason for ESRD (Hypertension, Diabetes, Other), and number of prior phosphate binders (1, 2 or more). Data are summarized in tables 23, 24, 25 and 26.

Table 23: Subgroup analysis based on gender and age: change in serum phosphorus in stage 1

	PA21				Sevelamer				p-value for Interaction with Treatment
	N	Mean [SD] Serum Phosphorus, mmol/L (mg/dL)			N	Mean [SD] Serum Phosphorus, mmol/L (mg/dL)			
		BL	Week 12 EP	Change from BL to Week 12 EP		BL	Week 12 EP	Change from BL to Week 12 EP	
All Subjects	461	2.5 (7.7) [0.59 (1.82)]	1.8 (5.5) [0.43 (1.32)]	-0.7 (-2.2) [0.62 (1.91)]	224	2.4 (7.6) [0.62 (1.92)]	1.7 (5.2) [0.42 (1.29)]	-0.8 (-2.4) [0.67 (2.07)]	N/A
Sex									0.643
Male	253	2.5 (7.7) [0.60 (1.84)]	1.8 (5.5) [0.42 (1.29)]	-0.7 (-2.2) [0.64 (1.98)]	136	2.4 (7.4) [0.58 (1.81)]	1.7 (5.2) [0.42 (1.29)]	-0.7 (-2.2) [0.61 (1.89)]	
Female	208	2.5 (7.7) [0.58 (1.78)]	1.8 (5.5) [0.44 (1.35)]	-0.7 (-2.2) [0.59 (1.83)]	88	2.5 (7.8) [0.67 (2.08)]	1.7 (5.2) [0.42 (1.29)]	-0.9 (-2.6) [0.75 (2.31)]	
Age									0.785
<65 years	346	2.5 (7.8) [0.61 (1.88)]	1.8 (5.6) [0.43 (1.33)]	-0.7 (-2.2) [0.63 (1.96)]	163	2.5 (7.7) [0.67 (2.08)]	1.7 (5.3) [0.42 (1.30)]	-0.8 (-2.4) [0.71 (2.19)]	
≥65 years	115	2.3 (7.2) [0.49 (1.51)]	1.6 (5.1) [0.39 (1.20)]	-0.7 (-2.1) [0.58 (1.78)]	61	2.3 (7.2) [0.44 (1.35)]	1.6 (4.9) [0.39 (1.21)]	-0.7 (-2.3) [0.56 (1.74)]	

(Sponsor table from PA-CL-05A study report)

Table 24: Subgroup analysis based on race and ethnicity: change in serum phosphorus in stage 1

	PA21				Sevelamer				p-value for Interaction with Treatment
	N	Mean [SD] Serum Phosphorus, mmol/L (mg/dL)			N	Mean [SD] Serum Phosphorus, mmol/L (mg/dL)			
		BL	Week 12 EP	Change from BL to Week 12 EP		BL	Week 12 EP	Change from BL to Week 12 EP	
Race									0.296
Black	70	2.5 (7.7) [0.66 (2.06)]	1.7 (5.3) [0.41 (1.28)]	-0.8 (-2.4) [0.71 (2.18)]	32	2.4 (7.5) [0.63 (1.97)]	1.6 (4.9) [0.46 (1.42)]	-0.8 (-2.6) [0.62 (1.93)]	
White	376	2.5 (7.7) [0.57 (1.77)]	1.8 (5.5) [0.43 (1.32)]	-0.7 (-2.2) [0.60 (1.85)]	187	2.4 (7.6) [0.62 (1.93)]	1.7 (5.3) [0.41 (1.27)]	-0.8 (-2.3) [0.68 (2.12)]	
Other	15	2.2 (6.9) [0.57 (1.77)]	1.9 (5.8) [0.47 (1.45)]	-0.4 (-1.1) [0.60 (1.87)]	5	2.4 (7.6) [0.58 (1.80)]	1.5 (4.7) [0.25 (0.79)]	-0.9 (-2.8) [0.45 (1.39)]	
Ethnicity									0.136
Hispanic or Latino	45	2.5 (7.8) [0.65 (2.01)]	1.8 (5.4) [0.38 (1.19)]	-0.8 (-2.4) [0.64 (1.97)]	23	2.3 (7.2) [0.48 (1.49)]	1.8 (5.5) [0.33 (1.01)]	-0.5 (-1.7) [0.55 (1.69)]	
Not Hispanic or Latino	416	2.5 (7.7) [0.58 (1.80)]	1.8 (5.5) [0.43 (1.33)]	-0.7 (-2.2) [0.62 (1.91)]	201	2.5 (7.6) [0.63 (1.96)]	1.7 (5.2) [0.42 (1.31)]	-0.8 (-2.4) [0.68 (2.10)]	

(Sponsor table from PA-CL-05A study report)

Velphoro (b) (4)

Table 25: Subgroup analysis based on region and dialysis status: Change in serum phosphorus in stage 1

	PA21				Sevelamer				p-value for Interaction with Treatment
	N	Mean [SD] Serum Phosphorus, mmol/L (mg/dL)			N	Mean [SD] Serum Phosphorus, mmol/L (mg/dL)			
		BL	Week 12 EP	Change from BL to Week 12 EP		BL	Week 12 EP	Change from BL to Week 12 EP	
Geographic Region									0.533
US	184	2.5 (7.6) [0.61 (1.88)]	1.8 (5.4) [0.41 (1.27)]	-0.7 (-2.2) [0.64 (1.97)]	87	2.4 (7.4) [0.54 (1.68)]	1.6 (5.1) [0.38 (1.18)]	-0.8 (-2.3) [0.57 (1.77)]	
EU	104	2.6 (7.9) [0.58 (1.80)]	1.7 (5.3) [0.43 (1.34)]	-0.8 (-2.6) [0.58 (1.81)]	47	2.5 (7.6) [0.58 (1.81)]	1.7 (5.2) [0.33 (1.03)]	-0.8 (-2.4) [0.60 (1.86)]	
ROW	173	2.5 (7.6) [0.57 (1.76)]	1.8 (5.6) [0.43 (1.34)]	-0.6 (-2.0) [0.61 (1.89)]	90	2.5 (7.7) [0.71 (2.19)]	1.7 (5.3) [0.48 (1.49)]	-0.8 (-2.4) [0.79 (2.44)]	
Dialysis Status									0.287
PD	41	2.3 (7.1) [0.46 (1.42)]	1.8 (5.5) [0.40 (1.25)]	-0.5 (-1.7) [0.58 (1.78)]	16	2.1 (6.5) [0.34 (1.05)]	1.5 (4.8) [0.30 (0.94)]	-0.5 (-1.7) [0.38 (1.19)]	
HD	420	2.5 (7.7) [0.59 (1.84)]	1.8 (5.5) [0.43 (1.32)]	-0.7 (-2.3) [0.62 (1.92)]	208	2.5 (7.7) [0.63 (1.95)]	1.7 (5.2) [0.42 (1.30)]	-0.8 (-2.4) [0.68 (2.12)]	

(Sponsor table from PA-CL-05A study report)

Table 26: Subgroup analysis based on medical history: change in serum phosphorus in stage 1

	PA21				Sevelamer				p-value for Interaction with Treatment
	N	Mean [SD] Serum Phosphorus, mmol/L (mg/dL)			N	Mean [SD] Serum Phosphorus, mmol/L (mg/dL)			
		BL	Week 12 EP	Change from BL to Week 12 EP		BL	Week 12 EP	Change from BL to Week 12 EP	
Previous Sevelamer Treatment									0.355
Yes	148	2.5 (7.7) [0.63 (1.94)]	1.7 (5.4) [0.41 (1.28)]	-0.7 (-2.3) [0.65 (2.00)]	76	2.4 (7.5) [0.55 (1.70)]	1.7 (5.2) [0.37 (1.15)]	-0.7 (-2.3) [0.57 (1.76)]	
No	313	2.5 (7.7) [0.57 (1.75)]	1.8 (5.5) [0.43 (1.33)]	-0.7 (-2.2) [0.61 (1.88)]	148	2.5 (7.6) [0.66 (2.03)]	1.7 (5.2) [0.44 (1.35)]	-0.8 (-2.4) [0.72 (2.22)]	
Time from first dialysis⁽¹⁾		—	—	—		—	—	—	0.287
Reason for ESRD⁽²⁾		—	—	—		—	—	—	0.493
Number of prior phosphate binders⁽³⁾		—	—	—		—	—	—	0.676

(Sponsor table from PA-CL-05A study report)

As in Stage 2, no significant differences in treatment effects on the change from baseline were observed for serum total calcium, calcium-phosphorus product, or iPTH for any of the subgroups in stage 1.

Reviewer comments: Although the sample size was limited in stage 2, based on the data from stage 1 and previous studies of other phosphate binders, there should be no difference in efficacy across these sub-populations.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Proposed dosing recommendations for PA21 are based on the results of the dose-rang finding study PA-CL-03A and the pivotal study PA-CL-05A, and on clinical practice with some approved phosphate binders. As many factors can affect serum phosphorus levels, phosphate

Velphoro (b) (4)

binders in general should be dose-titrated individually to achieve a target serum phosphorus level with minimum AEs.

Justification of Dosing Regimen: In Study PA-CL-03A, PA21 at doses of 1000 mg/day and 1500 mg/day were similar in efficacy and comparable to an approved starting dose of sevelamer (4.8 g/day). In PA-CL-05A, subjects were started at dose of 1000 mg/day and most subjects (82.7%) were up-titrated to 1500 mg/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 1000 mg/day and 88 (30.1%) subjects were taking 1500 mg/day. In comparison, of the sevelamer-treated subjects 160 (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. Given that very few dose-dependent or dose-limiting AEs were observed with PA21, it is therefore reasonable to recommend a starting dose of 1500 mg/day as more than 50% of subjects in PA-CL-05A who achieved controlled serum phosphorus levels would be expected to be controlled at a starting dose of 1500 mg/day. Furthermore, a starting dose of 1500 mg/day would necessitate taking 3 PA21 tablets per day instead of 2 tablets per day with a dose of 1000mg/day. Three tablets per day allows more flexibility and better distribution of drug administration during the day, thus ensuring that more meals can be consumed with a PA21 tablet.

As shown in both studies, 1000 mg/day PA21 was also effective for some subjects. Therefore, the dose of PA21 may be decreased or increased by 500 mg (1 tablet) per day, to a minimum of 1000 mg/day and a maximum of 3000 mg/day based on serum phosphorus level. As the serum phosphorus lowering effect of PA21 is rapid, it is also reasonable that dose titration can be started as early as 1 week after initiation of treatment or after any dose change. These data are summarized in table 27.

PA21 is equally efficacious in patients on HD and PD. PA21 is also equally efficacious across a number of sub-groups, and no interactions have been found with several baseline demographic and disease characteristics. Therefore, no special dosing recommendation is required for any sub-group of patients.

PA21 has not been studied in the pediatric population or in pregnant or lactating women and therefore is not recommended for use in these patients at this time.

Velphoro (b) (4)

Table 27: Dose distribution of PA21 and sevelamer in stage 1 of Study PA-CL-05A

Week Sub-group	PA21 (FAS, N=694)						Sevelamer (FAS, N=347)								
	No. Per Sub-group (% of All)	Mean Dose (SD), g/day	No. Per Sub-group (% of Sub-group) for Each Dose in g/day (tablets/day)					No. Per Sub-group (% of All)	Mean Dose (SD), g/day	No. Per Sub-group (% of Sub-group) for Each Dose in g/day (tablets/day)					
			5.0 (2) n (%)	7.5 (3) n (%)	10.0 (4) n (%)	12.5 (5) n (%)	15.0 (6) n (%)			2.4 (3) n (%)	4.8 (6) n (%)	7.2 (9) n (%)	9.6 (12) n (%)	12.0 (15) n (%)	14.4 (18) 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%)	325 (100%)	7.7 (2.50)	7 (2.2%)	87 (26.8%)	100 (30.8%)	94 (28.9%)	35 (10.8%)	2 (0.6%)
Controlled, KDOQI target ⁽¹⁾	292 (47.1%)	8.4 (2.55)	73 (25.0%)	88 (30.1%)	90 (30.8%)	39 (13.4%)	2 (0.7%)	160 (49.2%)	7.2 (2.17)	2 (1.3%)	51 (31.9%)	60 (37.5%)	39 (24.4%)	8 (5.0%)	0 (0.0%)
Uncontrolled, KDOQI target ⁽²⁾	328 (52.9%)	9.8 (2.54)	34 (10.4%)	76 (23.2%)	99 (30.2%)	116 (35.4%)	3 (0.9%)	165 (50.8%)	8.2 (2.70)	5 (3.0%)	36 (21.8%)	40 (24.2%)	55 (33.3%)	27 (16.4%)	2 (1.2%)
Controlled, KDIGO normal ⁽³⁾	104 (16.8%)	8.1 (2.63)	30 (28.8%)	37 (35.6%)	23 (22.1%)	12 (11.5%)	2 (1.9%)	75 (23.1%)	6.4 (1.95)	3 (4.0%)	32 (42.7%)	27 (36.0%)	13 (17.3%)	0 (0.0%)	0 (0.0%)
Uncontrolled, KDIGO normal ⁽⁴⁾	516 (83.2%)	9.4 (2.60)	77 (14.9%)	127 (24.6%)	166 (32.2%)	143 (27.7%)	3 (0.6%)	250 (76.9%)	8.1 (2.52)	4 (1.6%)	55 (22.0%)	73 (29.2%)	81 (32.4%)	35 (14.0%)	2 (0.8%)
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%)	311 (100.0%)	8.2 (3.16)	10 (3.2%)	78 (25.1%)	88 (28.3%)	65 (20.9%)	44 (14.1%)	26 (8.4%)
Controlled, KDOQI target ⁽¹⁾	258 (44.3%)	9.2 (3.07)	53 (20.5%)	64 (24.8%)	74 (28.7%)	44 (17.1%)	23 (8.9%)	170 (54.7%)	7.7 (2.81)	4 (2.4%)	48 (28.2%)	62 (36.5%)	28 (16.5%)	21 (12.4%)	7 (4.1%)

1. Subjects with controlled serum phosphorus according to KDOQI target range (3.5 to 5.5 mg/dL)).
2. Subjects with serum phosphorus outside the KDOQI target range.
3. Subjects with normal serum phosphorus (2.5-4.5 mg/dL).
4. Subjects with serum phosphorus outside the normal range.

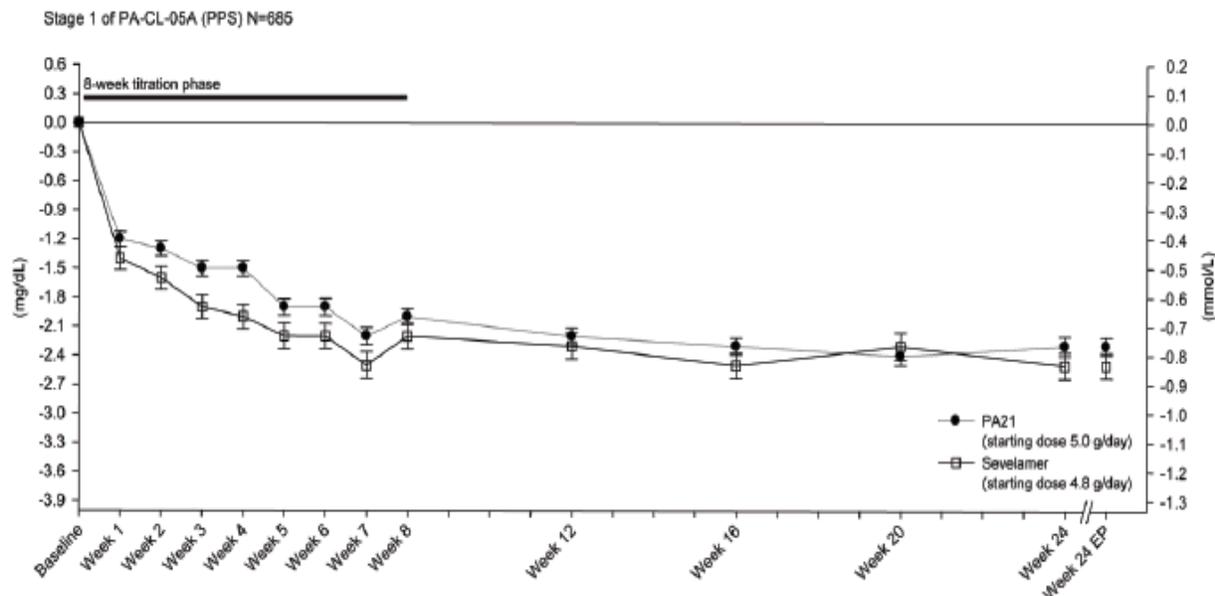
Notes: FAS = Full analysis set; doses of 5-15g/day represent 1000 mg/day to 3000 mg/day PA21
(Sponsor table from Summary of Efficacy)

Dosing Recommendations: Based on the aforementioned data, the recommended starting dose of PA21 should be 1500 mg (3 tablets) per day for the control of serum phosphorus in adult ESRD patients. Serum phosphorus levels should be monitored regularly, and the dose of PA21 may be decreased or increased by 500 mg (1 tablet) per day, to a minimum of 1000 mg/day and a maximum of 3000 mg/day until an acceptable serum phosphorus level is reached. Titration can be started as early as 1 week after treatment initiation or after any dose change.

6.1.9 Discussion of Persistence of Efficacy and/ Tolerance Effects

Persistence of efficacy of PA21 over 24 weeks was demonstrated in Stage 1 of PA-CL-05A. Following the rapid decrease in serum phosphorus in the 1 to 2 weeks during the initial dose-titration period, serum phosphorus levels remained relatively constant demonstrating persistence of effect up to 27 weeks (Stage 1 and Stage 2). The mean serum phosphorus levels returned towards baseline upon withdrawal of the effective dose to the non-effective low dose control in stage 2 confirming both persistence of efficacy and the lack of development of tolerance. These data are shown in figure 6.

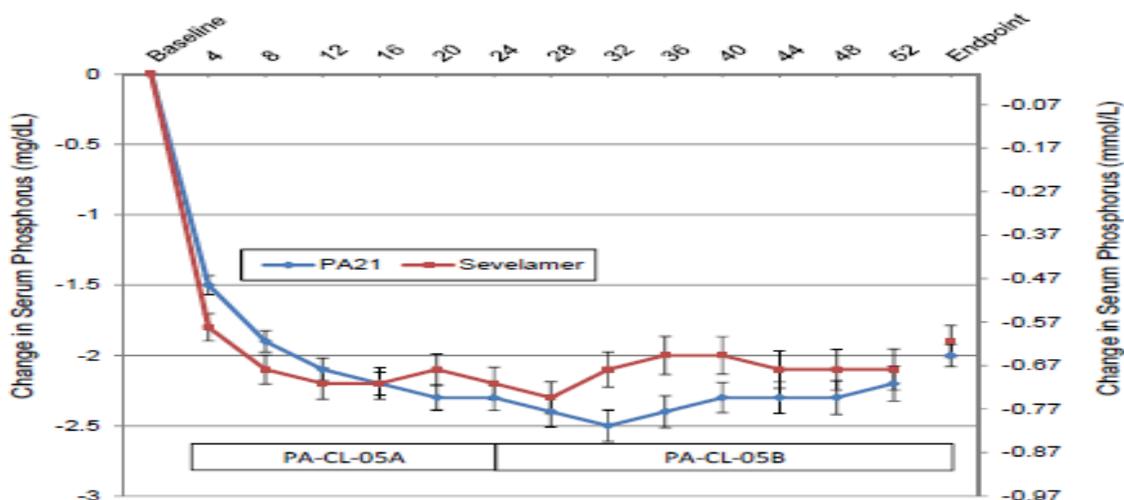
Figure 6: Mean change of serum phosphorus levels from baseline during Stage 1



Note: 5.0g/day is a total mass of the product meaning PA21 1000 mg/day (Sponsor figure from PA-CL-05A study report)

In the long-term extension study of the pivotal study, continued maintenance of serum phosphorus control for up to an additional 28 weeks (total 52 to 55 weeks) was also demonstrated as shown in figure 7 (PA21 (median 4.5 tablets/day) and sevelamer (median 10.3 tablets/day)).

Figure 7: Mean change of serum phosphorus levels from baseline in stages 1 and 2



(Sponsor figure from 120-day safety update report)

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety analyses focused on data from 4 clinical studies conducted in ESRD patients undergoing dialysis: the pivotal efficacy study, its extension trial (Study PA-CL-05A/05B), one phase 2 dose-ranging study (Study PA-CL-03A) and one phase 2 study conducted in Japanese patients (Study PA1201). Clinical pharmacology studies, including one study, Study Q-24120, which was conducted in patients with chronic kidney disease, were also utilized in safety analyses.

Overall, a total of 1953 subjects were included in the safety analysis including 1288 subjects who had received at least one dose of PA21. 1355 ESRD patients were included in short-term studies including 981 patients on PA21. A total of 659 ESRD patients were in an open-label, long-term study of up to 12 months including 391 ESRD patients in PA21.

Drug-related AEs were primarily limited to GI effects. In the pivotal study, diarrhea was the most common PA21-related adverse event (AE) and was also the major reason for AE-related patient withdrawal in the PA21 group. The incidence rate of diarrhea was higher in the PA21 group compared to the active control, sevelamer. The majority of these diarrhea AEs occurred early after starting treatment, were mild in severity, and resolved with continued treatment. A dose-dependent increase in the incidence rate of diarrhea was found in Japanese patients in Study PA1201. However, in the fixed dose ranging study, Study PA-CL-03A, the incidence rate of diarrhea was not related to dose and was similar in the PA21 and sevelamer treatment arms.

Other common GI AEs including nausea, vomiting and constipation occurred less frequently on PA21 than on sevelamer in the pivotal study. The incidence of common GI events was substantially reduced during continued treatment in the long-term extension study (Study PA-CL-05B). Hypophosphatemia was observed in some patients in both the dose-ranging study and the pivotal study. This is a dose-dependent drug-related AE. However, as this product will be started at a low dose and gradually titrated with careful monitoring, this AE should not be a major concern.

No new or significant safety signals have emerged with long-term treatment of up to one year duration. In general, the incidence of PA-21 related AEs was similar to that observed with the active control, sevelamer.

Because PA21 is an iron based phosphate binder, the effect of PA21 on systemic iron levels was evaluated in the pivotal study and its extension trial. Increases in serum ferritin and TSAT and decreases in transferrin were observed during the first 6 months of treatment with PA21 compared to both baseline and the active control (20.3% vs. 5.1% from baseline for transferrin, 18.4% vs. -3.6% from baseline for TSAT, and -2.3% vs. 8.3% for transferrin, in the PA21 vs. Sevelamer treatment arms, respectively) These effects were maintained but did not increase further with continued treatment up to one year. There was no evidence of iron accumulation with increased cumulative exposure. Concomitant use of IV iron and ESAs in these studies and regional differences in use complicate the interpretation of these events. The observed changes, however, are consistent with the minimal iron absorption from PA21 observed in the Phase 1 study and do not raise a major safety concern.

As with other phosphate binders, another concern is for potential effects of PA21 on the bioavailability of other drugs. In addition to the monitoring performed in the pivotal trial, several drug-drug interaction studies both in vitro and in vivo were performed. In the in vitro drug-drug interaction studies, there was no effect of PA21 on drugs including ciprofloxacin, enalapril, hydrochlorothiazide, metformin, metoprolol, nifedipine, and quinidine. However PA21 did show to bind to alendronate, doxycycline, levothyroxine, atorvastatin, and paricalcitol. (b) (4)

Considering the Tmax of paricalcitol is about 3 hours, the bioavailability of paricalcitol may still be affected if administered 2 hours after PA21. (b) (4)

In the pivotal study, Velphoro did not affect the lipid lowering effects of HMG-CoA reductase inhibitors. In in vivo studies conducted in healthy subjects, concomitant administration of PA21 did not affect the bioavailability of some commonly used drugs in ESRD patients including losartan, furosemide, digoxin, warfarin, and omeprazole based on measured AUC.

In conclusion, the size of the safety database and duration of exposure are adequate to assess safety for this product. Overall, the AE profile of PA21 is acceptable for the control of serum phosphorus levels in patients with end stage renal disease who are being treated with hemodialysis or peritoneal dialysis.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety analyses focused on 4 clinical studies conducted in patients with ESRD (see table 2 in Section 5.3). In addition, clinical pharmacology studies summarized in table 28 below were also utilized in the safety evaluation of PA-21.

Table 28: Summary of clinical pharmacology studies for safety evaluation

Study #	Design	N of patients	Control	Outcome	Other
Q-24120	open-label, repeat single-dose with ⁵⁹ Fe-labeled PA21 at 10g daily for 7 days	13M, 11F; CKD (16), or healthy with low iron stores (8)	None	ADME	Phase I
VIT-CL-01/02	Randomized, double-blind, single- and 3-day dose study. 7 dosing groups: 3.75, 5.0, 7.5, 8.75, 10, 11.25, and 12.5g/day. 6 on PA21 and 2 on placebo in each group	32 M, 25 F healthy volunteers	Placebo tablets	Safety and tolerability	Phase I
PA-DDI-001	Randomized, open-label, 3-period crossover study. Group 1: period 1, PA21 on Day -1 (5.0 g TID with meals) and on Day 0 a single dose of 5.0 g with breakfast) followed by a single dose of losartan (100 mg). Group 2: period 2, no	26 M, 15 F healthy volunteers	Losartan potassium tablet	DDI between PA21 and Losartan	Phase I

Velphoro (b) (4)

	<p>treatment on Day -1 and on Day 0 a single dose of losartan (100 mg) with breakfast. Group 3: period 3, PA21 on Day -1 (5.0 g TID with meals and on Day 0 a single dose of 5.0 g with breakfast followed by single dose of losartan (100 mg) 2 hours later and at least 1 hour prior to the next meal. After a 7-day washout period, Group 1 crossover to receive Period 2 dosing, Group 2 received Period 3 dosing, and Group 3 received Period 1 dosing. After a further 7-day washout period, subjects from Group 1 crossover to receive the Period 3 dosing, Group 2 received Period 1 dosing, and Group 3 received Period 2 dosing.</p>				
PA-DDI-002	Similar to 001, but using furosemide 40mg instead of losartan 100mg	28 M, 13 F Healthy volunteers	Furosemide 40mg tablet	DDI between PA21 and furosemide	Phase I
PA-DDI-003	Similar to 001, but using omeprazole 40mg instead of losartan 100mg	22 M, 21 F Healthy volunteers	Omeprazole 40mg tablet	DDI between PA21 and omeprazole	Phase I
PA-DDI-004	Similar to 001, but using digoxin 0.5mg instead of losartan 100mg	21 M, 21 F Healthy volunteers	Digoxin 0.25mg tablet	DDI between PA21 and digoxin	Phase I
PA-DDI-005	Similar to 001, but using warfarin 10mg instead of losartan 100mg	26 M, 17 F Healthy volunteers	Warfarin 10mg tablet	DDI between PA21 and warfarin	Phase I
PA1101	Randomized, double-blind, placebo-controlled, stepwise dose escalation study: placebo or PA21 at single doses of 1.25, 2.5, and 5.0 g fasting in mornings. Then placebo or PA21 at doses of 1.25, 2.5, and 5.0 g TID prior to each meal for 7 days.	30 Japanese Males Healthy volunteers	Placebo tablet	Safety and tolerability of single and multiple ascending doses	Phase I

(Reviewer table)

7.1.2 Categorization of Adverse Events

In the safety evaluation, data were presented according to MedDRA Version 13.1. Adverse event data cited in the proposed labeling were based on the MedDRA-based terminology analyses.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Given differences in study design, for the most part, data from studies were not pooled. Safety data are presented based on the following groups:

- Phase 2 dose-range finding study, Study PA-CL-03A
- Phase 3 pivotal study, Study PA-CL-05A and its extension, Study PA-CL-05B
- All of the 5 DDI clinical pharmacology studies.
- Others studies including Study VIT-CI-01/0 and Study Q-24120, and two Japanese studies including Study PA1101, and Study PA1201. Please see the section 7.1.1 for the brief summary of these studies.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 1953 subjects were included in the safety analysis of this clinical development program including 1288 subjects received PA21. 1355 ESRD patients were in short-term studies including 981 patients on PA21. A total of 659 ESRD patients were in an open-label, long-term study of up to 12 months including 391 ESRD patients on PA21.

Overall, the total number of patients and the duration of exposure seems adequate to evaluate the safety of this product. In both the pivotal study (including stage 1 and stage 2) and the supportive studies, the treatment groups and the placebo or active control groups were generally similar with respect to demographics and baseline characteristics, and reflected the intended target population. Data from individual studies are summarized in the following tables 29-35.

Table 29: Extent of exposure to PA21 or sevelamer in Study PA-CL-03A

	PA21					Sevelamer (HCl) (N=26)
	1.25 g/Day (N=26)	5.0 g/Day (N=26)	7.5 g/Day (N=25)	10.0 g/Day (N=27)	12.5 g/Day (N=24)	
Duration of exposure (days)						
n	26	26	25	27	24	26
Mean	39.2	37.3	38.2	32.1	35.8	35.8
SD	8.43	10.56	9.74	14.15	11.42	14.26
Median	42.0	42.0	43.0	42.0	42.0	42.5
Range	15-56	8-57	7-44	1-43	7-43	1-52
Average daily dose (g)						
n	25	24	24	25	24	26
Mean	1.2	4.5	7.0	8.5	11.1	4.2
SD	0.19	0.78	0.98	2.82	2.93	0.95
Median	1.3	4.8	7.3	9.7	12.1	4.6
Range	1-2	2-5	3-8	0-12	0-14	2-5

Note: the list doses were in the total mass. Its tablet is standardized to contain 500 mg iron (as PA21 drug substance (DS)) with a total nominal mass of 2.5g. Doses of 1.25, 5.0, 7.5, 10 and 12.5g represent 250, 1000, 1500, 2000, and 2500 mg iron of PA21. (Sponsor table from PA-CL-03A study report)

Table 30: Demographics including age, height, sex, and ethnic origin in Study PA-CL-03A

Demographic Variable	PA21						Sevelamer (HCl) (N=26)	Overall (N=154)
	1.25 g/day (N=26)	5 g/day (N=26)	7.5 g/day (N=25)	10 g/day (N=27)	12.5 g/day (N=24)	Total PA21 (N=128)		
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)		
Age (years)								
n	26	26	25	27	24	128	26	154
Mean	60.1	59.7	61.9	60.6	59.3	60.3	61.1	60.5
SD	12.29	13.80	13.71	12.74	12.32	12.82	11.00	12.50
Minimum	36	34	39	34	28	28	33	28
Median	63.0	57.5	63.0	61.0	62.0	62.0	63.0	62.0
Maximum	84	85	85	81	77	85	80	85
Height (cm)								
n	26	26	25	27	24	128	26	154
Mean	169.5	169.3	168.6	167.3	170.0	168.9	166.4	168.5
SD	10.93	8.97	11.65	7.23	9.45	9.63	9.32	9.59
Minimum	152	153	139	152	152	139	151	139
Median	171.0	169.0	172.0	168.0	170.5	170.0	166.0	170.0
Maximum	193	182	188	178	185	193	185	193
Sex								
Male	17 (65.4%)	19 (73.1%)	16 (64.0%)	17 (63.0%)	13 (54.2%)	82 (64.1%)	15 (57.7%)	97 (63.0%)
Female	9 (34.6%)	7 (26.9%)	9 (36.0%)	10 (37.0%)	11 (45.8%)	46 (35.9%)	11 (42.3%)	57 (37.0%)
Race								
White	24 (92.3%)	26 (100.0%)	24 (96.0%)	24 (88.9%)	24 (100.0%)	122 (95.3%)	25 (96.2%)	147 (95.5%)
Black	2 (7.7%)	0 (0.0%)	0 (0.0%)	2 (7.4%)	0 (0.0%)	4 (3.1%)	0 (0.0%)	4 (2.6%)
Asian	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (3.8%)	2 (1.3%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (0.6%)

Note: the list doses in were in the total mass. Its tablet is standardized to contain 500 mg iron (as PA21 drug substance (DS)) with a total nominal mass of 2.5g. Doses of 1.25, 5.0, 7.5, 10 and 12.5g represent 250, 1000, 1500, 2000, and 2500 mg iron of PA21. (Sponsor table from PA-CL-03A study report)

Table 31: Extent of exposure in stage 2 in Study PA-CL-05A

Parameter	PA21 MD (N=45)	PA21 LD (N=49)
Overall duration of exposure in Stage 2(days)		
N	45	49
Mean (SD)	22.9 (4.66)	21.2 (3.13)
Median	22.0	22.0
Min/max	15.0/43.0	9.0/33.0
Average daily dose (g/day) during Stage 2		
N	42	43
Mean (SD)	7.4 (3.62)	1.3 (0.81)
Median	7.4	1.3
Min/max	1.4/14.8	0.2/5.0

Note: the exact dose of PA21 iron should be divided by 5 from the whole masses list in above table. (Sponsor table from PA-CL-05A study report)

Table 32: Summary of extent of exposure to study treatment in Studies PA-CL-05A/05B

Parameter	Pooled PA-CL-05A/ PA-CL-05B (SS)		PA-CL-05B (SS5B)	
	PA21 (N=707)	Sevelamer (N=348)	PA21 (N=391)	Sevelamer (N=267)
Overall duration of exposure (days) ⁽¹⁾				
n	707	348	391	267
Mean (SD)	243.1 (130.59)	294.1 (112.45)	176.4 (49.52)	181.5 (41.90)
Median	253.0	364.0	197.0	197.0
Min/max	1.0/420.0	13.0/413.0	3.0/225.0	5.0/215.0
Total overall exposure (subject-years) ⁽²⁾	470.5	280.2	188.8	132.7
Overall total number of tablets taken				
n	707	348	391	267
Mean (SD)	864.3 (617.94)	2,633.5 (1,556.42)	713.1 (333.76)	1,769.7 (893.00)
Median	750.0	2,405.0	731.0	1,658.0
Min/max	2.0/2125.0	53.0/6782.0	6.0/1254.0	42.0/3780.0
Average daily dose (g/day)				
n	698	348	391	267
Mean (SD)	8.2 (3.15)	6.9 (2.84)	10.1 (3.69)	8.1 (5.27)
Median	7.8	6.5	10.1	7.1
Min/max	1.0/15.8	1.5/14.8	1.4/16.8	1.3/72.0
No. of subjects with at least 1 dose adjustment for efficacy	607 (85.9%)	299 (85.9%)	99 (25.3%)	89 (33.3%)
No. of subjects with at least 1 dose adjustment for tolerability	86 (12.2%)	49 (14.1%)	18 (4.6%)	5 (1.9%)
No. of subjects with at least 1 dose adjustment for efficacy and tolerability	23 (3.3%)	17 (4.9%)	5 (1.3%)	4 (1.5%)

(Sponsor table from 120-day safety update report)

Table 33: Duration of exposure by time intervals in Studies PA-CL-05A/05B

	PA21 (N=707)	Sevelamer (N=348)
Duration of Exposure		
≥24 weeks, n (%)	513 (72.6%)	293 (84.2%)
≥52 weeks, n (%)	319 (45.1%)	226 (64.9%)

(Sponsor table from 120-day safety update report)

Table 34: Summary of demography in Study PA-CL-05A/05B

Demographic Variable	Pooled PA-CL-05A/PA-CL-05B (SS)			PA-CL-05B (SS5B)		
	PA21 (N=707)	Sevelamer (N=348)	Total (N=1,055)	PA21 (N=391)	Sevelamer (N=267)	Total (N=658)
Age (years)						
Mean (SD)	56.3 (13.35)	55.8 (14.59)	56.2 (13.77)	55.2 (13.20)	55.6 (14.58)	55.4 (13.77)
Median	57.0	56.5	57.0	56.0	56.0	56.0
Min/max	21.0/89.0	21.0/88.0	21.0/89.0	22.0/87.0	21.0/88.0	21.0/88.0
Sex: n (%)						
Female	313 (44.3%)	129 (37.1%)	442 (41.9%)	171 (43.7%)	102 (38.2%)	273 (41.5%)
Male	394 (55.7%)	219 (62.9%)	613 (58.1%)	220 (56.3%)	165 (61.8%)	385 (58.5%)
Race: n (%)						
White	548 (77.5%)	264 (75.9%)	812 (77.0%)	324 (82.9%)	202 (75.7%)	526 (79.9%)
Black	130 (18.4%)	75 (21.6%)	205 (19.4%)	52 (13.3%)	58 (21.7%)	110 (16.7%)
Asian	9 (1.3%)	6 (1.7%)	15 (1.4%)	5 (1.3%)	6 (2.2%)	11 (1.7%)
American Indian/Alaskan Native	1 (0.1%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Native Hawaiian/Other Pacific Islander	6 (0.8%)	1 (0.3%)	7 (0.7%)	5 (1.3%)	0 (0.0%)	5 (0.8%)
Other	13 (1.8%)	2 (0.6%)	15 (1.4%)	5 (1.3%)	1 (0.4%)	6 (0.9%)
Ethnicity: n (%)						
Hispanic or Latino	90 (12.7%)	38 (10.9%)	128 (12.1%)	44 (11.3%)	32 (12.0%)	76 (11.6%)
Non Hispanic or Latino	617 (87.3%)	310 (89.1%)	927 (87.9%)	347 (88.7%)	235 (88.0%)	582 (88.4%)
Height (cm)						
Mean (SD)	168.8 (10.32)	169.4 (9.92)	169.0 (10.19)	168.8 (10.56)	168.9 (9.83)	168.8 (10.26)
Median	169.0	170.0	170.0	169.0	170.0	170.0
Min/max	110.0/195.6	132.1/200.7	110.0/200.7	110.0/195.6	132.1/194.0	110.0/195.6
Weight (kg)						
Mean (SD)	83.3 (20.99)	84.0 (20.78)	83.5 (20.92)	81.5 (19.80)	83.8 (20.92)	82.4 (20.28)
Median	80.3	81.2	80.5	79.0	80.4	79.5
Min/max	38.9/168.0	45.3/163.9	38.9/168.0	40.0/168.0	45.3/163.9	40.0/168.0

(Sponsor table from 120-day safety update report)

Table 35: Summary of dosing of PA21 in DDI studies

Study Treatment	Study					Overall (N=210) n (%)
	PA-DDI-001 (N=41) n (%)	PA-DDI-002 (N=41) n (%)	PA-DDI-003 (N=43) n (%)	PA-DDI-004 (N=42) n (%)	PA-DDI-005 (N=43) n (%)	
PA21 + reference drug	38 (92.7%)	41 (100%)	42 (97.7%)	42 (100%)	42 (97.7%)	205 (97.6%)
reference drug	36 (87.8%)	41 (100%)	38 (88.4%)	42 (100%)	42 (97.7%)	199 (94.8%)
PA21 + reference drug (2 hrs later)	37 (90.2%)	40 (97.6%)	40 (93.0%)	42 (100%)	41 (95.3%)	200 (95.2%)

(Sponsor table from safety summary table)

7.2.2 Explorations for Dose Response

Dose-related hypophosphatemia was reported in the phase 2 dose range finding study (Study PA-CL-03A). In this study, the proportions of subjects with hypophosphatemia were highest in the 2 higher-dose PA21 groups: 2000 mg/day (7 subjects, 25.9%) and 2500 mg/day (6 subjects, 25.0%). The proportions of subjects with treatment-related GI events were not closely correlated with PA21 dose. There were no clearly dose-related other AEs among the five dose groups including 250, 1000, 1500, 2000, and 2500 mg/day for 6 weeks.

In the pivotal study, there was no apparent dose-related increase in the overall incidence of AEs, withdrawals due to AEs, severity or seriousness of AEs or relationship to treatment in subjects who received the higher maximum daily doses. However, because subjects were started on a low dose with increases in dose permitted for tolerability or safety reasons and titrated based on the serum level of phosphorus, it is difficult to draw conclusions regarding any dose relationship for TEAEs. Dose related analyses are summarized in tables 36 and 37.

Table 36: Summary of treatment-related TEAEs with doses of PA21 and sevelamer in Study PA-CL-03A

System Organ Class Preferred Term	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 (%)	
Any TEAE	5 (19.2%) 6	9 (34.6%) 29	8 (32.0%) 15	12 (44.4%) 16	10 (41.7%) 12	44 (34.4%) 78	8 (30.8%) 8
Gastrointestinal Disorders	2 (7.7%) 2	3 (11.5%) 21	6 (24.0%) 10	6 (22.2%) 8	4 (16.7%) 5	21 (16.4%) 46	4 (15.4%) 4
Constipation	0 (0.0%) 0	1 (3.8%) 5	1 (4.0%) 1	0 (0.0%) 0	0 (0.0%) 0	2 (1.6%) 6	0 (0.0%) 0
Diarrhoea	0 (0.0%) 0	1 (3.8%) 7	2 (8.0%) 5	1 (3.7%) 1	1 (4.2%) 1	5 (3.9%) 14	3 (11.5%) 3
Faeces discoloured	2 (7.7%) 2	3 (11.5%) 3	3 (12.0%) 3	4 (14.8%) 4	3 (12.5%) 3	15 (11.7%) 15	0 (0.0%) 0
Flatulence	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (4.2%) 1	1 (0.8%) 1	0 (0.0%) 0
Vomiting	0 (0.0%) 0	1 (3.8%) 0	0 (0.0%) 0	1 (3.7%) 0	0 (0.0%) 1	2 (1.6%) 1	0 (0.0%) 0
Metabolism and Nutrition Disorders	3 (11.5%) 4	4 (15.4%) 5	4 (16.0%) 5	7 (25.9%) 7	6 (25.0%) 7	24 (18.8%) 28	4 (15.4%) 4
Hyperphosphataemia	3 (11.5%) 4	1 (3.8%) 1	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	4 (3.1%) 5	1 (3.8%) 1
Hypophosphataemia	0 (0.0%) 0	3 (11.5%) 4	2 (8.0%) 2	7 (25.9%) 7	5 (20.8%) 6	17 (13.3%) 19	2 (7.7%) 2

Note: the list doses in above figure were in the total mass. Its tablet is standardized to contain 500 mg iron (as PA21 drug substance (DS)) with a total nominal mass of 2.5g. Doses of 1.25, 5.0, 7.5, 10 and 12.5g represent 250, 1000, 1500, 2000, and 2500 mg iron of PA21. (Sponsor table from Study PA-CL-03A Study Report)

Table 37: Summary of TEAEs with doses of PA21 and sevelamer in Study PA-CL-05A

Parameter	PA21 Maximum Dose				
	PA21 5.0 g/day (N=97) n (%) E	PA21 7.5 g/day (N=116) n (%) E	PA21 10.0 g/day (N=144) n (%) E	PA21 12.5 g/day (N=110) n (%) E	PA21 15.0 g/day (N=240) n (%) E
Any TEAE	81 (83.5%) 419	102 (87.9%) 576	127 (88.2%) 763	100 (90.9%) 629	218 (90.8%) 1,434
Any related TEAE	47 (48.5%) 82	60 (51.7%) 127	71 (49.3%) 134	51 (46.4%) 84	91 (37.9%) 173
Any severe TEAE	14 (14.4%) 23	17 (14.7%) 28	28 (19.4%) 45	20 (18.2%) 42	34 (14.2%) 59
Any serious TEAE	23 (23.7%) 39	27 (23.3%) 58	43 (29.9%) 92	36 (32.7%) 69	59 (24.6%) 123
Withdrawal due to TEAE	36 (37.1%)	30 (25.9%)	29 (20.1%)	17 (15.5%)	36 (15.0%)
Death ⁽¹⁾	3 (3.1%)	4 (3.4%)	8 (5.6%)	2 (1.8%)	4 (1.7%)

Parameter	Sevelamer Maximum Dose				
	Sevelamer 4.8g/day (N=63) n (%) E	Sevelamer 7.2 g/day (N=79) n (%) E	Sevelamer 9.6 g/day (N=58) n (%) E	Sevelamer 12.0 g/day (N=58) n (%) E	Sevelamer 14.4 g/day (N=90) n (%) E
Any TEAE	55 (87.3%) 321	72 (91.1%) 507	47 (81.0%) 314	55 (94.8%) 336	79 (87.8%) 555
Any related TEAE	20 (31.7%) 45	18 (22.8%) 26	15 (25.9%) 27	13 (22.4%) 18	20 (22.2%) 36
Any severe TEAE	11 (17.5%) 20	17 (21.5%) 40	9 (15.5%) 16	8 (13.8%) 11	16 (17.8%) 33
Any serious TEAE	14 (22.2%) 24	28 (35.4%) 63	18 (31.0%) 40	17 (29.3%) 27	26 (28.9%) 64
Withdrawal due to TEAE	9 (14.3%)	8 (10.1%)	6 (10.3%)	2 (3.4%)	11 (12.2%)
Death	4 (6.3%)	4 (5.1%)	3 (5.2%)	1 (1.7%)	2 (2.2%)

Note: the list doses were in the total mass. Its tablet is standardized to contain 500 mg iron (as PA21 drug substance (DS)) with a total nominal mass of 2.5g. Doses of 5.0, 7.5, 10, 12.5 and 15g represent 1000, 1500, 2000, 2500 and 3000 mg iron of PA21. (Sponsor table from PA-CL-05A Study Report)

7.2.3 Special Animal and/or In Vitro Testing

No special animal studies were conducted.

In vitro testing for drug-drug interactions were performed to assess the potential for binding to other drugs. Potential interaction with PA21 in an aqueous solution was assessed for a range of drugs commonly used in ESRD patients. No significant binding/interaction of PA21 was revealed with a number of drugs which may be co-administered with the compound including ciprofloxacin, digoxin, enalapril, metoprolol, nifedipine, warfarin, hydrochlorothiazide, metformin, and quinidine. Extensive binding drugs with PA21 include furosemide, losartan, atorvastatin, doxycycline, alendronate, levothyroxine, and paricalcitol. Please see Section 7.5.5 drug-drug interaction and Section 4.4 clinical pharmacology for further discussion of *in vitro* and *in vivo* testing.

7.2.4 Routine Clinical Testing

Routine clinical testing including adverse event data collection and monitoring of laboratory parameters, vital signs, physical examinations and ECG was adequate.

Given the nature of the product (an iron based product with limited absorption) a thorough QT study was not required.

7.2.5 Metabolic, Clearance, and Interaction Workup

In clinical pharmacology studies PA21 was minimally absorbed from the GI tract. *In vitro* and *in vivo* studies were performed to evaluate PA-21's potential to bind co-administered drugs (see also Section 7.5.5 drug-drug interaction and Section 4.4 clinical pharmacology). As described in section 7.2.3, the *in vivo* DDI clinical program in healthy subjects was conducted to assess the effects of PA21 on the pharmacokinetics (PK) of the drugs that were shown to bind extensively with PA21 in the *in vitro* study. Results show that PA21 did not affect the AUCs of any of these drugs when given either concomitantly, or when the drugs were given 2 hours later. The ratios of all AUCs fell within the pre-defined bioequivalence range. The C_{max} ratios that fell outside the bioequivalence range are consistent with known food effects of these drugs (losartan, furosemide and omeprazole).

Paricalcitol was shown to bind extensively with PA21 in the *in vitro* study, but was not evaluated in an *in vivo* study. Please see the clinical pharmacology review for details.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Based on the safety profiles of other phosphate binders that have been being used in the ESRD population, the main concerns with this class of agents are GI tolerability and the potential to bind other agents. Please see Section 7.4.1 for further discussion.

7.3 Major Safety Results

7.3.1 Deaths

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 causes of death among the treatment groups and there was no dose correlation either. Given the nature of the drug (iron based) and lack of systemic absorption, there is no compelling reason to believe these deaths were causally related. The causes of death were generally consistent with the medical conditions of ESRD patients on dialysis. These deaths are briefly summarized in table 38.

Table 38: Listing of deaths in all studies

Study	Sex/age	Drug	Dose (day)	Reason(s)	Days from start of AE	Days from last dose to AE	Days from start to death
PA-CL-03A	M/59	PA21	1000 mg	Cardiac arrest, GI hemorrhage, MI	7	0	29
PA-CL-05A (stage 1)	F/74	PA21	2000 mg	Leriche syndrome, myocardium infarction	unknown	unknown	38
	M/75	PA21	2000 mg	AF, AMI, Pulmonary embolism	45, 47	0	47
	M/64	PA21	2000 mg	Cardiac arrest,	99	0	99
	M/67	PA21	2000 mg	Cerebrovascular accident	57	0	71
	F/67	PA21	2500 mg	Infection, acute respiratory failure	100	8	101
	M/78	PA21	1000 mg	dialysis discontinued	19	8	27
	F/58	PA21	1000 mg	Cardiogenic shock	114	19	114
	F/53	PA21	1500 mg	Internal hemorrhage (location unknown)	113	18	113
	M/64	PA21	2000 mg	Aortic stenosis	151	11	180
	M/55	PA21	1000 mg	Sepsis	159	0	162
	F/68	PA21	1000 mg	Cardiac arrest	64	1	65
	M/62	PA21	2000 mg	AV fistula hemorrhage, cardiorespiratory arrest	66	1	66
	M/61	PA21	2500 mg	AMI, GI hemorrhage	72	0	84
	M/77	Sevelamer	4.8 g	Hemorrhage shock, Pneumonia aspiration	64, 65	20	83
	M/67	Sevelamer	7.2 g	Aortic valve stenosis, Cardiac tamponade	99, 116	0	116
	M/70	Sevelamer	9.6 g	Sudden death	55	0	55
	F/65	Sevelamer	4.8 g	GI necrosis, Cardio-pulmonary failure	100, 105	5	105
F/58	Sevelamer	9.6 g	Myocardium infarction	168	0	168	
F/72	Sevelamer	7.2 g	Cardio-respiratory arrest	122	18	140	
M/56	Sevelamer	4.8 g	Cardiac arrest	107	8	108	
PA-CL-05A (Stage 2)	M/48	PA21	250 mg	Renal tubular necrosis after transplantation, circulatory failure	182	4	182
PA-CL-05B	F/85	PA21	1500 mg	Pneumonia	336	1	337

Velphoro (b) (4)

M/72	PA21	3000 mg	Circulatory collapse	276	0	276
M/65	PA21	3000 mg	Myocardium infarction	279	2	283
F/61	PA21	1500 mg	Hyperkalemia	212	1	212
F/69	PA21	1000 mg	Sepsis	226	46	249
M/63	PA21	3000 mg	Intracranial hemorrhage	226	1	227
M/79	PA21	3000 mg	Clostridium difficile colitis	335	1	339
F/57	Sevelamer	14.4g	unknown	231	1	231
M/69	Sevelamer	9.6g	Aneurysm ruptured	173	3	176
F/65	Sevelamer	7.2g	Septic shock	342	40	373
M/85	Sevelamer	4.8g	AV fistula hemorrhage	248	0	248
F/79	Sevelamer	14.4g	Lung cancer	291	14	379
F/72	Sevelamer	4.8g	Cardiac failure	268	0	268
M/67	Sevelamer	12g	Atherosclerosis	174		175
F/65	Sevelamer	14.4g	Cardio-respiratory arrest	397	32	397

(Reviewer table)

7.3.2 Non-fatal Serious Adverse Events

There were 3 subjects in PA-CL-05A, 2 in PA-CL-05B, and 1 in PA-CL-03A who experienced SAEs that were considered to be drug-related. All of these SAEs were GI related. 5 events (4 subjects) were in the PA21 group and 1 event (1 subject) was in the sevelamer group. All 5 subjects were on HD. There was no evidence to suggest a dose relationship between PA21 and the occurrence of these events. The narratives for these SAEs are provided below.

- A white male, 49 years old, experienced abdominal pain, nausea and vomiting on Day 44 of treatment in PA-CL-05A while taking PA21 2500 mg/day. On Day 45, he was hospitalized and PA21 was permanently discontinued. He was diagnosed with non-serious Mallory-Weiss syndrome (gastro-esophageal laceration syndrome), duodenal bulb ulcer, and also with a severe and life-threatening duodenal ulcer with GI bleeding. On Day 64, the Mallory-Weiss syndrome was recovered, the duodenum ulcer with GI bleeding was recovered with sequelae (duodenal ulcer and hemorrhagic iron deficiency anemia), and the subject was discharged from hospital on the same day. This duodenal ulcer may have been present for a long time without symptoms, but PA21's role cannot be excluded.
- A white male, 74 years old, experienced non-serious black stools during PA-CL-05A. On Day 35 while taking PA21 1500 mg/day, he was hospitalized with black stools after presenting to the emergency room. His hemoglobin level was normal and the stool analysis was negative for blood. Other laboratory results included hematocrit 0.4 (reference range 0.4 to 0.5) and glucose 6.5 mmol/L (reference range 3.9 to 5.6 mmol/L). No treatment was recorded for the event and the PA21 dose was maintained. On Day 36, the outcome of the black stools was reported as recovered without sequelae and the subject was discharged from hospital on the same day. The black stools may be related to study treatment.
- A white female, 49 years old, completed PA-CL-05A with 1 serious SAE of angina, from which she recovered. In addition to diabetes, she had a history of valvular heart disease, cardiac hypertrophy and hypertension. She was taking acetylsalicylic acid and clopidogrel for cardiac prophylaxis. On Day 169 she entered Study PA-CL-05B and received PA21 at a dose of 3000 mg/day. On Day 180, PA21 treatment was discontinued. On Day 181 she was admitted to the hospital with upper GI bleeding, and endoscopy revealed a Barrett's esophagus and a non-bleeding gastric ulcer. She received a blood transfusion and treatment with a proton pump

Velphoro (b) (4)

inhibitor and recovered. On Day 183, the outcome of the upper GI bleed was recovered without sequelae, and the subject was discharged from hospital on the same day. The outcome of the gastric lesion was considered ongoing at the end of the study. The upper GI bleed and gastric lesion may be related to study treatment due to the development of the new gastric lesion while on study treatment with PA21. The Investigator confirmed that the acetylsalicylic acid and heparin were considered as co-suspect drugs for the cause of the GI bleed.

- A black male, 79 years old, did not experience any SAEs during PA-CL-05A. On Day 248, while taking sevelamer 9.6 g/day, the subject was hospitalized with hemolysis. On Day 281, 28 days after his last dose of sevelamer, the subject was hospitalized with GI bleeding. Endoscopy revealed an actively bleeding vessel in duodenal bulb. The subject received aggressive IV fluid resuscitation, 2 units of packed red blood cells, and an Endo clip. On Day 283, his hemoglobin was 101.0 g/L. On Day 254, sevelamer was temporarily discontinued for SAEs of syncope and hypotension that were considered unrelated to study treatment; however, study treatment was not restarted due to the GI bleeding. On Day 283, the subject was considered to have recovered, without sequelae, from the GI bleeding and was discharged from the hospital on the same day. The GI bleeding may be related to study treatment, as bleeding duodenal ulcer can be a complication of phosphate binder use.
- One patient in this dose ranging study had a SAE of GI bleeding. This was a 59-year-old male who received PA21 1000 mg/day from Day 1 until Day 28. The subject had a medical history of diabetes mellitus and hypertension. On Day 7, during the treatment period, the subject experienced sudden shortness of breath and prolonged retrosternal chest pain. The subject was immediately referred to an emergency care unit where an ECG revealed acute myocardial infarction and the subject was admitted to hospital. No action was taken in regard to study treatment. On Day 26, during the treatment period, the subject experienced a gastrointestinal hemorrhage. The event was considered to be associated with the intake of clopidogrel and acetylsalicylic acid, which had been administered from Day 7 to Day 26. On Day 29, the subject had a cardiac arrest resulting in death.

The incidence rate of SAEs would be expected to be very high in this population because of the underlying condition (end stage renal disease and the dialysis process) and comorbidities. Cardiovascular events, stroke, and infection are expected events. The incidence rates of SAEs from the short-term studies and the long-term safety study are consistent with what would be expected in a chronic dialysis population. In my review of the narratives of each SAE from all available studies, I did not identify any potential drug-related SAEs of concern in either short-term or long-term studies except for above 5 cases (4 with PA21 and 1 with Sevelamer) of GI bleeding complications, which may be related to the phosphate binders. However, all of these 5 cases had also received anti-coagulants at the same time and GI bleeding complication is not a rare complication in ESRD patients. Other SAEs seem related to the primary diseases. All of the SAEs are summarized in the following tables as a reference.

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Table 39: Summary of SAEs in Studies PA-CL-05A/05B

MedDRA SOC Preferred Term	Pooled PA-CL-05A/PA-CL-05B (SS) ⁽¹⁾		PA-CL-05B (SS5B)	
	PA21 (N=707) n (%) E	Sevelamer (N=348) n (%) E	PA21 (N=391) n (%) E	Sevelamer (N=267) n (%) E
Any serious TEAE	188 (26.6%) 381	103 (29.6%) 218	78 (19.9%) 142	52 (19.5%) 106
Infections and Infestations	63 (8.9%) 86	34 (9.8%) 43	28 (7.2%) 34	18 (6.7%) 21
Pneumonia	13 (1.8%) 13	8 (2.3%) 8	6 (1.5%) 6	6 (2.2%) 6
Sepsis	7 (1.0%) 8	4 (1.1%) 4	3 (0.8%) 3	1 (0.4%) 1
Bronchitis	4 (0.6%) 4	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Cellulitis	4 (0.6%) 4	1 (0.3%) 1	2 (0.5%) 2	1 (0.4%) 1
Osteomyelitis	4 (0.6%) 4	1 (0.3%) 1	2 (0.5%) 2	0 (0.0%) 0
Gangrene	3 (0.4%) 3	2 (0.6%) 2	2 (0.5%) 2	0 (0.0%) 0
Gastroenteritis	2 (0.3%) 2	2 (0.6%) 2	1 (0.3%) 1	1 (0.4%) 1
Devised related infection	1 (0.1%) 1	2 (0.6%) 2	0 (0.0%) 0	0 (0.0%) 0
Septic shock	0 (0.0%) 0	2 (0.6%) 2	0 (0.0%) 0	2 (0.7%) 2
Lobar pneumonia	2 (0.3%) 2	0 (0.0%) 0	2 (0.5%) 2	0 (0.0%) 0
Staphylococcal bacteraemia	2 (0.3%) 2	1 (0.3%) 1	2 (0.5%) 2	0 (0.0%) 0
Cardiac Disorders	44 (6.2%) 53	23 (6.6%) 30	12 (3.1%) 15	10 (3.7%) 12
Acute myocardial infarction	10 (1.4%) 10	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0
Atrial fibrillation	3 (0.4%) 3	5 (1.4%) 5	1 (0.3%) 1	3 (1.1%) 3
Congestive cardiac failure	9 (1.3%) 10	2 (0.6%) 2	3 (0.8%) 4	1 (0.4%) 1
Myocardial infarction	3 (0.4%) 3	3 (0.9%) 3	1 (0.3%) 1	0 (0.0%) 0
Angina pectoris	4 (0.6%) 4	1 (0.3%) 1	2 (0.5%) 2	1 (0.4%) 1
Cardiac arrest	3 (0.4%) 3	2 (0.6%) 2	0 (0.0%) 0	1 (0.4%) 1
Coronary artery disease	3 (0.4%) 3	2 (0.6%) 2	1 (0.3%) 1	1 (0.4%) 1
Cardiorespiratory arrest	2 (0.3%) 2	2 (0.6%) 2	1 (0.3%) 1	1 (1.4%) 1
Bradycardia	1 (0.1%) 1	2 (0.6%) 2	1 (0.3%) 1	1 (0.4%) 1
Cardiac failure	0 (0.0%) 0	2 (0.6%) 2	0 (0.0%) 0	1 (0.4%) 1
Injury, Poisoning and Procedural Complications	31 (4.4%) 35	23 (6.6%) 28	14 (3.6%) 15	12 (4.5%) 14
AV fistula thrombosis	6 (0.8%) 6	4 (1.1%) 4	2 (0.5%) 2	2 (0.7%) 2
Vascular graft thrombosis	6 (0.8%) 7	0 (0.0%) 0	3 (0.8%) 3	0 (0.0%) 0
Post procedural haemorrhage	0 (0.0%) 0	2 (0.6%) 2	0 (0.0%) 0	2 (0.7%) 2
AV fistula site haemorrhage	3 (0.4%) 3	2 (0.6%) 2	0 (0.0%) 0	2 (0.7%) 2
AV fistula site complication	0 (0.0%) 0	2 (0.6%) 2	0 (0.0%) 0	0 (0.0%) 0
AV graft site haemorrhage	0 (0.0%) 0	2 (0.6%) 2	0 (0.0%) 0	1 (0.4%) 1
Vascular Disorders	28 (4.0%) 33	18 (5.2%) 22	11 (2.8%) 13	11 (4.1%) 12
Peripheral vascular disorder	1 (0.1%) 1	3 (0.9%) 3	0 (0.0%) 0	0 (0.0%) 0
Hypotension	3 (0.4%) 3	3 (0.9%) 3	0 (0.0%) 0	2 (0.7%) 2
Hypertension	6 (0.8%) 6	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
Haematoma	4 (0.6%) 4	0 (0.0%) 0	4 (1.0%) 4	0 (0.0%) 0
Peripheral ischaemia	1 (0.1%) 1	2 (0.6%) 2	1 (0.3%) 1	1 (0.4%) 1

Velphoro (b) (4)

Summary of SAEs in Studies PA-CL-05A/05B (Cont'd)

MedDRA SOC Preferred Term	Pooled PA-CL-05A/PA-CL-05B (SS) ⁽¹⁾		PA-CL-05B (SS5B)	
	PA21 (N=707) n (%) E	Sevelamer (N=348) n (%) E	PA21 (N=391) n (%) E	Sevelamer (N=267) n (%) E
Gastrointestinal Disorders	26 (3.7%) 30	13 (3.7%) 14	10 (2.6%) 11	8 (3.0%) 8
Peritonitis	6 (0.8%) 7	1 (0.3%) 1	3 (0.8%) 3	1 (0.4%) 1
Diarrhoea	3 (0.4%) 3	2 (0.6%) 2	1 (0.3%) 1	1 (0.4%) 1
Duodenal ulcer haemorrhage	1 (0.1%) 1	2 (0.6%) 2	0 (0.0%) 0	1 (0.4%) 1
Gastrointestinal haemorrhage	1 (0.1%) 1	2 (0.6%) 2	0 (0.0%) 0	2 (0.7%) 2
Vomiting	1 (0.1%) 1	2 (0.6%) 2	0 (0.0%) 0	1 (0.4%) 1
Upper gastrointestinal haemorrhage	2 (0.3%) 2	1 (0.3%) 1	2 (0.5%) 2	1 (0.4%) 1
Respiratory, Thoracic and Mediastinal Disorders	22 (3.1%) 25	15 (4.3%) 18	6 (1.5%) 8	7 (2.6%) 8
Dyspnoea	5 (0.7%) 5	5 (1.4%) 5	1 (0.3%) 1	1 (0.4%) 1
Pleural effusion	4 (0.6%) 4	1 (0.3%) 1	1 (0.3%) 1	0 (0.0%) 0
Pulmonary oedema	4 (0.6%) 5	3 (0.9%) 4	2 (0.5%) 2	3 (1.1%) 4
Acute respiratory failure	1 (0.1%) 1	2 (0.6%) 2	0 (0.0%) 0	1 (0.4%) 1
Metabolism and Nutrition Disorders	21 (3.0%) 24	11 (3.2%) 12	9 (2.3%) 11	7 (2.6%) 7
Fluid overload	8 (1.1%) 9	9 (2.6%) 10	4 (1.0%) 5	6 (2.2%) 6
Hyperkalaemia	5 (0.7%) 6	1 (0.3%) 1	2 (0.5%) 2	1 (0.4%) 1
General Disorders and Administration Site Conditions	18 (2.5%) 22	14 (4.0%) 15	6 (1.5%) 7	3 (1.1%) 3
Chest pain	11 (1.6%) 13	6 (1.7%) 7	3 (0.8%) 4	1 (0.4%) 1
Non-cardiac chest pain	1 (0.1%) 1	3 (0.9%) 3	0 (0.0%) 0	1 (0.4%) 1
Pyrexia	1 (0.1%) 2	2 (0.6%) 2	0 (0.0%) 0	1 (0.4%) 1
Thrombosis in device	1 (0.1%) 1	2 (0.6%) 2	1 (0.3%) 1	0 (0.0%) 0
Nervous System Disorders	18 (2.5%) 20	5 (1.4%) 5	9 (2.3%) 10	1 (0.4%) 1
Cerebrovascular accident	4 (0.6%) 4	1 (0.3%) 1	3 (0.8%) 3	0 (0.0%) 0
Neoplasms Benign, Malignant and Unspecified	8 (1.1%) 8	4 (1.1%) 4	5 (1.3%) 5	3 (1.1%) 3
Lung squamous cell carcinoma	1 (0.1%) 1	2 (0.6%) 2	1 (0.3%) 1	2 (0.7%) 2
Surgical and Medical Procedures	7 (1.0%) 8	2 (0.6%) 2	1 (0.3%) 1	1 (0.4%) 1
Hepatobiliary Disorders	6 (0.8%) 6	5 (1.4%) 5	4 (1.0%) 4	4 (1.5%) 4
Cholecystitis	0 (0.0%) 0	3 (0.9%) 3	0 (0.0%) 0	2 (0.7%) 2
Cholelithiasis	3 (0.4%) 3	0 (0.0%) 0	3 (0.8%) 3	0 (0.0%) 0
Blood and Lymphatic System Disorders	4 (0.6%) 4	8 (2.3%) 8	2 (0.5%) 2	5 (1.9%) 5
Anaemia	2 (0.3%) 2	6 (1.7%) 6	1 (0.3%) 1	3 (1.1%) 3
Investigations	4 (0.6%) 5	2 (0.6%) 2	1 (0.3%) 1	1 (0.4%) 1
Renal and Urinary Disorders	4 (0.6%) 4	3 (0.9%) 3	0 (0.0%) 0	3 (1.1%) 3
Skin and Subcutaneous Tissue Disorders	4 (0.6%) 4	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
Musculoskeletal and Connective Tissue Disorders	3 (0.4%) 3	5 (1.4%) 5	1 (0.3%) 1	2 (0.7%) 2
Systemic lupus erythematosus	0 (0.0%) 0	2 (0.6%) 2	0 (0.0%) 0	0 (0.0%) 0

¹ Also includes data for PA-CL-05A Stage 2 subjects.

(Sponsor table from 120-day safety update report)

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Table 40: Summary of SAEs in Study PA-CL-03A

System Organ Class Preferred Term	PA21					Total PA21 (N=128) n (%)	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 (%)		
	Any TEAE	2 (7.7%)	2 (7.7%)	1 (4.0%)	1 (3.7%)		
Cardiac Disorders	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Cardiac arrest	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Myocardial infarction	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Eye Disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
Diabetic retinopathy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
Gastrointestinal Disorders	1 (3.8%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.6%)	1 (3.8%)
Diverticular perforation	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Gastrointestinal haemorrhage	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Pancreatitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
Hepatobiliary Disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
Cholelithiasis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
Infections and Infestations	1 (3.8%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	3 (2.3%)	0 (0.0%)
Arteriovenous graft site abscess	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	1 (0.8%)	0 (0.0%)
Peritoneal infection	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Staphylococcal sepsis	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	2 (1.6%)	0 (0.0%)
Injury, Poisoning and Procedural Complications	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (4.2%)	2 (1.6%)	0 (0.0%)
Arteriovenous graft site haematoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	1 (0.8%)	0 (0.0%)
Rib fracture	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Metabolism and Nutrition Disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	1 (0.8%)	0 (0.0%)
Fluid overload	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	1 (0.8%)	0 (0.0%)
Nervous System Disorders	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Ischaemic stroke	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Respiratory, Thoracic and Mediastinal Disorders	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Asthma	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)

Note: the list doses in above figure were in the total mass. Its tablet is standardized to contain 500 mg iron (as PA21 drug substance (DS)) with a total nominal mass of 2.5g. Doses of 1.25, 5.0, 7.5, 10 and 12.5g represent 250, 1000, 1500, 2000, and 2500 mg iron of PA21. (Sponsor table from Study PA-CL-03A Study Report)

7.3.3 Dropouts and/or Discontinuations

In the pivotal Study and its extension, more subjects in the PA21 group compared with the sevelamer group were withdrawn from treatment for AEs (20.9% versus 10.3%, respectively). Gastrointestinal AEs were the most common class of AEs leading to withdrawal in both groups. Of those who withdrew, there were 70 of 148 withdrawals (47.3%) in the PA21 group and 11 of 36 (30.6%) in the sevelamer group who withdrew for a GI AE. Diarrhea was a common drug-related GI event in the PA21 arm and led to withdrawal in 25 (3.5%) subjects in the PA21 group

and 2 (0.6%) subjects in the sevelamer group. Other than GI events, the only AEs with an incidence $\geq 0.5\%$ in the PA21 group were abnormal product taste in 13 subjects (1.8%) and hyperphosphatemia in 23 subjects (3.3%).

In PA-CL-05B, a significantly lower proportion of subjects were withdrawn for AEs compared with the pivotal study, indicating that tolerability issues/AEs leading to discontinuation tend to manifest early in the course of therapy. In the long-term, the most common reason for discontinuation in both treatment groups was hyperphosphatemia, a predefined withdrawal criterion for the study. Hyperphosphatemia 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 AEs compared to 1 (0.4%) in the sevelamer group. All GI AEs leading to withdrawal were mild to moderate in severity except for a GI hemorrhage in sevelamer-treated Subject 883-917. Only 2 subjects, all in the PA21 group, withdrew because of diarrhea during PA-CL-05B. Data are summarized in the following table 41.

Table 41: Summary of AEs leading to withdrawal in Study PA-CL-05A/05B

MedDRA SOC Preferred term	Pooled PA-CL-05A/PA-CL-05B (SS) ⁽¹⁾		PA-CL-05B (SS5B)	
	PA21 (N=707) n (%) E	Sevelamer (N=348) n (%) E	PA21 (N=391) n (%) E	Sevelamer (N=267) n (%) E
Any TEAE leading to withdrawal	148 (20.9%) 187	36 (10.3%) 48	32 (8.2%) 33	13 (4.9%) 16
Gastrointestinal Disorders	70 (9.9%) 87	11 (3.2%) 16	7 (1.8%) 8	1 (0.4%) 1
Diarrhoea	25 (3.5%) 25	2 (0.6%) 2	2 (0.5%) 2	0 (0.0%) 0
Nausea	11 (1.6%) 11	2 (0.6%) 2	0 (0.0%) 0	0 (0.0%) 0
Constipation	7 (1.0%) 7	5 (1.4%) 5	0 (0.0%) 0	0 (0.0%) 0
Vomiting	7 (1.0%) 7	2 (0.6%) 2	0 (0.0%) 0	0 (0.0%) 0
Abdominal pain upper	5 (0.7%) 5	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
Faeces discoloured	5 (0.7%) 5	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
Abdominal pain	4 (0.6%) 4	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
Dyspepsia	4 (0.6%) 4	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
Flatulence	2 (0.3%) 2	2 (0.6%) 2	0 (0.0%) 0	0 (0.0%) 0
Metabolic and Nutritional Disorders	32 (4.5%) 33	8 (2.3%) 8	15 (3.8%) 15	7 (2.6%) 7
Hyperphosphataemia	23 (3.3%) 23	7 (2.0%) 7	11 (2.8%) 11	7 (2.6%) 7
Hypophosphataemia	3 (0.4%) 3	0 (0.0%) 0	2 (0.5%) 2	0 (0.0%) 0
General Disorders and Administration Site Conditions	20 (2.8%) 20	4 (1.1%) 4	3 (0.8%) 3	1 (0.4%) 1
Product taste abnormal	13 (1.8%) 13	1 (0.3%) 1	2 (0.5%) 2	0 (0.0%) 0
Product dosage form issue	2 (0.3%) 2	2 (0.6%) 2	0 (0.0%) 0	1 (0.4%) 1
Cardiac Disorders	10 (1.4%) 10	2 (0.6%) 2	3 (0.8%) 3	0 (0.0%) 0
Investigations	7 (1.0%) 7	1 (0.3%) 1	2 (0.5%) 2	1 (0.4%) 1
Blood phosphorus increased	4 (0.6%) 4	1 (0.3%) 1	1 (0.3%) 1	1 (0.4%) 1
Infections and Infestations	6 (0.8%) 7	2 (0.6%) 2	1 (0.3%) 1	0 (0.0%) 0
Skin and Subcutaneous Tissue Disorders	5 (0.7%) 5	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
Respiratory, Thoracic and Mediastinal Disorders	4 (0.6%) 4	3 (0.9%) 3	0 (0.0%) 0	1 (0.4%) 1
Nervous System Disorders	3 (0.4%) 3	2 (0.6%) 2	0 (0.0%) 0	1 (0.4%) 1
Vascular Disorders	2 (0.3%) 2	2 (0.6%) 2	0 (0.0%) 0	2 (0.7%) 2

1: PA21 treatment group also includes adverse events occurring in PA-CL-05A Stage 2. (Sponsor table from 120-day safety update report)

Velphoro (b) (4)

In the dose-ranging study, Study PA-CL-03A, the proportion of subjects experiencing AEs leading to discontinuation was similar between the PA21 and Sevelamer treatment groups as discussed in Section 7.5.1 dose dependency for adverse events.

AE related patients discontinuations in other studies were as follows:

- One subject was withdrawn from study medication due to a SAE (rhabdomyolysis) in Study PA-DDI-005 which was not considered drug-related.
- In the Japanese Phase 2 study (PA1201), a total of 18 of 146 subjects (12.3%) treated with PA21 and 2 of 37 subjects (5.4%) treated with placebo, had AEs that led to discontinuation of treatment. These AEs included: 2 cases of diarrhea in 2 subjects in the 1500 mg/day group, 5 cases of diarrhea, 1 case of constipation and 1 of tongue-discoloration reported in 7 subjects in the 2250 mg/day group, and 5 cases of diarrhea, 1 case of abdominal distension and 1 of epigastric discomfort in 6 subjects in the 3000 mg/day group. One case in the 750 mg/day group and two cases in the 2250 mg/day group were discontinued due to unknown AEs (the sponsor did not provide the data).

7.3.4 Significant Adverse Events

As discussed above, GI adverse events were the major drug related effect and were also the major reasons for patient dropout. In general, these AEs were mild, reversible and tolerated. There were 4 SAEs of GI bleeding with PA21 treatment including 3 in the pivotal study and 1 in the dose ranging study. These SAEs may be related to PA21 (please see the narratives in Section 7.3.2).

7.3.5 Submission Specific Primary Safety Concerns

Specific primary safety concerns include hypophosphatemia, hypocalcemia/hypercalcemia, iron accumulation, and severe GI events (please also see the discussion of AEs of special interest in Section 7.4.1 common adverse events).

Regarding hypophosphatemia, as this product is going to be titrated on a regular basis based on the serum phosphorus level, hypophosphatemia caused by high dose administration should not be a major safety concern.

No significant drug-related hypocalcemia/hypercalcemia was observed in the provided datasets. Increased serum ferritin and TSAT and decreased transferrin with PA21 were observed during the first 6 months of treatment compared to both baseline and the active control sevelamer (20.3% vs. 5.1% from baseline for transferrin, 18.4% vs. -3.6% from baseline for TSAT, and -2.3% vs. 8.3% for transferrin, in PA21 vs. Sevelamer, respectively). These effects were maintained but did not increase further with continued treatment up to one year. There was no evidence of iron accumulation with increased cumulative exposure. For further discussion, see section 7.4.2 laboratory findings.

Severe GI complications of GI hemorrhage were observed in 4 subjects with PA21 and 1 in Sevelamer as described in Section 7.3.2. These SAEs may be related to PA21. However, the incidence rate was very low (0.6% in PA21 and 0.3% in Sevelamer) and happened in the

Velphoro (b) (4)

combination with other anti-coagulation agents at the same time. In addition, severe GI bleeding is not an unexpected complications in ESRD patients.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In the pivotal study and its extension, Study PA-CL-05A/05B, the most commonly reported AEs in the PA21 group were diarrhea (167 subjects, 23.6%), hyperphosphatemia (113 subjects, 16.0%), discolored feces (114 subjects, 16.1%), hypertension (79 subjects, 11.2%), and arteriovenous (AV) fistula or graft complications (32 subjects, 4.5%). Diarrhea, hyperphosphatemia, discolored feces, and abnormal product taste were reported at a $\geq 2\%$ higher incidence on PA21 compared with sevelamer.

In the long-term safety study, the most commonly reported AEs in the PA21 group were hyperphosphatemia (42 subjects, 12.0%), hypertension (38 subjects, 9.7%), and diarrhea (32 subjects, 8.2%). AEs reported by a larger proportion (difference $\geq 2\%$) of subjects treated with PA21 versus sevelamer during the PA-CL-05B treatment period were hypertension, diarrhea, and headache. AEs reported by $\geq 2\%$ of subjects in either of the treatment groups in the pooled PA-CL-05B/05A data (SS) and PA-CL-05B (SS5B) are summarized in table 42.

Table 42: Summary of TEAEs in Studies PA-CL-05A/05B

Preferred Term	Pooled PA-CL-05A/PA-CL-05B (SS) ^(a)		PA-CL-05B (SS5B)	
	PA21 (N=707) n (%) E	Sevelamer (N=348) n (%) E	PA21 (N=391) n (%) E	Sevelamer (N=267) n (%) E
Diarrhoea	167 (23.6%) 231	40 (11.5%) 49	32 (8.2%) 43	15 (5.6%) 19
Hyperphosphataemia	113 (16.0%) 195	44 (12.6%) 86	47 (12.0%) 73	29 (10.9%) 47
Faeces discoloured	114 (16.1%) 116	1 (0.3%) 2	3 (0.8%) 3	1 (0.4%) 1
Hypertension	79 (11.2%) 112	41 (11.8%) 69	38 (9.7%) 53	20 (7.5%) 29
Nausea	69 (9.8%) 87	50 (14.4%) 53	23 (5.9%) 26	11 (4.1%) 12
Muscle spasms	48 (6.8%) 75	27 (7.8%) 36	26 (6.6%) 39	16 (6.0%) 20
Headache	43 (6.1%) 67	20 (5.7%) 31	20 (5.1%) 28	8 (3.0%) 19
Vomiting	42 (5.9%) 54	32 (9.2%) 37	14 (3.6%) 18	12 (4.5%) 14
Hypotension	41 (5.8%) 74	31 (8.9%) 51	19 (4.9%) 37	21 (7.9%) 38
Hypophosphataemia	40 (5.7%) 54	29 (8.3%) 34	22 (5.6%) 26	14 (5.2%) 14
Hyperkalaemia	38 (5.4%) 66	25 (7.2%) 40	17 (4.3%) 31	16 (6.0%) 28
Constipation	36 (5.1%) 44	29 (8.3%) 31	10 (2.6%) 11	5 (1.9%) 5
Hypocalcaemia	33 (4.7%) 43	22 (6.3%) 24	14 (3.6%) 16	8 (3.0%) 8
Pruritus	33 (4.7%) 39	14 (4.0%) 14	9 (2.3%) 10	6 (2.2%) 6
Pain in extremity	33 (4.7%) 35	12 (3.4%) 14	11 (2.8%) 12	5 (1.9%) 6
AV fistula or graft complications	32 (4.5%) 45	26 (7.5%) 31	8 (2.0%) 12	13 (4.9%) 15
Pyrexia	32 (4.5%) 37	19 (5.5%) 26	8 (2.0%) 8	11 (4.1%) 15
Hypercalcaemia	27 (3.8%) 38	10 (2.9%) 15	11 (2.8%) 14	6 (2.2%) 6
Hyperparathyroidism secondary	30 (4.2%) 33	31 (8.9%) 38	15 (3.8%) 15	23 (8.6%) 25
Nasopharyngitis	29 (4.1%) 34	20 (5.7%) 25	13 (3.3%) 13	8 (3.0%) 9
Back pain	28 (4.0%) 33	12 (3.4%) 12	7 (1.8%) 10	6 (2.2%) 6
Dyspnoea	28 (4.0%) 33	19 (5.5%) 20	10 (2.6%) 11	7 (2.6%) 7
Anaemia	28 (4.0%) 31	29 (8.3%) 32	15 (3.8%) 16	15 (5.6%) 17
Product taste abnormal	28 (4.0%) 28	3 (0.9%) 3	4 (1.0%) 4	1 (0.4%) 1
Bronchitis	27 (3.8%) 30	12 (3.4%) 14	8 (2.0%) 8	5 (1.9%) 5
Cough	27 (3.8%) 32	13 (3.7%) 15	9 (2.3%) 11	8 (3.0%) 9
Dyspepsia	26 (3.7%) 32	16 (4.6%) 18	6 (1.5%) 7	6 (2.2%) 7
Abdominal pain	26 (3.7%) 28	12 (3.4%) 13	8 (2.0%) 8	2 (0.7%) 2
Upper respiratory tract infection	25 (3.5%) 29	18 (5.2%) 22	5 (1.3%) 5	11 (4.1%) 13
Arthralgia	24 (3.4%) 26	10 (2.9%) 12	9 (2.3%) 10	6 (2.2%) 6
Abdominal pain upper	23 (3.3%) 33	10 (2.9%) 11	5 (1.3%) 8	2 (0.7%) 3
Chest pain	23 (3.3%) 27	20 (5.7%) 23	6 (1.5%) 7	8 (3.0%) 9
Dizziness	21 (3.0%) 25	16 (4.6%) 18	9 (2.3%) 9	9 (3.4%) 10
Urinary tract infection	21 (3.0%) 27	11 (3.2%) 14	10 (2.6%) 10	7 (2.6%) 9

Velphoro (b) (4)

Summary of TEAEs in Studies PA-CL-05A/05B (Cont'd)

Preferred Term	Pooled PA-CL-05A/PA-CL-05B (SS) ⁽¹⁾		PA-CL-05B (SS5B)	
	PA21 (N=707) n (%) E	Sevelamer (N=348) n (%) E	PA21 (N=391) n (%) E	Sevelamer (N=267) n (%) E
Blood parathyroid hormone increased	19 (2.7%) 23	9 (2.6%) 10	8 (2.0%) 9	5 (1.9%) 5
Fluid overload	19 (2.7%) 24	11 (3.2%) 12	8 (2.0%) 9	8 (3.0%) 8
Insomnia	19 (2.7%) 19	11 (3.2%) 11	6 (1.5%) 6	7 (2.6%) 7
Oedema peripheral	18 (2.5%) 18	12 (3.4%) 14	8 (2.0%) 8	8 (3.0%) 8
Pneumonia	17 (2.4%) 20	11 (3.2%) 12	7 (1.8%) 8	6 (2.2%) 6
Fall	16 (2.3%) 23	3 (0.9%) 3	3 (0.8%) 6	2 (0.7%) 2
Gastritis	16 (2.3%) 18	8 (2.3%) 9	4 (1.0%) 5	4 (1.5%) 4
Blood phosphorus increased	15 (2.1%) 20	8 (2.3%) 9	5 (1.3%) 6	6 (2.2%) 7
Decreased appetite	15 (2.1%) 18	16 (4.6%) 19	4 (1.0%) 4	6 (2.2%) 6
Serum ferritin increased	15 (2.1%) 22	8 (2.3%) 11	8 (2.0%) 10	3 (1.1%) 4
Atrial fibrillation	14 (2.0%) 20	8 (2.3%) 10	6 (1.5%) 6	4 (1.5%) 4
Gastroenteritis	14 (2.0%) 14	5 (1.4%) 7	4 (1.0%) 4	3 (1.1%) 3
Arteriovenous fistula thrombosis	13 (1.8%) 14	14 (4.0%) 14	3 (0.8%) 3	7 (2.6%) 7
Hyperparathyroidism	13 (1.8%) 13	10 (2.9%) 13	6 (1.5%) 6	5 (1.9%) 6
Rash	11 (1.6%) 13	8 (2.3%) 11	2 (0.5%) 2	5 (1.9%) 7
Fatigue	9 (1.3%) 10	8 (2.3%) 11	2 (0.5%) 2	5 (1.9%) 6
Asthenia	9 (1.3%) 9	10 (2.9%) 10	4 (1.0%) 4	3 (1.1%) 3
Flatulence	9 (1.3%) 9	8 (2.3%) 9	0 (0.0%) 0	0 (0.0%) 0
Abdominal discomfort	8 (1.1%) 9	10 (2.9%) 10	2 (0.5%) 2	1 (0.4%) 1
Neutropenia	8 (1.1%) 11	8 (2.3%) 8	3 (0.8%) 3	6 (2.2%) 6
Tachycardia	8 (1.1%) 8	8 (2.3%) 9	4 (1.0%) 4	5 (1.9%) 5
Blood pressure increased	6 (0.8%) 11	8 (2.3%) 20	3 (0.8%) 5	5 (1.9%) 11
Blood bicarbonate decreased	4 (0.6%) 5	7 (2.0%) 7	0 (0.0%) 0	3 (1.1%) 3
Neck pain	2 (0.3%) 3	7 (2.0%) 14	0 (0.0%) 0	4 (1.5%) 4

¹ PA21 treatment group includes PA-CL-05A Stage 2.
(Sponsor table from 120-day safety update report)

For treatment related common AEs, overall (pooled PA-CL-05A/PA-CL-05B data), more subjects in the PA21 group had treatment-related AEs than in the sevelamer group (45.3% versus 24.7%). This difference was driven primarily by treatment-related GI AEs. Specifically, there was a $\geq 2.0\%$ incidence in treatment-related discolored feces (15.6% PA21 versus 0.3% sevelamer), diarrhea (13.0% versus 2.3%), and abnormal product taste (3.8% versus 0.6%). Discolored feces and diarrhea are recognized effects of oral compounds containing iron.

In the long-term extension study, PA-CL-05B, TEAEs occurred in 57 (14.6%) subjects in the PA21 group and in 24 (9.0%) subjects in the sevelamer group. The incidence of GI disorders was lower during PA-CL-05B compared to the combined studies, indicating that these TEAEs became less common over time. Apart from hypophosphatemia, all individual TEAEs that were considered treatment related occurred at a very low incidence ($\leq 2.0\%$) during PA-CL-05B. The most common treatment-related events (incidence $\geq 1.0\%$) in the PA21 group that also occurred at a higher incidence on PA21 were hypophosphatemia (4.6% vs. 2.6% in sevelamer), hyperphosphatemia (2.0% vs. 1.2% in sevelamer), diarrhea (1.8% vs. 0 in sevelamer) and constipation (1.0% vs. 0.7% in sevelamer). These data are summarized in table 43.

Velphoro (b) (4)

Table 43: Summary of treatment-related AEs in Study PA-CL-05A/05B

MedDRA SOC Preferred Term	PA-CL-05A/PA-CL-05B(1) (SS)		PA-CL-05B (SS5B)	
	PA21 (N=707) n (%) E	Sevelamer (N=348) n (%) E	PA21 (N=391) n (%) E	Sevelamer (N=267) n (%) E
Any Treatment-related TEAE	320 (45.3%) 600	86 (24.7%) 152	57 (14.6%) 81	24 (9.0%) 30
Faeces discoloured	110 (15.6%) 112	1 (0.3%) 1	3 (0.8%) 3	0 (0.0%) 0
Diarrhoea	92 (13.0%) 131	8 (2.3%) 9	7 (1.8%) 10	0 (0.0%) 0
Hypophosphataemia	28 (4.0%) 38	13 (3.7%) 15	18 (4.6%) 22	7 (2.6%) 7
Hyperphosphataemia	24 (3.4%) 29	6 (1.7%) 6	8 (2.0%) 9	6 (2.2%) 7
Nausea	28 (4.0%) 30	18 (5.2%) 18	3 (0.8%) 3	0 (0.0%) 0
Product taste abnormal	27 (3.8%) 27	2 (0.6%) 2	4 (1.0%) 4	0 (0.0%) 0
Constipation	21 (3.0%) 23	17 (4.9%) 19	4 (1.0%) 4	2 (0.7%) 2
Vomiting	15 (2.1%) 16	4 (1.1%) 4	2 (0.5%) 2	0 (0.0%) 0
Dyspepsia	14 (2.0%) 17	6 (1.7%) 8	1 (0.3%) 1	2 (0.7%) 3
Abdominal pain	11 (1.6%) 12	4 (1.1%) 4	0 (0.0%) 0	0 (0.0%) 0
Tooth discolouration	10 (1.4%) 10	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0
Abdominal pain upper	8 (1.1%) 9	5 (1.4%) 5	1 (0.3%) 1	0 (0.0%) 0
Flatulence	7 (1.0%) 7	6 (1.7%) 7	0 (0.0%) 0	0 (0.0%) 0
Oral administration complication	7 (1.0%) 7	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Blood phosphorus increased	5 (0.7%) 5	4 (1.1%) 4	2 (0.5%) 2	4 (1.5%) 4
Decreased appetite	3 (0.4%) 3	4 (1.1%) 5	0 (0.0%) 0	0 (0.0%) 0

¹ PA21 group includes subjects in PA-CL-05A Stage 2.
(Sponsor table from 120-day safety update report)

Reviewer comments: The incidence rate of discolor feces was significantly reduced in Study PA-CL-05B. This was not because of the reduction of the real incidence rate but the reduction of the report rate as the patients did not consider that discolor feces caused by the iron in PA21 was an adverse event anymore.

In the phase 2 dose-ranging study, Study PA-CL-03A, no AEs were identified beyond those identified in the pivotal study. Of treatment-related TEAEs, hypo/hyper phosphatemia (24 subjects, 18.8%) and GI events were the most common events in the pooled PA21 group. In the sevelamer (HCl) group, the proportion of subjects with treatment-related TEAEs was similar to that seen in the pooled PA21 group. As expected, the proportion of subjects with hypophosphatemia was highest in the 2 higher-dose PA21 groups: 2000 mg/day and 2500 mg/day. Conversely, treatment-related hyperphosphatemia was reported only in the PA21 250 mg/day group, the PA21 1000 mg/day and sevelamer (HCl) groups. The proportion of subjects with treatment-related GI events was not closely correlated with PA21 dose. The treatment-related TEAEs that were reported for more than 1 subject in the pooled PA21 group were discolored feces and diarrhea. There were no relevant differences in the incidence among the PA21 groups. In the sevelamer (HCl) group, there were more patients with treatment-related diarrhea (11.5% vs. 3.9%) compared to the PA21 groups, which contrast with the findings in the pivotal trial. AEs considered to be treatment-related, and reported by 2 or more subjects in any of the PA21 or sevelamer (HCl) groups or in the pooled PA21 group, are summarized in table 44.

Velphoro (b) (4)

Table 44: Treatment-related TEAEs in Study PA-CL-03A

System Organ Class Preferred Term	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 (%)	
	# Events	# Events	# Events	# Events	# Events	# Events	
Any TEAE	5 (19.2%) 6	9 (34.6%) 29	8 (32.0%) 15	12 (44.4%) 16	10 (41.7%) 12	44 (34.4%) 78	8 (30.8%) 8
Gastrointestinal Disorders	2 (7.7%) 2	3 (11.5%) 21	6 (24.0%) 10	6 (22.2%) 8	4 (16.7%) 5	21 (16.4%) 46	4 (15.4%) 4
Constipation	0 (0.0%) 0	1 (3.8%) 5	1 (4.0%) 1	0 (0.0%) 0	0 (0.0%) 0	2 (1.6%) 6	0 (0.0%) 0
Diarrhoea	0 (0.0%) 0	1 (3.8%) 7	2 (8.0%) 5	1 (3.7%) 1	1 (4.2%) 1	5 (3.9%) 14	3 (11.5%) 3
Faeces discoloured	2 (7.7%) 2	3 (11.5%) 3	3 (12.0%) 3	4 (14.8%) 4	3 (12.5%) 3	15 (11.7%) 15	0 (0.0%) 0
Flatulence	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (4.2%) 1	1 (0.8%) 1	0 (0.0%) 0
Vomiting	0 (0.0%) 0	1 (3.8%) 5	0 (0.0%) 0	1 (3.7%) 1	0 (0.0%) 0	2 (1.6%) 6	0 (0.0%) 0
Metabolism and Nutrition Disorders	3 (11.5%) 4	4 (15.4%) 5	4 (16.0%) 5	7 (25.9%) 7	6 (25.0%) 7	24 (18.8%) 28	4 (15.4%) 4
Hyperphosphataemia	3 (11.5%) 4	1 (3.8%) 1	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	4 (3.1%) 5	1 (3.8%) 1
Hypophosphataemia	0 (0.0%) 0	3 (11.5%) 4	2 (8.0%) 2	7 (25.9%) 7	5 (20.8%) 6	17 (13.3%) 19	2 (7.7%) 2

Note: the list doses in above figure were in the total mass. Its tablet is standardized to contain 500 mg iron (as PA21 drug substance (DS)) with a total nominal mass of 2.5g. Doses of 1.25, 5.0, 7.5, 10 and 12.5g represent 250, 1000, 1500, 2000, and 2500 mg iron of PA21. (Sponsor table from the Study PA-CL-03A study report)

In the other phase 2 dose-ranging study conducted in Japanese patients (Study PA1201), treatment-related TEAEs experienced by 2 or more subjects in any PA21 dose group included the following:

1. A dose-dependent increase in diarrhea (750 mg group: 4 subjects (10.3%), 1500 mg group: 4 subjects (11.1%), 2250 mg group: 12 subjects (34.3%), 3000 mg group 12 subjects (33.3%) and placebo group: 3 subjects (8.1%))
2. Discolored feces (750 mg group: 10 subjects (25.6%), 1500 mg group: 11 subjects (30.6%), 2250 mg group: 10 subjects (28.6%), 3000 mg group: 10 subjects (27.8%) and placebo group: 1 subject (2.7%)).
3. Constipation (750 mg group: no subjects, 1500 mg group: 1 subject (2.8%), 2250 mg group: 2 subjects (5.7%), 3000 mg group: 1 subject (2.8%) and placebo group: no subjects).
4. Tongue discoloration (750 mg group: no subjects, 1500 mg group: no subjects, 2250 mg group: 2 subjects (5.7%), 3000 mg group: no subjects and placebo group: no subjects)

In the phase I studies, the major drug-related findings were mild to moderate GI events. Discolored feces was the most common event. In one study, it occurred in almost every actively treated subject. Other GI events included flatulence, diarrhea and various types of abdominal pain or discomfort.

In the DDI studies, discolored feces was reported by 25 subjects (12.2%) and 19 (9.5%) in the 2 PA21 groups, respectively, compared to none in the reference drug group. Other GI events

Velphoro (b) (4)

judged to be treatment-related and occurring with a frequency of 2% or greater in any one group included nausea, 4 subjects (2.0%) and 8 subjects (4.0%) in the PA21 groups, respectively, compared to no subjects in the reference drug group, and diarrhea with 5 (2.4%) and 4 (2.0%) subjects in the PA21 groups, respectively, compared to 1 subject (0.5%) in the reference drug alone group. Other GI events with a frequency of <2% which appeared as treatment-related in any group were constipation, abdominal pain, abdominal discomfort, abdominal distension, vomiting, and upper and lower abdominal pain. Other than GI events, there was a somewhat higher incidence of headache in the PA21 groups (14 subjects (6.8 %) and 11 subjects (5.5%) in the PA21 groups, respectively,) compared to the reference drug group (4 subjects (2.0%)). The reason of this difference is not clear and this difference was not observed in the other studies.

AEs of Special Interest in Studies PA-CL-05A/05B: Potential AEs of special interest include hyperphosphatemia, hypophosphatemia, hypocalcaemia, hypercalcemia, hyperparathyroidism, and GI events.

1. Hyperphosphatemia and Hypophosphatemia: In the pooled PA-CL-05A/PA-CL-05B studies the incidence of both hyperphosphatemia and hypophosphatemia was similar between the 2 treatment groups, the majority of events were mild and few led to discontinuation of study drug. Results from the long-term safety study, Study PA-CL-05B, were similar to those from the pooled analysis. These data are summarized in the following table 45.

Table 45: Summary of hyperphosphatemia and hypophosphatemia in Studies PA-CL-05A/05B

MedDRA SOC and Preferred Term	Pooled PA-CL-05A/ PA-CL-05B (SS)		PA-CL-05B (SS5B)	
	PA21 (N=707) n (%) E	Sevelamer (N=348) n (%) E	PA21 (N=391) n (%) E	Sevelamer (N=267) n (%) E
Hyperphosphataemia				
Any hyperphosphataemia ⁽¹⁾ TEAE	127 (18.0%) 215	50 (14.4%) 95	52 (13.3%) 79	34 (12.7%) 54
Any treatment-related hyperphosphataemia TEAE	29 (4.1%) 34	9 (2.6%) 10	10 (2.6%) 11	6 (2.2%) 7
Severity of hyperphosphataemia TEAE				
Mild	97 (13.7%)	35 (10.1%)	40 (10.2%)	23 (8.6%)
Moderate	26 (3.7%)	15 (4.3%)	10 (2.6%)	11 (4.1%)
Severe	4 (0.6%)	0 (0.0%)	2 (0.5%)	0 (0.0%)
Any hyperphosphataemia leading to withdrawal	27 (3.8%) 27	8 (2.3%) 8	12 (3.1%) 12	8 (3.0%) 8
Hypophosphataemia				
Any hypophosphataemia ⁽¹⁾ TEAE	45 (6.4%) 65	33 (9.5%) 38	25 (6.4%) 32	15 (5.6%) 15
Any treatment-related hypophosphataemia TEAE	30 (4.2%) 41	16 (4.6%) 18	19 (4.9%) 23	7 (2.6%) 7
Severity of hypophosphataemia TEAE				
Mild	37 (5.2%)	26 (7.5%)	22 (5.6%)	13 (4.9%)
Moderate	8 (1.1%)	7 (2.0%)	3 (0.8%)	2 (0.7%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Any hypophosphataemia leading to withdrawal	4 (0.6%)	0 (0.0%)	3 (0.8%)	0 (0.0%)

(Sponsor table from 120-day safety update report)

2. Hypocalcemia and Hypercalcemia: As a new phosphate binder, the serum level of calcium could be affected. In the studies, however, the incidence of both hypercalcemia and hypocalcemia was similar between the 2 treatment groups. The majority of events were mild, few were classed as related to treatment and very few led to discontinuation of study drug. Data are summarized in the following table 46.

Velphoro (b) (4)

Table 46: Summary of hypercalcemia and hypocalcemia in Studies PA-CL-05A/05B

MedDRA SOC and Preferred Term	Pooled PA-CL-05A/ PA-CL-05B (SS)		PA-CL-05B (SS5B)	
	PA21 (N=707) n (%) E	Sevelamer (N=348) n (%) E	PA21 (N=391) n (%) E	Sevelamer (N=267) n (%) E
Hypercalcaemia				
Any hypercalcaemia ⁽¹⁾ TEAE	30 (4.2%) 44	23 (6.6%) 25	11 (2.8%) 14	7 (2.6%) 7
Any treatment-related hypercalcaemia TEAE	1 (0.1%) 1	2 (0.6%) 2	0 (0.0%) 0	2 (0.7%) 2
Severity of hypercalcaemia TEAE				
Mild	25 (3.5%)	9 (2.6%)	9 (2.3%)	5 (1.9%)
Moderate	4 (0.6%)	2 (0.6%)	1 (0.3%)	2 (0.7%)
Severe	1 (0.1%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Any hypercalcaemia leading to withdrawal	2(0.3%) 2	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
Hypocalcaemia				
Any hypocalcaemia ⁽¹⁾ TEAE	34 (4.8%) 47	11 (3.2%) 16	15 (3.8%) 17	8 (3.0%) 8
Any treatment-related hypocalcaemia TEAE	5 (0.7%) 5	2 (0.6%) 2	2 (0.5%) 2	0 (0.0%) 0
Severity of hypocalcaemia TEAE				
Mild	23 (3.3%)	18 (5.2%)	10 (2.6%)	7 (2.6%)
Moderate	8 (1.1%)	5 (1.4%)	3 (0.8%)	1 (0.4%)
Severe	3 (0.4%)	0 (0.0%)	2 (0.5%)	0 (0.0%)
Any hypocalcaemia leading to withdrawal	1 (0.1%) 1	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0

(Sponsor table from 120day safety update report)

3. Hyperparathyroidism: The incidence of hyperparathyroidism was somewhat higher in the sevelamer group than in the PA21 group (14.1% and 8.6%, respectively). The majority of events were mild. No subjects were withdrawn for hyperparathyroidism. Data are summarized in the following table 47.

Table 47: Summary of TEAEs of hyperparathyroidism in Studies PA-CL-05A/05B

MedDRA SOC and Preferred Term	Pooled PA-CL-05A/ PA-CL-05B (SS)		PA-CL-05B (SS5B)	
	PA21 (N=707) n (%) E	Sevelamer (N=348) n (%) E	PA21 (N=391) n (%) E	Sevelamer (N=267) n (%) E
Any hyperparathyroidism ⁽¹⁾ TEAE	61 (8.6%) 69	49 (14.1%) 61	29 (7.4%) 30	33 (12.4%) 36
Any treatment-related hyperparathyroidism TEAE	3 (0.4%) 3	2 (0.6%) 3	3 (0.8%) 3	2 (0.7%) 2
Severity of hyperparathyroidism TEAE				
Mild	38 (5.4%)	26 (7.5%)	20 (5.1%)	17 (6.4%)
Moderate	21 (3.0%)	22 (6.3%)	8 (2.0%)	16 (6.0%)
Severe	2 (0.3%)	1 (0.3%)	1 (0.3%)	0 (0.0%)
Any hyperparathyroidism leading to withdrawal	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0

(Sponsor table from 120-day safety update report)

4. Gastrointestinal AEs: Gastrointestinal events were reported by 52.5% and 42.8% of subjects in the PA21 and sevelamer groups, respectively. In the PA21 group, the most common GI events (occurring in >5.0%) were diarrhea (23.6%), discolored feces (16.1%), nausea (9.8%) and constipation (5.1%). The higher proportion of PA21-treated subjects experiencing AEs in the GI compared with sevelamer-treated subjects was driven by the higher incidence of diarrhea and discolored feces. Discolored feces (black stool) was reported in 16.1% of PA21-treated subjects (versus 0.3% of sevelamer-treated subjects). Discolored feces was an expected occurrence because of the iron in PA21. 3 cases of diarrhea with PA21 and 2 cases with sevelamer were classified as serious AEs.

The incidence of GI events (especially diarrhea and discolored feces in the PA21 group) was lower in the long-term study compared with the combined studies, indicating that these events manifest early in the course of therapy (diarrhea) or possibly that subjects no longer perceived events such as discolored feces as an AE. The incidence of other GI events during PA-CL-05B was similar for the 2 treatment groups. Data are summarized in the following table 48.

Table 48: Summary of GI disorders in Studies PA-CL-05A/05B

MedDRA SOC Preferred Term	Pooled PA-CL-05A/PA-CL-05B ⁽¹⁾ (SS)		PA-CL-05B (SS5B)	
	PA21 (N=707) n (%) E	Sevelamer (N=348) n (%) E	PA21 (N=391) n (%) E	Sevelamer (N=267) n (%) E
Any GI Disorders	371 (52.5%) 811	149 (42.8%) 310	100 (25.6%) 170	51 (19.1%) 95
Diarrhoea	167 (23.6%) 231	40 (11.5%) 49	32 (8.2%) 43	15 (5.6%) 19
Faeces discoloured	114 (16.1%) 116	1 (0.3%) 2	3 (0.8%) 3	1 (0.4%) 1
Nausea	69 (9.8%) 87	50 (14.4%) 53	23 (5.9%) 26	11 (4.1%) 12
Abdominal pain ⁽²⁾	55 (7.8%) 73	32 (9.2%) 36	16 (4.1%) 19	5 (1.9%) 6
Vomiting	42 (5.9%) 54	32 (9.2%) 37	14 (3.6%) 18	12 (4.5%) 14
Constipation	36 (5.1%) 44	29 (8.3%) 31	10 (2.6%) 11	5 (1.9%) 5
Dyspepsia	26 (3.7%) 32	16 (4.6%) 18	6 (1.5%) 7	6 (2.2%) 7
Flatulence	9 (1.3%) 9	8 (2.3%) 9	0 (0.0%) 0	0 (0.0%) 0
Gastritis	16 (2.3%) 18	8 (2.3%) 9	4 (1.0%) 5	4 (1.5%) 4

1. PA21 treatment group includes PA-CL-05A Stage 2. (Sponsor table from 120-day safety update report)

A summary of the time to onset of GI TEAES in the pivotal study and its extension is shown in the following table 49. In both treatment groups the highest incidence of GI TEAES was during the first 4 weeks of treatment. In each time window, the incidence of GI TEAES was greater in the PA21 group than in the sevelamer arm; this difference was driven by a greater number of AEs of discolored feces and diarrhea on PA21. Discolored feces, which were reported almost exclusively in the PA21 group, were almost all reported during the first 4 weeks of treatment. In the PA21 group, diarrhea was also reported more frequently during the first 4 weeks of treatment, the incidence decreased over time to a level of around 4 to 5% at Week 24. Other common GI events, nausea, vomiting and constipation, occurred at a similar low incidence throughout the 52 weeks of treatment. The levels of constipation were consistent throughout the 52 weeks of treatment.

Table 49: Summary of time of onset of GI TEAES in Studies PA-CL-05A/05B

Preferred Term	PA21 (N=707)					Sevelamer (N=348)				
	<4 Weeks	4 to <12 Weeks	12 to <24 Weeks	24 to <36 Weeks	≥36 Weeks	<4 Weeks	4 to <12 Weeks	12 to <24 Weeks	24 to <36 Weeks	≥36 Weeks
	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E
Any GI TEAE	200 (28.3%) 299	130 (19.5%) 200	79 (13.3%) 120	63 (12.4%) 98	48 (13.5%) 71	55 (15.8%) 84	52 (15.2%) 80	34 (10.7%) 47	28 (9.7%) 52	28 (11.1%) 39
Faeces discoloured	102 (14.4%) 102	8 (1.2%) 9	1 (0.2%) 1	3 (0.6%) 3	1 (0.3%) 1	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (0.4%) 1
Diarrhoea	81 (11.5%) 88	51 (7.7%) 55	34 (5.7%) 40	22 (4.3%) 27	15 (4.2%) 18	16 (4.6%) 16	6 (1.8%) 6	7 (2.2%) 8	9 (3.1%) 11	5 (2.0%) 6
Nausea	21 (3.0%) 21	20 (3.0%) 20	10 (1.7%) 14	12 (2.4%) 14	12 (3.4%) 12	17 (4.9%) 18	17 (5.0%) 18	4 (1.3%) 4	9 (1.3%) 9	3 (1.2%) 4
Constipation	12 (1.7%) 12	16 (2.4%) 16	4 (0.7%) 4	3 (0.6%) 3	8 (2.2%) 8	7 (2.0%) 8	14 (4.1%) 14	3 (0.9%) 3	2 (0.7%) 2	3 (1.2%) 3
Vomiting	12 (1.7%) 13	14 (2.1%) 14	6 (1.0%) 6	9 (1.8%) 11	5 (1.4%) 6	9 (2.6%) 10	7 (2.1%) 8	4 (1.3%) 4	8 (2.8%) 8	6 (2.4%) 7

(Sponsor table from 120-day safety update report)

Velphoro (b) (4)

In combined PA-CL-05A/PA-CL-05B studies, there were more patients with mild and moderate diarrhea in the PA21 group than in the Sevelamer group. The incidence of severe cases was similar between the two groups (0.3% vs. 0.9%). In PA-CL-05B, the incidence of diarrhea was significantly reduced in both groups as previously noted. However, there were still more patients with diarrhea in the PA21 group than in the sevelamer group. These data are summarized in the following table 50.

Table 50: Summary of TEAEs of diarrhea Studies PA-CL-05A/05B

Parameter	Pooled PA-CL-05A/PA-CL-05B (SS)		PA-CL-05B (SS5B)	
	PA21 (N=707) n (%)	Sevelamer (N=348) n (%)	PA21 (N=391) n (%)	Sevelamer (N=267) n (%)
Any subjects with diarrhoea	167 (23.6%)	40 (11.5%)	32 (8.2%)	15 (5.6%)
Treatment-related diarrhoea	92 (13.0%)	8 (2.3%)	7 (1.8%)	0 (0.0%)
Severity				
Mild	119 (16.8%)	25 (7.2%)	26 (6.6%)	11 (4.1%)
Moderate	46 (6.5%)	12 (3.4%)	6 (1.5%)	3 (1.1%)
Severe	2 (0.3%)	3 (0.9%)	0 (0.0%)	1 (0.4%)
Diarrhoea leading to withdrawal	25 (3.5%)	2 (0.6%)	2 (0.5%)	0 (0.0%)
Serious diarrhoea	3 (0.4%)	2 (0.6%)	1 (0.3%)	1 (0.4%)

(Sponsor table from 120-day safety update report)

Reviewer's comments: The most common drug-related events were GI events. Diarrhea was the most common PA21-related adverse event (AE) and was also the major reason for AE-related patient withdrawal in the PA21 group. In the pivotal study, the incidence rate of diarrhea was higher in the PA21 group compared to the active control, sevelamer. The majority of these diarrhea AEs occurred early after starting treatment, were mild in severity, and resolved with continued treatment. Other common GI AEs including nausea, vomiting and constipation occurred at a lower incidence on PA21 than on sevelamer. The incidence of the more common GI events was substantially reduced during continued treatment in the long-term extension study (Study PA-CL-05B).

Hypophosphatemia was observed in some patients in both the dose-ranging study and the pivotal study. This is a dose-dependent drug-related AE and is expected given the intended pharmacologic effect. Since this product will be started at a low dose and gradually titrated with careful monitoring, this AE should not be a major concern.

7.4.2 Laboratory Findings

Laboratory data from Study PA-CL-05A, its extension 05B, and Study PA-CL-03A were analyzed. When clinically meaningful abnormal findings were observed, data from other studies were analyzed to confirm these findings.

Hematology: In the pivotal study, mean changes in hemoglobin were small and similar compared to baseline in both PA-21 and sevelamer groups. Anemia was reported as an AE in 37 subjects (5.2%) in the PA21 group and in 35 subjects (10.1%) in the sevelamer group. All of these cases were reported to be related to end stage renal disease and not to study treatment. These data are summarized in the following table 51.

Velphoro (b) (4)

Table 51: Summary of change of hemoglobin from baseline in Studies PA-CL-05A/05B

Time Point	PA-CL-05A/PA-CL-05B (SS)				Completers (PA-CL-05A and PA-CL-05B)			
	PA21 (N=707)		Sevelamer (N=348)		PA21 (N=322)		Sevelamer (N=227)	
	Actual (g/dL)	Change from Baseline	Actual (g/dL)	Change from Baseline	Actual (g/dL)	Change from Baseline	Actual (g/dL)	Change from Baseline
Baseline⁽¹⁾								
n	707	–	348	–	322	–	227	–
Mean (SD)	11.31 (1.298)	–	11.33 (1.347)	–	11.25 (1.412)	–	11.36 (1.327)	–
Median	11.40	–	11.40	–	11.40	–	11.50	–
Min/max	6.30/16.10	–	5.90/17.20	–	6.30/16.10	–	5.90/14.70	–
Week 24								
n	504	504	282	282	306	306	217	217
Mean (SD)	11.42 (1.373)	0.10 (1.471)	11.25 (1.419)	-0.10 (1.260)	11.40 (1.460)	0.13 (1.488)	11.28 (1.352)	-0.08 (1.171)
Median	11.50	0.0	11.30	-0.10	11.50	0.00	11.40	-0.20
Min/max	6.40/16.10	-4.30/5.50	5.40/14.60	-5.40/4.10	6.40/16.10	-4.10/5.50	5.40/14.60	-3.60/4.10
Week 52								
n	317	317	225	225	315	315	223	223
Mean (SD)	11.39 (1.390)	0.12 (1.551)	11.27 (1.273)	-0.09 (1.276)	11.39 (1.394)	0.13 (1.552)	11.25 (1.248)	-0.10 (1.272)
Median	11.30	0.1	11.30	-0.20	11.30	0.10	11.30	-0.20
Min/max	6.70/16.10	-5.10/5.80	7.20/15.60	-2.80/5.60	6.70/16.10	-5.10/5.80	7.20/15.60	-2.80/5.60
Combined endpoint⁽²⁾								
n	681	681	344	344	322	322	227	227
Mean (SD)	11.36 (1.300)	0.05 (1.486)	11.22 (1.332)	-0.11 (1.299)	11.39 (1.389)	0.15 (1.576)	11.26 (1.249)	-0.10 (1.263)
Median	11.30	0.10	11.25	-0.10	11.30	0.10	11.30	-0.20
Min/max	6.00/16.10	-5.10/5.80	7.20/16.20	-3.40/5.60	6.70/16.10	-5.10/5.80	7.20/15.60	-2.80/5.60

1. Baseline was defined as the last non-missing value prior to or on the date of the first PA-CL-05A study drug intake.
2. Combined endpoint was defined as the last post-baseline non-missing value across both studies (for PA-CL-05A only Stage 1 values are considered). (Sponsor table from 120-safety update report)

Abnormal white blood cell counts (mostly increases) were reported in >4.0% of subjects during the study but no distinct pattern was observed in either treatment group, and the events were generally not serious and were not considered to be drug related. Mild leukopenia led to withdrawal of a sevelamer treated subject and one case of thrombocytopenia (moderate) was reported as an SAE in the PA21 group but did not lead to withdrawal. No dose-related changes in hematology parameters were observed in either treatment group.

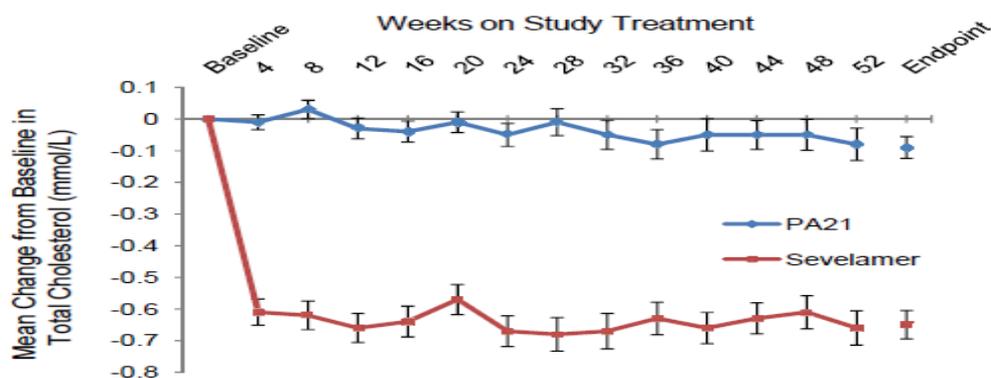
In Study PA-CL-03A, there were no differences in hematology parameters between the pooled PA21 group and the sevelamer group compared to baseline values. From baseline to Week 9, there was a statistically significant decrease in eosinophils in the PA21 1500 mg/day group; the values, however, were within the normal range at both time points. There were no significant changes in any other dose group. From baseline to Week 4 there was a statistically significant decrease in MCHC in the PA21 1000 mg/day group, but no significant changes occurred in any other group. From baseline to Week 4 and to Week 9, there was a statistically significant increase in mean corpuscular volume in the PA21 1000 mg/day group and the pooled PA21 group. There were no significant changes in any other individual PA21 group or in the sevelamer group. No pattern was observed for changes in any hematology parameter across the individual PA21 groups or the sevelamer group.

In all other studies, there were no clinically meaningful PA-21 related changes in hematological parameters compared to baseline in either healthy subjects or ESRD patients.

Clinical chemistry: In the pivotal study, overall there were no clinically meaningful differences in clinical chemistry parameters between the two treatment groups compared to baseline including bicarbonate, bilirubin, BUN, high density lipoprotein cholesterol, C-reactive protein, chloride, creatine kinase, creatinine, glucose, potassium, sodium, total protein, and urate.

A significant decrease in mean cholesterol (total and low density lipoprotein) was observed in the sevelamer group by Week 4 with mean values gradually decreasing further through Week 12. In the sevelamer group, mean values were significantly lower than those in the PA21 group at all time points throughout the 52 weeks of treatment. The reduction in total and low density lipoprotein cholesterol is a known effect of sevelamer treatment. These data are shown in the following figure. There were no differences in triglyceride levels between treatment groups.

Figure 8: Mean serum total cholesterol change from baseline at each time point in Studies PA-CL-05A/05B



(Sponsor figure from 120 safety update report)

As expected, significant changes were seen in serum phosphorus levels (see the efficacy section and common AE section). In addition to TEAEs related to serum phosphorus and calcium levels, clinically significant serum chemistry values that were reported as TEAEs included abnormal glucose levels, hyperkalemia, increased and decreased international normalized ratio (INR), increased creatinine phosphokinase, and GGT. These AEs likely reflect the underlying disease and disease related clinical complications. There were no significant differences between PA21 and sevelamer for these findings.

Changes seen in serum chemistry parameters in the subgroups were generally consistent with the changes seen in the overall treatment groups. There were no clinically meaningful differences between treatment groups or in any of the subgroups by region, age, sex, race, and dialysis status. There was a single report of a severe decreased INR and a moderate increased INR in the PA21 group; they were classified as serious but not considered drug related and neither resulted in withdrawal.

In the phase 2 dose-range finding study, PA-CL-03A, there were no clinically meaningful changes at the end of Week 4 and the 2-week follow up compared to baseline for albumin, bicarbonate, C-reactive protein, chloride, cholesterol, creatine phosphokinase, creatinine, glucose, potassium, sodium, total bilirubin, high density lipoproteins, low density lipoproteins, total protein, triglycerides, urea and uric acid. There was no observed pattern in mean changes from baseline across the individual PA21 groups and the sevelamer group for any of these parameters.

Changes in other laboratory parameters of interest are discussed below.

Velphoro (b) (4)

Calcium and calcium-phosphorus product: In the pivotal study, there were no notable changes from baseline in serum total calcium and no differences between treatment groups were observed. Changes in ionized and corrected calcium were very similar to changes in total calcium. Serum total calcium-phosphorus product changes mirrored changes in serum phosphorus and no significant differences were observed between treatment groups. Changes from baseline in total calcium are summarized in table 52.

Table 52: Summary of changes of serum total calcium from baseline in Studies PA-CL-05A/05B

Parameter/ Time Point	PA21 (N=707)		Sevelamer (N=348)	
	Actual	Change from Baseline	Actual	Change from Baseline
Total Calcium (mg/dL)				
PA-CL-05A baseline⁽¹⁾				
n	707	–	348	–
Mean (SD)	8.80 (0.740)	–	8.79 (0.794)	–
Median	8.80	–	8.80	–
Min/max	6.30/11.32	–	5.96/12.16	–
PA-CL-05A Week 24				
n	493	493	282	282
Mean (SD)	8.97 (0.796)	0.18* (0.841)	8.94 (0.713)	0.13* (0.817)
Median	8.90	0.10	8.92	0.12
Min/max	6.92/14.80	-2.44/7.56	5.70/11.68	-4.40/3.68
PA-CL-05B Week 28 (Week 52)				
n	297	297	214	214
Mean (SD)	9.03 (0.761)	0.20* (0.793)	9.02 (0.797)	0.22* (0.911)
Median	9.04	0.20	9.08	0.24
Min/max	6.40/11.32	-2.20/3.40	4.00/11.10	-5.30/3.12
Combined endpoint⁽²⁾				
n	701	701	348	348
Mean (SD)	8.97 (0.829)	0.17* (0.856)	8.99 (0.723)	0.20* (0.840)
Median	9.00	0.16	9.00	0.20
Min/max	6.40/14.80	-3.12/7.56	5.30/11.10	-3.50/3.76

1. Baseline was defined as the last non-missing value prior to or on the date of the first PA-CL-05A study drug intake.
2. Combined endpoint was defined as the last post-baseline non-missing value across both studies (for PA-CL-05A only Stage 1 values are considered). (Sponsor table from 120-safety update report)

In the dose-ranging study, PA-CL-03A, mean changes from baseline in serum calcium levels were generally not significant among the PA21 groups. There was no clear dose-relationship for hyper/hypocalcemia.

iPTH: Mean iPTH values were high in both treatment groups at baseline. Changes in serum iPTH were quite variable among subjects in both treatment groups throughout the studies. There were no clinically relevant changes from baseline at Week 52 and no difference between treatment groups.

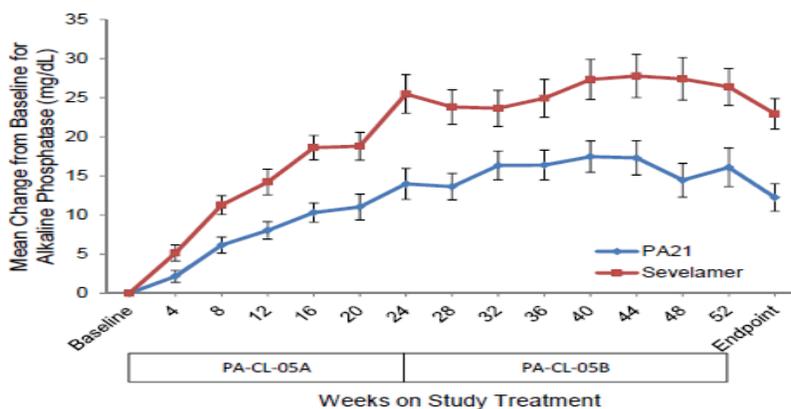
In the dose-ranging study, serum iPTH showed statistically significant decreases from baseline at Week 2 in the 4 higher-dose PA21 groups and the sevelamer group, and at Week 3 in the PA21 2000 mg/day, 2500 mg/day and the sevelamer groups. In the PA21 2500 mg/day group, mean decreases from baseline in serum iPTH remained statistically significant at Weeks 4, 5 and 6, and in the sevelamer group the mean decreases were significant at Weeks 5 and 7. Mean serum phosphorus and iPTH levels returned towards baseline at the end of follow up.

Bone related enzyme: Alkaline phosphatase increased significantly from baseline in both treatment groups and the increases in the sevelamer group were significantly higher than the PA21 group. Similar changes were also observed in all subgroups but were less pronounced in

Velphoro (b) (4)

the “Other” race subgroup. These changes were driven by changes in bone-specific alkaline phosphatase. These data are shown in the following figure.

Figure 9: Changes in mean serum alkaline phosphatase from baseline at each time point in Studies PA-CL-05A/05B



(Sponsor figure from 120-safety update report)

Iron status: In the pivotal study, mean changes from baseline in serum ferritin and TSAT were significantly greater 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 but no further increase was observed. There was no evidence of accumulation of iron during one year of treatment with PA21.

Mean transferrin levels decreased slightly from baseline in the PA21 group, and mean values increased slightly in the sevelamer group. The increase in serum iron levels from baseline was not meaningful. No clinically meaningful changes in hemoglobin levels were observed in either treatment group as discussed in the hematology section.

The majority of subjects with baseline serum ferritin values that were $>2 \times \text{ULN}$ had values that remained above the ULN during the studies. Shifts to higher serum ferritin in a higher proportion of subjects in the PA21 group were seen during the first 24 weeks of treatment, but differences between treatment groups were less evident in Study PA-CL-05B. Increases from baseline in serum ferritin were higher in the US subjects, followed by EU subjects and least in the ROW subjects. In addition, HD subjects had higher increases in serum ferritin compared to PD subjects. These serum ferritin data are most likely related to the pattern of IV iron use in these subgroups, where the proportion of US subjects and HD subjects receiving concomitant IV iron was the highest compared to the other subgroups. Other iron parameter changes in the subgroups were generally consistent with the overall treatment groups. Summary statistics for iron parameter values and changes from baseline at key time points are shown in the following table. In the dose-ranging study, a similar trend in iron parameters was observed but was less pronounced when compared to the pivotal study (data not shown here).

Velphoro (b) (4)

Table 53: Summary of iron parameters in Studies PA-CL-05A/05B

Parameter Time Point	(PA-CL-05A/PA-CL-05B) (SS)				(PA-CL-05A and PA-CL-05B) (Completers)			
	PA21 (N=707)		Sevelamer (N=348)		PA21 (N=322)		Sevelamer (N=227)	
	Actual	Change from Baseline	Actual	Change from Baseline	Actual	Change from Baseline	Actual	Change from Baseline
Ferritin (ng/mL)								
Baseline ⁽¹⁾								
n	707	—	348	—	322	—	227	—
Mean (SD)	666.6 (439.55)	—	714.5 (521.89)	—	621.5 (423.19)	—	710.1 (461.14)	—
Median	603.9	—	650.9	—	574.8	—	680.0	—
Min/max	9.8/3,043.2	—	9.3/4,742.8	—	9.8/2,115.7	—	9.3/2,186.0	—
Week 24								
n	512	512	287	287	310	310	221	221
Mean (SD)	780.7 (492.80)	135.0 ⁺⁺ (340.33)	753.8 (494.81)	36.3 ⁺ (384.00)	722.0* (458.97)	116.7* (316.99)	763.1 (475.40)	51.0* (344.35)
Median	722.0	108.0	726.7	18.0	660.7	95.5	743.0	32.0
Min/max	8.9/2,975.5	-1,613.7/2,654.2	4.0/3,061.4	-3,320.0/1,690.0	8.9/2,061.9	-1,613.7/1,174.9	9.8/2,917.0	-1,234.0/1,690.0
Week 52								
n	321	321	229	229	319	319	227	227
Mean (SD)	776.7 (473.82)	152.4 ⁺ (354.11)	776.7 (518.03)	70.9* (394.41)	776.1 (475.25)	152.7* (353.69)	781.6 (517.31)	71.5* (396.09)
Median	757.0	145.0	766.4	54.0	753.0	145.0	768.0	56.5
Min/max	15.6/2,468.0	-1,605.3/1,370.0	12.9/3,514.9	-1,302.0/2,397.9	15.6/2,468.0	1,605.3/1,370.0	12.9/3,514.9	-1,302.0/2,397.9
Combined endpoint ⁽²⁾								
n	685	685	344	344	322	322	227	227
Mean (SD)	810.7 (510.69)	145.0 ⁺⁺ (378.16)	722.8 (532.66)	61.0 ⁺⁺ (409.91)	775.2 (477.37)	153.7* (358.09)	782.5 (517.20)	395.56* (395.56)
Median	768.0	105.5	735.7	45.4	751.2	144.8	769.0	56.5
Min/max	11.1/3,279.0	-2,082.8/2,654.2	7.6/3,514.9	-3,479.8/2,397.9	15.6/2,468.0	1,605.3/1,370.0	12.9/3,514.9	-1,302.0/2,397.9
Iron (mcg/dL)								
Baseline ⁽¹⁾								
n	707	—	348	—	322	—	227	—
Mean (SD)	64.7 (31.12)	—	67.1 (29.06)	—	65.3 (25.61)	—	66.5 (25.61)	—
Median	58.0	—	63.0	—	59.9	—	62.0	—
Min/max	10.1/250.0	—	11.2/239.0	—	10.1/207.8	—	11.2/157.5	—
Week 24								
n	511	511	287	287	309	309	221	221
Mean (SD)	75.4 (32.15)	10.6 ⁺ (36.96)	72.1 (35.25)	4.4 (38.54)	75.0 (30.62)	9.9 ⁺ (34.85)	73.3 (34.12)	7.0* (34.97)
Median	69.0	11.0	64.8	2.0	69.0	10.6	66.0	3.4
Min/max	20.0/268.7	-162.6/235.2	17.3/217.0	-201.0/183.0	20.0/196.0	-162.6/128.0	17.3/217.0	-70.9/183.0
Week 52								
n	321	321	229	229	319	319	227	227
Mean (SD)	73.1 (33.66)	7.8 ⁺ (39.46)	73.7 (33.59)	7.1 ⁺ (32.75)	73.1 (33.68)	7.7 ⁺ (39.50)	73.6 (33.71)	7.1 ⁺ (32.88)
Median	65.4	7.0	67.0	3.0	65.4	7.00	66.5	3.0
Min/max	17.3/217.0	-116.0/177.0	21.0/198.0	-71.5/149.0	17.3/217.0	-116.0/177.0	21/198.0	-71.5/149.0
Combined endpoint ⁽²⁾								
n	685	685	344	344	322	322	227	227
Mean (SD)	73.8 (38.99)	9.3 ⁺ (43.99)	71.9 (35.98)	4.7 ⁺ (37.41)	73.3 (33.85)	8.0* (39.85)	74.1 (34.04)	7.7* (33.57)
Median	66.0	6.1	64.5	2.0	65.2	6.9	67.0	3.4
Min/max	11.7/518.0	-121.0/482.0	15.6/293.0	-201.0/149.0	17.3/217.0	-116.0/177.0	21/198	-71.5/149
Transferrin Saturation (mcg/dL)								
Baseline ⁽¹⁾								
n	707	—	348	—	322	—	227	—
Mean (SD)	2,288.8 (481.69)	—	2,274.9 (456.59)	—	2,314.5 (482.83)	—	2,291.4 (462.16)	—
Median	2,218.8	—	2,238.2	—	2,296.2	—	2,244.6	—
Min/max	967.5/5,200.0	—	1,290.0/4,500.0	—	967.5/5,200.0	—	1,290.0/4,500.0	—
Week 24								
n	510	510	287	287	308	308	221	221
Mean (SD)	2,238.7 (432.61)	-53.6 ⁺⁺ (295.74)	2,472.9 (496.76)	189.3 ⁺⁺ (311.06)	2,248.1 (428.31)	-63.7 ⁺⁺ (306.46)	2,463.8 (481.41)	176.6 ⁺⁺ (310.89)
Median	2,186.6	-51.6	2,400.0	200.0	2,218.8	-77.4	2,400.0	200.0
Min/max	967.5/4,300.0	-1,200.0/800.0	1,431.9/4,300.0	-1,900.0/1,400.0	967.5/4,300.0	-1,200.0/800.0	1,431.9/4,300.0	-1,900.0/1,400.0
Week 52								
n	321	321	229	229	319	319	227	227
Mean (SD)	2,196.5 (404.54)	-121.6 ⁺⁺ (324.47)	2,450.3 (460.63)	150.9 ⁺⁺ (341.76)	2,192.7 (402.90)	-121.3 ⁺⁺ (325.44)	2,445.4 (457.33)	154.0 ⁺⁺ (341.15)
Median	2,100.0	-100.0	2,400.0	154.8	2,100.0	-100.0	2,400.0	154.8
Min/max	967.5/4,000.0	-1,600.0/900.0	1,600.0/3,900.0	-1,800.0/1,032.0	967.5/4,000.0	-1,600.0/900.0	1,600.0/3,900.0	-1,800.0/1,032.0
Combined endpoint ⁽²⁾								
n	685	685	344	344	322	322	227	227
Mean (SD)	2,202.7 (431.24)	-87.7 ⁺⁺ (322.21)	2,435.0 (475.89)	157.9 ⁺⁺ (332.38)	2,194.5 (402.96)	-120.0 ⁺⁺ (323.52)	2,445.7 (457.72)	154.3 ⁺⁺ (341.15)
Median	2,100.0	-64.5	2,400.0	167.7	2,100.0	-100.0	2,400.0	154.8
Min/max	967.5/4,166.7	-2,200.0/1,000.0	900.0/4,000.0	-1,800.0/1,100.0	967.5/4,000.0	-1,600.0/900.0	1,600.0/3,900.0	-1,800.0/1,032.0
Transferrin Saturation (%)								
Baseline ⁽¹⁾								
n	706	—	348	—	321	—	227	—
Mean (SD)	26.6 (13.70)	—	27.8 (13.78)	—	26.5 (13.28)	—	27.4 (12.25)	—
Median	24.0	—	25.5	—	24.0	—	25.0	—
Min/max	2.0/95.0	—	3.0/117.0	—	2.0/95.0	—	3.0/90.0	—
Week 24								
n	509	509	287	287	307	307	221	221
Mean (SD)	31.4 (14.09)	4.9 ⁺⁺ (16.12)	27.5 (15.29)	-0.6 ⁺⁺ (17.30)	31.2 (13.91)	4.6 ⁺⁺ (15.76)	28.1 (15.06)	0.7 ⁺ (15.24)
Median	29.0	5.0	24.0	-1.0	29.0	5.0	25.0	-1.0
Min/max	7.0/101.0	-66.0/72.0	4.0/101.0	-98.0/74.0	7.0/101.0	-66.0/71.0	4.0/101.0	-44.0/74.0
Week 52								
n	320	320	229	229	318	318	227	227
Mean (SD)	31.0 (15.17)	4.6 ⁺ (17.93)	28.4 (14.97)	1.0 (14.72)	31.0 (15.19)	4.5 ⁺ (17.97)	28.4 (15.02)	1.0 (14.78)
Median	28.0	4.0	26.0	-1.0	28.0	4.0	26.6	-1.0
Min/max	6.0/95.0	-60.0/78.0	7.0/109.0	-38.0/87.0	6.0/95.0	-60.0/78.0	7.0/109.0	-38.0/87.0
Combined endpoint ⁽²⁾								
n	684	684	344	344	321	321	227	227
Mean (SD)	31.2 (16.66)	4.7 ⁺ (18.81)	27.6 (14.90)	-0.2 ⁺ (16.62)	31.1 (15.25)	4.7 ⁺ (18.10)	28.6 (15.09)	1.2 (14.96)
Median	28.0	4.0	25.0	-1.0	28.0	4.0	26.0	-1.0
Min/max	4.0/194.0	-60.0/180.0	6.0/109.0	-98.0/87.0	6.0/95.0	-60.0/78.0	7.0/109.0	-38.8/87.0

1. Baseline was defined as the last non-missing value prior to or on the date of the first PA-CL-05A study drug intake.
2. Combined endpoint was defined as the last post-baseline non-missing value across both studies (for PA-CL-05A only Stage 1 values are considered). (Sponsor table from 120-safety update report)

Vitamins: There were no clinically meaningful changes from baseline in Vitamin A, 1,25 hydroxy Vitamin D, Vitamin E, and Vitamin K and there were no significant differences between treatment groups in both the pivotal study and the dose-ranging study.

Bone related markers: Bone markers including bone-specific alkaline phosphatase, osteocalcin, tartrate-resistant acid phosphatase, carboxyl terminal crosslinking telopeptide, and fibroblast

Velphoro (b) (4)

growth factor- 23 were evaluated. Significant increases from baseline in bone-specific alkaline phosphatase were observed in both treatment groups during treatment but values returned to near baseline at the end of the studies. Increases were generally greater in the sevelamer group. Mean values were greater for female subjects at baseline, and mean changes during treatment were greater for female subjects than male subjects in both treatment groups.

Osteocalcin increased slightly during the first 24 weeks in both groups; increases were larger during the subsequent weeks. Although increases were larger in the sevelamer group, there was no significant difference between two groups.

Tartrate resistant acid phosphatase values were significantly decreased from baseline throughout the studies in both groups. There was no significant difference between groups.

Carboxyl Terminal Crosslinking Telopeptide (CTX) increased during the first 24 weeks. The increases were comparable between groups. CTX values leveled off during PA-CL-05B and had returned to near baseline at Week 52.

FGF-23 was significantly decreased from baseline during PA-CL-05A, but differences between treatment groups were not significant. No relationship between other bone markers and FGF-23.

In the dose ranging study, mean changes from baseline to Week 7 and the end of follow up in beta-CTX and osteocalcin were not statistically significant in any treatment group. Mean increases from baseline to Week 7 in tartrate-resistant acid phosphatase-5b were statistically significant in the PA21 1000 mg/day, 1500 mg/day and sevelamer groups. At the end of follow up, these increases from baseline were statistically significant in the PA21 250 mg/day, 1000 mg/day, 1500 mg/day and sevelamer groups. Increases from baseline in bone-specific alkaline phosphatase were statistically significant at Week 7 in the 4 higher-dose PA21 treatment groups and in the sevelamer group. At the end of follow up, mean increases from baseline were statistically significant in the PA21 250 mg/day and the sevelamer group.

In other studies, there were no notable changes in serum or urinary phosphorus concentrations between active treatment groups and the placebo group in healthy volunteers. This may be because normal homeostatic mechanisms keep these levels within normal limits in these healthy subjects. There were no clinically meaningful changes in clinical chemistry parameters in these studies.

Reviewer comments: Although PA21 was minimally absorbed in clinical pharmacology studies, increases in ferritin and TSAT, and decreases in transferrin were observed in the PA21 treatment group compared to both baseline values and relative to the sevelamer treatment arm, especially in Study PA-CL-05A. These changes were maintained without further significant increase in the long-term study (05B). Hence, this should not be a major safety concern, however patients will need to be carefully monitored, especially those who are on iron replacement therapy.

Although the incidence rate of anemia in PA21 group was lower than in sevelamer group (5.2% vs. 10.1%), overall, there was no significant difference in hemoglobin levels in the PA21 group

Velphoro (b) (4)

compared to either baseline values or the sevelamer group. As more than 80% of patients in both groups had received IV iron supplements and ESA, it is difficult to determine the effect of PA21 on hemoglobin from this development program.

There were no other obvious drug-related abnormal findings in laboratory examinations. The changes in laboratory parameters among the different study groups were similar. There was no laboratory parameter related AE report or drug discontinuation. Because of abnormal baseline values and different group sizes, many of the observed differences are not clinically relevant.

7.4.3 Vital Signs

There were changes from baseline in blood pressure, heart rate, and body temperature. However, these changes were likely related to the underlying disease and not to study treatments. There were no notable differences between PA21 and the sevelamer control.

Hypertension and hypotension were among the most commonly reported TEAEs, with a similar proportion of subjects reporting these events in both treatment groups. No subjects were withdrawn from treatment for hypertension. One subject treated with sevelamer was withdrawn for hypotension in the pivotal study. Hence, it does not appear that PA21 has a significant impact on the efficacy of anti-hypertensive drugs when compared to sevelamer.

The proportion of subjects with a finding on physical examination at baseline was similar to the proportion of subjects with a finding on physical examination at the end of study.

7.4.4 Electrocardiograms (ECGs)

In the pivotal study, mean changes in PQ, QRS, QT, and RR intervals and heart rate from baseline were not statistically significant in either the PA21 or sevelamer treatment groups, and no differences were observed between treatment groups.

In the dose-ranging study, Study PA-CL-03A, mean changes in PQ, QRS, QT and RR intervals as well as heart rate did not differ significantly between the 2 treatment groups. Fluctuations in the QTc interval or calculated QTcB and QTcF values were seen across all 5 PA21 dose groups as well as in the sevelamer group. The number of subjects showing a longer QTc interval between baseline and Week 4 in any PA21 group was generally similar to, or lower than, the number in the sevelamer group. There was no indication of any dose response with PA21.

Reviewer comments: ESRD patients frequently exhibit clinical abnormalities in vital signs and ECGs as a consequence of electrolyte and metabolic disturbances. 7.4.5 Special Safety Studies/Clinical Trials

7.4.6 Immunogenicity

PA21 is a small molecule and is not expected to have immunogenic potential. Neither the non-clinical studies nor the clinical studies suggest an increase in adverse events of potential immunogenic etiology.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose-dependency for AEs was evaluated by calculating AE rates for each dosage. In the pivotal trial, dose was titrated based on the serum level of phosphorus, thus making it difficult to use data from this trial to understand the dose dependency for adverse events. In the dose-ranging studies, other than dose-dependent hypophosphatemia, no obvious dose-related AEs were observed among the five dose groups: 1.25 g/day (250 mg PA21 iron), 5 g/day (500 mg PA21 iron), 7.5 g/day (1500 mg PA21 iron), 10 g/day (2000 mg PA21 iron) and 12.5 g/day (2500 mg PA21 iron) administered for 6 weeks.

In PA-CL-03A, the dropout rate was similar in the two groups (21.1% of subjects (27/128) in the pooled PA21 group and 23.1% (6/26) in the sevelamer (HCl) group). Hypophosphatemia was the most frequent cause of discontinuation, occurring in 10.2% (13/128) of the pooled PA21 group and 7.7% of the sevelamer (HCl) group. Within the PA21 group there was a dose-response relationship for hypophosphatemia with more subjects withdrawing due to hypophosphatemia in the 2 highest dose groups (6 subjects (22.2%) in the 2000 mg/day group and 4 subjects (16.7%) in the PA21 2500 mg/day group) when compared to the lower dose groups. Data are summarized in table 54 below.

Table 54: Summary of AEs leading to withdrawal in Study PA-CL-03A

System Organ Class Preferred Term	PA21					Total PA21 (N=128) n (%)	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 (%)		
Subjects reporting any TEAE	5 (19.2%)	5 (19.2%)	4 (16.0%)	8 (29.6%)	5 (20.8%)	27 (21.1%)	6 (23.1%)
Cardiac Disorders	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Cardiac arrest	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Gastrointestinal Disorders	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	3 (11.5%)
Diarrhoea	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	2 (7.7%)
Pancreatitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
Infections and Infestations	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	1 (0.8%)	0 (0.0%)
Arteriovenous graft site abscess	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	1 (0.8%)	0 (0.0%)
Staphylococcal sepsis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	1 (0.8%)	0 (0.0%)
Injury, Poisoning and Procedural Complications	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (4.2%)	2 (1.6%)	0 (0.0%)
Arteriovenous graft site haematoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	1 (0.8%)	0 (0.0%)
Rib fracture	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Metabolism and Nutrition Disorders	5 (19.2%)	4 (15.4%)	3 (12.0%)	7 (25.9%)	4 (16%)	23 (18.0%)	3 (11.5%)
Hypercalcaemia	2 (7.7%)	2 (7.7%)	0 (0.0%)	1 (3.7%)	1 (4.2%)	6 (4.7%)	0 (0.0%)
Hyperphosphataemia	2 (7.7)	2 (7.7%)	0 (0.0%)	1 (3.7%)	0 (0.0%)	5 (3.9%)	1 (3.8%)
Hypoglycaemia	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Hypophosphataemia	1 (3.8%)	0 (0.0%)	2 (8.0%)	6 (22.2%)	4 (16.7%)	13 (10.2%)	2 (7.7%)

Note: the list doses in above figure were in the total mass. Its tablet is standardized to contain 500 mg iron (as PA21 drug substance (DS)) with a total nominal mass of 2.5g. Doses of 1.25, 5.0, 7.5, 10 and 12.5g represent 250, 1000, 1500, 2000, and 2500 mg iron of PA21. (Sponsor table from Study PA-CL-03A study report)

With regard to drug-related TEAEs, as expected, the proportion of subjects with TEAEs of hypophosphatemia was highest in the 2 higher-dose PA21 groups: 2000 mg/day and 2500 mg/day. Conversely, treatment-related hyperphosphatemia was reported only in the PA21 250 mg/day group, the PA21 1000 mg/day and sevelamer (HCl) groups. The proportion of subjects with treatment-related GI events was not closely correlated with PA21 dose. For further details, see Section 7.4.1.

7.5.2 Time Dependency for Adverse Events

Incidence rates of GI AEs, especially product-related diarrhea, were highest early in the course of treatment (within four weeks). Other events likely associated with underlying disease and unrelated to study treatment were generally more evenly distributed. No other obvious time-dependent adverse event was observed with this product either in short-term or long-term studies. For further discussion of GI AEs, see Section 7.4.1.

7.5.3 Drug-Demographic Interactions

To evaluate the possible effect of demographic factors on the safety of PA21, subgroup analyses were performed in the pivotal trial by gender, age, race, ethnicity and region (US, EU and ROW) for safety parameters including AE incidence, laboratory parameters (hematology and clinical chemistry) evaluations, and vital signs. In general, there was no suggestion of a drug-demographic interaction. Older patients (> 65 years of age) reported more adverse events, likely reflecting greater underlying disease burden. These data are discussed briefly below:

1. AEs by Region: The incidence of treatment-related AEs was highest in the EU versus the US or ROW (46.2%, 36.3% and 36.3%, respectively). This pattern was also seen in the PA21 group (EU 53.5%; US 45.4%; ROW 38.5%); the pattern was somewhat different in the sevelamer group (EU 31.2%; US 17.6%; ROW 31.7%).

When compared to the EU and ROW, US subjects tended to report more severe AEs (13.1% and 11.4% versus 21.1%, respectively). This pattern was observed in both the PA21 group and the sevelamer group. Subjects in the US reported the most serious AEs (34.7%) followed by subjects in the EU (26.3%) and ROW (16.7%). Again, this pattern was observed in both the PA21 group and the sevelamer group. In all regions, the number of subjects reporting serious AEs was similar across the treatment groups.

More EU subjects withdrew due to their TEAEs (24.2%) than subjects from the US (17.0%) and the ROW (13.1%). This pattern was observed in the PA21 group and the sevelamer group. In all 3 regions, TEAEs leading to withdrawal were higher in the PA21 treatment subjects than in the sevelamer treated subjects.

2. AEs by gender: Over 52 weeks of study treatment, the incidence of subjects with any AE, severe AEs, serious AEs, deaths and/or withdrawals due to AEs were generally similar between males and females. Within the PA21 group, the incidence of these AEs was similar between males and females. More PA21 subjects reported treatment-related TEAEs versus sevelamer subjects (males: 47.0% versus 20.1%, respectively; females: 43.1% versus 32.6%, respectively).

3. AEs by Age: Over 52 weeks of study treatment, the incidence of treatment related TEAEs (36.3% and 43.9%), severe TEAEs (14.8% and 20.8%), serious TEAEs (25.7% and 32.3%), deaths (1.7% and 7.3%) and TEAEs leading to withdrawal (15.4% and 22.4%) were all higher in the older age group (> 65 years old). This pattern was seen in both the PA21 and sevelamer groups. In both age groups, drug related TEAEs and TEAEs leading to withdrawal occurred at a higher incidence in the PA21 group versus the sevelamer group.

4. AEs by Race: Over 52 weeks of study treatment, the incidence of treatment-related TEAEs, severe TEAEs and serious TEAEs was comparable across the races examined.

7.5.4 Drug-Disease Interactions

Adverse events were analyzed in patients with different primary diseases (diabetes, hypertension and others), dialysis modality (HD versus PD), dialysis duration, etc. AEs reported in association with PA21 or sevelamer for patients were similar across these conditions/settings. The limited number of PD patients makes it difficult to compare AEs on HD versus PD.

7.5.5 Drug-Drug Interactions

In the pivotal study, PA21 did not affect the lipid lowering effects of HMG-CoA reductase inhibitors. The results of *in vitro* and *in vivo* interaction studies are discussed in section 4.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

In the one year study, 1 of 707 patients (0.1%) in the PA21 group and 2 of 348 patients (0.6%) in the sevelamer group reported lung squamous cell carcinoma. No other malignant tumor was reported.

7.6.2 Human Reproduction and Pregnancy Data

There is no information on drug exposure in pregnant or lactating woman.

7.6.3 Pediatrics and Assessment of Effects on Growth

No pediatric studies have been conducted.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose: There were no reports of overdose with PA21. As absorption of PA21 is low, the risk of systemic iron toxicity is expected to be very low.

Abuse potential and withdrawal symptoms: Not applicable given the drug's mechanism of action/therapeutic class.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

There is no postmarketing experience with this product.

9 Appendices

9.1 Literature Review/References

I searched Pubmed using the key words: “phosphate binders”, “iron”, “end stage renal disease” and “dialysis” with “adverse events”. No additional safety concerns associated with iron containing phosphate binders were identified, beyond those described above.

9.2 Labeling Recommendations

Labeling recommendations will be discussed separately.

9.3 Advisory Committee Meeting

No Advisory Committee Meeting was held.

9.4 Additional clinical study information

9.4.1 Study PA-CL-03A: Demographic information and patient disposition

In this phase 2 dose range finding study, in general, the demographic characteristics of the groups were well matched. There were no notable differences among the groups regarding age, height and race, although the majority of the subjects were male and the proportion of male subjects was higher in the PA21 5.0 g/day group as compared to the other groups. The majority of subjects included in the study were from Eastern European countries, and this is reflected in the high percentage of white subjects. Data are summarized in the following table 55. There were no significant differences among the PA21 groups, and between the PA21 and the sevelamer group regarding the factors that may potentially affect the drug efficacy including the underlying causes and duration of CKD, medical history, prior medications, and concomitant medications.

Velphoro (b) (4)

Table 55: Demographic characteristics in Study PA-CL-03A

Demographic Variable	PA21						Sevelamer (HCl) (N=24) 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=25) n (%)	12.5 g/Day (N=24) n (%)	Total PA21 (N=126) n (%)	
Age (yrs)							
Mean	60.1	59.7	61.9	60.8	59.3	60.4	61.6
SD	12.29	13.80	13.71	13.21	12.32	12.91	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
Height (cm)							
Mean	169.5	169.3	168.6	166.8	170.0	168.8	166.4
SD	10.93	8.97	11.65	7.29	9.45	9.69	9.70
Median	171.0	169.0	172.0	167.0	170.5	170.0	166.0
Range	152-193	153-182	139-188	152-178	152-185	139-193	151-185
Sex							
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%)
Race							
White	24 (92.3%)	26 (100.0%)	24 (96.0%)	22 (88.0%)	24 (100.0%)	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%)

Note: the list doses were in the total mass. Its tablet is standardized to contain 500 mg iron (as PA21 drug substance (DS)) with a total nominal mass of 2.5g. (Sponsor table Study PA-CL-03A study report)

The majority of the subjects were from Eastern Europe. Overall, 417 subjects were screened, 154 subjects were randomized. Of the 154 randomized subjects, 103 subjects (66.9%) completed the study and 51 subjects (33.1%) were withdrawn from the study. Patient disposition is summarized in the following table 56.

Table 56: Subject disposition in Study PA-CL-03A

Reason	PA21					Sevelamer (HCl) (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 (%)		
Subjects randomised	26 (100.0%)	26 (100.0%)	25 (100.0%)	27 (100.0%)	24 (100.0%)	26 (100.0%)	154 (100.0%)
Subjects randomised but not treated	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subjects treated	26 (100.0%)	26 (100.0%)	25 (100.0%)	27 (100.0%)	24 (100.0%)	26 (100.0%)	154 (100.0%)
Subjects who withdrew	8 (30.8%)	9 (34.6%)	5 (20.0%)	12 (44.4%)	9 (37.5%)	8 (30.8%)	51 (33.1%)
Subjects completed ⁽¹⁾	18 (69.2%)	17 (65.4%)	20 (80.0%)	15 (55.6%)	15 (62.5%)	18 (69.2%)	103 (66.9%)

1. Number of subjects completed the study based on the end of study CRF.

Note: the list doses were in the total mass which equal 250 mg/day to 2500 mg/day PA 21(1.25 g/day to 12.5 g/day)
(Sponsor table from Study PA-CL-03A study report)

The proportions of withdrawn subjects were highest in the PA21 10.0 g/day and 12.5 g/day groups, and lowest in the PA21 7.5 g/day group. The higher withdrawal rates in the two highest PA21 dose groups were mainly due to higher incidences of hypophosphatemia (25.9% for the 10.0 g/day group and 25.0% for the 12.5 g/day group, which was based on the pre-defined withdrawal criterion). Reasons for patient withdrawal are summarized in the following table 57.

Velphoro (b) (4)

Table 57: Summary of primary reasons for study discontinuation in Study PA-CL-03A

Reason	PA21					Total PA21 (N=128) n (%)	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 (%)		
	Prohibited medication	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		
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%)

Note: the list doses were in the total mass which equal 250 mg/day to 2500 mg/day PA 21(1.25 g/day to 12.5 g/day)
(Sponsor table from Study PA-CL-03A study report)

Major difference between the PA-CL-03A and the pivotal study (Study PA-CL-05A):

1. PA-CL-03A included only subjects undergoing HD; 05A included both PD and HD in Stage 1.
2. Study PA-CL-03A used a threshold for hyperphosphatemia based on the upper limit of the KDOQI target range (serum phosphorus >5.5 mg/dL), 05A used slightly more stringent criteria (≥ 6.0 mg/dL).
3. Study PA-CL-03A excluded uncontrolled hyperphosphatemia or known history of non-responsiveness to phosphate binders, but 05A did not.
4. Study PA-CL-03A excluded subjects treated with sevelamer (either as Renagel or Renvela) within 3 months prior to screening, 05A allowed these treatments up to the time of the screening visit.
5. PA-CL-03A excluded subjects with iron deficiency anemia. Patients in both studies, however, had the similar Hb levels.
6. Unlike PA-CL-03A, Study PA-CL-05A permitted treatment with intravenous iron.
7. The exclusion criterion for iPTH in Study PA-CL-03A was iPTH >600 ng/L and in 05A was increased to 800 ng/L.
8. Demographic features in both studies were roughly comparable, with the exception of region and race.
9. Previous phosphate binders: In PA-CL-03A, calcium based phosphate binders were used by 87.3% (110/126) and 91.7% (22/24) of subjects in the pooled PA21 group and sevelamer group, respectively. Subjects with prior exposure to lanthanum at any time in their life were excluded from entry. Treatment with sevelamer (as Renagel or Renvela) within 3 months before screening was also excluded. In Stage 1 of PA-CL-05A, calcium-based phosphate binders were used by 72.5% (334/461) and 72.3% (162/224) of subjects in the PA21 and sevelamer group, respectively. Lanthanum was used by 5.0% (23/461) and 3.6% (8/224) in the PA21 and sevelamer groups, respectively.

9.4.2 Study PA-CL-05B: Demographic information and patient disposition

Study PA-CL-05B study was conducted in 143 of 174 centers that conducted the PA-CL-05A study and these centers enrolled 659 subjects. Of the 659 subjects enrolled in PA-CL-05B, 549 (83.3%) completed the study and 110 (16.7%) prematurely discontinued (1 Study PA-CL-05B). The demographics and characteristics of this study were collected at entry to Study PA-CL-05A. Primary demographic characteristics are summarized in the following table 58. The mean age of subjects was 55.4 years (range 21 to 88 years), and the mean weight was 82.3 kg (range 40.0 to 170.0 kg). The majority of subjects were male (58.8%) and White (79.8%). There was a good representation of the Black/African American race (16.8%) and subjects of Hispanic or Latino ethnicity (11.0%). The 2 treatment groups were generally comparable except there was an imbalance in the sex of the 2 groups, with a greater proportion of female subjects in the PA21 group (43.4%) than in the sevelamer group (37.9%).

Table 58: Summary of demography in Study PA-CL-05B

Demographic Variables	PA21 (N=387)	Sevelamer (N=261)	Total (N=648)
Age (years)			
n	387	261	648
Mean (SD)	55.3 (13.27)	55.6 (14.51)	55.4 (13.77)
Median	56.0	56.0	56.0
Min/Max	22.0/88.0	21.0/88.0	21.0/88.0
Sex, n (%)			
Female	168 (43.4%)	99 (37.9%)	267 (41.2%)
Male	219 (56.6%)	162 (62.1%)	381 (58.8%)
Race, n (%)			
White	320 (82.7%)	197 (75.5%)	517 (79.8%)
Black/African American	52 (13.4%)	57 (21.8%)	109 (16.8%)
Asian	5 (1.3%)	6 (2.3%)	11 (1.7%)
American Indian/Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)
Native Hawaiian/Other Pacific Islander	5 (1.3%)	0 (0.0%)	5 (0.8%)
Other	5 (1.3%)	1 (0.4%)	6 (0.9%)
Ethnicity, n (%)			
Hispanic or Latino	42 (10.9%)	29 (11.1%)	71 (11.0%)
Not Hispanic or Latino	345 (89.1%)	232 (88.9%)	577 (89.0%)
Weight (kg)			
n	385	258	643
Mean (SD)	81.9 (19.74)	83.0 (20.43)	82.3 (20.01)
Median	79.7	79.7	79.7
Min/Max	40.0/170.0	44.9/163.7	40.0/170.0

(Sponsor table from the 120-day safety update study report)

The most common reasons for ESRD overall and in the individual treatment groups were hypertension, glomerulonephritis, and diabetic nephropathy. There were fewer subjects with hypertension in the PA21 treatment group (76 subjects (19.6%)) than in the sevelamer treatment group (71 subjects (27.2%)), and slightly more with polycystic kidney disease (10.9% and 6.1%, respectively) but for the other causes of ESRD, the 2 groups were well matched. Other factors

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were similar to the Study PA-CL-05A. Data are summarized in the following table 59. The other relevant medical history, prior medications, and the concomitant medications were similar between the two groups and were also similar to the Study PA-CL-05A.

Table 59: Summary of ESRD in Study PA-CL-05 B

Parameter	PA21 (N=387)	Sevelamer (N=261)	Total (N=648)
Reason for ESRD, n (%)			
Hypertension	76 (19.6%)	71 (27.2%)	147 (22.7%)
Glomerulonephritis	97 (25.1%)	66 (25.3%)	163 (25.2%)
Diabetic nephropathy	95 (24.5%)	68 (26.1%)	163 (25.2%)
Pyelonephritis	15 (3.9%)	9 (3.4%)	24 (3.7%)
Polycystic kidney disease	42 (10.9%)	16 (6.1%)	58 (9.0%)
Interstitial nephritis	14 (3.6%)	8 (3.1%)	22 (3.4%)
Hydronephrosis	6 (1.6%)	3 (1.1%)	9 (1.4%)
Congenital	8 (2.1%)	5 (1.9%)	13 (2.0%)
Other	34 (8.8%)	15 (5.7%)	49 (7.6%)
Time from start of ESRD (months)⁽¹⁾			
n	386	261	647
Mean (SD)	70.1 (62.16)	75.1 (70.35)	72.1 (65.58)
Median	50.4	53.9	51.1
Min/Max	9.6/388.9	7.0/403.4	7.0/403.4
Dialysis, n (%)			
HD	345 (89.1%)	244 (93.5%)	589 (90.9%)
PD	42 (10.9%)	17 (6.5%)	59 (9.1%)
Time from the first dialysis (months)⁽²⁾			
n	387	261	648
Mean (SD)	56.3 (47.85)	61.5 (57.56)	58.4 (52.00)
Median	39.4	44.8	41.6
Min/Max	7.7/295.0	1.1/403.4	1.1/403.4

1. Time from start of ESRD is the difference between the date of Visit 1 (Week 0) and the date of ESRD diagnosis.
 2. Time from start of first dialysis is the difference between the date of Visit 1 (Week 0) and the date of first dialysis.
- (Sponsor table from the 120-day safety update study report)

The patient disposition in PA-CL-05B is summarized in the following table 60. In the PA21 group, 322 (82.4%) completed the study and 69 (17.6%) prematurely discontinued. The primary reasons for premature discontinuation of PA21-treated subjects were TEAEs other than phosphorus or calcium level TEAEs (24.6% of withdrawals), hyperphosphatemia (17.4%), renal transplant (15.9%) and withdrawn consent (13.0%). The percentage withdrawn for hyperphosphatemia was similar for the 2 groups, but higher proportion of the withdrawals in PA21-treated subjects was for AEs other than phosphorus or calcium TEAEs (24.6% PA21 versus 9.8% sevelamer).

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Table 60: Subject disposition in Study PA-CL-05B

Parameter	All Randomised Subjects (PA-CL-05A/PA-CL-05B)			Enrolled Subjects in PA-CL-05B		
	PA21 (N=710) n (%)	Sevelamer (N=349) n (%)	Total (N=1,059) n (%)	PA21 (N=391) n (%)	Sevelamer (N=268) n (%)	Total (N=659) n (%)
Treated in PA-CL-05B	391(55.1%)	267 (76.5%)	658 (62.1%)	391(100%)	267(99.6%)	658 (99.8%)
Completed PA-CL-05B	322 (45.4%)	227 (65.0%)	549 (51.8%)	322 (82.4%)	227 (84.7%)	549 (83.3%)
Withdrawn from PA-CL-05B	69 (9.7%)	40 (11.5%)	109 (10.3%)	69 (17.6%)	41 (15.3%)	110 (16.7%)
Withdrawn from PA-CL-05A or PA-CL-05B ⁽⁵⁾	342 (48.2%)	122 (35.0%)	464 (43.8%)	–	–	–
Reason for premature discontinuation of treatment (study withdrawal)⁽⁶⁾						
Death ⁽⁷⁾	16 (4.7%)	10 (8.2%)	26 (5.7%)	6 (8.7%)	5 (12.2%)	11 (10.0%)
Adverse event other than phosphorus or calcium levels	112 (33.2%)	24 (19.7%)	136 (29.6%)	17 (24.6%)	4 (9.8%)	21 (19.1%)
Pregnancy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Withdrew consent	41 (12.2%)	23 (18.9%)	64 (13.9%)	9 (13.0%)	8 (19.5%)	17 (15.5%)
Investigator decision	14 (4.2%)	6 (4.9%)	20 (4.4%)	6 (8.7%)	3 (7.3%)	9 (8.2%)
Hyperphosphataemia ⁽⁸⁾	24 (7.1%)	7 (5.7%)	31 (6.8%)	12 (17.4%)	7 (17.1%)	19 (17.3%)
Hypophosphataemia ⁽⁹⁾	4 (1.2%)	0 (0.0%)	4 (0.9%)	2 (2.9%)	0 (0.0%)	2 (1.8%)
Hypercalcaemia ⁽¹⁰⁾	2 (0.6%)	0 (0.0%)	2 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

5. The percentages of reasons for withdrawals were computed based on the total number of withdrawals.

6. Subjects not treated in PA-CL-05A are counted as withdrawn in this section of the table.

7. This represents only subjects whose reason for withdrawal was listed as death and the percentage represents the percentage of withdrawals. Other subjects in the study also had fatal TEAEs.

8. Hyperphosphatemia was defined per protocol as serum phosphorus >8.5 mg/dL despite appropriate dose adjustments.

9. Hypophosphatemia was defined per protocol as serum phosphorus <2.5 mg/dL despite appropriate dose adjustments.

10. Hypercalcemia was defined by protocol as serum calcium >11.0 mg/dL despite appropriate rescue interventions.

(Sponsor table from the 120-day safety update report)

9.4.3 Study PA1201: Summary of protocol, demographic information and patient disposition

Study PA 1201 was a Phase 2, parallel-group, randomized, double-blind, placebo-controlled, multicenter, dose-ranging study which enrolled 183 Japanese ESRD patients on stable, maintenance hemodialysis.

This study was conducted in 14 centers in Japan. The first patient was enrolled on January 11, 2012 and the last patient completed the study on July 3, 2012.

The objectives in this study were to investigate dose-response efficacy and safety, when orally administering PA21 at doses of 250, 500, 750 or 1000mg, 3 times daily immediately prior to meals for 6 weeks, in hemodialysis patients having hyperphosphatemia. The primary endpoint was defined as change from baseline in serum phosphate concentrations at final evaluation.

Secondary endpoints included the following:

- Serum calcium concentrations
- Serum calcium × phosphate product
- Serum intact-PTH concentrations

Safety endpoints:

- Adverse events
- Adverse drug reactions

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- Laboratory tests (hematological, blood chemistry, iron parameters, vitamins)
- Vital sign (blood pressure, pulse rate) and body weight
- Twelve-lead ECG

Inclusion criteria:

1. Having been receiving stable maintenance hemodialysis 3 times weekly, for 12 weeks or more
2. Not having changed their phosphate binder agent dose, for 4 weeks or more before their observation period start
3. Serum phosphate concentration is > 6.0 mg/dL, and serum phosphate concentration is ≤ 10.0 mg/dL
4. Not having changed, for 4 weeks or more before their observation period start, the dose of any vitamin D, vitamin D metabolite, calcium receptor agonist (calcimimetic) or osteoporosis drug
5. Dialysate calcium concentrations have not been changed, for 4 weeks or more before their observation period
6. Able to discontinue their current therapy for hyperphosphatemia for 3 weeks
7. Age 20 or older (at the time their consent is obtained)

Exclusion criteria

1. Serum calcium concentration is ≤ 7.5 mg/dL, or serum calcium concentration is > 11.0 mg/dL
2. iPTH concentration is > 800 pg/mL or > 500 pg/mL with poor control
3. Planning to have a parathyroidectomy (PTx) or percutaneous ethanol injection therapy (PEIT) during the study period, or PTx or PEIT is performed, 24 weeks or less before their observation period start
4. Having a history of hemochromatosis, or any other iron overload disorder, or patients whose serum ferritin is > 800 ng/mL or TSAT is $> 50\%$
5. Having the following clinically significant gastrointestinal disorders: an active peptic ulcer, Crohn's disease, ulcerative colitis, irritable bowel syndrome, an intestinal motility disorder (e.g. symptomatic gastroparesis (whether being treated or un-treated), a bowel obstruction, pronounced constipation, a pseudo-obstruction, megacolon or mechanical obstruction)
6. Having a history of a clinically significant digestive tract procedure (e.g. a gastric or intestinal resection)
7. Having a clinically significant hepatic disorder (e.g. patients with an ALT or AST of 100 U/L or more, or a total bilirubin of ≥ 3.0 mg/dL at their observation period start)
8. Having a history of a pronounced brain / cardiovascular disorder (e.g. myocardial infarct, unstable angina, cerebral infarct, cerebral hemorrhage)
9. Malignant tumors
10. Any patients living with HIV
11. Drink alcohol habitually, or have a previous history of alcoholism
12. A history of heightened drug sensitivity, or patients having an allergy to iron products
13. Female patients who are pregnant, nursing, or desire pregnancy during the study period, or who cannot strictly comply with a physician's contraception instructions
14. Patients having taken another investigational product, in the 12 weeks before their consent is obtained

Study design: This is a phase 2, randomized, double-blind, placebo-controlled, multicenter, dose-range-finding study conducted in Japanese patients. The study included a washout period and a

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treatment period. In the washout period, a period of 3 weeks was established for any phosphate binders that have been taken before study start.

In the treatment Period, placebo or PA21 at doses of 250, 500, 750, and 1000 mg were orally administered 3 times per 1 day, immediately prior to meals for 6 weeks. The number of patients in each group included PA21 at 750mg/day (N=39), 1500mg/day (N=35), 2250mg/day (N=33), or 3000mg/day (N=34), or placebo (N=37) for 6 weeks.

Demographic information is summarized in the following table 61. There were no notable differences among the treatment groups regarding age, gender, major medical history, dialysis prescriptions, and baseline parameters of calcium, phosphate and iPTH. In addition, the prior medications including the phosphate binders, concomitant medications, and patient compliance were also similar.

Table 61: Demographic information in Study PA1201

		Overall		PA21 3.75 g		PA21 7.5 g		PA21 11.25 g		PA21 15 g		Placebo		Fisher's exact test
		n	%	n	%	n	%	n	%	n	%	n	%	
N		178	---	39	---	35	---	33	---	34	---	37	---	---
Sex	Male	115	64.6	27	69.2	23	65.7	23	69.7	19	55.9	23	62.2	P=0.745
	Female	63	35.4	12	30.8	12	34.3	10	30.3	15	44.1	14	37.8	
Primary disease	Diabetic nephropathy	52	---	14	---	9	---	5	---	10	---	14	---	---
	Chronic glomerulonephritis	56	---	12	---	8	---	11	---	14	---	11	---	
	Nephrosclerosis	23	---	7	---	6	---	6	---	1	---	3	---	
	Polycystic kidney disease	10	---	2	---	2	---	2	---	1	---	3	---	
	Chronic pyelonephritis	1	---	0	---	0	---	1	---	0	---	0	---	
	Others	11	---	0	---	2	---	3	---	3	---	3	---	
	Unknown	26	---	4	---	8	---	6	---	5	---	3	---	
Mode of dialysis	HD	176	98.9	38	97.4	35	100.0	32	97.0	34	100.0	37	100.0	---
	HDF	2	1.1	1	2.6	0	0.0	1	3.0	0	0.0	0	0.0	
Complication	No	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	---
	Yes	178	100.0	39	100.0	35	100.0	33	100.0	34	100.0	37	100.0	
Medical history	No	55	30.9	11	28.2	12	34.3	12	36.4	7	20.6	13	35.1	---
	Yes	123	69.1	28	71.8	23	65.7	21	63.6	27	79.4	24	64.9	
Alcohol intake	No	116	65.2	28	71.8	22	62.9	21	63.6	20	58.8	25	67.6	---
	Occasionally	52	29.2	8	20.5	12	34.3	12	36.4	10	29.4	10	27.0	
	Everyday	10	5.6	3	7.7	1	2.9	0	0.0	4	11.8	2	5.4	
Smoking	No	143	80.3	31	79.5	30	85.7	25	75.8	27	79.4	30	81.1	---
	Yes	35	19.7	8	20.5	5	14.3	8	24.2	7	20.6	7	18.9	
Age by category 1 (years)	<50	31	17.4	9	23.1	5	14.3	5	15.2	7	20.6	5	13.5	---
	50≤<60	35	19.7	8	20.5	5	14.3	6	18.2	6	17.6	10	27.0	
	60≤<70	67	37.6	16	41.0	11	31.4	13	39.4	13	38.2	14	37.8	
	70≤	45	25.3	6	15.4	14	40.0	9	27.3	8	23.5	8	21.6	
Age by category 2 (years)	<65	111	62.4	26	66.7	20	57.1	21	63.6	20	58.8	24	64.9	---
	65≤	67	37.6	13	33.3	15	42.9	12	36.4	14	41.2	13	35.1	

		Overall		PA21 3.75 g		PA21 7.5 g		PA21 11.25 g		PA21 15 g		Placebo		Fisher's exact test
		n	%	n	%	n	%	n	%	n	%	n	%	
Dialysis vintage (months)	<60	79	44.4	21	53.8	16	45.7	14	42.4	11	32.4	17	45.9	---
	60≤	99	55.6	18	46.2	19	54.3	19	57.6	23	67.6	20	54.1	
Dialysis time (hr)	<4	20	11.2	4	10.3	4	11.4	3	9.1	6	17.6	3	8.1	---
	4≤	158	88.8	35	89.7	31	88.6	30	90.9	28	82.4	34	91.9	
P (mg/dL)	≤6	18	10.1	3	7.7	3	8.6	1	3.0	5	14.7	6	16.2	---
	6< ≤7	55	30.9	14	35.9	8	22.9	13	39.4	8	23.5	12	32.4	
	7< ≤8	52	29.2	12	30.8	10	28.6	13	39.4	8	23.5	9	24.3	
	8< ≤9	34	19.1	6	15.4	8	22.9	5	15.2	8	23.5	7	18.9	
	9< ≤10	14	7.9	3	7.7	4	11.4	1	3.0	4	11.8	2	5.4	
	10<	5	2.8	1	2.6	2	5.7	0	0.0	1	2.9	1	2.7	
Ca (mg/dL)	<8.4	66	37.1	16	41.0	9	25.7	15	45.5	11	32.4	15	40.5	---
	8.4≤ <10	108	60.7	23	59.0	26	74.3	17	51.5	22	64.7	20	54.1	
	10≤	4	2.2	0	0.0	0	0.0	1	3.0	1	2.9	2	5.4	
Ca×P (---)	<60.0	78	43.8	19	48.7	13	37.1	15	45.5	12	35.3	19	51.4	---
	60.0≤	100	56.2	20	51.3	22	62.9	18	54.5	22	64.7	18	48.6	
intact-PTH (pg/mL)	<60	7	3.9	2	5.1	2	5.7	0	0.0	2	5.9	1	2.7	---
	60≤ ≤240	77	43.3	16	41.0	18	51.4	12	36.4	14	41.2	17	45.9	
	240<	94	52.8	21	53.8	15	42.9	21	63.6	18	52.9	19	51.4	

Note: the list doses were in the total mass. Its tablet is standardized to contain 500 mg iron (as PA21 drug substance (DS)) with a total nominal mass of 2.5g. (sponsor table from summary report of Study PA1201)

The patient disposition in study PA1201 is summarized in the following table 62. Of the 183 randomized subjects, 136 subjects (74.3%) completed the study and 47 subjects (25.7%) were withdrawn from the study. The proportions of withdrawn subjects were higher in groups at doses of PA21 2500 mg/day and 3000 mg/day than in the placebo group. This is mainly due to the adverse events and drug-related hypophosphatemia.

Table 62: Patient disposition and reason for discontinuation in Study PA1201

Analysis Set	Category	PA21 3.75 g		PA21 7.5 g		PA21 11.25 g		PA21 15 g		Placebo		Fisher's exact test
		n	%	n	%	n	%	n	%	n	%	
All allocated subjects	---	39	---	36	---	35	---	36	---	37	---	---
Study completion	Completed	37	94.9	31	86.1	23	65.7	15	41.7	30	81.1	P<0.001
	Discontinued	2	5.1	5	13.9	12	34.3	21	58.3	7	18.9	
Reason for discontinuation	Adverse events	1	---	2	---	9	---	6	---	2	---	---
	P increase	0	---	0	---	0	---	0	---	2	---	
	P decrease	0	---	2	---	3	---	12	---	0	---	
	Ca decrease	0	---	0	---	0	---	1	---	1	---	
	Others	1	---	1	---	3	---	3	---	2	---	

Note: the list doses were in the total mass which equal 750 mg/day to 3000 mg/day PA 21(3.75 g/day to 15 g/day) (Sponsor table from summary report of Study PA 1201)

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/s/

SHEN XIAO
10/10/2013

ALIZA M THOMPSON
10/11/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Hyperphosphotemia Pivotal Study #2 Indication: Hyperphosphotemia	x			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	x			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (<i>e.g.</i> , QT interval studies, if needed)?			x	The product has very minimal absorption should not have this effect.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	x			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	x			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	x			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			x	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Shen Xiao

Reviewing Medical Officer Date

Clinical Team Leader Date

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/s/

SHEN XIAO
03/15/2013