An Open-label, Randomised, Active-controlled, Parallel Group, Multicentre, Phase 3 Study to Investigate the Safety and Efficacy of PA21 (Velphoro®) and Calcium Acetate (Phoslyra®) in Paediatric and Adolescent CKD Patients with Hyperphosphataemia

Clinical Protocol Number:	PA-CL-PED-01
Date:	22 September 2015
Version:	2.0
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IND Number:	75610
EudraCT Number:	2015-004155-43
Co-ordinating Investigator:	To be confirmed
Sponsor Contact:	PPD
Sponsor Address:	Vifor Fresenius Medical Care Renal Pharma France 7-13, Boulevard Paul-Emile Victor 92521 Neuilly-sur-Seine France

SIGNATURE PAGE

Declaration of Sponsor

Title: An Open-label, Randomised, Active-controlled, Parallel Group, Multicentre, Phase 3 Study to Investigate the Safety and Efficacy of PA21 and Calcium Acetate (Phoslyra®) in Paediatric and Adolescent CKD Patients with Hyperphosphataemia

Version Number/Date: Version 2.0, 22 September 2015

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and the International Conference on Harmonisation Guidelines on Good Clinical Practice.

PPD _____ PPD _____

Clinical Representative, Vifor Pharma — Date (day month year)

PPD _____ _____

Trial Statistician, Vifor Pharma — Date (day month year)

PPD _____ _____

Regulatory Representative, Vifor Pharma — Date (day month year)

PPD _____ PPD _____

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SYNOPSIS

PA-CL-PED-01

Title:	An Open-label, Randomised, Active-controlled, Parallel Group, Multicentre, Phase 3 Study to Investigate the Safety and Efficacy of PA21 and Calcium Acetate (Phoslyra®) in Paediatric and Adolescent CKD Patients with Hyperphosphataemia
Short Title:	PA21 safety and efficacy, paediatrics
Study Product:	PA21
Indication:	Control of serum phosphorus levels in paediatric and adolescent subjects with chronic kidney disease (CKD).
Phase:	3
Sponsor:	Vifor Fresenius Medical Care Renal Pharma, France
Study Code:	PA-CL-PED-01
Co-ordinating Investigator:	To be confirmed
Objectives:	<u>Primary Objective</u> • To evaluate the efficacy of PA21 in reducing serum phosphorus levels in paediatric and adolescent subjects with CKD at the end of Stage 1. <u>Secondary Objectives</u> • To evaluate the efficacy of PA21 in maintaining the serum phosphorus lowering effects in paediatric and adolescent subjects with CKD at the end of Stage 2. • To evaluate the safety of PA21 in paediatric and adolescent subjects with CKD. • To evaluate the efficacy of Phoslyra in reducing and maintaining serum phosphorus levels in paediatric and adolescent subjects with CKD at the end of Stages 1 and 2. • To evaluate the safety of Phoslyra in paediatric and adolescent subjects with CKD.
Design:	The study has a 2-stage design. In total, approximately 100 subjects will be randomised to PA21 treatment and approximately 30 subjects to Phoslyra treatment. In addition, the study will aim to randomise a minimum number of subjects from each age group as detailed in Table A. **Table A Minimum Number of Randomised Subjects by Age Group**

Age	PA21	Phoslyra
0 to <1 year	4	1
≥1 year to <6 years	10	3
≥6 years to <9 years	10	3
≥9 years to <18 years	10	3

- Screening period: up to 4 weeks.
- Washout period: up to 3 weeks.

Design: (Cont'd)	• Stage 1: Open-label, randomised, active-controlled, dose titration of PA21 and Phoslyra: up to 10 weeks. • Stage 2: Open-label long-term safety extension: 24 weeks. • Follow-up: 14 days.
Treatment:	The study formulations are detailed in Table B. **Table B Summary of Formulations** See table below. Note: PET=Polyethylene terephthalate. PA21 contains approximately 20% m/m of elemental iron. PA21 (sucroferric oxyhydroxide) is a mixture of polynuclear iron (III)-oxyhydroxide (about 33% m/m), sucrose (about 30% m/m), and starches (about 28% m/m) and contains ≤10% m/m water. Hence, PA21 125 mg (iron) powder will contain approximately 625 mg PA21 drug substance, a PA21 250 mg (iron) tablet/powder will contain approximately 1.25 g PA21 drug substance and a PA21 500 mg (iron) tablet/powder will contain approximately 2.5 g PA21 drug substance Each 5 mL of Phoslyra contains 667 mg calcium acetate equal to 169 mg calcium i.e., each 1 mL contains 33.8 mg of elemental calcium. At any time during the study, subjects randomised to receive PA21 will be provided with the formulation considered to be the most appropriate for them i.e., either powder for oral suspension (for subjects <6 years) or chewable tablet (for subjects ≥6 years). Due to the increments for dose changes subjects in the 6 to 9 year age group will ideally receive powder for oral suspension throughout the study. If required, subjects in the older age groups may change to the alternative PA21 formulation, but should remain on the same dose. For example, a subject may begin treatment with the chewable tablet but at a subsequent study visit change to the powder for oral suspension. Stage 1: Open-Label Dose Titration Subjects will be randomised to receive either PA21 or Phoslyra. PA21 subjects will receive PA21 at a starting dose based on their age, as detailed in Table C. Phoslyra subjects will receive Phoslyra either at a starting dose, as detailed in Table F, or, if considered more appropriate by the Investigator, at an equivalent dose of their previous phosphate binder (PB), calcium-based or sevelamer.

Age	PA21		Phoslyra Oral Solution (mL)
	Powder for Oral Suspension (mg Iron)	Chewable Tablet (mg Iron)	
0 to <1 year	125, 250, 500	–	Multiple-dose PET bottles 473 mL with a child-resistant closure
≥1 year to <6 years	125, 250, 500	–	
≥6 years to <9 years	125, 250, 500	250, 500	
≥9 years to <18 years	250, 500	250, 500	

Treatment: (Cont'd)

Dose of PA21 (100 subjects) or Phoslyra (30 subjects) will be increased or decreased as required for efficacy (to achieve age specific target serum phosphorus level as indicated in Table D), provided a subject has been receiving that dose for a minimum of 2 weeks, and for safety or tolerability reasons at any time. Increases or decreases in dose and maximum doses are detailed in Table E, Table F and Table G. From Week 4, once a subject achieves the age specific target serum phosphorus level, as indicated in Table D, they can move to Stage 2.

Table C Stage 1 Starting Dose of PA21

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

Table D Age Related Serum Phosphorus Targets Post-Randomisation

Age	mmol/L	mg/dL
0 to <1 year	1.62-2.52	5.0-7.8
≥1 year to <6 years	1.45-2.10	4.5-6.5
≥6 years to <13 years	1.16-1.87	3.6-5.8
≥13 years to <18 years	0.74-1.45	2.3-4.5

Source: National Kidney Foundation Kidney Disease Outcomes Quality Initiative Nutrition Guidelines, 2008.

Table E PA21 Dosing Regimens

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

Table F Stage 1 Starting Dose and Dosing Regimen of Phoslyra (All Age Group)

Initial Dose	Dose Increase or Decrease	Maximum Dose (up to 35 kg)	Maximum Dose (above 35 kg)
0.45 mL/kg/day	0.1 to 0.2 mL/kg/day	1.25 mL/kg/day	44 mL/day

Treatment: (Cont'd)

Table G Maximum Daily Dose of Phoslyra

Body Weight (kg)	Phoslyra Maximum Dose mL/day
5	6.0
10	12.5
15	18.5
20	25
25	31.0
30	37.5
35	43.5
40	44
45	44
50	44
60	44
70	44

Stage 2: Open-Label Safety Extension

All subjects will enter this safety extension stage. Subjects will continue on the dose received at the end of Stage 1, unless a dose change is required.

For all subjects, doses may be titrated for efficacy (to achieve age specific target serum phosphorus levels, see Table D), provided a subject has been receiving that dose for a minimum of 2 weeks, and for safety or tolerability reasons at any time during Stage 2. Increases or decreases in dose and maximum doses are detailed in Table E, Table F and Table G.

Inclusion Criteria:

1. Subjects 0 to <18 years at time of consent.
2. Subjects with hyperphosphataemia i.e., with serum phosphorus levels indicated in Table H.
3. Subjects who are PB naïve or have been receiving stable doses of a PB(s) for at least 1 month prior to screening. Subjects may be on stable doses of a maximum of 2 PBs. Subjects who have been receiving PBs will enter an obligatory washout period and may be randomised once their serum phosphorus levels are as indicated in Table H. Subjects already receiving a PB but with serum phosphorus levels indicated in Table H may be eligible for randomisation without a washout period.
4. Subjects ≥1 year with CKD Stages 4-5 defined by a glomerular filtration rate <30 mL/min/1.73 m^2 or with CKD Stage 5D receiving adequate maintenance haemodialysis (HD) or peritoneal dialysis (PD) for at least 2 months prior to screening.
5. Subjects <1 year must have CKD.
6. PD subjects must have had 1 month of unchanged PD prescription (volume and number of exchanges). Home HD subjects may be included (no nocturnal HD (overnight stay at site) will be allowed).
7. Appropriate written informed consent and, where appropriate/required assent, have been provided. Written informed consent (and, where appropriate/required, assent) must be provided before any study-specific procedures are performed, including screening procedures.

Inclusion Criteria: (Cont'd)	8. Parents/legal guardians and, where appropriate/required, subjects with the ability to provide written informed consent, and where appropriate/required, assent, to understand the requirements of the study and abide by the study restrictions, and who agree to return for the required assessments, in the Investigator's opinion.
Exclusion Criteria:	1. Subjects with hypercalcaemia at screening as indicated in Table J. 2. Subjects with intact parathyroid hormone (iPTH) levels >700 pg/mL at screening. 3. Subjects who are PB naïve who weigh <5 kg at screening. Subjects receiving stable doses of PBs who weigh <6 kg at screening (in order to comply with maximum blood sample volumes in paediatric clinical trials). 4. Subjects requiring feeding tube sizes ≤6 FR (French catheter scale). 5. Subjects with planned or expected parathyroidectomy within the next 12 months, in the Investigator's opinion. 6. Subjects with history of: • Major gastrointestinal surgery which, in the Investigator's opinion, is likely to influence the outcome of treatment with PBs. • Significant gastrointestinal disorders. 7. Subjects with estimated life expectancy of less than 12 months. 8. Subjects with known seropositivity to human immunodeficiency virus. 9. Subjects with a history of haemochromatosis or other iron accumulation disorders. 10. Subjects on PD with a history of peritonitis in the last 3 months or ≥3 episodes in the last 12 months. 11. Subjects with hypocalcaemia (serum total corrected calcium <1.9 mmol/L; <7.6 mg/dL) at screening. 12. Subjects with raised alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of the normal range based on central laboratory results at screening. 13. Subjects taking more than 2 PBs concomitantly prior to screening. 14. Subjects taking any prohibited medication(s) (See Section 7.7). 15. Subject has known hypersensitivity and/or intolerance to any of the active substances or to any of the excipients to be administered. 16. Subject has previously been randomised into this study. 17. Subject is currently enrolled in or has completed any other investigational device or drug study <30 days prior to screening, or is receiving other investigational agent(s). 18. Subject is pregnant (e.g., positive human chorionic gonadotropin test) or breast feeding.

Exclusion Criteria: (Cont'd)	19. If of child-bearing potential, subject is not using adequate contraceptive precautions. Subject must agree to use a highly effective method of birth control during the study and for 1 month after the last dose of study medication. Adequate methods of birth control are defined as those which result in a low failure rate (i.e., <1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intra-uterine devices, sexual abstinence or vasectomised partner. Non-child-bearing potential includes being surgically sterilised at least 6 months prior to the study. 20. Subject has a history of drug or alcohol abuse within 2 years prior to screening. 21. Subject has a significant medical condition(s) e.g., uncontrolled diabetes, known hepatitis B surface antigen positivity and/or hepatitis C virus ribonucleic acid positivity or anticipated need for major surgery during the study, or any other kind of disorder that may be associated with increased risk to the subject, or may interfere with study assessments or outcomes.
Primary and Secondary Endpoints:	<u>Primary Efficacy Endpoint</u> • Change in serum phosphorus from baseline in the PA21 group at the end of Stage 1. <u>Primary Safety Endpoint</u> • Adverse events (AEs) profile. • Percentage of withdrawals due to AEs. <u>Secondary Efficacy Endpoints</u> • Change in serum phosphorus from baseline in the Phoslyra group at the end of Stage 1. • Change in serum phosphorus from baseline in the PA21 and Phoslyra groups at the end of Stage 2. • Percentage of subjects in each stage during which the subject has serum phosphorus levels in the age dependent target ranges. • Serum phosphorus levels at each time point and change from baseline. <u>Secondary Safety Endpoints</u> • Serum total corrected calcium levels at each time point and change from baseline. • Percentage of subjects that develop at least 1 episode of sustained hypercalcaemia (as indicated in Table J) during study participation (confirmed by repeat sample 1 week later). • Serum total corrected calcium x phosphorus levels at each time point and change from baseline. • Serum iPTH levels at each time point and change from baseline. • Biochemical/haematological laboratory tests (including blood iron parameters, Vitamin D parameters and bone markers). <u>Additional Assessments</u> • Patient reported outcomes on palatability and acceptability.

Procedures:

See Schedule of Events, Table 1 for full details of protocol required procedures, visits and timings.

Table 2 (Summary of Blood Samples) details visits where blood samples must be analysed at a central laboratory and visits where there is the option of having blood samples analysed by a local laboratory

Screening Period

Subjects for whom signed and dated informed consent (and, where appropriate/required, assent) has been provided will be enrolled in the study and screened.

Washout Period

Subjects who are PB Naïve

Subjects who are PB naïve and whose serum phosphorus levels values are as indicated in Table H will be eligible for randomisation when the results from the screening visit are available for assessment of study eligibility. In centre HD subjects must be randomised after a maximum interdialytic period of 48 hours, once qualifying screening results are received. Home HD, pre-dialysis and PD subjects should be randomised as soon as feasible after qualifying screening results are received, and preferably within 4 days.

Subjects Taking PBs

Subjects already receiving a PB but with serum phosphorus levels indicated in Table H may be randomised without a washout period when the results from the screening visit are available for assessment of study eligibility. For subjects taking PBs the washout period cannot begin until the results from the screening visit are available for assessment of study eligibility. Subjects who are eligible for inclusion (or their parent/legal guardian) will then be contacted by the site and asked to stop taking their current PBs. The dose of previous PB treatment should remain stable until the subject, or their parent/legal guardian, is contacted by the site. Subjects who are eligible for inclusion will then undergo a washout from their previous PBs for up to 3 weeks. Serum phosphorus levels will be monitored weekly for up to 3 weeks of washout.

Table H Age Related Serum Phosphorus Targets for Washout Period

Age	mmol/L	mg/dL
0 to < 6 months	>2.62	>8.1
≥6 months to <1 year	>2.29	>7.1
≥1 year to <6 years	>2.02	>6.3
≥6 years to <13 years	>1.77	>5.5
≥13 years to <18 years	>1.36	>4.2

Note: Adapted from National Kidney Foundation Kidney Disease Outcomes Quality Initiative Nutrition Guidelines, 2008 and personal communication.

Subjects whose serum phosphorus levels have risen to the values indicated in Table H will be eligible for randomisation at any time during the washout period. Subjects who have serum phosphorus levels below the values indicated in Table H can continue in the washout period for up to 3 weeks. As soon as their serum phosphorus level has risen to the value indicated in Table H they can be randomised into the study.

Procedures: (Cont'd)	In centre HD subjects must begin their washout after a maximum interdialytic period of 48 hours, once qualifying screening results are received. Subsequent visits during the washout period should take place after a maximum interdialytic period of 48 hours. Home HD, pre-dialysis and PD subjects should begin their washout as soon as feasible after qualifying screening results are received, and preferably within 4 days. If, after 3 weeks of washout, the serum phosphorus remains below the values indicated in Table H the subject is not eligible for randomisation and must be withdrawn from the study. **Randomisation and Study Visits** Subjects who are eligible will be randomised via an IRT to either PA21 (100 subjects) or Phoslyra (30 subjects), and will enter Stage 1, the open-label, dose titration period. For in centre HD subjects study visits must be planned after a maximum interdialytic period of 48 hours and on the same day and same session each week, as far as possible. Collection of laboratory samples and completion of all other procedures required by the protocol, except the physical examination and the patient reported palatability and acceptability will be completed before dialysis is initiated. Subjects that are on home HD, pre-dialysis or on PD will be free to select a weekday for the study visits that coincides best with their weekly routine, preferably in the first half of the week. All subsequent study visits will be scheduled on the same weekday, wherever possible. For these subjects all laboratory samples and other procedures required by the protocol will, where possible, be taken at a consistent time for each visit. Concomitant medications that have a direct influence on serum phosphorus levels (e.g., Vitamin D, Vitamin D analogues and calcimimetics), dietary restrictions (e.g., phosphate and calcium intake) and dialysis regimens (e.g., duration of dialysis, number of HD sessions per week, number of PD exchanges/day, modality of dialysis, calcium concentration) should remain unchanged as far as possible in both the PA21 and Phoslyra groups throughout the study in accordance with local clinical practice. This does not apply if changes are indicated for safety or tolerability reasons. AEs and concomitant medication will be recorded from screening (following informed consent, and where appropriate/required, assent signature) to the end of study participation. <u>Stage 1: Open-Label Dose Titration Period</u> Visits and assessments will be as detailed in the Schedule of Events, Table 1. During this period, dose titrations will be based on laboratory values taken at regular study intervals. If a dose adjustment is indicated, i.e., the serum phosphorus level is outside the target serum phosphorus levels indicated in Table D, the Investigator will inform the subject and, where appropriate, parent/legal guardian (either directly or by phone) whether a dose increase or a dose decrease is indicated. Subjects will thereafter follow the new dose regimen for a minimum of 2 weeks. <u>Stage 2: Open-Label Safety Extension</u> Visits and assessments will be as detailed in the Schedule of Events, Table 1. During this period, dose titrations will be based on laboratory values taken at regular study intervals. If a dose adjustment is indicated, i.e., if the serum phosphorus level is outside the target serum phosphorus levels indicated in Table D, the Investigator will inform the subject and, where appropriate, parent/legal guardian (either directly or by phone) whether a dose increase or a dose decrease is indicated. Subjects will thereafter follow the new dose regimen for a minimum of 2 weeks.

Procedures: (Cont'd)

Early Discontinuation and Stopping Rules

Phosphorus

At any time during the study, if a subject's phosphorus level exceeds or is below the safety limits indicated in Table I:

Table I Age Related Safety Limits of Serum Phosphorus

Age	Upper Safety Limit		Lower Safety Limit	
	mmol/L	mg/dL	mmol/L	mg/dL
0 to <1 year	2.91	9.0	1.62	5.0
≥1 year to <6 years	2.42	7.5	1.45	4.5
≥6 years to <13 years	2.26	7.0	1.13	3.5
>13 years to <18 years	2.26	7.0	0.81	2.5

Note: Limits calculated as upper limit of normal ±20% based on National Kidney Foundation Kidney Disease Outcomes Quality Initiative Nutrition Guidelines, 2008.

- The subject's study medication must be adjusted and the subject must be asked to return for a visit 1 week after the value outside the safety limits indicated in Table I was first seen i.e., irrespective of whether this was during Stage 1 or 2.
- At the next visit, 1 week after the value outside the safety limits indicated in Table I was first seen a blood sample for serum phosphorus will be taken. Once the site receives the blood sample result, if the serum phosphorus level is outside the target safety limits indicated in Table I, the Investigator will inform the subject and, where appropriate, parent/legal guardian, (either directly or by phone) whether a dose increase or a dose decrease of study medication is indicated. The subject must return for a visit 1 week after the change in study medication dose.
- At the next visit, 1 week after the change in study medication dose, a blood sample for serum phosphorus will be taken. Once the site has the blood sample result, if the subject's phosphorus level still exceeds or is below the safety limits indicated in Table I, then the subject must be withdrawn from the study.

In addition, at each of the above visits, if the subject's phosphorus level exceeds the upper safety limit indicated in Table I, the site must advise the subject and parent/carer regarding a low phosphorus diet.

The subject does not need to be withdrawn if the 2 follow-up results are outside of the safety limit, but in the opposite direction (i.e., one too high and one too low). In this situation, the subject's PB dose must be adjusted and the subject must return in 1 week to provide a blood sample for serum phosphorus. Once the site has the blood sample result, if the subject's phosphorus level still exceeds or is below the safety limits indicated in Table I, then the subject must be withdrawn from the study.

Calcium

At any time during the study, subjects will be withdrawn immediately if their serum corrected total calcium level exceeds 3.0 mmol/L (12 mg/dL) or is below 1.63 mmol/L (6.5 mg/dL).

Procedures: (Cont'd)

At any time during the study if a subject's corrected total calcium level exceeds or is below the safety limits indicated in Table J:

- The subject should receive appropriate rescue intervention and must be asked to return for a visit 1 week after the value outside the safety limits indicated in Table J was first seen.
- At the next visit, 1 week after the value outside the safety limits indicated in Table J was first seen, a blood sample for serum corrected total calcium will be taken. Once the site has the blood sample result, if the level is outside the target safety limits indicated in Table J, the Investigator will inform the subject and, where appropriate, parent/legal guardian, (either directly or by phone) whether a dose increase or a dose decrease in rescue medication or an alternative rescue medication is indicated. The subject must return for a visit 1 week after the change in rescue medication.
- At the next visit, 1 week after the change in rescue medication, a blood sample will be taken. Once the site has the blood sample result, if the subject's corrected total calcium level still exceeds or is below the safety limits indicated in Table J, then the subject must be withdrawn from the study.

The subject does not need to be withdrawn if the 2 follow-up results are outside of the safety limit, but in the opposite direction (i.e., one too high and one too low). In this situation, the subject's rescue medication must be adjusted and the subject must return in 1 week to provide a blood sample for serum total corrected calcium. Once the site has the blood sample result, if the subject's serum corrected total calcium level still exceeds or is below the safety limits indicated in Table J, then the subject must be withdrawn from the study

Appropriate rescue intervention for hypercalcaemia may include:

- Reduce or stop dose of active Vitamin D metabolite
- Increase dose of calcimimetic
- Reduce calcium content in dialysate
- Reduce the dose of Phoslyra

Appropriate rescue intervention for hypocalcaemia may include:

- Increase dose of active Vitamin D metabolite
- Decrease dose of calcimimetic
- Increase calcium content in dialysate

Table J Age Related Safety Limits for Total Calcium

Age	Upper Safety Limit		Lower Safety Limit	
	mmol/L	mg/dL	mmol/L	mg/dL
0 to <1 year	2.75	11.0	<1.9	<7.6
≥1 year to <6 years	2.70	10.8	<1.9	<7.6
≥6 years to <13 years	2.60	10.3	<1.9	<7.6
≥13 years to <18 years	2.60	10.2	<1.9	<7.6

Note: Upper safety limits based on National Kidney Foundation Kidney Disease Outcomes Quality Initiative Nutrition Guidelines, 2008. Lower limit based on literature (Paediatric Nephrology, 2nd edition) and personal communication.

Procedures: (Cont'd)	**General** Subjects will also be withdrawn if it is necessary to add an additional PB to the treatment regimen or if they receive a kidney transplant, or they initiate dialysis during the study. All withdrawn subjects will be asked to complete the end of study assessments. **Follow-Up** Any subject who has been treated with study medication, whether completing the study or withdrawn prematurely, will be followed up 14 days after their last scheduled study visit to collect any new AEs and concomitant medications. **External Data and Safety Monitoring Board** There will be an external Data and Safety Monitoring Board. **Post Study Treatment** The Investigator is responsible for ensuring that consideration is given to the appropriate post study care of the subject's medical condition.
Sample Size:	One hundred-thirty subjects will be randomised in the study (PA21: 100, Phoslyra: 30). The study will aim to randomise the number of subjects from each age group as detailed in Table A.
Statistical Methods:	The primary efficacy analysis will be conducted on the change from baseline in the PA21 group at the end of Stage 1. The change from baseline in the PA21 group will be analysed using a paired t-test, and also summarised descriptively. Additional descriptive analyses will be conducted on the serum phosphorus changes from baseline to the end of Stage 1(Phoslyra) and to the end of Stage 2 (both PA21 and Phoslyra treatment groups). Demographic and baseline disease characteristics will be summarised and compared between the PA21 and Phoslyra groups. Subject exposure and compliance will be calculated and summarised by treatment groups, and by stage. AE, laboratory values, vital signs and other safety parameters will be summarised. Patient palatability and acceptability assessments will be summarised and analysed by treatment groups. All analyses will be described in a statistical analysis plan that will be finalised before database lock.

Figure 1 Study Design

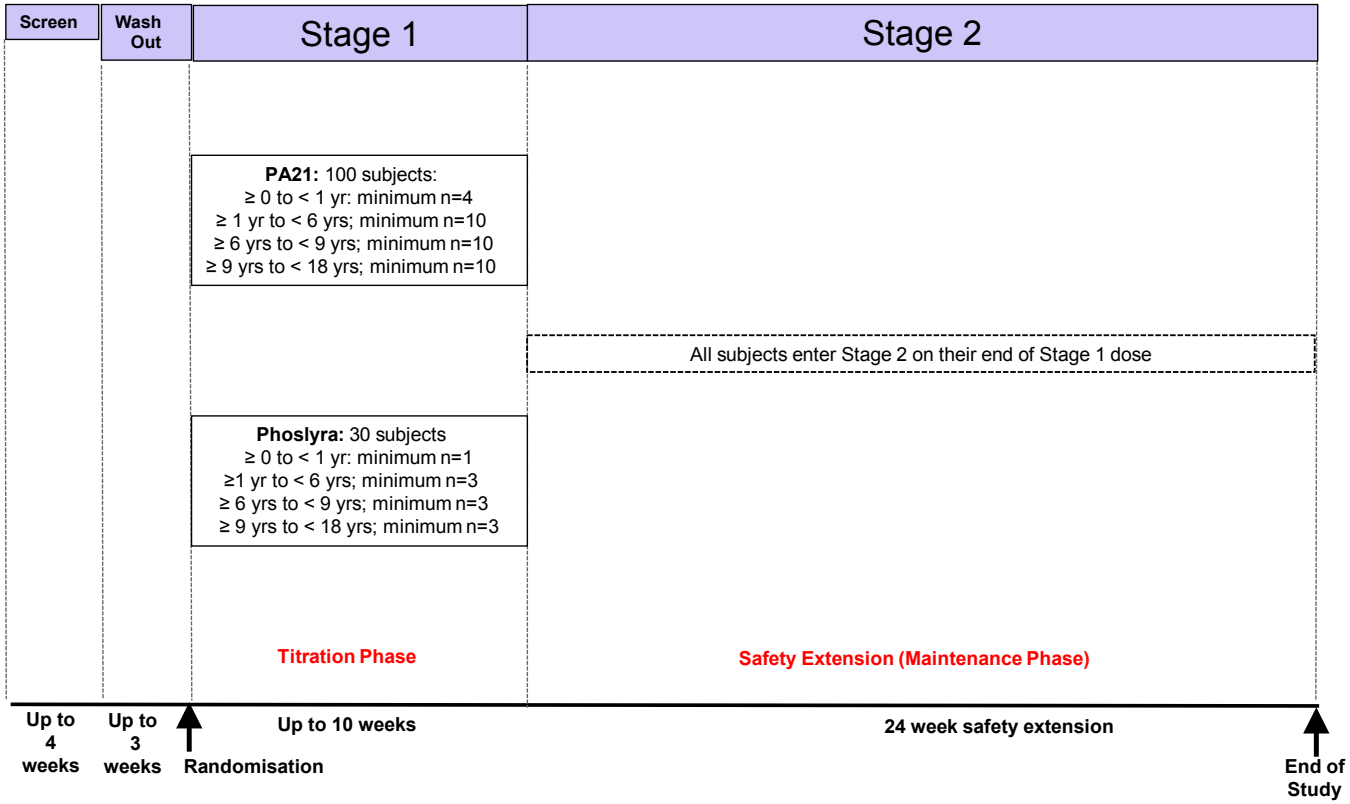

Table 1 Schedule of Events

	Screen[1,2,3]	Washout[2] (Visits Only for Subjects on PBs)			Treatment Period												Follow-Up: 2 Weeks After Last Visit[4]
					Stage 1[4,5] Titration Period							Stage 2 Safety Extension[4]					
Week (PB washout)[2]	**Up to -7**	**-3**	**-2**	**-1**	**BL**	**1**	**2**	**4**	**6**	**8**	**10**	**14**	**18**	**22**	**28**	**34**	**36**
Week (PB naïve)[3]	**Up to -4**	**Not Required**															
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16[6]**	**17[7]**
Informed consent/assent	X																
Eligibility criteria	X				X												
Demography	X																
Medical/surgical history	X																
Physical examination	X											X				X	
Height and weight	X				X			X			X	X		X		X	
Vital signs (blood pressure, heart rate, temperature)	X				X			X			X	X		X		X	
Blood samples: details in Table 2																	
Call to IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense subject identification card					X												
Dialysis parameters	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dialysis parameters for Kt/V[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomization					X												
Dispense study medication					X	X	X	X	X	X	X	X	X	X	X		
Returned study medication count						X	X	X	X	X	X	X	X	X	X	X	
Patient reported palatability and acceptability								X								X	
AE/SAE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1 Schedule of Events (Cont'd)

	Screen[1,2,3]	Washout[2] (Visits Only for Subjects on PBs)			Treatment Period												Follow-Up: 2 Weeks After Last visit[4]
					Stage 1[4,5] Titration Period							Stage 2 Safety Extension[4]					
Week (PB washout)[2]	**Up to -7**	**-3**	**-2**	**-1**	**BL**	**1**	**2**	**4**	**6**	**8**	**10**	**14**	**18**	**22**	**28**	**34**	**36**
Week (PB naïve)[3]	**Up to -4**	**Not Required**															
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16[6]**	**17[7]**
Discuss and advise on subject's diet	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

1 Laboratory data must be available prior to washout and randomization to check that all laboratory eligibility criteria have been met. Subjects may be rescreened once if, for example, they have a positive pregnancy test, have an active infection or if they are taking antibiotics. Subjects who need to be rescreened will be withdrawn from the study (as screen failures) and enrolled again.
2 For subjects requiring a washout period, Visit 2 to be scheduled 5 to 28 days after the screening visit. Washout visits to be scheduled in relation to Visit 2: Visit 3 is 7 ±2 days, Visit 4 is 14 ±2 days, and baseline is 21 ±2 days. The washout period, if required, is up to 3 weeks ±2 days and cannot begin until the results from the screening visit are available for assessment of study eligibility.
3 For subjects not requiring a washout period, the baseline visit to be scheduled 5 to 28 days after the screening visit. These subjects will not be required to attend Visits 2, 3 and 4.
4 All other visits should be scheduled in relation to baseline Visit ±3 days.
5 From Visit 8, subjects can move to Stage 2 if they have been on a stable dose for a minimum of 2 weeks.
6 All subjects must complete the assessments for this visit on completion of the study or early discontinuation/withdrawal at any time (Stage 1 and Stage 2).
7 Visit 17 can be conducted by a telephone call.
8 Any visit where this value is available from routine clinical assessment.
Notes: AE=Adverse event; BL=Baseline; PB=Phosphate binder; SAE=Serious adverse event.

Table 2 Summary of Blood Samples

	Screen	Washout (Visits Only for Subjects on PBs)			Treatment Period												Follow-Up: 2 Weeks After Last Visit[1]
					Stage 1 Titration Period							Stage 2 Safety Extension					
Week (PB washout)	**Up to -7**	**-3**	**-2**	**-1**	**BL**	**1**	**2**	**4**	**6**	**8**	**10**	**14**	**18**	**22**	**28**	**34**	**36**
Week (PB naïve)	**Up to -4**	**Not Required**															
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16[2]**	**17**
Central laboratory blood sample required	X				X			X			X		X			X	
Option to use local laboratory		X	X	X		X	X		X	X		X		X	X		
Pregnancy test[3]	X												X			X	
Haematology	X							X			X	X	X	X	X	X	
Intact parathyroid hormone	X							X			X	X	X	X	X	X	
Clinical chemistry, iron status (excluding ferritin)	X							X			X	X	X	X	X	X	
Separate serum phosphorus, serum total corrected calcium and albumin[4,5]		X	X	X	X		X		X	X							
Bone markers and vitamins (excluding 1,25(OH)2D)[6]					X						X			X		X	
Ferritin[6]					X			X			X			X		X	
Coagulation and Vitamin 1,25(OH)2D[7]																	

1 Visit 17 can be conducted by a telephone call.
2 All subjects must complete the assessments for this visit on completion of the study or early discontinuation/withdrawal at any time (Stage 1 and Stage 2).
3 In females of child-bearing potential, the serum pregnancy tests will be performed at site. Positive pregnancy tests will be repeated 2 weeks later, to check for false positive results.
4 Where clinical chemistry test is conducted, serum phosphorus, serum total corrected calcium and albumin will be included therefore separate tests are not required at these visits.
5 Wherever possible a sample for central laboratory analysis of these parameters should be obtained at the final visit of Stage 1.
6 Exclude these blood tests in subjects <36 months but provide value if available from routine clinical assessment. Samples for bone marker assessment will be obtained and may be stored (frozen) for later analysis.
7 Any visit where this value is available from routine clinical assessment.
Notes: BL=Baseline; PB=Phosphate binder.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
ADR	Adverse drug reaction
AE	Adverse event
CKD	Chronic kidney disease
CRF	Case report form
CRO	Contract Research Organisation
DDI	Drug-drug interaction
DRI	Dietary referenced intake
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ESRD	End-stage renal disease
EU	European Union
FAS	Full analysis set
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HCl	Hydrochloride
HD	Haemodialysis
HP	Hyperphosphataemia
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
iPTH	Intact parathyroid hormone
IRB	Institutional Review Board
IRT	Interactive response technology
KDOQI	Kidney Disease Outcomes Quality Initiative
Kt/V	K=Dialyser clearance of urea; t=Dialysis time; V=Patient's total body water
LD	Low dose

m/m	Mass fraction
MD	Maintenance dose
NKF	National Kidney Foundation
PB	Phosphate binder
PD	Peritoneal dialysis
PG	Propylene glycol
PPS	Per-protocol set
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event
UK	United Kingdom
US	United States
Vifor Pharma	Vifor Pharma/Vifor International Ltd.
WMA	World Medical Association

1. INTRODUCTION AND BACKGROUND

1.1 Background of the Disease and Treatment Options

Hyperphosphataemia (HP) is a common and serious complication in patients with chronic kidney disease (CKD), particularly those with end-stage renal disease (ESRD) requiring dialysis. In the paediatric population, CKD is most commonly caused by congenital anomalies of the kidney and urinary tract such as aplasia/hypoplasia/dysplasia and obstructive uropathy. The frequency of such conditions is low. Glomerular diseases of various aetiologies, (e.g., polycystic kidneys, pyelonephritis) can also cause CKD, but with a lower frequency [1,2,3,4]. HP plays an important role in the pathophysiology of major CKD complications for example secondary hyperparathyroidism [5,6,7], renal bone disease [8,9] and cardiovascular disease [10,11,12,13], and appears to promote the progression of CKD towards ESRD [3]. High levels of serum phosphorus are considered to be a risk factor for mortality, morbidity and hospitalisation in patients with ESRD. [14,15,16,17]. Complications most relevant to the paediatric population are renal bone disease, also called renal osteodystrophy (sometimes referred to as mineral bone disease), cardiovascular disease and growth failure [18-22].

In 2011, in 14 European countries, the prevalence of dialysis and transplantation in the age group 0-19 years was 2,098 patients [23]. The incidence gradually increases after the age of 5 years, reaching a maximum in adolescents. In the US, 751 prevalent cases of ESRD were reported in 2010 in patients aged 0-19. Thirty-eight per cent receive a transplant in the first year of being on the transplant list [24]. Again, the incidence increases with age. A study on the epidemiology of CKD conducted in several Latin American countries showed a wide variation in incidence that ranged from 2.8 to 15.8 new cases per million of the age related population [25]. CKD is a major health problem in Southeast Asia where the true prevalence is unknown but estimates suggest that it may be more than reported in Western societies. The majority of the affected individuals are young, in the most productive years of their lives [26]. Malaysia is the only country in Southeast Asia with a national registry [27]. According to the European Paediatric Dialysis Working Group, HP has been observed in children at glomerular filtration rate <40 mL/min/1.73 m^2, and is almost always present in children on dialysis [28].

Phosphorus concentrations vary with age, with the normal range declining from birth to adult levels. The concentrations are higher in children than in adults, since phosphorus is necessary for growth. Phosphorus levels defining HP vary with age. In adults, HP is defined as a fasting serum phosphorus concentration >1.8 mmol/L (5.5 mg/dL) [29], whereas in children HP is characterised by a level of serum phosphorus above the upper normal limit for an age group [30].

Transplantation is the preferred treatment in the paediatric population, and dialysis is used for the relatively limited period of time waiting for the transplant, or in patients not qualifying for renal transplantation [3,31]. However, the time interval waiting for transplantation is variable. Kovalski et al, 2007 [32] reported that more than 75% of

children require chronic dialysis while awaiting transplantation, with waiting periods varying between a few months and several years.

HP cannot be satisfactorily controlled by dietary restriction alone in these patients. In children protein restriction was shown not to be effective in slowing progression of CKD and is generally not recommended due to the concern of adverse outcomes on growth and development [2,33]. In addition, dialysis is not particularly effective in removing phosphate (as phosphates are largely stored intracellularly after gastrointestinal (GI) absorption), therefore it is necessary to employ therapeutic means of binding phosphate to reduce dietary uptake.

A number of phosphate binders (PBs) are currently available for treating HP in adults with chronic renal failure and/or dialysis (haemodialysis (HD), peritoneal dialysis (PD)). The use of PBs for treatment of HP in paediatric patients with advanced CKD is widespread [28,34,35,36,37]. Although the active substances are not approved in paediatrics for this indication, National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) Guidelines and the UK National Institute for Health and Clinical Excellence recommend use of PBs in children [35,38]. These guidelines recommend calcium-based PBs as the first choice, in addition to dietary management. Dosing instructions for the paediatric population are included for some calcium carbonate PBs [39,40]. To date, there is experience with the use of calcium-containing phosphate adsorbents in paediatric patients [41,42], although their use is associated with the risk of hypercalcaemia. Calcium salts (carbonate, citrate, acetate) can significantly reduce (but not completely prevent) the uptake of phosphate into the blood [43]. None of the newer aluminium-free, calcium-free PBs (sevelamer or lanthanum carbonate) are approved for use in the paediatric population. To date clinical investigations have been conducted with results available on 18 and 15 patients treated with sevelamer hydrochloride (HCl) in 2 studies [44,45].

In adults, although widely used [46], calcium salts are limited by the development of hypercalcaemia, which has been reported to occur in over 50% of CKD patients on HD [47]. Furthermore, calcium salts exacerbate hypercalcaemia caused by resorption of calcium from the bones, particularly in patients receiving active Vitamin D metabolites (which increase intestinal calcium absorption) or when bone turnover is low [48]. In conjunction with raised phosphorus levels, this may contribute to vascular calcification and arterial and coronary sclerosis [10,11,12,49]. For this reason it has been suggested that calcium-based PBs should be avoided in many, if not most, patients who are undergoing dialysis [50]. Use of calcium salts may also result in over suppression of parathyroid hormone [49]. Aluminium salts are less often used and should be avoided because of toxicity due to aluminium absorption which may lead to Vitamin D-resistant osteomalacia and various neurological problems including encephalopathy and dementia [51,52]. Newer products include a cationic polymer (sevelamer HCl, sevelamer carbonate) and lanthanum carbonate. Sevelamer is a non-absorbable, cationic polymer capable of reversibly binding anions such as phosphate [53,54]. It is effective in reducing

phosphorus levels [9], but has a relatively high pill burden, requires swallowing of large tablets without chewing, and can lead to GI problems [55,56], all of which in turn potentially lead to compliance problems, thereby reducing efficacy. Lanthanum carbonate is another PB which appears to be well tolerated and has a reduced pill burden compared to sevelamer [57,58]; however, low but measurable absorption of lanthanum has been observed [59,60], raising potential toxicity concerns.

Due to the clinical limitations of the available phosphate adsorbents, there is a therapeutic need to develop a phosphate adsorbent which is free from aluminium and unlikely to induce hypercalcaemia and has thus less potential for hypercalcaemic events. Hence, an improved PB with a lower pill burden, better safety and tolerability profile, and improved compliance could contribute to better control of serum phosphorus in both adult and paediatric patients with CKD.

Vifor Pharma has developed a new non calcium-based, oral iron containing PB, PA21 (sucroferric oxyhydroxide), for therapeutic use in the control of serum phosphorus levels in patients with CKD undergoing dialysis [61]. The PA21 drug substance is practically insoluble and possesses a high phosphate adsorption capacity in combination with a low iron release. Following oral administration, PA21 adsorbs the dietary phosphate in the GI tract, preventing its uptake into the blood, thereby reducing the serum level of phosphorus. The phosphate bound to PA21 is subsequently eliminated through the faeces.

1.2 Summary of Nonclinical and Clinical Data

Details regarding the nonclinical and clinical data which support the rationale for the indication under investigation can be found in the current PA21 Investigator's Brochure (IB).

In vitro data show that PA21 has a high, pH-dependant phosphate-binding capacity optimised at a pH of 3 to 8 [62]. It exhibits minimal release of iron across the range of pH values found in the GI tract. A dose of 500 mg (iron) binds a minimum of phosphate corresponding to 105 mg phosphorus under validated laboratory conditions at pH 3 [63].

The safety and efficacy of PA21 has been assessed in over 65 nonclinical studies. Generally, the nonclinical studies have demonstrated unremarkable findings and do not raise potential safety issues in humans. PA21 was shown to be well tolerated in mice, rats, dogs, and rabbits at doses exceeding the maximal expected clinical dose for adults and children. The only findings of note in the nonclinical programme were findings in carcinogenicity studies performed in mice and rats. There was no clear evidence of a carcinogenic effect in mice. Mucosal hyperplasia, with diverticulum/cyst formation was observed in the colon and caecum of mice after 2 years treatment, but this was considered a species-specific effect with no diverticula/cysts seen in long-term studies in rats or dogs. In rats, there was a slightly increased incidence of benign C-cell adenoma in the thyroid of male rats given the highest dose of PA21. This is thought to be most likely an adaptive

response to the pharmacological effect of the drug, and not clinically relevant. Further details of these studies can be found in the current PA21 IB.

Given the insolubility and degradation characteristics of PA21, and the minimal absorption of the active moiety (sucroferric oxyhydroxide) conventional clinical pharmacology studies are not possible. The Phase 1 clinical programme has therefore focussed on measures for phosphate binding capacity, iron release and resorption, and drug-drug interactions (DDIs).

The Vifor Pharma clinical development programme comprises 1,112 adult subjects treated with PA21 in 7 Phase 1 clinical studies with PA21 and 2 pivotal efficacy and safety studies (Phase 2 study PA-CL-03A and Phase 3 study PA-CL-05A with its safety extension study, PA-CL-05B). A preliminary, Investigator-initiated Phase 1 study has also been published [64]. In addition, 2 supportive Phase 3 studies (PA1301, PA1304) have been conducted by Vifor's Japanese partner, Kissei Pharmaceuticals, Co., Ltd.

Early evidence of the efficacy and safety of PA21 was demonstrated in the initial Phase 1 studies. In the Phase 1 absorption, distribution, metabolism and elimination study Q-24120, a significant reduction in serum phosphorus levels was seen in CKD subjects treated with PA21 2,000 mg iron/day for 7 days, but not in healthy subjects. Similarly, no significant changes in serum phosphorus were seen in any of the Phase 1 studies conducted in healthy subjects, including dose-ranging/dose-escalation tolerability studies and DDI studies. Across studies in healthy volunteers, the phosphorus lowering potential of PA21 was suggested with a trend towards slightly reduced urinary phosphorus excretion. PA21 was well tolerated in these studies with mainly mild GI adverse events (AEs) reported (e.g., diarrhoea and discoloured faeces). Furthermore, in Study Q-24120, absorption of iron from PA21 was low in CKD patients (e.g., 0.04%) indicating that the potential for iron accumulation is expected to be low in CKD patients.

Efficacy and safety have been further established in 2 pivotal clinical studies: PA-CL-03A and PA-CL-05A/PA-CL-05B which included 835 PA21-treated CKD patients on dialysis. A rapid reduction in serum phosphorus levels was demonstrated in both these studies at doses of ≥1,000 mg iron/day PA21 and was maintained over 52 weeks in PA-CL-05A/05B.

Study PA-CL-03A was a 6-week open-label, randomised, active-controlled, dose-ranging study (250 to 2,500 mg iron/day PA21) in CKD patients on HD. PA21 doses of 1,000 to 2,500 mg iron/day were shown to significantly reduce serum phosphorus in a dose-dependent manner whereas the 250 mg iron/day low dose (LD) was shown to be ineffective. Pair-wise comparisons of the PA21 LD (250 mg iron/day) to each of the higher PA21 doses for the primary endpoint (change from baseline in serum phosphorus) were statistically significant for the 2,000 mg iron/day and 2,500 mg iron/day dose groups in the full analysis set (FAS), and for all of the higher dose groups in the per-protocol set (PPS). The 1,000 and 1,500 mg iron/day doses of PA21 showed similar efficacy to 4.8 g/day of sevelamer HCl (Renagel®).

Study PA-CL-05A was a confirmatory, 27-week, 2-stage, re-randomisation, withdrawal study demonstrating maintenance of efficacy and safety of PA21 in CKD patients on HD and non-inferiority compared to sevelamer carbonate (Renvela®) in CKD patients on HD or PD. In Stage 1, subjects received PA21 (N=707) at a starting dose of 1,000 mg iron/day, or sevelamer carbonate (N=348) at a starting dose of 4.8 g/day. (Note: As both sevelamer HCl and sevelamer carbonate contain the same active moiety, and are therapeutically equivalent, "sevelamer" will be used throughout the remainder of the protocol.)

Dosing of both drugs was titrated to effect, based on the upper limit of the KDOQI target serum phosphorus range of 1.13 to 1.78 mmol/L (3.5 to 5.5 mg/dL), after which subjects were continued on a maintenance dose (MD) of either PA21 or sevelamer. The maximum dose of PA21 administered was 3,000 mg iron/day.

A rapid reduction in serum phosphorus levels was observed in both treatment groups, and at Week 12, PA21 was shown to be non-inferior to sevelamer, with a markedly reduced pill burden. Efficacy was maintained through Week 24 (end of Stage 1). In Stage 2, the continued effect of the Week 24 MD in subjects on HD was demonstrated in the 3-week withdrawal phase in which the PA21 MD (mean of 1,480 mg iron/day (2.9 tablets/day) was shown to be superior ($p<0.001$) to the non-effective LD control (which in this study essentially functioned as a placebo control), thereby confirming the long-term efficacy of PA21 in lowering serum phosphorus. The effectiveness of PA21 was further supported by the Japanese Phase 3 studies.

The long-term maintenance of treatment effect over 52 weeks was demonstrated in the extension study, PA-CL-05B, in which subjects continued treatment with the same PB and at the same dose as at the end of Study PA-CL-05A. Minimal changes in serum phosphorus levels were observed in both treatment groups, with mean serum phosphorus levels remaining controlled at around the upper limit of the KDOQI target range (i.e., 1.78 mmol/L (5.5 mg/dL)). Based on subgroup analyses, efficacy was not affected by age, gender, race, or dialysis modality (HD or PD). The mean daily dose of PA21 in PA-CL-05B was 2,020 mg iron/day (4.0 tablets/day) compared to 8.1 g/day sevelamer (10.1 tablets/day).

Together, the combined studies PA-CL-05A/05B demonstrated the efficacy of PA21 in control of serum phosphorus levels, both in initially lowering, and then maintaining, serum phosphorus levels through 52 weeks of treatment, and with a reduced pill burden compared to sevelamer. Over the combined studies, the mean (median) number of tablets/day was 3.3 (3.1) and 8.7 (8.1), for PA21 and sevelamer, respectively.

PA21 was well tolerated in these pivotal studies at doses of up to 3,000 mg iron/day for up to 55 weeks duration. With the exception of common GI events of diarrhoea and faeces discolouration, recognised effects of oral compounds containing iron, the overall AE profile of PA21 was broadly similar to sevelamer, and consistent with background disease in this population of CKD patients on dialysis.

In studies PA-CL-05A/05B combined, treatment-emergent adverse events (TEAEs) of diarrhoea were reported in 23.6% of PA21-treated subjects (versus 11.5% of sevelamer-treated subjects). The majority of these diarrhoea TEAEs occurred early after starting treatment, were mild in severity, and resolved with continued use of PA21. The second most common GI TEAE in the PA21 group was discoloured faeces (16.1%). No safety concerns were raised by a comprehensive assessment of laboratory tests which included electrocardiograms, haematology, and chemistry tests.

There were no remarkable differences in the incidence of severe AEs, serious adverse events (SAEs), or deaths between PA21 and sevelamer groups over 52 weeks of treatment. Very few of the severe TEAEs and SAEs were considered related to study medications with no differences between groups. Thirty-five (3.3%) subjects died during the study/follow-up: 21 (3.0%) in the PA21 treatment group and 14 (4.0%) in the sevelamer group. No deaths were considered related to study treatments.

2. RATIONALE

As the efficacy and safety of PA21 has been confirmed in adult patients with CKD on dialysis, the aim of this Phase 3 clinical study is to demonstrate similar efficacy of PA21 in paediatric and adolescent patients with CKD, and to provide safety and dosing information for this patient population. The Phoslyra group provides information for a descriptive comparison of PA21 against a commonly used calcium-based phosphate binder (calcium acetate). Approximately130 patients (PA21:100 subjects; Phoslyra: 30 subjects) will be recruited and randomised in a 2-stage study design.

A Data and Safety Monitoring Board (DSMB) will oversee the study to protect the safety of study participants.

The screening period is up to 4 weeks and the washout period is up to 3 weeks.

Stage 1 is an open-label, randomised, active-controlled, dose titration of PA21 and Phoslyra® for up to 10 weeks.

Stage 2 is an open-label, long-term safety extension of PA21 and Phoslyra for 24 weeks.

Follow-up is 14 days after the final on-treatment visit.

An open-label design has been employed as it is not considered essential or necessary to conduct the study in a double-blind fashion to obtain the required safety and efficacy data. In addition, a double-dummy design comparing PA21 with Phoslyra would lead to an unreasonably high number of doses to be taken by the subjects who typically are already taking a large number of medications to treat other co-existing diseases/morbidities. Dialysis patients have been reported to have one of the highest daily medication burdens of any chronic disease state, and in 1 study the median daily pill burden was 19 [65]. In addition, the key efficacy parameter - serum phosphorus level - is an objective, precise and reproducible blood assay routinely performed in clinical laboratories and is not subject to bias as a consequence of the open design. Finally, to minimise selection bias, a central global randomisation procedure (using interactive response technology (IRT)) will be employed.

A dose titration scheme is used for both PA21 and Phoslyra since this reflects normal clinical practice. In order to protect study participants, controlled starting doses of both treatment groups will be administered at the beginning of Stage 1, as detailed in Table 3 and Table 5. Phoslyra subjects in each age group will all receive either the same mg/kg dose or receive an equivalent dose of their previous PB, calcium-based or sevelamer, whichever is considered most appropriate by the Investigator. Subjects can have their dose titrated for efficacy reasons, provided they have received that dose for a minimum of 2 weeks. Titration can occur at any time for safety or tolerability reasons. Since many factors affect serum phosphorus levels (such as diet and dialysis) doses of PBs have to be individualised for each patient. Experience from Vifor Pharma studies in adults show that maximum phosphorus lowering effects of PA21 are usually seen within 1-2 weeks of

PA21 treatment. Moreover, in published paediatric trials with various PBs, dose titration intervals of 1 to 4 weeks are used [44,45,66,67,68].

Table 3 Stage 1 Starting Dose of PA21: Total Daily Dose

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

In addition, maximum doses per day, plus maximum dose increases and decreases, for both treatments (for each age group) will be controlled as detailed in Table 4, Table 5 and Table 6.

Table 4 PA21 Dosing Regimens

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

Table 5 Stage 1 Starting Dose and Dosing Regimen of Phoslyra (All Age Group)

Initial Dose	Dose Increase or Decrease	Maximum Dose (up to 35 kg)	Maximum Dose (above 35 kg)
0.45 mL/kg/d	0.1 to 0.2 mL/kg/d	1.25 mL/kg/d	44 mL/d

Note: Individual doses will be administered in 0.5 mL increments.

Table 6 Maximum Daily Dose of Phoslyra

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

1 Acceptable daily intake of 25 mg/kg/day for propylene glycol.
2 Limit of the calcium intake (1,500 mg/day).

Table 7 Age Related Safety Limits of Serum Phosphorus

Age	Upper Safety Limit		Lower Safety Limit	
	mmol/L	mg/dL	mmol/L	mg/dL
0 to <1 year	2.91	9.0	1.62	5.0
≥1 year to <6 years	2.42	7.5	1.45	4.5
≥6 years to <13 years	2.26	7.0	1.13	3.5
>13 years to <18 years	2.26	7.0	0.81	2.5

Note: Limits calculated as upper limit of normal ±20% based on National Kidney Foundation Kidney Disease Outcomes Quality Initiative, 2008.

Throughout the study stopping rules will apply if a subject's serum phosphorus level exceeds, or is below, the safety limits detailed in Table 7 (see Section 5.4).

A period of 1-3 weeks for the washout period is considered appropriate to allow sufficient time for washout of previous PBs before subjects are randomised into Stage 1. HP is an asymptomatic condition and its adverse consequences require many years to develop. Therefore this short period should not lead to adverse clinical effects. Subjects will continue to receive their regular dialysis sessions and will be advised to adhere to their phosphate restricted diet; both measures in themselves will limit the rise in serum phosphorus levels. Furthermore, a serum phosphorus safety withdrawal limit detailed in Table 7 will ensure that subjects do not have excessively high serum phosphorus levels during this short period.

Clinical data to date have shown that PA21 is generally well tolerated in adults and there have been no safety signals to indicate that a paediatric study should not be conducted.

Overall, the safety profile of PA21 in the paediatric population is expected to be comparable to that in adults, similar to calcium containing PBs and sevelamer, for which a similar safety profile between adult and paediatric patients has been shown [8,35,44].

The starting doses of PA21 have been determined using the known phosphate-binding capacity of PA21, and the recommendations of the NKF KDOQI nutrition guidelines for children with CKD [69]. The phosphate binding capacity is expressed as mg phosphorus, bound by 1 mg of the iron content of PA21. The biochemistry of phosphate binding has been well characterised. Results from the nonclinical studies have provided robust information allowing calculation of the appropriate dose of PA21 for the investigation of the phosphate binding capacity in vivo. PA21 has been shown to bind in vivo approximately 0.2 mg of phosphorus for each mg of iron at pH 3.0 (IB). A dose of 500 mg iron would therefore be expected to bind 100 mg phosphorus.

In addition to the amount of dietary phosphate to be bound by the starting doses, consideration has also been given to clinical experience with PA21. In the Phase 3 studies (PA-CL-05A and PA-CL-05B), a maximum dose of 3,000 mg iron/day has been safely given to adult patients with CKD, equating to an exposure of approximately 43 mg iron/kg (assuming a 70 kg person). It should be noted that the AE profile of PA21 is mainly defined by GI events, primarily diarrhoea which are mainly mild and not treatment limiting. The proposed starting doses of PA21 are similar or below this exposure level. For example, with reference to growth charts (e.g., Centers for Disease Control and Prevention growth charts), a baby of approximately 5.0 kg would be exposed to approximately 25.0 mg iron/kg of PA21. In the event that the starting dose is not well tolerated, the protocol will allow downward titration.

For Phoslyra, the phosphate binding capacity in vivo of calcium acetate is expected to be 45 mg of phosphorus bound for each 1 g of calcium acetate [35]. Each 5 mL of Phoslyra contains 667 mg calcium acetate (equal to 169 mg calcium i.e., each 1 mL contains 33.8 mg of calcium). A dose of 6.0 mL of Phoslyra would therefore be expected to bind approximately 36 mg phosphorus.

The starting dose of Phoslyra was selected as 0.45 mL/kg/day, i.e., divided into 3 meals per day with approximately 0.15 mL/kg for each meal. The recommended Phoslyra starting dose in adults as per Phoslyra package insert is 10 mL with each meal or 0.14 mL/kg/meal for a 70 kg adult, and most adult patients require 15 mL to 20 mL per meal [70] (0.21 to 0.28 mL/kg/meal). This dose range includes the estimated Phoslyra dose (0.27 mL/kg/meal) derived from the Pieper publication. On the basis of the publication by Pieper and the starting dose in adult patients (0.14 mL/kg/meal for a 70 kg adult), an initial paediatric starting dose for the titration stage was as 0.45 mL/kg/day, i.e., divided into 3 meals per day with approximately 0.15 mL/kg for each meal. The proposed starting doses for both PA21 and Phoslyra are shown in Table 3 and Table 5.

Pieper et al, 2006 [44] reported that an adequate calcium acetate dose in paediatric patients is 110 mg/kg/day with a standard deviation of 44 mg/kg/day. The calcium acetate

concentration in Phoslyra is 133.4 mg/mL; a Phoslyra volume of 0.82 mL contains 110 mg of calcium acetate. Thus, based on the publication by Pieper, an estimated adequate daily dose of Phoslyra would be 0.82 mL/kg/day and assuming 3 meals per day, the estimated dose per meal would be 0.27 mL/kg/meal.

The dietary referenced intake (DRI) of phosphorus in children with CKD is shown in Table 8 [69], along with an estimate of the amount of phosphorus required to be bound per day in each of the age groups. In hyperphosphataemic children it is recommended that the phosphorus intake be limited to ≤80% of the DRI.

Table 8 Recommended Maximum Oral and/or Enteral Phosphorus Intake for Children with CKD

Age	DRI (mg/d)	Recommended Phosphorus Intake (mg/d)		VFMCRP Estimate PB Required to Bind Approx. (mg/day) (DRI Minus High PTH/High Phosphorus)
		High PTH and Normal Phosphorus[1]	High PTH and High Phosphorus[2]	
0-6m	100	≤100	≤80	20
7-12m	275	≤275	≤220	55
1-3 y	460	≤460	≤370	90
4-8 y	500	≤500	≤400	100
9-18 y	1,250	≤1,250	≤1,000	250

1 ≤100% of the DRI.
2 ≤80% of the DRI.
Notes: CKD=Chronic kidney disease; DRI=Dietary referenced intake; PB=Phosphate binder; PTH=Parathyroid hormone; VFMCRP=Vifor Fresenius Medical Care Renal Pharma.
Source: Adapted from Kidney Disease Outcomes Quality Initiative Clinical Practice Guideline for Nutrition in Children with CKD: 2008 Update [69].

Vifor Fresenius Medical Care Renal Pharma has estimated the amount of phosphorus required to be bound in each of the age groups based on the phosphorus intakes in Table 8. In establishing the daily maximum dose for Phoslyra, the maximum daily intake of calcium was also taken into consideration. The publication by Pieper et al, 2006 does not identify a maximum calcium acetate dose in the paediatric population. However, the paediatric KDOQI guidelines for patients with CKD (Stage 5) on dialysis recommend that the calcium intake from phosphate binders should be limited to 1,500 mg/day, equivalent to 45 mL of Phoslyra.

As detailed in Table 17, the formulation of Phoslyra consists of propylene glycol (PG) USP. The PG concentration of Phoslyra is 20 mg/mL. Propylene glycol (PG) is a clear, colourless, water-soluble alcohol (1, 2-propanediol) used as a co-solvent in parenteral and non-parenteral pharmaceutical formulations containing active substances that are not highly soluble in water. It is also used in cosmetics products and in the food industry as a humectant, as a preservative and as a vehicle for flavours in preference to ethanol [71].

On the basis of metabolic and toxicological data, the Joint Food and Agriculture Organization of the United Nations/World Health Organization Expert Committee on Food Additives, International Programme on Chemical Safety, Chemical Safety

Information from Intergovernmental Organizations [72] defined an acceptable daily intake (ADI) of 25 mg/kg/day for PG from all sources. (The ADI value is based on the no observed effect level in a long-term toxicity study in rats of 2,500 mg/kg body weight/day). The ADI of 25 mg/kg/day has been used to evaluate the PG exposure in this paediatric study. The PG concentration of Phoslyra is 20 mg/mL. A Phoslyra dose greater than 1.25 mL/kg/day would therefore exceed the PG ADI for food products. Based on the limit of the calcium intake (1,500 mg/day), and ADI of PG (25 mg/kg/day), the maximum Phoslyra dose was determined in Table 5 and Table 6.

A calcium–based PB (Phoslyra: calcium acetate) has been chosen as an active control to provide assay sensitivity and comparison with respect to the serum phosphorus lowering effects and AE profile of PA21 against a PB in a drug class commonly used in clinical practice. Although calcium acetate is not specifically approved for use in the paediatric population it has been chosen as the active comparator since calcium-based PBs are considered "gold-standard" for the treatment of HP in the paediatric patients under evaluation in this study [35,38]. No formal sample size has been calculated for the comparison with Phoslyra. The number of subjects that would be required to demonstrate equivalence or non-inferiority of PA21 against an active control would be too high and not feasible in a paediatric population.

In order to reduce the risk of hypercalcaemia and hypocalcaemia, stopping rules will apply throughout the study if, a subject's serum total corrected calcium exceeds, or is below the safety limits detailed in Table 9 (see Section 5.4).

Table 9 Age Related Safety Limits for Total Calcium

Age	Upper Safety Limit		Lower Safety Limit	
	mmol/L	mg/dL	mmol/L	mg/dL
0 to <1 year	2.75	11.0	<1.9	<7.6
≥1 year to <6 years	2.70	10.8	<1.9	<7.6
≥6 years to <13 years	2.60	10.3	<1.9	<7.6
≥13 years to <18 years	2.60	10.2	<1.9	<7.6

Note: Upper safety limits based on National Kidney Foundation Kidney Disease Outcomes Quality Initiative Nutrition Guidelines, 2008. Lower limit based on literature (Paediatric Nephrology, 2nd edition) and personal communication.

A recent study has shown that more frequent dosing of a PB throughout the day is more effective than once daily dosing [73]. In this study, subjects will be advised to take their treatment 3 times per day, where possible. This dosing regimen will allow more flexibility and better spread of drug administration during the day, thus ensuring that more meals can be consumed with a study treatment.

In the Phase 2 and 3 adult studies only subjects undergoing dialysis were studied. This study, however, will recruit CKD Stage 4, 5 and 5D paediatric patients. This is considered appropriate since all types of patients are essentially similar with respect to causes and natural history of their renal failure. In addition, NKF KDOQI Guideline 6 [35]

recommends treatment with PBs for hyperphosphataemic paediatric patients with CKD Stages 2-5 and UK National Institute for Health and Clinical Excellence recommends use of PBs in hyperphosphataemic paediatric patients with CKD Stages 4-5 [38].

3. STUDY OBJECTIVES

3.1 Primary Objective

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

3.2 Secondary Objectives

- To evaluate the efficacy of PA21 in maintaining the serum phosphorus lowering effects in paediatric and adolescent subjects with CKD at the end of Stage 2.

- To evaluate the safety of PA21 in paediatric and adolescent subjects with CKD.

- To evaluate the efficacy of Phoslyra in reducing and maintaining serum phosphorus levels in paediatric and adolescent subjects with CKD at the end of Stages 1 and 2.

- To evaluate the safety of Phoslyra in paediatric and adolescent subjects with CKD.

4. INVESTIGATIONAL PLAN

4.1 Overall Study Design

This is a Phase 3, multicentre, randomised, prospective, open-label controlled study performed at global study centres.

See Study Design (Figure 1) and Schedule of Events (Table 1).

The study will aim to randomise approximately 130 subjects into the study via IRT.

The study will also aim to randomise a minimum number of subjects from each age group (Table 10).

Table 10 Minimum Number of Randomised Subjects by Age Group

Age	PA21	Phoslyra®
0 to <1 year	4	1
≥1 year to <6 years	10	3
≥6 years to <9 years	10	3
≥9 years to <18 years	10	3

Subjects for whom signed and dated informed consent (and, where appropriate/required, assent) has been provided will be enrolled in the study and screened.

The screening period is up to 4 weeks.

The washout period is up to 3 weeks.

Stage 1 is an open-label, randomised, active-controlled, dose titration period of PA21 and Phoslyra for up to 10 weeks. One hundred subjects will be randomised to receive PA21 and 30 subjects will be randomised to receive Phoslyra. PA21 subjects will receive PA21 at a starting dose based on their age, as detailed in Table 3. Phoslyra subjects will receive Phoslyra, either at a starting dose as detailed in Table 5, or, if considered more appropriate by the Investigator, at an equivalent dose of their previous PB, calcium-based or sevelamer. Doses of PA21 or Phoslyra will be increased or decreased as required for efficacy (to achieve age specific target serum phosphorus level as indicated in Table 11), provided a subject has been receiving that dose for a minimum of 2 weeks, and for safety or tolerability reasons at any time. Increases or decreases in dose and maximum doses are detailed in Table 4 for PA21, and Table 5 and Table 6 for Phoslyra. From Week 4, once a subject achieves the age specific target serum phosphorus level, as indicated in Table 11, they can move to Stage 2.

Table 11 Age Related Serum Phosphorus Targets Post-Randomisation

Age	mmol/L	mg/dL
0 to <1 year	1.62-2.52	5.0-7.8
≥1 year to <6 years	1.45-2.10	4.5-6.5
≥6 years to <13 years	1.16-1.87	3.6-5.8
≥13 years to <18 years	0.74-1.45	2.3-4.5

Source: National Kidney Foundation Kidney Disease Outcomes Quality Initiative Nutrition Guidelines, 2008.

Stage 2 is an open-label, long-term safety extension for 24 weeks. All subjects will enter this safety extension stage. During Stage 2:

- Subjects will continue on the dose they received at the end of Stage 1, unless a dose change is required.
- All subjects may have their dose titrated for efficacy to achieve age-specific target serum phosphorus levels as indicated in Table 11 (provided the subject has taken the dose for a minimum of 2 weeks) and safety or tolerability reasons at any time during Stage 2. Maximum doses and dose increases/decreases of PA21 and Phoslyra are detailed in Table 4, Table 5 and Table 6.

The follow-up period will be 14 days after end of study treatment.

The schedule of assessments is provided in the Schedule of Events (Table 1).

Table 2 (Summary of Blood Samples), details visits where blood samples must be analysed by a central laboratory and visits where there is the option of having blood samples analysed by a local laboratory.

Since subjects may become 18 years old during the study, all values quoted in the protocol for subjects <18 years will also apply to these subjects. Once a subject is 18 years old they must provide informed consent, as described in the inclusion criteria (Section 5.2).

The Investigator is responsible for ensuring that consideration is given to the post study care of the subject's medical condition.

There will be an external DSMB for this study.

Protocol waivers or exemptions are not allowed, with the exception of immediate safety concerns. Therefore adherence to the study design requirements, including those specified in the Schedule of Events, Table 1 are essential and required for study conduct.

4.2 Duration of Subject Participation and Study

The expected duration of subject participation is a maximum of 43 weeks including up to 4 weeks screening period; up to 3 weeks washout period, up to 10 weeks dose titration

period; 24 weeks safety extension. All subjects, whether completing the study or withdrawn prematurely, will be followed up 14 days after their last study visit.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Number of Subjects

For detailed justification of the sample size please refer to Section 12.2.

Approximately 130 subjects will be randomised into the Stage 1 titration period of this study: 100 subjects will receive PA21 and 30 subjects will receive Phoslyra. The randomisation into Stage 1 will be stratified by age group with the objective of randomising a minimum number of subjects from each age group as detailed in Table 10.

All eligible subjects will enter Stage 2, the safety extension stage.

Recruitment will be on a competitive basis.

No replacement of subjects will be allowed in Stages 1 or 2.

5.2 Inclusion Criteria

Investigators must maintain a screening log of all potential study candidates that includes limited information about the potential candidate, date, and outcome of the screening process (e.g., enrolled into study, reason for ineligibility, or refused to participate). The following inclusion criteria must be met for each subject:

1. Subjects 0 to <18 years at time of consent.

2. Subjects with hyperphosphataemia i.e., with serum phosphorus levels indicated in Table 28.

3. Subjects who are PB naïve or have been receiving stable doses of a PB(s) for at least 1 month prior to screening. Subjects may be on stable doses of a maximum of 2 PBs. Subjects who have been receiving PBs will enter an obligatory washout period and may be randomised once their serum phosphorus levels are as indicated in Table 28. Subjects already receiving a PB but with serum phosphorus levels indicated in Table 28 may be eligible for randomisation without a washout period.

4. Subjects ≥1 year with CKD Stages 4-5 defined by a glomerular filtration rate <30 mL/min/1.73 m2 or with CKD Stage 5D receiving adequate maintenance HD or PD for at least 2 months prior to screening.

5. Subjects <1 year must have CKD.

6. PD subjects must have had 1 month of unchanged PD prescription (volume and number of exchanges). Home HD subjects may be included (no nocturnal HD (overnight stay at site) will be allowed).

7. Appropriate written informed consent and, where appropriate/required assent, have been provided. Written informed consent (and, where appropriate/required, assent) must be provided before any study-specific procedures are performed, including screening procedures.

8. Parents/legal guardians and, where appropriate/required, subjects with the ability to provide written informed consent, and where appropriate/required, assent, to understand the requirements of the study and abide by the study restrictions, and who agree to return for the required assessments, in the Investigator's opinion.

5.3 Exclusion Criteria

1. Subjects with hypercalcaemia at screening as indicated in Table 9.

2. Subjects with intact parathyroid hormone (iPTH) levels >700 pg/mL at screening.

3. Subjects who are PB naïve who weigh <5 kg at screening. Subjects receiving stable doses of PBs who weigh <6 kg at screening. (In order to comply with maximum blood sample volumes in paediatric clinical trials [75]).

4. Subjects requiring feeding tube sizes ≤6 FR (French catheter scale).

5. Subjects with planned or expected parathyroidectomy within the next 12 months, in the Investigator's opinion.

6. Subjects with history of:

   - Major GI surgery which, in the Investigator's opinion, is likely to influence the outcome of treatment with PBs.

   - Significant GI disorders.

7. Subjects with estimated life expectancy of less than 12 months.

8. Subjects with known seropositivity to human immunodeficiency virus.

9. Subjects with a history of haemochromatosis or other iron accumulation disorders.

10. Subjects on PD with a history of peritonitis in the last 3 months or ≥3 episodes in the last 12 months.

11. Subjects with hypocalcaemia (serum total corrected calcium <1.9 mmol/L; <7.6 mg/dL) at screening.

12. Subjects with raised alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of the normal range based on central laboratory results at screening.

13. Subjects taking more than 2 PBs concomitantly prior to screening.

14. Subjects taking any prohibited medication(s) (See Section 7.7).

15. Subject has known hypersensitivity and/or intolerance to any of the active substances or to any of the excipients to be administered.

16. Subject has previously been randomised into this study.

17. Subject is currently enrolled in or has completed any other investigational device or drug study <30 days prior to screening, or is receiving other investigational agent(s).

18. Subject is pregnant (e.g., positive human chorionic gonadotropin test) or breast feeding.

19. If of child-bearing potential, subject is not using adequate contraceptive precautions. Subject must agree to use a highly effective method of birth control during the study and for 1 month after the last dose of study medication. Adequate methods of birth control are defined as those which result in a low failure rate (i.e., <1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intra-uterine devices, sexual abstinence or vasectomised partner. Non-child-bearing potential includes being surgically sterilised at least 6 months prior to the study.

20. Subject has a history of drug or alcohol abuse within 2 years prior to screening.

21. Subject has a significant medical condition(s) e.g., uncontrolled diabetes, known hepatitis B surface antigen positivity and/or hepatitis C virus ribonucleic acid positivity or anticipated need for major surgery during the study, or any other kind of disorder that may be associated with increased risk to the subject, or may interfere with study assessments or outcomes.

5.4 Withdrawal of Subjects

Subjects may voluntarily withdraw, or their parents/legal guardian may withdraw them, from study participation at any time without having to provide a reason. Subjects may be withdrawn because of the appearance of a new health condition requiring care or medications prohibited by the protocol, unacceptable AEs, refusal to continue treatment, or at the Investigator's discretion if it is in the subject's best interest.

5.4.1 Stopping Rules for Serum Phosphorus Levels

At any time during the study if a subject's phosphorus level exceeds or is below the safety limits indicated in Table 7:

- The subject's study medication must be adjusted and the subject must be asked to return for a visit 1 week after the value outside the safety limits indicated in Table 7 was first seen i.e., irrespective of whether this was during Stage 1 or 2.

- At the next visit, 1 week after the value outside the safety limits indicated in Table 7 was first seen; a blood sample for serum phosphorus will be taken. Once the site receives the blood sample result, if the serum phosphorus level is outside the target safety limits indicated in Table 7, the Investigator will inform the subject and, where appropriate, parent/legal guardian, (either directly or by phone) whether a dose increase or a dose decrease of study medication is indicated. The subject must return for a visit 1 week after the change in study medication dose.

- At the next visit, 1 week after the change in study medication dose, a blood sample for serum phosphorus will be taken. Once the site has the blood sample result, if the subject's phosphorus level still exceeds or is below the safety limits indicated in Table 7 then the subject must be withdrawn from the study.

In addition, at each of the above visits, if the subject's phosphorus level exceeds the upper safety limit indicated in Table 7, the site must advise the subject and parent/carer regarding a low phosphorus diet.

The subject does not need to be withdrawn if the 2 follow-up results are outside of the safety limit, but in the opposite direction (i.e., one too high and one too low). In this situation, the subject's PB dose must be adjusted and the subject must return in 1 week to provide a blood sample for serum phosphorus. Once the site has the blood sample result, if the subject's phosphorus level still exceeds or is below the safety limits indicated in Table 7, then the subject must be withdrawn from the study.

5.4.2 Stopping Rules for Serum Corrected Total Calcium Levels

At any time during the study, subjects will be withdrawn immediately if their serum corrected total calcium level exceeds 3.0 mmol/L (12 mg/dL) or is below 1.63 mmol/L (6.5 mg/dL).

At any time during the study if a subject's corrected total calcium level exceeds or is below the safety limits indicated in Table 9:

- The subject should receive appropriate rescue intervention and must be asked to return for a visit 1 week after the value outside the safety limits indicated in Table 9 was first seen.

- At the next visit, 1 week after the value outside the safety limits indicated in Table 9 was first seen; a blood sample will be taken. Once the site has the blood sample result, if the serum corrected total calcium level is outside the target safety limits indicated in Table 9, the Investigator will inform the subject and, where appropriate, parent/legal guardian, (either directly or by phone) whether a dose increase or a dose decrease in rescue medication or an alternative rescue medication is indicated. The subject must return for a visit 1 week after the change in rescue medication.

- At the next visit, 1 week after the change in rescue medication, a blood sample will be taken. Once the site has the blood sample result, if the subject's corrected total calcium level still exceeds or is below the safety limits indicated in Table 9 then the subject must be withdrawn from the study.

The subject does not need to be withdrawn if the 2 follow-up results are outside of the safety limit, but in the opposite direction (i.e., one too high and one too low). In this situation, the subject's rescue medication must be adjusted and the subject must return in 1 week to provide a blood sample. Once the site has the blood sample result, if the subject's serum corrected total calcium level still exceeds or is below the safety limits indicated in Table 9, then the subject must be withdrawn from the study.

Appropriate rescue intervention for hypercalcaemia may include:

- Reduce or stop dose of active Vitamin D metabolite.
- Increase dose of calcimimetic.
- Reduce calcium content in dialysate.
- Phoslyra subjects: reduce dose of Phoslyra.

Appropriate rescue intervention for hypocalcaemia may include:

- Increase dose of active Vitamin D metabolite.
- Decrease dose of calcimimetic.
- Increase calcium content in dialysate.

5.4.3 Other Reasons for Withdrawal

Subjects will also be withdrawn if:

- It is necessary to add an additional PB to the treatment regimen.
- They receive a kidney transplant.
- Dialysis is initiated in pre-dialysis subjects.
- They become pregnant. Subject must be withdrawn immediately (pregnancy is to be recorded with the same timelines as an SAE). In case of pregnancy the procedure described in Section 10.3.3 must be followed.

Any measures taken must be documented by the Investigator in the appropriate sections of the subject's case report form (CRF) and source documentation.

If a subject withdraws from the study at any time either at his or her request, or at his or her parents/legal guardian request, or at the Investigator's discretion, the reason(s) for withdrawal must be recorded on the relevant page of the subject's CRF and source documentation. Subjects who are withdrawn from the study prematurely should, if possible, undergo all end of study assessments.

Any subject who has been treated with study medication, whether completing the study or withdrawn prematurely, will be followed up 14 days after their last scheduled study visit to collect any new AEs and concomitant medications.

It is vital to obtain follow-up data on any subject withdrawn because of an AE. Every effort must be made to undertake protocol-specified safety follow-up procedures (see Section 10.3). If a subject is discontinued due to an AE, the event should be followed by the Investigator through contact with the subject until resolution or stabilisation has occurred. All drug related AEs should be followed until resolution, stabilisation or the subject is lost to follow-up and cannot be contacted. If a subject and/or his/her parent/legal guardian refuses to continue study procedures, the reason for refusal should be fully documented in the subject's source document and recorded in the study-specific CRF. It is the subject's right to withdraw (and/or his/her parents/legal guardian right to withdraw the subject) from the trial without providing a reason. In this case, the source documents and the CRF should document the reason for discontinuation as "withdrawal of consent" or "withdrawal of assent".

6. RANDOMISATION PROCEDURES

6.1 Randomisation

All screened subjects must be identifiable throughout the study by a unique subject number. The Investigator will maintain a list of these subject numbers and subject names to enable records to be found at a later date.

In Stage 1, at the end of screening or washout (where required), approximately 130 eligible subjects will be randomised via IRT to either PA21 (100 subjects) or to Phoslyra (30 subjects), respectively, and will enter the treatment period. Each subject will receive a randomisation number which they will retain for the duration of their participation. The randomisation list will be stratified by age group to satisfy the criteria described in Section 5.1. Subjects in each age group will receive their allocated dose as detailed in Table 3.

Randomisation will be performed based on a predefined randomisation list. Randomised subjects who terminate their study participation for any reason regardless of whether the study drug was taken or not, will retain their randomisation number.

In Stage 2, subjects continue on either PA21 or Phoslyra for a further 24 weeks safety extension.

Details on IRT will be provided in the study documentation

6.2 Blinding

The study is open-label.

7. STUDY TREATMENTS

7.1 Dosage Forms/Formulation

All investigational medicinal products used in this study have been manufactured in accordance with current Good Manufacturing Practice (GMP) [74]. The study formulations are summarised in Table 12.

Table 12 Overview of Formulations

API	PA21	PA21	Phoslyra®
Dosage form	Powder for oral suspension	Chewable tablet	Oral solution
Appearance	Red-brown powder	Red-brown tablet	Pale to light greenish-yellow clear liquid
Dosage strengths (mg)	125, 250, 500	250, 500	Each 5 mL contains 667 mg calcium acetate, equal to 169 mg (8.45 mEq) calcium
Primary packaging	CR sachet	PP tube with CR closure	Amber-coloured, multiple-dose PET bottles with a CR closure.

Notes: API=Active pharmaceutical ingredient; CR=Child-resistant; PET=Polyethylene terephthalate; PP=Polypropylene.

Responsibility for manufacture, quality control, primary packaging and batch release of investigational treatment are summarised in Table 13.

Table 13 Responsibility for Manufacture, Quality Control, Primary Packaging and Batch Release

API	PA21	PA21	Phoslyra®
Dosage form	Powder for oral suspension	Chewable tablet	Oral solution
Manufacture (bulk)	Patheon	Catalent	Lyne Laboratories, Inc.
Primary packaging	Patheon	Catalent	Lyne Laboratories, Inc.
Quality control	Vifor Int.	Vifor Int.	Vifor or CMO
Batch release	Vifor Int.	Vifor Int.	Vifor or CMO

Notes: API=Active pharmaceutical ingredient; CMO=Clinical Manufacturing Organisation.

Addresses of the drug manufacturers are provided in Table 14.

Table 14 Addresses of Drug Product Manufacturers

Catalent Germany Schorndorf GmbH, Steinbeissstrasse 1 and 2, 73614 Schorndorf, Germany
Vifor (International) Inc., Rechenstrasse 37, 9014 St. Gallen, Switzerland
Patheon France S.A.S., 40 Boulevard de Champaret, 38317 Bourgoin-Jallieu, France
Lyne Laboratories Inc., Brockton, MA 02301, US

7.1.1 PA21 Chewable Tablet

The composition of PA21 chewable tablets is provided in Table 15.

Table 15 Composition of PA21 Chewable Tablet

Product Code		**YT318**	**YT326**	
Component	**Function**	**Quantity per Tablet (mg)**	**Quantity per Tablet (mg)**	**Test Method**
PA21-2 drug substance (sucroferric oxyhydroxide), corresponding to iron(III)	Active ingredient	2,500.00[(1)] 500.00	1,250.00[(1)] 250.00	In-house method
Silica (colloidal, anhydrous)	Flow aid	12.49	6.245	Ph. Eur./USP/NF
Woodberry flavour	Flavour	40.00	20.00	In-house method
Neohesperidin dihydrochalcone	Sweetener	0.01	0.005	Ph. Eur.
Magnesium stearate	Lubricant	25.00	12.50	Ph. Eur./USP/NF
Total		**2,577.50**	**1,288.75**	

1 Each tablet is adjusted to 500 mg or 250 mg iron, respectively.
Notes: NF=National Formulary; Ph. Eur.=European Pharmacopoeia; USP=United States Pharmacopeia.

7.1.2 PA21 Powder for Oral Suspension

The composition of PA21 powder for oral suspension is provided in Table 16.

Table 16 Composition of PA21 Powder for Oral Suspension

Product Code		**ZF001**	**ZF002**	**ZF003**	
Component	**Function**	**Quantity per Sachet (mg)**	**Quantity per Sachet (mg)**	**Quantity per Sachet (mg)**	**Test Method**
PA21-2 drug substance (sucroferric oxyhydroxide), corresponding to iron(III)	Active ingredient	2,500[(1)] 500	1,250[(1)] 250	625[(1)] 125	In-house method
Maltodextrin	Filler/binder	1,180	590	295	Ph. Eur./USP/NF
Microcrystalline cellulose	Filler/binder	200	100	50	Ph. Eur./USP/NF
Xanthan gum	Viscosity enhancer	80	40	20	Ph. Eur./USP/NF
Silica (colloidal, anhydrous)	Flow aid	20	10	5	Ph. Eur./USP/NF
Magnesium stearate[(2)]	Lubricant	20	10	5	Ph. Eur./USP/NF
Purified water[(3)]	Solvent	–	–	–	Ph. Eur./USP/NF
Total		**4,000**	**2,000**	**1,000**	

1 Each sachet is adjusted to 500 mg, 250 mg or 125 mg iron respectively.
2 Of vegetable origin.
3 The solvent for granulation is not present in the drug product.
Notes: NF=National Formulary; Ph. Eur.=European Pharmacopoeia; USP=United States Pharmacopeia.

7.1.3 Phoslyra Oral Solution (Comparator Group)

The composition of Phoslyra oral solution is provided in Table 17.

Table 17 Summary of Quantitative Composition and Function for Phoslyra

Ingredient	Concentration per 5 mL	% w/v	Function
Calcium acetate USP	667.0 mg/5 mL[(1)]	13.34[(1)]	Active
Crystalline maltitol NF	1,000 mg/5 mL	20	Sweetener
Glycerin USP	250.0 mg/5 mL	5	Sweetener
Propylene glycol USP	100.0 mg/5 mL	2	Solvent
Magnasweet 110	125.0 mg/5 mL	2.5	Sweetener
Sucralose NF	17.5 mg/5 mL	0.35	Sweetener
Methylparaben NF	10.0 mg/5 mL	0.2	Preservative
Providone K25 USP	37.5 mg/5 mL	0.75	Solubiliser
Artificial black cherry flavour #825.083	10.0 mg/5 mL	0.2	Flavouring agent
Menthol flavour, natural #875.017	10.0 mg/5 mL	0.2	Flavouring agent
Purified water USP	Qs 5 mL		Solvent

1 On anhydrous basis.
Notes: NF=National Formulary; USP=United States Pharmacopeia.

7.1.3.1 Primary Packaging

PA21 chewable tablets (dosage strength: 500 mg iron) are stored in polypropylene tubes with a child-resistant closure, containing an integral desiccant sleeve (molecular sieve), cotton and a polypropylene insert. One tube contains 12 chewable tablets.

PA21 chewable tablets (dosage strength: 250 mg iron) are stored in polypropylene tubes with a child-resistant closure, containing an integral desiccant sleeve (molecular sieve) and cotton. One tube contains 24 chewable tablets.

PA21 powder for oral suspension (all dosage strengths) is stored in child-resistant sachets with aluminium as water-vapour barrier.

Phoslyra solution is stored in multiple-dose polyethylene terephthalate bottles 473 mL with a child-resistant closure.

7.2 Drug Dosage and Administration

7.2.1 Treatment Arms

The study will aim to randomise a minimum number of subjects from each age group as detailed in Table 10.

Throughout the study subjects randomised to receive PA21 will be provided with the most appropriate formulation i.e., either powder for oral suspension (for subjects <6 years) or chewable tablet (for subjects ≥6 years). Due to the possibility of a 125 mg/day increment for dose changes subjects in the 6 to 9 year age group will ideally

receive powder for oral suspension throughout the study. If required, subjects may change to the alternative PA21 formulation, but should remain on the same dose. For example, a subject may begin treatment with the chewable tablet but at a subsequent study visit change to the powder for oral suspension.

Stage 1 is up to 10-weeks, and is an open-label, randomised, active-controlled, parallel group, dose titration period. Subjects will be randomised to receive either PA21 or Phoslyra:

- PA21 subjects will receive PA21 at a starting dose based on their age, as detailed in Table 3.

- Phoslyra subjects will receive Phoslyra, either at a starting dose as detailed in Table 5, or, if considered more appropriate by the Investigator, at an equivalent dose of their previous PB, calcium-based or sevelamer.

Dose of PA21 (100 subjects) or Phoslyra (30 subjects) will be increased or decreased as required for efficacy (to achieve age specific target serum phosphorus level as indicated in Table 11), provided a subject has been receiving that dose for a minimum of 2 weeks, and for safety or tolerability reasons at any time. Increases or decreases in dose and maximum doses are detailed in Table 4 for PA21, and Table 5 and Table 6 for Phoslyra. From Week 4, once a subject achieves the age specific target serum phosphorus level, as indicated in Table 11, they can move to Stage 2.

Stage 2 is a 24-week, open-label, long-term safety extension period. All eligible subjects will enter this safety extension stage.

During Stage 2 all subjects will continue on the dose received at the end of Stage 1, unless a dose change is required.

- For all subjects, doses may be titrated for efficacy (to achieve age specific target serum phosphorus levels, see Table 11), provided a subject has been receiving that dose for a minimum of 2 weeks, and for safety or tolerability reasons at any time during Stage 2. Increases or decreases in dose and maximum doses are detailed in Table 4, Table 5 and Table 6.

Dose adjustments are described in Section 7.6.

Due to the large variation in feed types, volumes and regimens in the study population the protocol is not prescriptive regarding when and how the total daily dose of study drug will be administered to subjects. Investigators (in collaboration with dieticians where this is local practice) should decide the optimal way to give the total daily dose of study drug to individual subjects. This should also be discussed with the parent/legal guardian (and, where appropriate, subject).

Dosing tables (Table 18 to Table 25) are provided as a guideline only. Please also refer to Stage 1 starting doses (Table 3 and Table 5) and maximum doses per day, plus maximum dose increases and decreases (Table 4, Table 5 and Table 6).

(Note: Main meal(s) refers to meal(s) with the highest phosphate content).

7.2.1.1 Dosing of PA21 Powder for Oral Suspension

Table 18 Dosing of PA21 Powder for Oral Suspension: Subjects Age 0 to <1 Year

Total Daily Dose PA21 (mg Iron/Day)	Powder for Oral Suspension (mg Sachet)		
	Main Meal	Meal	Meal
125	125 across the day		
250	125	125 across remaining meals	
375	125	125	125
500	250	125	125
625	250	250	125
750	250	250	250
875	250 + 125	250	250
1,000	250 + 125	250 + 125	250

Table 19 Dosing of PA21 Powder for Oral Suspension: Subjects Age ≥1 Year to <6 Years

Total Daily Dose PA21 (mg Iron/Day)	Powder for Oral Suspension (mg Sachet)		
	Main Meal	Meal	Meal
500	250	125	125
625	250	250	125
750	250	250	250
875	250 + 125	250	250
1,000	250 + 125	250 + 125	250
1,125	250 + 125	250 + 125	250 + 125
1,250	500	250 + 125	250 + 125

Table 20 Dosing of PA21 Powder for Oral Suspension: Subjects Age ≥6 Years to <9 Years

Total Daily Dose PA21 mg Iron/Day)	Powder for Oral Suspension (mg Sachet)		
	Main Meal	Meal	Meal
750	250	250	250
875	250 + 125	250	250
1,000	250 + 125	250 + 125	250
1,125	250 + 125	250 + 125	250 + 125
1,250	500	250 + 125	250 + 125

Table 20 Dosing of PA21 Powder for Oral Suspension: Subjects Age ≥6 Years to <9 Years (Cont'd)

Total Daily Dose PA21 mg Iron/Day)	Powder for Oral Suspension (mg Sachet)		
	Main Meal	Meal	Meal
1,375	500	500	250 + 125
1,500	500	500	500
1,625	500 + 125	500	500
1,750	500 + 125	500 + 125	500
1,875	500 + 125	500 + 125	500 + 125
2,000	500 + 250	500 + 125	500 + 125
2,125	500 + 250	500 + 250	500 + 125
2,250	500 + 250	500 + 250	500 + 250
2,375	500 + 500	500 + 250	500 + 125
2,500	500 + 500	500 + 250	500 + 250

Table 21 Dosing of PA21 Powder for Oral Suspension: Subjects Age ≥9 Years to <18 Years

Total Daily Dose PA21 (mg Iron/Day)	Powder for Oral Suspension (mg Sachet)		
	Main Meal	Meal	Meal
1,250	500	250 + 125	250 + 125
1,500	500	500	500
1,750	500 + 250	500	500
2,000	500 + 250	500 + 250	500
2,250	500 + 250	500 + 250	500 + 250
2,500	500 + 500	500 + 250	500 + 250
2,750	500 + 500	500 + 500	500 + 250
3,000	500 + 500	500 + 500	500 + 500

7.2.1.2 Dosing of PA21 Tablet

Table 22 Dosing of PA21 Tablet: Subjects Age ≥6 Years to <9 Years

Total Daily Dose PA21 (mg Iron/Day)	Chewable Tablet (mg)		
	Main Meal	Meal	Meal
750	250	250	250
1,000	500	250	250
1,250	500	500	250
1,500	500	500	500
1,750	500 + 250	500	500
2,000	500 + 250	500 + 250	500
2,250	500 + 250	500 + 250	500 + 250
2,500	500 + 500	500 + 250	500 + 250

Table 23 Dosing of PA21 Tablet: Subjects Age ≥9 Years to <18 Years

Total Daily Dose PA21 (mg Iron/Day)	Chewable Tablet (mg)		
	Main Meal	Meal	Meal
1,250	500	500	250
1,500	500	500	500
1,750	500 + 250	500	500
2,000	500 + 250	500 + 250	500
2,250	500 + 250	500 + 250	500 + 250
2,500	500 + 500	500 + 250	500 + 250
2,750	500 + 500	500 + 500	500 + 250
3,000	500 + 500	500 + 500	500 + 500

7.2.1.3 Dosing of Phoslyra

The starting dose of Phoslyra is 0.45 mL/kg/day, equivalent to 0.15 mL/kg/meal, 3 meals per day (detailed in Table 5). The dose of Phoslyra will be increased or decreased as required to achieve age specific target serum phosphorus level as indicated in Table 11. Table 24 provides Phoslyra dose ranges per body weight, the doses take into consideration propylene glycol and calcium intakes in Table 6. Individual doses will be rounded to 0.5 mL increments to allow accurate measurement, as shown in Table 25.

Table 24 Total Daily Dose Phoslyra® (mL/Day)

Body Weight	Daily Dose Phoslyra (mL/kg/day)								
	0.45	0.55	0.65	0.75	0.85	0.95	1.05	1.15	1.25
5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0
10	4.5	5.5	6.5	7.5	8.5	9.5	10.5	11.5	12.5
15	6.5	8.0	9.5	11.0	12.5	14.0	15.5	17.0	18.5
20	9	11	13	15	17	19	21	23	25
25	11.0	13.5	16.0	18.5	21.0	23.5	26.0	28.5	31.0
30	13.5	16.5	19.5	22.5	25.5	28.5	31.5	34.5	37.5
35	15.5	19.0	22.5	26.0	29.5	33.0	36.5	40.0	43.5
40	18	22	26	30	34	38	42	44[1]	44[1]
45	20.0	24.5	29.0	33.5	38.0	42.5	44[1]	44[1]	44[1]
50	22.5	27.5	32.5	37.5	42.5	44[1]	44[1]	44[1]	44[1]
60	27	33	39	44[1]	44[1]	44[1]	44[1]	44[1]	44[1]
70	31.5	38.5	44[1]	44[1]	44[1]	44[1]	44[1]	44[1]	44[1]

1 Dose adjusted according to Table 5.

Table 25 Dosing of Phoslyra®

Total Daily Dose Phoslyra (mL/Day)	Main Meal (mL)	Meal (mL)	Meal (mL)
2.0	1.0	0.5	0.5
2.5	1.0	1.0	0.5
3	1.0	1.0	1.0
3.5	1.5	1.0	1.0
4	1.5	1.5	1.0
4.5	1.5	1.5	1.5
5	2.0	1.5	1.5
5.5	2.0	2.0	1.5
6	2.0	2.0	2.0
6.5	2.5	2.0	2.0
7	2.5	2.5	2.0
7.5	2.5	2.5	2.5
8	3.0	2.5	2.5
8.5	3.0	3.0	2.5
9	3.0	3.0	3.0
9.5	3.5	3.0	3.0
10	3.5	3.5	3.0
11	4.0	3.5	3.5
12	4.0	4.0	4.0
13	4.5	4.5	4.0
14	5.0	4.5	4.5
15	5.0	5.0	5.0
16	55	5.5	5.0
17	6.0	5.5	5.5
18	6.0	6.0	6.0
19	6.5	6.5	6.0
20	7.0	6.5	6.5
21	7.0	7.0	7.0
22	7.5	7.5	7.0
23	8.0	7.5	7.5
24	8.0	8.0	8.0
25	8.5	85.	8.0
26	9.0	8.5	8.5
27	9.0	9.0	9.0
28	9.5	9.5	9.0
29	10.0	9.5	9.5
30	10.0	10.0	10.0
31	10.5	10.5	10.0
32	11.0	10.5	10.5
33	11.0	11.0	11.0

Table 25 Dosing of Phoslyra® (Cont'd)

Total Daily Dose Phoslyra (mL/Day)	Main Meal (mL)	Meal (mL)	Meal (mL)
34	11.5	11.5	11.0
35	12.0	11.5	11.5
36	12.0	12.0	12.0
37	12.5	12.5	12.0
38	13.0	12.5	12.5
39	13.0	13.0	13.0
40	13.5	13.5	13.0
41	14.0	13.5	13.5
42	14.0	14.0	14.0
43	14.5	14.5	14.0
44	15.0	14.5	14.5

All remaining tablets, sachets and liquid (and any empty containers) dispensed to the subject will be returned at each study visit for tablet, sachet and volume of liquid counts to check compliance. The Investigator will count the returned tablets, sachets and volume of liquid and, taking into account the dose prescribed, will assess the subjects' compliance.

This tablet and sachet count and volume of liquid will be documented in the CRF and source documentation.

7.2.2 Dosing and Administration Guidelines

7.2.2.1 PA21 – Investigational Treatment

PA21 tablets will be chewed or crushed. They must not be swallowed whole.

PA21 powder for oral suspension should be combined with a suitable food/drink prior to administration, for example water, apple sauce, nutritional supplements for renal patients or infant formula milk in the following approximate volumes:

- 500 mg iron: 20 mL
- 250 mg iron: 10-20 mL
- 125 mg iron: 5-20 mL

The suspension should be ingested within 30 minutes after being prepared.

PA21 powder for oral suspension may be given by feeding tube.

PA21 must not be taken on an empty stomach. The daily dose will be taken orally with meals and with no additional water above the amount usually taken by the subject with meals.

7.2.2.3 Phoslyra Oral Solution - Active Control

Phoslyra should be administered on its own, unless administering by feeding tube when it should be combined with a small volume of water and flushed down the feeding tube before the feed.

7.3 Package and Labelling

All study medications will be packaged and labelled by Vifor Pharma (or designee) according to all local legal requirements and applicable regulatory requirements. All packaging and labelling operations will be performed according to GMP and Good Clinical Practice (GCP). Containers provided to centres and to subjects will be labelled in the appropriate local language. Container label information will be appropriately documented in the drug accountability form after the container has been dispensed to the subject.

7.4 Study Treatment Allocation

Each eligible subject will be assigned to the treatment arms via a secure IRT.

7.5 Site Supply, Storage, Accountability

7.5.1 Site Supply

Once a site has been approved to receive study drug, the site will be supplied with an initial stock of PA21 and Phoslyra. The need for drug resupply will be assessed on a regular basis taking into account the number of subjects enrolled, and the number of subjects in screening at the site. This will be managed via the IRT.

7.5.2 Storage

The Investigator at each site is responsible for the appropriate storage of study drug supplies.

PA21 should be stored in a locked area at 25°C (77°F) with excursions permitted at 0°C to 35°C (32 to 95°F).

The study drug supplies should be protected from moisture. The containers should be tightly closed.

Phoslyra should be stored in a locked area at 25°C (77°F) with excursions permitted at 15°C to 30°C (59 to 86°F).

Maintenance of a temperature log is mandatory. The log should be updated by site personnel daily whenever possible. This log must be available for review by the Monitor during on-site monitoring visits.

7.5.3 Accountability

The Investigator at each site is responsible for study drug supplies. The Investigator will ensure that adequate records of the receipt, administration and return of the study drug are kept and that the study drug is used only for subjects enrolled in the study. All data regarding the study drug must be recorded on the relevant forms provided.

Each study site will maintain a drug inventory/dispensing record for all drugs dispensed and returned. At the end of the study, 1 copy of the drug inventory/dispensing record should be sent to the Sponsor or designee for the central study file. The original will be kept in the site files.

After completion of the study, or if it is prematurely terminated, all unused materials will be returned to the Sponsor or designee. Vifor Pharma's policy is not to have materials destroyed by sites. However, if there are exceptional cases and the study medication is destroyed at site, the Investigator will forward the certificate of destruction to the Sponsor or designee. The decision to destroy study medication at site must be made by the Sponsor or designee.

7.6 Drug Dose Modification

During the study, dose titrations of PA21 or Phoslyra (increases or decreases) will be allowed, for efficacy, provided that the subject has received that dose for a minimum period of 2 weeks, and safety or tolerability reasons at any time. Blood samples will be taken at these visits in order to obtain serum phosphorus values for dose titration purposes. If a dose adjustment is indicated i.e., if the serum phosphorus level is outside the target serum phosphorus levels detailed in Table 11, the Investigator will inform the subject or legal representative (either directly or by phone) whether a dose increase or a dose decrease is indicated. Subjects will thereafter follow the new dose regimen.

Maximum doses of PA21 and Phoslyra and dose increases or decreases permitted are detailed in Table 4, Table 5 and Table 6.

Rules for stopping study drug are detailed in Section 5.4.

7.6.1 Procedures for Overdose

Any instances of hypophosphataemia due to PB overdose should be treated by stopping the drug immediately and by standard clinical practice.

There is no rescue medication for this study.

7.6.1.1 PA21

There are no reports of overdose with PA21 in patients. Since the absorption of iron from PA21 is low, the risk of systemic iron toxicity is negligible. Any instances of hypophosphataemia due to PB overdose should be treated by stopping the drug

immediately and by standard clinical practice. PA21 will be provided in child-proof containers to avoid unintentional ingestion of study medication by children.

7.6.1.2 Phoslyra

Administration of Phoslyra in excess of the appropriate daily dosage may result in hypercalcaemia (refer to Section 5.4). Phoslyra will be provided in a child-proof container to avoid unintentional ingestion of study medication by children.

7.7 Prohibited Therapy and Concomitant Treatment

Prohibited therapies in this study include the following:

- Oral calcium supplements.
- Antacids containing aluminium, calcium or magnesium.
- PB binders (i.e., PBs in addition to the study medications: PA21 or Phoslyra).
- Subjects receiving growth hormone who have not been on a stable dose for 2 months.
- Subjects taking anti-arrhythmic medications for the control of arrhythmias and anti-seizure medications for the control of seizure disorders.
- In subjects randomised to PA21, oral iron products, oral vitamins containing iron and other oral iron containing supplements or medications should be discontinued at the start of the study. Iron status should then be monitored and iron therapy initiated if indicated as part of routine care. If iron therapy is indicated, intravenous iron is the preferred formulation. If oral iron is prescribed, however, the subject should be instructed to take it between meals and not at the same time as PA21.

Concomitant medications that have a direct influence on serum phosphorus levels (e.g., Vitamin D, Vitamin D analogues and calcimimetics), dietary restrictions (e.g., phosphate and calcium intake) and dialysis regimens (e.g., duration of dialysis, number of HD sessions per week, number of PD exchanges/day, modality of dialysis, calcium concentration) should remain unchanged as far as possible in both the PA21 and Phoslyra groups throughout the study in accordance with local clinical practice. This does not apply if changes are indicated for safety and tolerability reasons.

For HD subjects, details of the subject's dialysis, date, duration and the day of dialysis must be documented in the CRF and in the subject's medical records. As far as possible, dialysis parameters should remain stable throughout the study. All changes must be documented in the CRF and in the subject's medical records.

Any concomitant treatment given for any reason during the course of the study must be recorded on the CRF and in the subject's medical records, including dosage, start and stop dates and reason for use.

7.7.1 PA21 Interactions

Human DDI studies have shown no interactions with 5 commonly used medications (losartan, furosemide, digoxin, warfarin, and omeprazole) in adult healthy subjects.

Interaction has been observed in in vitro studies with the following drugs: alendronate, cephalexin, doxycycline, levothyroxine, atorvastatin.

Data from clinical studies, however, have shown that PA21 does not affect the lipid lowering effects of HMG-CoA (3-hydroxy-3-methyl-glutaryl-CoA) reductase inhibitors (e.g., atorvastatin and simvastatin). In addition, clinical studies demonstrated no impact of PA21 on iPTH lowering effect of oral Vitamin D analogues. Vitamin D and 1,25-dihydroxy Vitamin D levels remained unchanged.

In vitro studies with the following drugs did not show any relevant interaction: acetylsalicylic acid, cephalexin, cinacalcet, ciprofloxacin, clopidogrel, enalapril, hydrochlorothiazide, metformin, metoprolol, nifedipine, pioglitazone, simvastatin and quinidine.

When administering any medicinal product that is known to interact with iron, the medicinal product should be administered at least 1 hour before or 2 hours after PA21.

7.7.2 Phoslyra Interactions

Phoslyra may decrease the bioavailability of tetracyclines, fluroquinolones or levothyroxine. When clinically significant drug interactions are expected, separate dosing from Phoslyra, or consider monitoring blood levels of drug.

Table 26 Oral Drugs that Have to be Separated From Phoslyra®

	Dosing Recommendations
Flouroquinolones	Take at least 2 hours before or 6 hours after Phoslyra
Tetracyclines	Take at least 1 hour before Phoslyra
Levothyroxine	Take at least 4 hours before or 4 hours after Phoslyra

Oral Medications Not Listed in the Table

There are no empirical data on avoiding drug interactions between Phoslyra and most concomitant oral drugs. For oral medications where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, consider separation of the timing of the administration of the 2 drugs. The duration of separation depends upon the absorption characteristics of the medication concomitantly administered, such as the time to reach peak systemic levels and whether the drug is an immediate release or an extended release product. Consider monitoring clinical responses or blood levels of concomitant medications that have a narrow therapeutic range.

8. RISKS/PRECAUTIONS

The required procedures in the study are appropriate for paediatric and adolescent patients, including blood sampling which will be in line with current guidelines [75].

Study subjects will have phosphorus and calcium levels monitored at frequent intervals (weekly during the washout stage of the study) see Section 4. The dose will be adjusted at regular intervals to optimise serum phosphorus levels (Section 7.2). Stopping rules are in place to ensure withdrawal of subjects whose phosphorus or calcium levels are not controlled within required limits (Section 5.4). In addition, the study has an external DSMB (Section 11).

8.1 PA21 – Investigational Treatment

Details regarding risks and precautions can be found in the current PA21 IB.

PA21 is indicated for the control of serum phosphorus levels in adult patients with CKD on dialysis.

The only findings of note in the nonclinical programme were positive findings in rodent carcinogenicity studies. Administration of PA21 to mice for up to 2 years resulted in a dosage-related increase in mucosal epithelial hyperplasia and development of diverticula with cysts. There was no clear evidence of a tumourigenic response in male mice and no evidence of a tumourigenic response in female mice in this study. These low grade proliferative changes in the caecum and colon of mice are considered species specific and not considered a clinically relevant risk to humans. Follicular C-cell adenomas of the thyroid were seen in the rat study and these were considered likely to represent an exaggerated pharmacological response to the effects of PA21 treatment on calcium and phosphate homeostasis. Further details can be found in the PA21 IB.

The effectiveness of PA21 in lowering serum phosphorus levels in adult patients with ESRD on dialysis has been confirmed in 2 adequate and well controlled studies (PA-CL-03A and PA-CL-05A). A 6 month safety extension study to PA-CL-05A has also been completed (PA-CL-05B), thereby providing PA21 exposure data for up to 1 year.

Throughout the studies in the adult clinical development programme, PA21 was well tolerated at the proposed clinical doses. The most frequent patient-reported adverse drug reactions (ADRs) were GI AEs, consisting mainly of diarrhoea, faeces discoloured, and other mild to moderate GI AEs.

Diarrhoea occurred in 11.6% of patients in clinical trials (PA-CL-03A, PA-CL-05A and PA-CL-05B). In the 55 weeks long-term studies, the majority of these treatment-related diarrhoea events were mild (59.8%) and transient, occurred early during treatment initiation and led to treatment discontinuation in 3.1% of patients.

PA21 can cause discoloured (black) stools. Discoloured (black) stool may visually mask GI bleeding. The usage of a faecal occult blood test will be able to distinguish discoloured (black) stools caused by PA21 from those due to a GI bleed. PA21 does not affect guaiac based (Haemoccult®) or immunological based (iColo Rectal®, and Hexagon Obti®) faecal occult blood tests.

In combined studies PA-CL-05A/05B, temporary tooth discolouration was reported with a higher frequency in the PA21 group compared to the sevelamer group (1.4% versus no subjects, respectively).

The use of PA21 is contraindicated in patients with (1) hypersensitivity to the active substance or any of the excipients, and (2) haemochromatosis and any other iron accumulation disorders.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltose insufficiency should not take PA21.

One tablet of PA21 is equivalent to 0.116 bread units (equivalent to approximately 1.4 g of carbohydrates).

No safety concerns were raised by a comprehensive assessment of laboratory tests which included electrocardiograms, haematology and chemistry tests in adult subjects.

Human DDI studies have shown no interactions with 5 commonly used medications (losartan, furosemide, digoxin, warfarin, and omeprazole) in adult healthy subjects. Data from clinical studies have shown that PA21 does not affect the lipid lowering effects of HMG-CoA reductase inhibitors (e.g., atorvastatin and simvastatin). In addition, clinical studies demonstrated no impact of PA21 on iPTH lowering effect of oral Vitamin D analogues. Vitamin D and 1, 25-dihydroxy Vitamin D levels remained unchanged. When administering any medicinal product that is known to interact with iron, the medicinal product should be administered at least 1 hour before or 2 hours after PA21.

The rationale for the PA21 starting dose and age-specific dosing are described in Section 2.

The safety and efficacy of PA21 in children below the age of 18 years has not yet been established.

8.2 Phoslyra – Active Control

Details regarding risks and precautions can be found in the current Phoslyra IB.

Patients with ESRD may develop hypercalcaemia when treated with calcium, including calcium acetate (Phoslyra). Avoid the concurrent use of calcium supplements, including calcium-based non-prescription antacids, with Phoslyra. An overdose of Phoslyra may lead to progressive hypercalcaemia, which may require emergency measures. Therefore,

early in the treatment phase during the dosage adjustment period, monitor serum calcium levels regularly. Should hypercalcaemia develop, reduce the Phoslyra dosage or discontinue the treatment, depending on the severity of hypercalcaemia. More severe hypercalcaemia (calcium >12 mg/dL) is associated with confusion, delirium, stupor and coma. Severe hypercalcaemia can be treated by acute HD and discontinuing Phoslyra therapy. Mild hypercalcaemia (10.5 to 11.9 mg/dL) may be asymptomatic or manifest as constipation, anorexia, nausea, and vomiting. Mild hypercalcaemia is usually controlled by reducing the Phoslyra dose or temporarily discontinuing therapy. Decreasing or discontinuing Vitamin D therapy is recommended as well. Chronic hypercalcaemia may lead to vascular calcification and other soft-tissue calcification. Radiographic evaluation of suspected anatomical regions may be helpful in early detection of soft tissue calcification. The long-term effect of Phoslyra on the progression of vascular or soft tissue calcification has not been determined. Hypercalcaemia (>11 mg/dL) was reported in 16% of patients in a 3-month study of a solid dose formulation of calcium acetate; all cases resolved upon lowering the dose or discontinuing treatment.

Phoslyra contains maltitol (1 g per 5 mL) and may induce a laxative effect, especially if taken with other products containing maltitol.

In subjects randomised to Phoslyra, hypercalcaemia may aggravate digitalis toxicity.

The safety and efficacy of Phoslyra in children below the age of 18 years has not yet been established.

9. STUDY PROCEDURES

9.1 Description of Study Assessments

9.1.1 Laboratory Assessments

Laboratory assessments are detailed in Table 27. Some laboratory assessments will be excluded for subjects <36 months of age, and some will only be collected if the results are available from routine clinical management of the subject (see Summary of Blood Samples, Table 2).

Wherever possible, blood samples should be analysed at the central laboratory. Specifically, a central laboratory sample for serum phosphorus, calcium and albumin should be obtained at the final study visit in Stage 1 if possible. Table 2 gives details of those visits at which local laboratory analysis of blood samples is permitted. Standard validated methods must be used. Contact details for the central laboratory will be provided in the study documentation Laboratory Manual.

For HD subjects, study visits after washout (or after screening for those subjects not requiring washout) will be planned after a maximum interdialytic period of 48 hours. Collection of laboratory samples will be completed before dialysis is initiated, using the dialysis access.

Home HD, pre-dialysis and PD subjects will be free to select a weekday for the study visits that coincides best with their weekly routine, preferably in the first half of the week. All subsequent study visits will be scheduled on the same weekday thereafter, wherever possible. Collection of laboratory samples will, where possible, be completed at a consistent time for each visit.

Blood samples for the following efficacy and safety assessments will be drawn in accordance with the Summary of Blood Samples, Table 2.

Table 27 Laboratory Assessments

Haematology:	• Erythrocytes • Mean corpuscular volume • Mean corpuscular haemoglobin • Mean corpuscular haemoglobin concentration • Haemoglobin • Haematocrit • Reticulocyte count • White blood cells • White blood cell differential (% and absolute value) • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes • Platelets • Leukocytes	Clinical Chemistry:	• Phosphorus • Calcium (total, corrected) • Intact parathyroid hormone • Creatinine • Glucose • Triglycerides • Total protein • Albumin • Urea • Uric acid • Total bilirubin • Total cholesterol (differentiated in high density lipoproteins and low density lipoproteins) • Creatine phosphokinase • C-reactive protein • Bicarbonate • Sodium • Potassium • Chloride
Coagulation:(1)	• Activated partial thromboplastin time • Prothrombin time	Clinical Chemistry: Liver Enzymes:	• Alkaline phosphatase • Aspartate transaminase • Alanine transaminase • Lactate dehydrogenase • Gamma-glutamyl transpeptidase
Iron Status Parameters:	• Iron • Ferritin(2) • Transferrin • Transferrin saturation	Vitamins:(2)	• A • 25(OH)D • $1,25(OH)_2D$(1) • E • K
Bone Markers:(2)	• Carboxyterminal cross-linking telopeptide of bone collagen • Tartrate-resistant acid phosphatase 5b • Bone-specific alkaline phosphatase • Osteocalcin • Fibroblast growth factor 23		

1 These assessments will only be collected if taken as part of the routine clinical management of the subjects.
2 These assessments will be excluded in subjects <36 months of age (but will be collected if available from routine clinical assessment).

Samples for bone marker assessment will be obtained and may be stored (frozen) for later analysis.

The total amount of blood (including efficacy endpoints) that will be collected during the study from an individual subject will comply with current paediatric guidelines [75]. Over a period of approximately 41 weeks the amount of blood taken will be up to approximately 53.5 mL for subjects <36 months and up to approximately 78.2 mL for subjects ≥36 months of age. In addition, female subjects of child bearing potential will have approximately 3 x 1.5 mL pregnancy tests. The exact volume will depend on, for example, how many visits the subject has during Stage 1, whether the subject requires washout visits and the techniques/tubes used to collect blood.

Serum pregnancy tests in females of child-bearing potential will be performed by the central laboratory. Positive pregnancy tests will be repeated 2 weeks later, to check for false positive results.

For details on whether laboratory abnormalities should be reported as AEs and on the follow-up required in such cases, see Section 10.2.5.

9.1.2 Physical Examinations

Physical examinations will be performed in accordance with the Schedule of Events, Table 1.

Body systems to be assessed as part of the physical examination will include general appearance, head (eyes, ears, nose, and throat), cardiovascular, respiratory, abdomen, musculoskeletal, neurological, lymph nodes, and skin.

Body weight and height will be measured as part of the physical examinations and, in addition, in accordance with the Schedule of Events, Table 1.

9.1.3 Vital Signs

The following vital signs will be measured in accordance with the Schedule of Events, Table 1.

- Resting blood pressure (systolic and diastolic)
- Resting heart rate
- Body temperature (°C; oral, otic or axillary)

Blood pressure and heart rate will be measured using age-appropriate equipment.

9.1.4 Patient Reported Palatability and Acceptability Assessments

Patient reported palatability and acceptability assessments will be performed in accordance with the Schedule of Events, Table 1.

Age-appropriate assessments will be used based on already-established and standardised versions of the combined facial hedonic facial and 10 cm visual analogue scale. Site staff

will be trained to give standardised, age-appropriate, brief, clear instructions to the subjects or, where appropriate, the parents/carers.

9.1.5 Dialysis Parameters

Dialysis parameters will be recorded in accordance with the Schedule of Events, Table 1. As far as possible, dialysis parameters should remain stable throughout the study. All changes must be documented in the CRF and in the subject's medical records.

For HD subjects, the following parameters must be documented in the CRF and in the subject's medical records at each visit: date, duration of dialysis and the day of dialysis.

Kt/V will only be recorded by the Investigator where these data are collected as part of the routine management of the subject.

9.1.6 Diet

Investigators will discuss and advise on the subject's diet at every visit.

9.2 Schedule of Assessments

For a detailed schedule of visits and assessments (including visit windows) please refer to the Schedule of Events, Table 1.

9.2.1 Screening Visit (Visit 1) Procedures

No study related assessments will be performed until signed and dated informed consent (and, where applicable/required, assent) has been provided for the subject.

Subjects for whom signed and dated informed consent (and, where applicable/required, assent) has been provided will be enrolled in the study and screened. By signing and dating the informed consent form (ICF), the parent/legal guardian (and by signing the assent form where applicable/required, the subject) consent for a possible participation in screening, washout (where applicable), Stages 1 and 2 and follow-up of this clinical trial.

As far as possible, all assessments (except for palatability and acceptability assessment and physical examinations) should be completed prior to dialysis sessions. Subjects previously taking PBs who are eligible for inclusion will continue into the washout phase. Subjects previously taking PBs but with serum phosphorus levels indicated in Table 28 may be randomised without a washout period when the results from the screening visit are available for assessment of study eligibility.

Subjects who are PB naïve and whose serum phosphorus levels values are as indicated in Table 28 will be eligible for randomisation when the results from the screening visit are available for assessment of study eligibility. In centre HD subjects must be randomised after a maximum interdialytic period of 48 hours, once qualifying screening results are received. Home HD, pre-dialysis and PD subjects should be randomised as soon as feasible after qualifying screening results are received, and preferably within 4 days.

Table 28 Age Related Serum Phosphorus Targets for Washout Period

Age	mmol/L	mg/dL
0 to <6 months	>2.62	>8.1
≥6 months to <1 year	>2.29	>7.1
≥1 year to <6 years	>2.02	>6.3
≥6 years to <13 years	>1.77	>5.5
≥13 years to <18 years	>1.36	>4.2

Note: Adapted from National Kidney Foundation Kidney Disease Outcomes Quality Initiative Nutrition Guidelines, 2008 and personal communication.

During the screening visit the following procedures will be undertaken:

- Informed consent
- Inclusion/exclusion criteria review to confirm eligibility
- Demography
- Medical/surgical history
- Prior medication history
- Physical examination
- Height and body weight
- Vital signs
- Blood sample
- Confirmation of screening using IRT
- Dialysis parameters
- Dialysis parameters for Kt/V (when available from routine clinical assessment)
- Adverse events
- Concomitant medication
- Discuss and advise on the subject's diet

9.2.2 Washout Visit (Visits 2 to 4) Procedures

For subjects taking PBs, the washout period cannot begin until the results from the screening visit are available for assessment of study eligibility. The dose of previous PB treatment must remain stable until the subject, or their parent/legal guardian, is contacted

by the site. Subjects who are eligible for inclusion (or their parent/legal guardian) will then be contacted by the site and asked to stop taking their current PBs. The subject will then undergo a washout from their previous PBs for up to 3 weeks. Serum phosphorus levels will be monitored weekly up to 3 weeks of washout. At the end of the first week of the washout period subjects whose serum phosphorus levels have risen to those detailed in Table 28 will be eligible for randomisation and enter the treatment period.

Subjects who have serum phosphorus levels below those detailed in Table 28 at this time can continue in the washout period for an additional 2 weeks. As soon as their serum phosphorus levels have risen to those detailed in Table 28 they can be randomised into the treatment period. In centre HD subjects must be randomised after a maximum interdialytic period of 48 hours, once qualifying screening results are received. Home HD, pre-dialysis and PD subjects should be randomised as soon as feasible after qualifying results are received, and preferably within 4 days. If, after 3 weeks of washout, the serum phosphorus remains below those detailed in Table 28 the subject is not eligible for randomisation.

During the washout visits the following procedures will be undertaken:

- Blood sample
- Call to IRT
- Dialysis parameters
- Dialysis parameters for Kt/V (when available from routine clinical assessment)
- Adverse events
- Concomitant medications
- Discuss and advise on the subject's diet

9.2.3 Baseline Visit (Visit 5) Procedures

- Inclusion/exclusion criteria review to confirm eligibility
- Height and body weight
- Vital signs
- Blood sample
- Call to IRT: randomisation into Stage 1
- Dispense subject identification card

- Dialysis parameters
- Dialysis parameters for Kt/V (when available from routine clinical assessment)
- Dispense study medication
- Adverse events
- Concomitant medication
- Discuss and advise on the subject's diet

9.2.4 Treatment Visit (Visits 6 to 16) Procedures

For in centre HD subjects study visits must be planned after a maximum interdialytic period of 48 hours and on the same day and same session each week, as far as possible. Collection of laboratory samples and completion of all other procedures required by the protocol, except the physical examination and the patient reported palatability and acceptability will be completed before dialysis is initiated.

Subjects who are on home HD, pre-dialysis or on PD will be free to select a weekday for the study visits that coincides best with their weekly routine, preferably in the first half of the week. All subsequent study visits will be scheduled on the same weekday thereafter, wherever possible. For these subjects, where possible, all laboratory samples and other procedures required by the protocol will be taken at a consistent time for each visit.

AEs and concomitant medication will be recorded prior to the conduct of other study assessments at each visit.

For dosing and dose titration procedures see Section 7.

9.2.4.1 Stage 1 Visit (Visits 6 to 11) Procedures

9.2.4.1.1 Visit 6 Procedures

During Visit 6 the following procedures will be undertaken:

- Call to IRT
- Dialysis parameters
- Dialysis parameters for Kt/V (when available from routine clinical assessment)
- Dispense study medication
- Returned study medication count
- Adverse events

- Concomitant medication
- Discuss and advise on the subject's diet

9.2.4.1.2 Visits 7, 9 and 10 Procedures

Subjects attending site Visits 7, 9 and 10 will undergo the following procedures:

- Blood sample
- Call to IRT
- Dialysis parameters
- Dialysis parameters for Kt/V (when available from routine clinical assessment)
- From Visit 8, subjects can move to Stage 2 if they have been on a stable dose of study drug for a minimum of 2 weeks
- Dispense study medication
- Returned study medication count
- Adverse events
- Concomitant medication
- Discuss and advise on the subject's diet

9.2.4.1.3 Visits 8 and 11 Procedures

During Visits 8 and 11 the following procedures will be undertaken:

- Height and body weight
- Vital signs
- Blood sample
- Call to IRT
- Dialysis parameters
- Dialysis parameters for Kt/V (when available from routine clinical assessment)
- From Visit 8, subjects can move to Stage 2 if they have been on a stable dose of study drug for a minimum of 2 weeks

- Dispense study medication
- Returned study medication count
- Visit 8 only: patient reported palatability and acceptability
- Adverse events
- Concomitant medication
- Discuss and advise on the subject's diet

9.2.4.2 Stage 2 Visit (Visits 12 to 16) Procedures

9.2.4.2.1 Visit 12 and 14 Procedures

During Visit 12 and 14 the following procedures will be undertaken:

- Visits 12 only: physical examination
- Height and body weight
- Vital signs
- Blood sample
- Call to IRT
- Dialysis parameters
- Dialysis parameters for Kt/V (when available from routine clinical assessment)
- Dispense study medication
- Returned study medication count
- Adverse events
- Concomitant medication
- Discuss and advise on the subject's diet

9.2.4.2.2 Visit 13 and 15 Procedures

During Visits 13 and 15 the following procedures will be undertaken:

- Blood sample
- Call to IRT

- Dialysis parameters
- Dialysis parameters for Kt/V (when available from routine clinical assessment)
- Dispense study medication
- Returned study medication count
- Adverse events
- Concomitant medication
- Discuss and advise on the subject's diet

9.2.4.2.3 Visit 16 End of Study (or Early Discontinuation) Procedures

On completion of the study or early discontinuation/withdrawal, the following procedures will be undertaken. See also Section 5.4, for further information on withdrawal procedures and criteria.

- Physical examination
- Height and body weight
- Vital signs
- Blood sample
- Call to IRT: confirmation of subject completion/discontinuation
- Dialysis parameters and dietary habits
- Dialysis parameters for Kt/V (when available from routine clinical assessment)
- Returned study medication count
- Patient reported palatability and acceptability
- Adverse events
- Concomitant medication
- Discuss and advise on the subject's diet

9.2.5 Visit 17 Follow-Up Procedures

All subjects, whether completing the study or who have withdrawn prematurely, will be followed up 14 days after their last study visit to collect any new AEs and concomitant

medications. This visit may be conducted by telephone call or as an in-clinic visit. If the Investigator has not seen the subject at a clinic visit at the end of the reporting period, the Investigator must attempt 2 telephone calls to the subject, and if there is no response, a registered letter will be mailed, with return receipt requested.

See Section 10.3.1 and Section 10.3.2 for instructions on follow-up of AEs, SAEs and pregnancies.

9.2.6 Post Study Treatment

The Investigator is responsible for ensuring that consideration is given to the appropriate post study care of the subject's medical condition.

10. EVALUATION, RECORDING AND REPORTING OF AEs AND SAEs

10.1 Definitions

10.1.1 Reference Safety Information

The Reference Safety Information is a document covering information relating to safety, indications, dosing, pharmacology, warnings, precautions, contraindications and other information concerning the product. As a minimum, it contains the Company Core Safety Information, which consists of the information on Contraindications, Warnings and Precautions, Use in Special Populations, Undesirable Effects and Overdose from the Company Core Data Sheet.

In the context of this study, for both PA21 and Phoslyra the Reference Safety Information is the current version of the IB.

10.1.2 Adverse Event

Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

10.1.3 Adverse Drug Reaction

In the pre-approval clinical experience with a new medical product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered ADRs. This definition also covers medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product. The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

10.1.4 Unexpected AE/ADR

An AE/ADR, the nature (i.e., specificity/seriousness/outcome/frequency) or severity of which is not consistent with the applicable product information (IB for both PA21 and Phoslyra).

10.1.5 Serious Adverse Event

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death

- Is life-threatening (the term life-threatening in the definition of serious refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe)

- Requires inpatient hospitalisation or prolongation of existing hospitalisation (unless elective surgery (a planned, non-emergency medical procedure))

- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect

- Is an important medical event (i.e., medically significant)

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events should also be considered as serious.

Conversely, some hospitalisations, particularly those which are the result of elective or previously scheduled surgery for pre-existing conditions should not automatically be classed as SAEs. For example, an admission for a previously scheduled ventral hernia repair or kidney transplant surgery would not be classed as an SAE. Previously scheduled hospitalisations must be documented in the subject's source documents before the parents/legal guardian signs the ICF and the subject, where appropriate/required, signs the assent form. Any worsening of a pre-existing medical condition or any new medical condition that meets the above SAE criteria should be considered as an SAE.

Any suspected transmission of any infectious agent via a medicinal product should be considered as an important medical event (i.e., medically significant) and therefore documented as an SAE.

The Investigator is encouraged to discuss with the Sponsor, or designee, any AEs for which the issue of seriousness is unclear or questionable.

10.1.6 Suspected Unexpected Serious Adverse Reaction

Any ADR that is both serious and unexpected (per the Reference Safety Information) that, based on the opinion of the Investigator or Sponsor, or designee, is felt to have a reasonable suspected causal relationship to a medicinal product.

10.2 AE Descriptors

10.2.1 Intensity/Severity Categorisation

The term severe is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); however the event itself may be of

relatively minor medical significance (such as severe headache). This is not the same as serious, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

In general, the intensity of a particular AE to be recorded is the worst intensity experienced by the subject during the course of the event. The medical assessment of intensity will be determined by using the following definitions:

Mild: The AE is easily tolerated and does not interfere with usual activity.

Moderate: The AE interferes with daily activity, but the subject is still able to function.

Severe: The AE is incapacitating and the subject is unable to work or complete usual activity.

10.2.2 Causal Relationship Categorisation

An Investigator who is qualified in medicine must make the determination of relationship to investigational product for each AE and SAE. The Investigator should decide whether, in his or her medical judgement, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE/SAE should be classified as unrelated or unlikely related. Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a cause-and-effect relationship between the investigational product and the occurrence of the AE/SAE, then the AE/SAE should be considered certainly, probably/likely, or possibly related.

For additional guidance refer to Table 29.

Table 29 Causal Relationship Categories

Term	Relationship	Definition
Certain	Yes	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary

Table 29 Causal Relationship Categories (Cont'd)

Term	Relationship	Definition
Probable/likely	Yes	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	Yes	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	No	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Unrelated	No	• Event or laboratory test abnormality which is clearly related to circumstances not connected with the drug intake.

If the causal relationship between an AE/SAE and the investigational product is determined to be "certainly, probably/likely, or possibly related", the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting. In circumstances where the Investigator has not provided his/her assessment about the relationship, the event will be considered as related and will qualify for expedited regulatory reporting

10.2.3 Outcome Categorisation

Outcome may be classified as: recovered/resolved; recovering/resolving, not recovered/not resolved/ongoing, recovered/resolved with sequelae; fatal; or unknown (if follow-up is not possible).

If the outcome of an SAE is reported as recovered/resolved with sequelae, the Investigator should specify the kind of sequelae on the SAE form. If the outcome of an SAE is reported as unknown, the Investigator should specify (on the SAE form) the rationale why unknown was selected.

10.2.4 Symptoms and Signs of the Disease under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation of the disease.

Worsening of the symptoms however, should be recorded as an AE, and clearly marked as worsening.

10.2.5 Clinical Laboratory Evaluations

A change in the value of a safety laboratory investigation can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to a pathological value, or a further worsening of an already pathological value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are pathological laboratory values which were not present at baseline, further clinical or laboratory investigations should be performed until the values return to within reference range or until a plausible explanation (e.g., concomitant disease) is found for the pathological laboratory values.

The Investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a laboratory parameter is clinically significant and therefore represents an AE. If the Investigator considers such an AE as serious (e.g., medically significant event fulfilling criteria per Section 10.1.5) it must be reported as an SAE.

At the end of the study period, all pathological laboratory findings/values diagnosed throughout the treatment period should be reviewed by the Investigator to provide a final clinical assessment in view of the dynamic of laboratory changes/abnormalities.

10.2.6 Abuse, Misuse, Overdose and Medication Error

All special events such as study medication abuse, misuse, overdose and medication errors have to be documented in the subject's CRF and source documents. If any abuse, misuse, overdose, or medication errors lead to an SAE (see Section 10.1.5), then the event has to be reported per standard guidelines.

10.3 Reporting Procedure for AEs, SAEs and Pregnancy

10.3.1 Adverse Events

All AEs either observed by the Investigator or one of his/her medical collaborators, or reported by the subject spontaneously, or in response to a direct question, will be noted in the AE section of the subject's CRF and source documentation. This applies to all AEs regardless of presumed relationship to the study treatment, including the investigational product, active comparator and no treatment period (e.g., screening and washout periods). AEs leading to discontinuation of study treatment should also be collected.

If any AE is reported, the date of onset, relationship to study medication or treatment, any action taken, date of resolution (or the fact that it is still continuing or has become chronic), outcome, and whether the AE is serious or not will be recorded. Where possible,

the Investigator should report a diagnosis rather than signs and symptoms or abnormal laboratory values.

The AE reporting/recording period begins at the time the ICF (and where required/appropriate, assent) is signed. The AE reporting/recording period ends at the last study/follow up visit.

All AEs persisting at the time of study completion will be followed by the Investigator through contact with the subject until resolution or stabilisation, or the subject is lost to follow-up and cannot be contacted. The outcome must be documented in the subject's source documents.

If the subject reports an AE, it is the Investigator's responsibility to acquire sufficient information in order to assess causality. This may require additional laboratory testing, physical examinations, telephone contacts, etc.

In order to avoid bias in eliciting AEs, subjects, where appropriate/required, and their parents/legal guardian should be asked a non-leading question, such as "How are you/is the subject feeling?" It is also important to question the subject, where appropriate/required, and their parents/legal guardian in a non-leading way about changes in the subject's health or concomitant medication usage since their last visit. This information should be collected prior to completion of assessments at all study visits. In addition, any symptoms/conditions reported during assessments and deemed to be clinically significant by the Investigator will be assessed as AEs.

As GI AEs (e.g., nausea, vomiting, diarrhoea, constipation and dyspepsia) are associated with the use of all phosphate binders, it should be ensured that all occurrences of GI events are appropriately reported.

10.3.2 Serious Adverse Events

The occurrence of an SAE must be immediately reported to Vifor Pharma or designee, within 24 hours of awareness by facsimile, email or telephone.

A safety contact sheet will be provided by the Sponsor, or designee, to the Investigator (prior to first subject providing informed consent) detailing all applicable contact information. This will be kept up to date with any changes being provided to the Investigator immediately.

The detailed SAE reporting procedures will be provided in the study documentation (SAE Processing and Reporting Plan). The SAE should be reported using the Vifor Pharma, or designee, SAE report form provided by Vifor Pharma, or designee (see Appendix 1). The Investigator must complete, sign and date the SAE pages, and verify the accuracy of the information recorded on the SAE pages with the corresponding AE CRF page(s) and source documents. The Vifor Pharma, or designee, SAE report form must be completed in

capital letters, in medical terms, in English and to the best extent possible given the time constraints.

Where possible, the Investigator should report a diagnosis rather than signs and symptoms. In case of a fatal outcome, the Investigator should provide a working diagnosis (event which caused outcome, e.g., death due to fatal myocardial infarction) instead of reporting only death; an autopsy report should be provided where possible.

Where the SAE report form cannot be transmitted due to technical problems, the Investigator must inform Vifor Pharma, or designee, about the SAE by phone. As soon as technical problems are resolved, the Investigator will send a copy of the SAE report form to the Vifor Pharma, or designee.

All SAEs (regardless of relationship to investigational product) will be reported from the time the informed consent (and where required/appropriate, assent) is signed until 30 days following the last study visit (including the follow-up visit if applicable) or until 30 days after last study drug administration, whichever is longer. No formal study visit is required but the Investigator must report any SAEs that occur during this period using the SAE form. If the Investigator has not seen the subject at a clinic visit at the end of the reporting period, the Investigator must attempt 2 telephone calls to the subject to inquire about SAEs, and if there is no response, a registered letter will be mailed, with return receipt requested. SAEs starting before first administration of study drug must be identified as such on the CRF and source documentation.

A death occurring during the study or which comes to the attention of the Investigator within 30 days after the last study visit (including the follow-up visit if applicable) or until 30 days after the last study drug administration, whichever is longer, whether considered treatment-related or not, must be reported to Vifor Pharma, or designee, using the Vifor Pharma, or designee, SAE form. Preliminary reports will be followed by detailed descriptions which will include copies of hospital case reports, autopsy reports/certificates and other documents when requested and applicable.

Contact information for reporting of SAEs will be provided in the study documentation (SAE Processing and Reporting Plan).

The onset date of the AE is defined as the onset of signs and symptoms or a change from baseline. The onset date of the SAE is defined as the date the signs and symptoms/diagnosis became serious, i.e., met at least 1 of the International Conference on Harmonisation (ICH)) criteria for serious. The resolution date of the SAE is defined as when the symptoms resolve (subject recovering), or the event is considered chronic (e.g., sequelae) or stable, and/or if the seriousness criteria are no longer applicable. Serious AEs that are ongoing at the time of death are considered unresolved.

All recorded SAEs, regardless of relationship to investigational product, will be followed up until resolution, stabilisation, or the subject is lost to follow-up and cannot be

contacted. In circumstances where the Investigator is unable to make contact with the subject (or his/her relatives/legal guardian), the Investigator must provide a written statement (recorded in the subject's source documents) to Vifor Pharma, or designee, confirming that the subject is lost to follow-up.

At a minimum the following should be provided at the time of the initial SAE report:

- Study name and/or number
- Subject number, age and gender/sex
- SAE description (including onset date of the SAE, outcome and reason for it being considered serious)
- Relationship to investigational product (i.e., causality)
- Name of the investigational product (including drug dose and administration dates)
- Investigator name and address
- Name of the reporter (including site name or number and country), and,
- Dated signature of the Investigator or Sub-/Co-Investigator

Additional follow-up information, if required or available, must be faxed immediately (within 24 hours of awareness) following Investigator (or site) awareness of the information. The follow-up information must be completed on a Vifor Pharma, or designee, SAE report form (marked follow-up) and placed with the original in the appropriate section of the study file.

Preliminary reports will be followed by detailed descriptions which will include copies of hospital case reports, autopsy reports/certificates (in case of death) and other documents when requested and applicable.

The Investigator is encouraged to discuss with Contract Research Organisation (CRO)/Sponsor any AEs for which the issue of seriousness is unclear or questionable.

Vifor Pharma, or designee, is responsible for expedited reporting to the relevant Regulatory Authorities, to Investigators and to local and central Institutional Review Board/Ethics Committee/Independent Ethics Committee (IRB/EC/IEC) as per local regulations.

Any SAE considered to have a causal relationship (i.e., related) to the investigational product and discovered by the Investigator at any time after the study should be reported. A rationale for the assessment of a causal relationship must be provided by the Investigator together with the Vifor Pharma, or designee, SAE report form. Any safety

information that is obtained after database lock of the clinical database will be documented only in the safety database.

Additional detail regarding SAE reporting is available in the SAE Processing and Reporting Plan, which will be provided in the study documentation.

10.3.2.1 Elective Surgery/Routine Examination

Elective surgery (a pre-planned, non-emergency medical procedure) and in-patient routine examination for a pre-existing condition do not qualify as SAEs but must be recorded in the subject's source documents. However, AEs which occur during the elective hospitalisation will need to be collected and reported.

10.3.3 Pregnancy

When a female subject becomes pregnant during the study and study treatment has been administered to the subject, the outcome of the pregnancy needs to be monitored and the safety of the mother and unborn child need to be safeguarded (as per protocol, pregnancy is an exclusion criteria). Therefore, the outcome of all such pregnancies (including normal births) must be followed up and documented, even if the subject was withdrawn from the study.

Women of child-bearing potential should have a negative serum pregnancy test prior to randomisation. Study medication should not be initiated by the Investigator until a report of a negative pregnancy test has been obtained.

Subjects with CKD may experience false positive results in serum pregnancy tests. Women with a positive pregnancy test at screening will be withdrawn from the study and can be rescreened about 2 weeks later if subsequent test is negative. Women who have a positive pregnancy test during the study will be withdrawn from the study immediately, and the procedures for withdrawal will be completed (see Section 5.4). Positive pregnancy tests during the study will be repeated 2 weeks later, in order to eliminate false positive results.

Effective contraception must be used (in sexually mature male and female subjects) before beginning study medication, during study dosing, and for 30 days following discontinuation of study medication even when there has been a history of infertility, unless due to hysterectomy. A reliable form of contraception (i.e., with a failure rate of <1% per year) must be used unless abstinence is the chosen method or subject has been surgically sterilised. Please refer to the exclusion/inclusion criteria (Section 5) for additional information.

A female subject must immediately inform the Investigator if she becomes pregnant during the study and be instructed to stop taking study medication. The Investigator should counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the foetus.

The Investigator/Sponsor, or designee, is responsible for monitoring the subject and pregnancy outcome. Every effort should be made to gather information regarding the pregnancy outcome until 90 days postpartum (or otherwise as appropriate). It will be the responsibility of the Sponsor, or designee, together with the appropriate support of the Investigator, to obtain this information.

Any report of pregnancy recorded for any female subject should be reported to Vifor Pharma, or designee, within the same timelines as SAE reporting, i.e., immediately (within 24 hours of awareness). The Investigator should complete a Vifor Pharma, or designee, Report on Exposure to Medicines during Pregnancy form (see Appendix 2) and forward to Vifor Pharma, or designee. Complications of pregnancy such as abortion (spontaneous or induced), premature birth or congenital abnormality are considered SAEs and should be reported using the Vifor Pharma, or designee, SAE report form.

All pregnancies occurring in a female subject within 30 days after discontinuation of investigational product should be reported within the same timelines as SAE reporting to Vifor Pharma, or designee.

11. DSMB PROCEDURES

A DSMB will be constituted to protect the safety of study participants. A DSMB is a group of independent experts external to a study assessing the progress, safety data and, if needed, critical efficacy endpoints of a clinical study. The DSMB will be composed of clinicians with expertise in relevant clinical specialties and at least 1 biostatistician knowledgeable about statistical methods for clinical trials and sequential analysis of trial data.

The DSMB will receive CRF data in the form of tables and listings. The data should include, but is not limited to, demographics, subject enrolment, baseline characteristics, AE data, SAE data (by severity and causality), laboratory data, dose adjustments, protocol adherence, and subject withdrawals. The DSMB will evaluate participant benefit versus risk. In addition the DSMB will monitor external factors relevant to the trial, for example scientific and therapeutic developments that may affect participant safety. Based on the observed benefits or adverse effects, the DSMB will make recommendations to the Sponsor concerning continuation, termination or modifications of the trial.

The Sponsor will establish a charter document explaining the working procedures for the DSMB.

12. STATISTICAL ANALYSIS

12.1 Statistical Methods

All statistical analyses will be performed using SAS Version 9.2 or later (SAS Institute Inc. SAS/STAT, Cary, NC, US). Detailed methodology (including handling of missing data, data from subjects receiving a kidney transplant and data from subjects moving from pre-dialysis to dialysis) for summary and statistical analyses of the data collected in this trial will be documented and finalised prior to study completion. A general description of the planned methods is provided below.

12.2 Sample Size and Power Calculations

In the PA21 treatment group, assuming a mean change in serum phosphorus levels from baseline to end of Stage 1 of 1.2 mg/dL, a standard deviation for the change of 2.0 and to further allow for an approximate drop-out rate of 30%, 100 randomised subjects will provide more than 90% power.

The sample size estimation is based on conservative values from the Phase 3 study, and performed using nQuery Version 6.0.

One hundred subjects should also be sufficient to provide robust safety and dosing information for PA21 in the paediatric and adolescent patients with CKD.

12.3 Populations

12.3.1 FAS Population

The FAS population will consist of all subjects who satisfy the following criteria:

- Randomised to treatment at Stage 1
- Received at least 1 dose of randomised treatment
- Had at least 1 post-baseline assessment of the efficacy endpoint (serum phosphorus)
- The FAS will be analysed based on the treatment to which the subject was randomised.

12.3.2 PPS Population

The PPS population consists of all subjects who, in addition to the FAS criteria, had no major protocol violations.

12.3.3 Safety Population

The safety population consists of all randomised subjects who have taken at least 1 dose of study medication. The subjects in this group will be analysed based on the treatment they received.

12.4 Background and Demographic Characteristics

Demographic and baseline disease characteristics will be summarised and compared between the PA21 and Phoslyra groups.

12.5 Study Medication

The total amount of drug given will be calculated for each subject and will be compared to the amount expected to be given for each subject. Treatment compliance will be calculated for each subject and summarised by treatment group.

Results will be summarised by means of descriptive statistics (n, mean, standard deviation, median, minimum and maximum) and frequency tables, stratified by treatment group.

12.6 Concomitant Therapy

Concomitant medications will be categorised according to a standard dictionary (World Health Organization Anatomical Therapeutic Chemical Drug Reference List classification – the version will be provided in the study report). Counts and percentages of subject use for each medication will be computed and summarised by treatment group.

12.7 Efficacy Evaluations

12.7.1 Primary

The primary efficacy analysis will be performed on the change in serum phosphorus levels from baseline to the end of Stage 1 in the PA21 and group. The change from baseline in the PA21 group will be analysed for the subjects of the FAS, using a paired t-test. The changes from baseline will also be summarised descriptively.

Analyses will generally be based on the results from the central laboratory. Depending on availability of data, the change from baseline may be computed using pre- and post-treatment values from the local laboratory. Summary of Blood Samples (see Table 2).

12.7.2 Secondary

Additional secondary efficacy endpoints that will be analysed include:

- Change in serum phosphorus from baseline in the Phoslyra group at the end of Stage 1.
- Change in serum phosphorus from baseline in PA21 and Phoslyra groups at the end of Stage 2.
- Serum phosphorus values at each visit during Stage 1and 2.

- Percentage of subjects in each period during which the subject has serum phosphorus levels in the age dependent target ranges at each visit.

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

The secondary efficacy endpoints will be summarised by visits, and changes from baseline will be analysed with descriptive statistics.

12.8 Safety Evaluations

Primary safety endpoint:

- AE profile

- Percentage of withdrawals due to AEs

Secondary safety endpoints:

- Serum total corrected calcium at each time point and change from baseline

- Percentage of subjects that develop at least 1 episode of sustained hypercalcaemia during study participation (confirmed by repeat sample 1 week later; see Section 5.4.2)

- Serum total corrected calcium-phosphorus product at each time point and change from baseline

- Serum iPTH levels at each time point and change from baseline

- Routine biochemical/haematological laboratory tests

AEs, laboratory values, vital signs and other safety parameters will be summarised. AEs of special interest will be summarised separately. Descriptive comparisons will be made for changes from baseline where appropriate.

AEs will be coded using the latest available version of the Medical Dictionary for Regulatory Activities, the version of which will be provided in the Clinical Study Report.

AEs will be summarised by system organ class and preferred term for the incidence and prevalence of the AEs. SAEs, SAEs that led to death and (S)AEs that led to withdrawal will also be summarised and listed.

Only AEs and concomitant medications which started on or after written and dated informed consent have been provided (and, where appropriate/required, assent) will be summarised for this study. All AE summaries will be done for all of the subjects in a

treatment group combined and by the maximum dose received during the trial. All AEs will be listed.

12.9 Other Evaluations

12.9.1 Patient Reported Palatability and Acceptability

Patient reported palatability and acceptability assessments will be summarised by treatment group.

13. STUDY ETHICAL CONSIDERATIONS

13.1 Ethical Conduct of the Study

The study will be conducted according to the principles of the World Medical Association's (WMA) Declaration of Helsinki (as amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013) [76], and the ICH guidelines for GCP [77]. Vifor Pharma, or designee, will ensure that the study complies with all local, federal or country regulatory requirements.

The Investigator must ensure the anonymity of all subjects participating in the study. Each subject will be assigned a unique subject number and this should be used on all forms associated with the subject's documents or samples that will be supplied to the Sponsor or any party completing testing on behalf of the Sponsor (e.g., blood for central laboratory assessments).

All anonymous data remains the property of Vifor Pharma.

13.2 Informed Consent and Assent

The ICF used for the study must comply with the Declaration of Helsinki, federal regulations, and ICH guidelines; and must have been approved by the appropriate IRB/EC/IEC prior to use. The age-appropriate assent forms must comply with all relevant regulations for the centre and must also have also been approved by the appropriate IRB/EC/IEC prior to use. The Investigator or an authorised associate must explain orally and in writing the nature of the study and the treatment in such a manner that the subject, where appropriate/required, and their parent/legal guardian are aware of potential benefits and risks. Subjects, where appropriate/required, and their parent/legal guardian must also be informed that participation is voluntary and that the subject may withdraw, or be withdrawn by their parents/legal guardian, from the study at any time, without prejudice. Subjects and their parent/legal guardian must be provided sufficient time to consider participation, including discussion with other family members prior to signing the ICF, and, where applicable, assent. Documentation of the discussion and the date of informed consent, and where applicable assent, must be recorded in the source documentation. Subjects, parents/legal guardian must give informed consent (and where appropriate/required, subjects must give assent) in writing.

A guideline on how to administer informed consent, is attached in Appendix 3 and should be followed by all site staff administering informed consent to subject's parents/legal guardian (and where appropriate/required, subjects), when an equivalent process is not available at the site.

13.3 Institutional Review Board or EC/IEC

The protocol, any protocol amendments, consent and assent forms for the proposed clinical study and any other documents required by the local IRB/EC/IEC must be submitted by the Investigator for review and approval to the IRB/EC/IEC. The

Investigator must also ensure that the IRB/EC/IEC reviews the progress of the study on a regular basis and, if necessary, renews its approval of the study on an annual basis. A copy of the approval letter must be forwarded to Vifor Pharma or designee before the study is implemented.

14. QUALITY CONTROL AND QUALITY ASSURANCE

The Investigator must ensure that all trial related site source data, study related documents and reports will be available, and that the provision of direct access for monitoring and auditing by Vifor Pharma or its designees will be permitted. In addition, the Investigator must ensure that all trial related site source data, study related documents and reports will be made available for inspection by the appropriate Regulatory Authority and review by the IRB/EC/IEC.

Accurate and reliable data collection will be assured by verification and cross-check of the CRFs against the Investigator's records by the Study Monitor (source document verification), and the maintenance of a drug dispensing log by the Investigator. The data collected will be entered (electronic data capture) into the study database and will be verified by the Monitor. A comprehensive validation check program will verify the data and queries will be generated for resolution by the Investigator. Throughout the study, Vifor Pharma or its designee may review data as deemed necessary.

15. ADMINISTRATIVE PROCEDURES

15.1 Sponsor's Responsibilities

15.1.1 Study Supplies

Sites will be provisioned with supplies required to manage this study. This will include but not be limited to:

- Investigator file(s) (for filing of all study related documentation)
- Kits for collection, storage and transportation of applicable samples required for central laboratories. This will also include all applicable guidelines and contact details
- Contact list of all relevant study personnel
- Documentation and directions for use of relevant study questionnaires
- Access to electronic CRF and completion guidelines
- Access to IRT and user guidelines
- Study Reference Manual
- All study forms (e.g., SAE, pregnancy, drug accountability, etc.)

15.1.2 Insurance

Vifor Pharma confirms that it carries liability insurance which protects non-employee physicians or Investigators against claims for which they may become liable as a result of damages caused by Vifor Pharma products used in clinical studies. Insurance coverage is not extended to damages that the Investigators or third parties may suffer by reason of acts of commission or omission on the part of such Investigators or third parties and that are not in accordance with accepted common medical practices (*lege artis* procedures). Vifor Pharma will reimburse the subject for all study-related injuries provided that the injury does not arise from the subject's misuse of the study drug or failure to follow the Investigator's instructions.

15.1.3 Investigator Training

All Investigators and their study personnel will receive training regarding the study procedures and GCP/regulations specific to the conduct of clinical trials. This training will take place prior to enrolment of the first subject at the study centre.

15.1.4 Study Monitoring

The study will be monitored by representatives of Vifor Pharma, or designee, which may include a CRO and/or partner company.

It is understood that the responsible Vifor Pharma Monitor (or designee) will contact and visit the Investigator regularly and will be allowed, on request, to inspect the various records of the trial (CRFs and other pertinent data) provided that subject confidentiality is maintained in accordance with local requirements.

It will be the Monitor's responsibility to inspect the CRFs at frequent regular intervals throughout the study, to verify adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The Monitor must have access to laboratory test reports and other subject records needed to verify the entries on the CRF. The Investigator (or his/her deputy) agrees to co-operate with the Monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

15.2 Investigator's Responsibilities

15.2.1 Reporting and Recording of Data

All required study data must be entered in the CRF created for the study. Training on the system will be provided to all sites, including instructions on how to address missing data, corrections, query procedures and electronic signatures. Only individuals who are identified on the authorised signature page may enter/correct data in the CRF. For those subjects who withdraw before completion of the study, all available efficacy and safety data must be entered in the CRF. Incomplete or inconsistent data on the CRF will result in data queries addressed to the Investigator for resolution.

15.2.2 Source Documentation

All data for the study must be available in source documentation. The Investigator must maintain adequate and accurate source documents upon which case reports for each subject are based. They are to be separate and distinct from CRFs. These records should include detailed notes on:

- The medical history prior to participation in the study
- The basic identifying information, such as demographics, that link the subject's source documents with the CRFs
- The results of all diagnostic tests performed, diagnoses made, therapy provided and any other data on the condition of the subject
- The subject's exposure to study treatment
- All AEs
- The subject's exposure to any concomitant therapy (including date and quantity dispensed)
- All relevant observations and data on the condition of the subject throughout the study

- The oral and written communication with the subject's parent/legal guardian and, where appropriate/required, the subject regarding the study treatment (including the risks and benefits of the study). The date of informed consent, and where applicable assent, must be recorded in the source documentation.

15.2.3 Records Retention

The Investigator must arrange for the retention of all study documentation (such as CRF data, research files, and master files) for the duration specified in their respective site contract or as specified by the applicable Regulatory Authority, whichever is longer. The Sponsor will inform the Investigator in writing when files can be destroyed. Archived data may be held on microfiche or electronic record, provided that a back-up copy exists and that a hard copy can be generated if required.

The Investigator must inform Vifor Pharma or designee immediately if any documents are lost, to be transferred to a different facility, or to be transferred to a different owner.

15.2.4 Site Documentation

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

16. PROCEDURE FOR MODIFICATION OF PROTOCOL OR PREMATURE TERMINATION OF THE STUDY

16.1 Protocol Waivers, Deviations and Violations

Protocol waivers shall not be permitted except where necessary to eliminate an immediate hazard to subjects.

Deviations from the protocol including violations of inclusion/exclusion criteria will be assessed as minor or major on a case-by-case basis. The criteria describing the deviation(s) and how they will be handled will be documented.

16.2 Protocol Amendments

Protocol amendments, except where necessary to eliminate an immediate hazard to subjects, must be made only with the prior approval of Vifor Pharma. Each applicable Regulatory Authority/IRB/EC/IEC will review and approve amendments prior to their implementation. Regulatory Authority/IRB/EC/IEC approval need not be obtained prior to removal of an immediate hazard to subjects.

16.3 Study Termination

Vifor Pharma reserves the right to terminate the study in its entirety or at a site at any time. Reasons for termination may include (but are not limited to) unsatisfactory subject enrolment with respect to quality and/or quantity, site is unable to comply with the requirements of the protocol or GCP, or data recording is inaccurate and/or incomplete.

In terminating the study, Vifor Pharma and the Investigator will assure that adequate consideration is given to the protection of the subject's interests. Both parties will arrange the procedures on an individual basis after review and consultation and in accordance with the study contract.

17. POLICY FOR PUBLICATION AND PRESENTATION OF DATA

Vifor Pharma is committed to the timely communication of data from clinical research trials, following the Pharmaceutical Research and Manufacturers of America principles [78]. Where possible, authorship will be agreed at the beginning of the study. The authors will form a publication committee and this committee will propose and develop appropriate scientific manuscripts or abstracts from the study data. Investigators may not present or publish partial or complete study results individually. Any manuscript or abstract proposed by the Investigators must be reviewed and approved in writing by Vifor Pharma before submission for publication. Names of all Investigators participating in the study will be included in the publication.

The publication committee for a study will comprise of authors selected in adherence with the International Committee of Medical Journal Editors criteria [79] for authorship. That is, all authors must meet each of the following 3 criteria:

1. Substantial contribution to conception and design or acquisition of data, or analysis and interpretation of data

2. Drafted the article or revised it critically for important intellectual content

3. Approved the final version for publication

Members of the study steering committee generally fulfil the authorship criteria through their involvement in protocol design and review, monitoring of and sometimes direct involvement with recruitment, and thus they will usually be part of the publication committee. If studies are multicentre, it may be appropriate to assign group authorship.

In addition, certain Vifor Pharma employees involved in the design and conception of the protocol, study management and data analysis and interpretation are qualified authors and will be included in the publication committee e.g., the lead physician, statistician and study project manager or their equivalents.

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Appendix 1 Serious Adverse Event Form (Sample)

Vifor Pharma

FOR 107: SAE REPORT

FORM

VIFOR (Int.) ONLY: *Coding number:*_____

1 Vifor Study: CRO No. : EudraCT No.:	Initial Report ❑ Follow-up Report ❑ Follow-up Number:_____	Date of Report **:** (dd/mmm/yyyy)

2 **Patient information**	Year of birth: (yyyy) If unknown, age at onset: (Years) Gender: Male ❑ Female ❑ Patient No.: Screening No.: Random No.: Weight: _____ kg Height: _____ cm Hb Value _____ mg/dl (at Baseline)
3 **Study Medication**	Treatment drug: ❑ VIFOR DRUG ❑ COMPARATOR ❑ PLACEBO Total calculated dose: _____ mg First Application of Study Drug: (dd/mmm/yyyy) Last Application of Study Drug: (dd/mmm/yyyy) Most recent Application of Study Drug before onset of SAE: (dd/mmm/yyy) Dilution: _____ Duration of infusion: _____ Total dose of study drug until start of event: _____ mg Will study drug treatment be continued? ❑ No, If no: Why was study drug stopped? _____ ❑ Yes, If yes: Date of next drug administration:_____ Next originally planned date of drug administration if it is different from the date above: _____
4 **Event Verbatim**	Serious Adverse Event Term: _____
5 **SAE Information**	Event start date: (dd/mmm/yyyy) Event stop date: (dd/mmm/yyyy) OR ongoing ❑
6 **SAE Description**	(incl. signs, symptoms, most important reaction(s), diagnosis, relevant tests, relevant lab data)
7 **Concomitant Drugs and Diseases**	Please attach a copy of "Prior and Concomitant Medication" and "Medical and Surgical History" CRF page. - Please continue on next page -

Page 2 of: Initial Report ❑ Follow-up Report ❑ Patient No.:	
8 Action Taken	SAE treatment medication given ? ❑ No ❑ Yes If yes, provide medication number(s) of attached CRF: _____ Non-drug treatment, specify: _____ Withdrawal from study due to event ❑ Yes ❑ No
9 Outcome	❑ Recovered without sequelae ❑ Recovered with sequelae ❑ Not yet recovered ❑ Death ❑ Unknown
10 SAE category	❑ **Death, date:** (dd/mmm/yyyy) **Autopsy: ❑ No ❑ Yes** **Cause of death: _____ If yes, please attach a copy of the autopsy report** ❑ **Life-threatening** ❑ **Persistent or significant disability/incapacity** ❑ **Inpatient hospitalization……..from** (dd/mmm/yyyy) **to** (dd/mmm/yyyy) ❑ **Prolongation of existing inpatient hospitalisation** ❑ **Congenital anomaly/birth defect** ❑ **Important medical event** Premature births will be considered SAEs up to gestational week 35.
11 Causality Assessment	Which one of the following best describes the role of the investigational product in causing this SAE?: Certain ❑ Probable/Likely ❑ Possible ❑ Unlikely ❑ Unrelated ❑ Please describe reason for your opinion: _____
12 Intensity	❑ Mild ❑ Moderate ❑ Severe
13 Reporter Identifier	**Reporter's Name, Profession (speciality): _____** Name & Address of Institution: _____ Phone/Fax: _____ **Signature of Reporter: _____ Date:** (dd/mmm/yyyy) **Site Number: Investigator's Name (if different form Reporter's Name):_____**
VIFOR ONLY	**Date report received:** (dd/mmm/yyyy) **Name Recipient:** _____ **Signature Recipient:** _____

Appendix 2 Report on Exposure to Medicines During Pregnancy (Sample)

Vifor Pharma

FOR GDS 171: PREGNANCY REPORT V01

REPORT ON EXPOSURE TO MEDICINES DURING PREGNANCY Part 1

Name of Vifor Drug (Trade name / IMP): _____

Clinical Trial Protocol Identifier (if applicable): #####

Patients Initials / No: ##### Country: ##### Local Reference No: #####

Details of Mother and Pregnancy

Date / Year of Birth: ##/###/ (dd/mmm/yyyy) Age: Occupation:

Previous Pregnancy

Yes ☐ No ☐ Total no. of pregnancies: _____ Normal Deliveries: _____

Abortions (Spontaneous): _____ Abortions (performed): _____

Relevant Medical History:
(including pregnancy risk factors, Pre-eclampsia, eclampsia, smoking, alcohol, environmental & occupational exposures etc.)

Relevant Family History:
(hereditary diseases e.g. hypertension, diabetes)

Current Pregnancy

First day of Last Menstruation: ##/###/ (dd/mmm/yyyy) Expected Delivery Date: ##/###/ (dd/mmm/yyyy)

Gestational age of foetus (specify at time of exposure / time of reporting) : _____

Ultrasound performed? Yes ☐ No ☐ If yes, findings if any: _____

Any complications, infections or illnesses during pregnancy? Yes ☐ No ☐

If yes, elaborate: _____

Drug Exposure during Pregnancy

Mother /Father Exposure	Suspect Drug/ Concomitant medication	Product Name (Trade / IMP) Batch no.	Total Daily Dose (Units)	Therapy Start date	Therapy Stop date	Indication for use	Route of application (oral, infusion, injection)
					#####		
					#####		
					#####		
					#####		

_____ _____

Place, Date (dd/mmm/yyyy) **Name/ Signature/Stamp of Reporter**

REPORT ON EXPOSURE TO MEDICINES DURING PREGNANCY Part 2

Information on Outcome of Pregnancy

Name of Vifor Drug (Trade name/IMP)**:** _____

Clinical Trial Protocol Identifier (if applicable): #####

Patients Initials / No: _____ Country: _____ Local Reference No: _____

Outcome of Pregnancy

☐ Full Term — Normal delivery or Caesarean: _____

☐ Premature Birth — If premature birth, gestational age: _____ weeks

☐ Spontaneous Miscarriage

☐ Elective termination — Medical Reason? ☐ Yes ☐ No

If yes, specify: _____

Details / Comments (if any): _____

☐ Healthy Baby ☐ Multiple Births

☐ Sick Baby (e.g. Birth trauma, infection etc.) ☐ Congenital anomaly or Birth defect ☐ Still Birth

Date of Birth ##/###/ (dd/mmm/yyyy) Sex ☐ Male ☐ Female

Size: _____ Weight: _____ APGAR scores, if provided (Birth/5/10 mins.) _____

Details / Comments (if any): _____

Please comment on any abnormal condition or occurrence regarding outcome of pregnancy and/or birth/delivery.

Is there a suspicion that adverse outcome of pregnancy is related to exposure to Product?

☐ Yes ☐ No

Please elaborate: _____

_____ _____

Place, Date (dd/mmm/yyyy) **Name/ Signature/Stamp of Reporter**

Please always send both Part I and Part II of the form to safety.VIT@viforpharma.com or fax to: +0041 58851 8659

Vifor Pharma

Administrating Informed Consent

These guidelines apply to all study site personnel administrating informed consent to a potential subject *or* their legally acceptable representative, which must be done ***prior*** to conducting any study related functions, including verifying eligibility.

These guidelines are to be used when your site IRB does not provide you with an equivalent documented consent process; or when your site does not have an equivalent written process (like an SOP).

1. Present the potential subject or legally acceptable representative with:
   - The most up-to-date version of the IRB/REB/EC approved informed consent form (ICF)
   - The Subject Information Sheet (PIS) (if any)

2. Explain the following to the potential subject:
   - That the trial involves research
   - The purpose of the trial
   - The trial treatments, procedures to be followed and (if randomized) the probability of each treatment
   - Alternative procedures or treatment that may be available
   - The subject's responsibilities
   - All aspects of the trial which are experimental
   - Reasonably foreseeable risks
   - Reasonably expected benefits
   - Compensation and/or treatment available in the event of trial-related injury
   - Anticipated payment to the subject, and expenses (if applicable)
   - The subject's participation is voluntary; the subject may withdraw consent at anytime. In the USA and whenever possible the withdrawal of consent must be done in writing.
   - Monitor(s), auditor(s) and the IRB/EC and Regulatory Authorities may be allowed direct access to the subjects' medical records.
   - Records identifying the subject will be kept confidential
   - If any information becomes available which may be relevant to the subject's willingness to continue in the trial, he/she should be informed in a timely manner
   - The person(s) to contact for further information regarding the trial and the subject's rights
   - The foreseeable circumstances and/or reasons whereby the subject may be withdrawn from the trial
   - The foreseeable circumstances and/or reasons whereby the trial may be terminated
   - The expected duration of the subject's participation in the trial
   - The approximate number of subjects in the trial

3. Throughout the process, ensure that:

   - The potential subject is not coerced or unduly influenced to participate in the trial

- There is ample opportunity and time for the subject to ask questions and to receive satisfactory answers.
- If the subject (or representative) is unable to read, an impartial witness is present during the entire consent discussion. By signing the consent form, the witness confirms that the trial was fully explained and verbal consent willingly given.
- The consent form is **signed** and **dated** by the subject (or representative), the person explaining the study and the witness (if applicable).
- The subject (or representative) receives a copy of the signed and dated consent form and all other written subject information.

IT IS THE PRINCIPAL INVESTIGATOR'S RESPONSIBILITY TO DOCUMENT THIS PROCESS

4. Tips on documentation of the informed consent process

- There should be a "contextual" statement in the source document to show exactly how and when IC was administered - including the time (even if it is on the ICF).