STATISTICAL ANALYSIS PLAN

Protocol PA-CL-PED-01

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

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SAP SIGNATURE PAGE

Protocol Title:	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
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Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

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LIST OF IN-TEXT TABLES

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse events
ATC	Anatomic Therapeutic Chemical
BLQ	Below Limit of Quantification
BMI	Body mass index
BP	Blood pressure
CDC	Centers for Disease Control
CI	Confidence interval
CKD	Chronic kidney disease
CRF	Case report form
CSR	Clinical study report
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case report form
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
FAS	Full analysis set
HP	Hyperphosphataemia
ICH	International Conference on Harmonisation
iPTH	Intact parathyroid hormone
IxRS	Interactive Voice/Web Response System
LOQ	Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not Applicable
PB	Phosphate binder
PPS	Per-protocol set
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS®	Statistical Analysis System
SMQ	Standardised MedDRA Query
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TSAT	Transferrin saturation
UIBC	Unsaturated iron binding capacity
WHO	World Health Organisation

DOCUMENT HISTORY

Version	Date	Modification
Final v1.0	27-DEC-2018	N/A
Final v2.0	13-FEB-2019	- Typo corrected in abbreviations section on ATC. N/A added. - Tables 4, 5 and 6: Last category extended to include 18 years. Indeed, we may have subjects enrolled at less than 18, but aged of 18 years during the study. Footnote added. - Section 3.2: missing compliance added on the first programmable protocol violation. - Section 4.2.6: Last category for the age at randomisation extended to include 18 years. Indeed, we may have subjects enrolled at less than 18, but aged of 18 years at the time of randomisation. - Sections 4.2.8.1 and 4.2.8.2: Precisions added on the derived analysis visits (applying windowing as defined in section 4.2.9) to be used. - Section 4.2.8.4: Imputation rule added if value > X for laboratory parameters. - Section 4.2.9: Column "Analysis visit" added to be consistent with the reference in sections 4.2.8.1 and 4.2.8.2. Precisions added on the CRF visits to be used to derive "End of stage 1" and "End of stage 2" for safety analysis, and the fact that the last non missing assessment collected in each period will be reported under "End of Stage 1" and "End of Stage 2". - Section 4.6: Details added on the compliance calculation for Stage 1 and Stage 2. - Section 4.7: details added regarding conversion factor to convert mmol/L into mg/dL for serum phosphorus. - Section 4.9.1: Slashes removed from System/Organ/Class in order to be system organ class. Addition of AE table by SOC and PT, and by age. - Section 4.9.2: details added for the derivation of an episode of sustained hypercalcaemia. - Section 4.9.3: Formula added to derive Transferrin Saturation (%) laboratory parameter. Unsaturated Iron Binding Capacity parameter added in Table 10. - Section 4.9.4: BMI parameter added in the descriptive table. - Section 7.1: Numbering updated in AE section due to duplicate numbering. Addition of 2 tables related to Serum total corrected calcium (Table 14.4.3.1 and 14.4.4.1), numbering updated on the Calcium-Phosphorus product tables. Addition of 2 tables related to TEAE by SOC and PT, and by Age (Table 14.3.1.30 and 14.3.1.31). - Section 7.2: Addition of listing 16.1.6.2: Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used. Numbering updated on Listing 16.1.6.2 to become Listing 16.1.6.3.
Final v3.0	20-MAR-2019	- Addition of updates detailed in the SAP Addendum dated of 22 February 2019:

		• Section 4.2.8.5: imputation of missing or partial dates on disease history • Section 4.6: addition of new exposure to study drug tables by age group • Section 4.9.1: (a) addition of a new listing of AEs occurring in patients randomized but not treated; (b) in the tables by SOC and PT and by time of onset, the denominator is the number of patients at risk at the beginning of the period (excluding those who have withdrawn or completed). • Section 4.9.3: (a) TSAT will not be derived and presented; (b) In Table 11, last age category for the eGFR formula extended to include 18 years. Indeed, we may have subjects enrolled at less than 18, but aged of 18 years during the time of the study; (c) For the shift tables, a list of parameters has been added for which we will not produce shift tables due to normal ranges not available. • Sections 7.1 and 7.2: new tables and listing added per the above updates. - Section 4.4: addition of the early termination and reasons table by age group. - Section 4.6: (a) Addition of exposure to PA21 drug tables during Stage 1, Stage 2 and overall by gender, by region and by formulation (tablets only, sachets only, both); (b) Addition of details regarding exposure variables for patients with all dispensed tablets/sachets or bottles unused, reported as lost and no tablets/sachets or bottles returned dates. - Section 4.7.1: addition of change from baseline sP in PA21 Group – end of stage 1 table (FAS population) by formulation, by serum phosphorus at baseline according to the age related normal range (Above vs. within + below), and by age group*serum phosphorus at baseline according to the age related normal range (first age group will be excluded as no subject in). - Section 4.9.1: (a) In the tables by SOC and PT and by age group, the denominator is the number of patients in each age group. (b) Removal of the additional listing of AEs occurring in patients randomized but not treated -Sections 7.1 and 7.2: new tables added or listing removed per the above updates.

1. INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1. Introduction

Hyperphosphataemia (HP) is a common and serious complication in subjects 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. HP plays an important role in the pathophysiology of major CKD complications for example secondary hyperparathyroidism, renal bone disease and cardiovascular disease, and appears to promote the progression of CKD towards ESRD. High levels of serum phosphorus are considered to be a risk factor for mortality, morbidity and hospitalisation in patients with ESRD.

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.

As the efficacy and safety of PA21 has been confirmed in adult subjects with CKD on dialysis, the aim of this Phase 3 clinical study is to demonstrate similar efficacy of PA21 in paediatric and adolescent subjects with CKD, and to provide safety and dosing information for this subject population. The Phoslyra group provides information for a descriptive comparison of PA21 against a commonly used calcium-based phosphate binder (calcium acetate).

This Statistical Analysis Plan (SAP) has been developed for the final analyses of protocol PA-CL-PED-01 (Version 2.0, 22 September 2015), prior to final database lock. It outlines the efficacy and safety analyses, including tables, listings, and graphical presentations to be included in the Clinical Study Report (CSR). A complete draft SAP has been developed and approved by the sponsor statistician before any significant accumulation of data.

1.2. Objectives of Statistical Analysis

The primary objective of this study is:

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

The secondary objectives of this study are:

- 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.

This SAP is designed to outline the methods to be used in the analysis of study data in order to answer the study objectives as defined above. Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and

summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

2. STUDY DESIGN

2.1. Synopsis of Study Design

This study is a prospective, open-label, randomised, active-controlled, parallel group, multicenter, phase 3 study investigating the safety and efficacy of PA21 (Velphoro®) and calcium acetate (Phoslyra®) in paediatric and adolescent CKD subjects with hyperphosphataemia.

Approximately 130 subjects will be randomised to either PA21 (approximately 100 subjects) or to Phoslyra (approximately 30 subjects) with age as stratification factor.

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). For Phoslyra, only oral solution will be dispensed.

The study will consist of a maximum of 43 weeks including a screening period, a washout period, a treatment period split into 2 stages, and a follow-up period. Screening should be up to 4 weeks. The washout period should be of 1-3 weeks to allow sufficient time for washout of previous Phosphate Binders (PBs). Of note, subjects already receiving a PB but with age related serum phosphorus levels (Table H of the protocol) may be eligible for randomisation without a washout period. Treatment period will be split in 2 stages:

- **Stage 1** is a dose titration period of PA21 and Phoslyra for up to 10 weeks. PA21 subjects will receive PA21 at a starting dose based on their age, as detailed in Table 3 from protocol. Phoslyra subjects will receive Phoslyra, either at a starting dose as detailed in Table 5 from protocol, 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 from protocol), 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 from protocol for PA21, and Table 5 and Table 6 from protocol for Phoslyra. From Week 4, once a subject achieves the age specific target serum phosphorus level, as indicated in Table 11 from protocol, they can move to Stage 2.
- **Stage 2** is a long-term safety extension of PA21 and Phoslyra for 24 weeks. All subjects will enter this safety extension and will continue on the dose they received at 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 and safety or tolerability reasons at any time during Stage 2.

All subjects, whether completing the study or withdrawn prematurely, will be followed up 14 days after their last study visit.

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

2.2. Randomisation Methodology

Approximately 130 subjects will be randomised via interactive response technology to either receive PA21 (approximately 100 subjects) or to Phoslyra (approximately 30 subjects).

The randomisation will be stratified by age group and will also aim to randomise at least the minimum number of subjects from each age group as outlines in Table A from study protocol synopsis and as shown in Table 1 below:

Table 1 Minimum Number of Randomised Subjects by Age Group

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

2.3. Stopping Rules and Unblinding

The study will be conducted in an open-label manner. However, the sponsor will not receive any IxRS data or data summarised by treatment groups before the database lock in order to preserve the integrity of the trial. In particular during the DSMB meeting, the sponsor will not attend the closed session of the meeting where data splitted by treatment could be presented.

2.4. Study Procedures

The schedule of assessments and blood samples, as outlined in the Tables 1 and 2 from study protocol, is provided in Table 2 and Table 3 below.

Table 2 Schedule of Assessments

	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
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 3 Schedule 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.

2.5. Efficacy, Pharmacokinetic, and Safety Variables

2.5.1. Efficacy Variables

2.5.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change in serum phosphorus levels from baseline to the end of Stage 1 in PA21 group. It is based on central laboratory data; in case of missing data, the change from baseline will be computed using pre- and post-treatment values from the local laboratory (see Section 4.2.8).

2.5.1.2. Secondary Efficacy Endpoints

The following secondary endpoints based on central laboratory measurement are planned for analysis:

- Change in serum phosphorus levels from baseline to the end of Stage 1 in Phoslyra group
- Change in serum phosphorus levels from baseline to the end of Stage 2 in both groups

In case of missing central laboratory data, the change from baseline will be computed using pre- and post-treatment values from the local laboratory (see Section 4.2.8).
The following secondary endpoints based on both central and local laboratory measurements are planned for analysis:

- Serum phosphorus values at each visit during Stages 1 and 2
- Percentage of subjects with serum phosphorus level in the age related target range (Table D from the study protocol synopsis; Table 4 below) at each visit.
- Percentage of subjects with serum phosphorus level within the age related normal range (Table 5) at each visit.

Table 4 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

Note: This table comes from National Kidney Foundation Kidney Disease Outcomes Quality Initiative Nutrition Guidelines, 2008, and was slightly modified to include 18 year in the last category.

Table 5 Age Related Normal Range of Serum Phosphorus

Age	mmol/L		mg/dL	
	Lower Limit	**Upper Limit**	**Lower Limit**	**Upper Limit**
0 to <1year	1.36	2.62	4.2	8.1
≥1 year to <6 years	1.03	1.97	3.2	6.1
≥6 years to <9 years	1.03	1.97	3.2	6.1
≥9 years to <10 years	1.03	1.97	3.2	6.1
≥10 years to <15 years	1.00	1.94	3.1	6.0
≥15 years to ≤18 years	0.71	1.65	2.2	5.1

Note: This table comes from Covance central laboratory normal range, and was slightly modified to include 18 year in the last category.

2.5.2. Pharmacokinetic Variables

Not applicable.

2.5.3. Safety Variables

2.5.3.1. Primary Safety Endpoint

The primary safety endpoint is the AE profile, and percentage of treatment withdrawals due to AEs (treatment withdrawals due to AEs information will be retrieved from the Treatment Termination eCRF page).

2.5.3.2. Secondary Safety Endpoints

The following safety secondary endpoints are planned for analysis:

- Serum total corrected calcium at each time point and change from baseline
- Percentage of subjects who develop at least 1 episode of sustained hypercalcaemia (defined as total calcium value>upper safety limit from Table 6 (Table J from the study protocol synopsis) confirmed by repeat sample 1 week later) after start of treatment
- Serum total corrected calcium-phosphorus product at each time point and change from baseline, where serum total corrected calcium-phosphorus product correspond to the product of serum total calcium and Phosphorus, expressed in $mmol^2/L^2$ (serum total calcium and Phosphorus units must be the same).
- Serum iPTH levels at each time point and change from baseline
- Routine biochemical/haematological laboratory tests (blood iron parameters, Vitamin D parameters and bone markers)
- Vital signs

Table 6 Age Related Safety Limits of Total Calcium

Age	Upper Safety Limit		Lower Safety Limit	
	mmol/L	mg/dL	mmol/L	mg/dL
0 to <1year	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 were based on National Kidney Foundation Kidney Disease Outcomes Quality Initiative Nutrition Guidelines, 2008. Lower limit were based on literature (Paediatric Nephrology, 2nd edition) and personal communication. Both limits were slightly modified to include 18 year in the last category.

2.5.3.3. Other Safety Endpoints

Safety assessments performed during the study including physical examinations.

2.5.4. Other Variables

2.5.4.1. Subject Reported Palatability and Acceptability

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

3. SUBJECT POPULATIONS

3.1. Population Definitions

The following subject populations will be evaluated and used for presentation and analysis of the data:

- **Full Analysis Set (FAS) Population**: all subjects randomised to treatment at Stage 1, who received at least one dose of randomised treatment and who had at least one post-baseline assessment of the efficacy endpoint (serum phosphorus level). FAS population will be analysed according to treatment randomised. This population will be analysed for the protocol deviations, demographics and baseline characteristics, medical history and efficacy endpoints.
- **Per Protocol Set (PPS) Population**: all subjects in the FAS population who had no statistical major protocol violations. This population will be analysed for the demographics and baseline characteristics, medical history as well as for the primary and secondary efficacy endpoints
- **Safety Population**: all subjects who have taken at least one dose of study medication. Safety population will be analysed according to treatment received.
- **Stage 2 Safety Population:** all subjects who have taken at least one dose of study medication during stage 2.

If a subject switches from a treatment to the other by mistake, then other safety populations will be created to report the adverse events under each received treatment.

The FAS Population is the primary population for the analysis of efficacy parameters. A subset of efficacy parameters will be evaluated for the PPS Population. The Safety Population is the population for the analysis of safety endpoints. If a subject switches from a treatment to the other by mistake, further adverse events summary tables will be generated using additional safety populations.

3.2. Protocol Violations

The sponsor trial statistician with the Clinical Research Manager and the Clinical Trial Manager using the SAP and the final and consolidated versions of the Important and Non-important Protocol Deviations Designation and Escalation files (produced by Covance) will produce a protocol deviation criteria list to review, assess all protocol deviations (programmable deviations and deviations captured by the CRA) and classify as major deviations those which lead to exclusion of a subject's data from the PPS Population.

Covance will be responsible to review programmable PDs listing provided by Cytel on a quarterly basis and reconcile them to produce the final protocol deviation file (formatted as a Microsoft Excel file). This file will include the Important and Non-important Protocol Deviations Designation and Escalation lists as well as the programmable PDs. The protocol deviation file reconciled by Covance will include subject number, deviation code and a description of the protocol deviation.
The protocol deviation criteria list provided by the sponsor will specify the list of all protocol deviations and for each deviation a deviation code, and will identify whether or not the deviation

may warrant exclusion from the PPS Population. The final and reconciled protocol deviation file provided by Covance will be sent to the sponsor.
The sponsor will be in charge to review, update this file with the information coming from protocol deviation criteria list and send back to Cytel. This final file will be reviewed during the blinded data review meeting and finalised prior to hard database lock.

The major protocol deviations are as follows:

- Subject with insufficient compliance, i.e. missing, <70% or >120% during stage 1 or stage 2, (programmatically derived)
- Randomized subjects not fulfilling inclusion criterion number 2 on Hyperphosphatemia values (according to age) before randomisation (programmatically derived)
- Subjects with no baseline serum phosphorus value (programmatically derived)
- Subject with End of stage 1 visit date outside of allowed visit windows (section 4.2.9) (programmatically derived)
- Incorrect study treatment (not compliant with the IxRS randomisation) given to the subject (programmatically derived)
- Subjects who received both PA21 and Phoslyra (programmatically derived)
- Subject was randomised but did not meet inclusion criterion 4 or 5 (programmatically derived).
- Subject was randomised but met exclusion criterion 1, 2, 11 or 12 (programmatically derived).
- ICF not signed or signed by parents/guardian after randomisation date and if child is 7 or older, assent not obtained or obtained after randomisation date (programmatically derived).
- Other from deviations identified during the study which may lead to classification of "Major" as per clinical judgment during the blinded Data Review Meeting. If these deviations could not be programmatically derived, then an excel file will be provided by the sponsor with the corresponding major deviation information.

All protocol deviations will be presented in the data listings.

4. STATISTICAL METHODS

4.1. Sample Size Justification

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 subjects with CKD.

4.2. General Statistical Methods and Data Handling

4.2.1. General Methods

All outputs will be incorporated into rtf files, sorted and labelled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

For all outputs, the order and labelling of the treatment groups will be maintained as shown below:

1. PA21

2. Phoslyra

A 'Total' column will be used in all the outputs, which will present a total over both treatment groups, with the exception of exposure data where data will be presented separately for each drug.

Tabulations will be produced for appropriate demographic, baseline, efficacy and safety parameters. For categorical variables, summary tabulations of the number and missing observations as well as the number and percentage within each category of the parameter will be presented. For continuous variables, the number and missing observations, mean, median, standard deviation, Q1, Q3, minimum, and maximum values will be presented.

For the laboratory parameters, the number of the decimal places (dp) will be determined using the following rules based on the number of dp from the raw data:

- mean, median, q1 and q3 = raw + 1
- sd = raw + 2
- Min and max = raw

Formal statistical hypothesis testing will be performed on the primary endpoint only with test conducted at the 2-sided, 0.05 level of significance. Summary statistics will be presented, as well as confidence intervals on selected parameters, as described in the sections below. Some other statistical tests within each group may be performed for the secondary efficacy endpoints depending on the observed clinical differences.

Baseline will be defined as the latest measurement collected prior to first dose of study treatment.

Stage 1 data will be defined as all data collected until the last visit in the titration phase (prior to visit 12 and when "Yes" is responded to the question "Will subject enter the Stage 2 Safety Extension period after the current visit?"). Of note, if subject withdrew during stage 1 (i.e. no stage 2 initiated), visit 16 will be considered as part of stage 1.

Stage 2 data will be defined as all data collected from the day after the last visit in the titration phase.

Both local and central laboratory data will be reported using SI units, unless otherwise specify.

4.2.2. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.4 or later), unless otherwise noted. Medical History and adverse events will be coding using MedDRA (version 19.1 or later). Concomitant medications will be coded using World Health Organisation (WHO) Drug Dictionary (version June 2016 or later).

4.2.3. Methods of Pooling Data

Not applicable to the present study.

4.2.4. Adjustments for Covariates

The primary and secondary efficacy endpoints including change in serum phosphorus levels from baseline will be analysed through a linear mixed model with baseline serum phosphorus value, age (in categories) at randomisation, region and gender as covariates.

4.2.5. Multiple Comparisons/Multiplicity

Multiplicity is not of concern for this study with a single primary efficacy endpoint.

4.2.6. Subpopulations

The following subgroups will be considered:

- Age at randomisation: 0 to <2 year/ ≥2 year to <6 years/ ≥6 years to <12 years/ ≥12 years to ≤18 years
- Gender: Male/Female
- Region: Europe/Rest of the World/United States

Europe and Rest of the World maybe pooled under Non-US if Rest of the World represents a low number of subjects (e.g. less than 5% of the overall Safety Population).

In case of imbalance between treatment groups regarding baseline characteristics, other subgroup analyses may be performed.

4.2.7. Withdrawals, Dropouts, Loss to Follow-up

Subjects who withdrew from the study were not to be replaced.

4.2.8. Missing, Unused, and Spurious Data

All data recorded on the CRF will be included in data listings that will accompany the clinical study report.

In general there will be no imputation of missing data. There are a few exceptions where data imputation will be implemented see paragraph below.

4.2.8.1. Primary endpoint and secondary efficacy endpoints related to change in serum phosphorus levels from baseline to the end of Stage 1

To compute the change from baseline in serum phosphorus at end of stage 1, the laboratory values post-baseline and at baseline should be from the same source (i.e. either both central or both local). In addition, the following steps will be followed regarding the value to be considered at end of stage 1 for serum phosphorus:

- Step 1: Take central laboratory value at Visit 11 (visit n) if available.
- Step 2: If central laboratory value at Visit 11 is not available, then the central laboratory value at the previous visit, if available, is to be used. The previous visit to be called visit (n-1) will be the latest visit between Visit 16 (if subject early withdrew during stage 1) and Visit 10.
- Step 3: If central laboratory value at visit (n-1), as defined above, is not available, if local laboratory values at Visit (n-1) and at baseline are both available for the subject, then local laboratory value at Visit (n-1) is to be used.
- Step 4: If local laboratory value at Visit (n-1) is not available or if local laboratory value at baseline is not available, then the central laboratory value at visit (n-2) will be considered.
- Step 5: Repeat step 3 considering Visit (n-2)
- Step 6: Repeat step 3 and 4 considering visit (n-3),
    - until visit 1 for PB naive subjects
    - until visit 2 for subjects on PB

Note: “Visit 11”, “Visit 16” and more generally “Visit x” will refer to the derived analysis visits (applying windowing as defined in section 4.2.9).

4.2.8.2. Secondary efficacy endpoints related to change in serum phosphorus levels from baseline to the end of Stage 2

To compute the change from baseline in serum phosphorus at end of stage 2, the laboratory values post-baseline and at baseline should be from the same source (i.e. either both central or both local). In addition, the following steps will be followed regarding the value to be considered at end of stage 2 for serum phosphorus. Of note Visit 16 will be taken into account only if subject did not early withdraw during stage 1:

- Step 1: Take central laboratory value at Visit 16 (visit n) if available.
- Step 2: If central laboratory value at Visit 16 is not available then the central laboratory value at the previous visit, Visit (n-1) (i.e. visit 15), is to be used, if available.
- Step 3: If central laboratory value at Visit (n-1) is not available, if local laboratory values at Visit (n-1) and at baseline are both available for the subject, then local laboratory value at Visit (n-1) is to be used.

- Step 4: if local laboratory value at Visit (n-1) or local baseline are not available, central laboratory value at Visit (n-2) is to be used.
- Step 5: Repeat step 3 considering Visit (n-2)
- Step 6: Repeat step 4 and 5 for Visit (n-3), until Visit 12

Note: "Visit 16", "Visit 15" and more generally "Visit x" will refer to the derived analysis visits (applying windowing as defined in section 4.2.9).

4.2.8.3. Glomerular Filtration Rate

For subjects on dialysis values of glomerular filtration rate will not be deemed interpretable. Therefore all eGFR values for subjects on dialysis at screening as well as eGFR values after dialysis for subjects requiring dialysis for the first time during the study will not be part of the summary statistics over time of eGFR, they will be listed only.

4.2.8.4. Laboratory parameters

Clinical laboratory values as "<X" where X is the numerical value of the limit of quantification (LOQ) established by the laboratory will be imputed by LOQ/2 for summaries in the tables.

Clinical laboratory values as ">X" where X is the numerical value of the limit of quantification (LOQ) established by the laboratory will be imputed by LOQ for summaries in the tables.

Laboratory data below the lower limit of quantification (BLQ) should be labelled as such in the data listings.

4.2.8.5. Missing and partially missing dates

For identification of AEs as treatment-emergent, partial or missing dates for adverse events will be imputed as follows:

- Incomplete start date: if the day and month are missing and year is the same as first drug administration, or if only the day is missing and month and year are the same as first drug administration then the start date will be replaced by the minimum between first drug administration and AE resolution date. In all other cases the missing start day or start month will be replaced by 01.

- Complete missing start date: the start date will be replaced by the minimum between first drug administration and AE resolution date.

- Incomplete stop dates (Month and year available or only year available): these dates will be imputed to the last day of the corresponding month, or the last day of the corresponding year if not resulting in a date later than the date of subject's death. In the latter case the date of death will be used to impute the incomplete stop date. In all other cases the incomplete stop date will not be imputed.

For medications and procedures, imputation of missing or partial dates will be done to identify concomitant medications and procedures as follows:

- If the start date of the medication/procedure is unknown (i.e. complete missing date), the worst-case scenario will be assumed. The medication/procedure will be considered as both a prior medication/procedure and a concomitant medication/procedure (i.e. the medication will be assumed to start on January, 1st 2016).

- If the month and the day of the start date of the medication/procedure are missing, the month and the day will be imputed to January, 1st of the year specified.

- If the day of the start date of the medication/procedure is missing, the day will be imputed to the first day of the month specified.

- If the end date is unknown (i.e. missing), the date will be kept as missing however the medication/procedure will be considered concomitant.

- If the month and the day of the end date of the medication/procedure are missing, the month and the day will be imputed to December, 31st of the year specified.

- If the day of the end date of the medication/procedure is missing, the day will be imputed to the last day of the month specified.

For disease history, imputation of missing or partial dates (date of onset of CKD and date of first dialysis) will be done as follows:

- If the month and the day of the date are missing, the month and the day will be imputed to January, 1st of the year specified.

- If the day of the date is missing, the day will be imputed to the first day of the month specified.

- In case of missing date, no imputation will be performed.

No other dates will be imputed.

The original incomplete, missing or partial dates will be presented in the listings, not the imputed dates.

4.2.9. Visit Windows

The below windowing will be applied for summary tables with descriptive statistics over time, label of the visit will be derived as below.

Analysis visit	Week number	Windowing
Visit 5	Day 1 (Baseline) Stage 1	Day 1 (Visit 5)
Visit 6	Week 1 - Stage 1	Day 8 (+/- 3 days)
Visit 7	Week 2 - Stage 1	Day 15 (+/- 3 days)
Visit 8	Week 4 - Stage 1	Day 29 (+/- 3 days)
Visit 9	Week 6 - Stage 1	Day 43 (+/- 3 days)

Visit 10	Week 8 - Stage 1	Day 57 (+/- 3 days)
Visit 11	Week 10 - Stage 1	Day 71 (+/- 7 days)
N/A	Day 1 (Baseline) Stage 2	Day 1 (last visit in the titration phase + 1)
Visit 12	Week 4 - Stage 2	Day 29 (+/- 3 days)
Visit 13	Week 8 - Stage 2	Day 57 (+/- 3 days)
Visit 14	Week 12 - Stage 2	Day 85 (+/- 3 days)
Visit 15	Week 18 - Stage 2	Day 127 (+/- 7 days)
Visit 16	Week 24 - Stage 2	Day 169 (+/- 7 days)

If several values are falling into the same time window then the nearest value compared to the pre-defined week window as per protocol will be considered for efficacy and safety, if they are still 2 or more values then the first one in time among the nearest value will be considered. In case of 2 values at the same time (planned visit and unscheduled one), then the planned visit will be considered.

In addition, visit 11 or earlier (visit when “Yes” is responded to the question “Will subject enter the Stage 2 Safety Extension period after the current visit?”) and visit 16 or earlier data will be reported with the corresponding label in the summary tables "End of Stage 1" and "End of Stage 2", respectively. If subject withdrew during stage 1, visit 16 will be displayed with the corresponding label in the summary tables "End of Stage 1".

For "End of Stage 1" and "End of Stage 2" reported visits of the safety analyses, the original visits (as collected in the EDC system and not derived) will be used. The last non missing assessment collected in each period will be reported under “End of Stage 1” and “End of Stage 2”.

4.3. Interim Analyses

No interim analysis is planned for this study. A DSMB will review regularly the safety data to protect the safety of study participants. The procedures and analyses provided to DSMB are described in the DSMB Charter document.

4.4. Subject Disposition

Number of subjects treated at each site, country and region will be tabulated by treatment group and overall. A study populations table will describe the different populations used for analysis (FAS, PPS, Safety Population and Stage 2 Safety Population).

Subject disposition will be tabulated and will include the number of subjects randomised in Stage 1, the number of subjects treated, the number of subjects who enter the Stage 2, the number of subjects who completed the study, the number who withdrew prior to completing the treatment overall, during stage 1 and during stage 2, and reason(s) for withdrawal. The number of subjects who withdrew prior to completing the treatment overall, during stage 1 and during stage 2, and reason(s) for withdrawal will be also provided by age group. Summary data will be presented by treatment group and overall.

A by-subject listing of treatment completion information, including the reason for premature treatment withdrawal, if applicable, will be presented.

4.5. Demographic and Baseline Characteristics

Baseline, demographic, medical history and surgery history information will be summarised for the safety, Stage 2 safety, FAS and PPS Populations by treatment group and overall using descriptive statistics. No formal statistical comparisons will be performed.

Demographics and baseline disease characteristics will also be summarised by subgroups (age, gender, and region) for the safety, Stage 2 safety, FAS and PPS Populations.

Demographic and baseline data will be provided in data listings.

4.5.1. Demographics

Summary statistics will be provided for age at randomisation (years) as continuous and categorical variables (section 4.2.6; the 0 to <2 year category will be divided in two categories: 0 to <1 year and 1 to <2 year) and below), sex, race, ethnicity, region, baseline height (cm), baseline weight (kg), and baseline body mass index (BMI; kg/m^2).

The following age categories will be considered:

- New borns (0-27 days)
- Infants and toddlers (28 days-23 months)
- Children (2-11 years)
- Adolescents (12-17 years)
- Adults (18-64 years)

4.5.2. Baseline Disease Characteristics

Summary statistics will be provided for baseline disease characteristics including reason or cause of CKD, CKD stage, time since onset of CKD (years), time since first dialysis (years), baseline type of dialysis (haemodialysis, peritoneal dialysis, none), PB naïve (yes/no), Washout period needed (yes/no), baseline serum phosphorus (central laboratory in both Standard and Conventional units).
Time since onset of CKD (years) will be derived as: (date of informed consent - date of onset of CKD +1)/365.25
Time since first dialysis (year) will be derived as: (date of informed consent - date of first dialysis +1)/365.25

4.5.3. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 19.1 or later) and displayed in tables and listings using System Organ Class (SOC) and Preferred Term.

4.5.4. Surgery History

Surgery history will be displayed in listing only.

4.6. Exposure to Study Drug

Exposure to study drug will be summarised for each drug separately and for stage 1, stage 2 and overall study using descriptive statistics. Summary tables will be generated on the Safety Population for stage 1 and overall study exposure and on the Stage 2 Safety Population for stage 2 exposure data. They will include:

- For PA21 drug:
    - total number of tablets[(1)] taken / total number of sachets taken,
    - actual average daily number of tablets[(1)] taken / actual average daily number of sachets taken
    - actual average daily dosage (mg),
    - prescribed average daily dosage (mg),
    - duration of exposure (weeks),
    - compliance
    - maximum prescribed daily dose,
    - and reason of dose change.
- For Phoslyra drug:
    - actual average daily dosage (mL),
    - prescribed average daily dosage (mL),
    - duration of exposure (weeks),
    - compliance,
    - maximum prescribed daily dose,
    - and reason of dose change.

[(1)] Note: Tablets may have different strengths.

These tables for the PA21 group will be repeated by age group at randomisation, by gender, by region and by formulation (tablets only/sachets only/both).

The total and actual average daily number of tablets/sachets taken will be defined as

- For PA21 Drug:

Number of tablets/sachets dispensed – sum(Number of tablets/sachets returned or lost)

The actual average daily number of tablets/sachets taken will be defined as:

Total number of tablets/sachets taken / (last date of administration - start date of administration + 1)

The average daily dosage (g or mL) will be defined as

- For PA21 Drug:

(Total number of tablets/sachets taken × strength in g PA21) / (last date of administration - start date of administration + 1)

- For Phoslyra Drug:

(Total content of bottles taken) / (last date of administration - start date of administration + 1)

The prescribed average daily dosage (mg or mL) will be defined as:

$$\frac{\sum_{i=1}^{n} (\text{end date - start date of administration}_{(i)} +1) * \text{Prescribed Total Daily dosage of administration}_{(i)}}{\text{last date administration - start date of administration + 1}}$$

i being the i^{th} subject's administration and n the last subject's administration, i will be incremented from 1 until n by 1.

All subject's administrations will be considered for the overall study prescribed average daily dosage, whereas only subject's administration during the stage 1 or during the stage 2 will be considered for the prescribed average daily dosage for the stage 1 and for the stage 2, respectively.

Duration of exposure (days) for stage 1 will be defined as: (date of last administration in stage 1 (i.e. last administration until the last visit in the titration phase) – date of first administration in stage 1+1).

Duration of exposure (days) for stage 2 will be defined as: (date of last administration in stage 2– date of first administration in stage 2 (i.e. from the day after the last visit in the titration phase) +1).

Overall duration of exposure (days) will be defined as: (date of last administration in the study – date of first administration in stage 1+1).

Overall compliance (%) will be defined as:

- For PA21 drug: [[total number of mg corresponding to sachets/tablets dispensed - (total number of mg corresponding to unused sachets/tablets returned + total number of mg corresponding to unused sachets/tablets reported as lost)]/ total prescribed dose (in mg)]*100, where the total number of mg corresponds to the number of sachets/tablets * the dosage of the corresponding sachets/tablets and the total prescribed dose corresponds to $\sum_{i=1}^{n}$ (end date - start date of administration$_{(i)}$ +1) * Prescribed Total Daily dosage of administration$_{(i)}$ (in mg) as defined earlier. The prescribed total daily dosage (in mg) from the PA21 dosing eCRF page will be considered.
- For Phoslyra drug:[[473* total number of bottles dispensed - (473* total number of unused bottles + 473* total number of bottles reported as lost + sum of mL left from the total number of partially used bottles returned)] / total prescribed dose (in mL)]*100, where the total prescribed dose corresponds to $\sum_{i=1}^{n}$ (end date - start date of administration$_{(i)}$ +1) * Prescribed dose of administration$_{(i)}$ (in mL/day) as defined earlier. The prescribed dose (in mL/day) from the Phoslyra dosing eCRF page will be considered. Of note for the partially used bottles, eCRF collect only millimetres left, the information from table 7 will be used to convert approximately the millimetres to millilitres. Each bottle will be assumed to contain 473mL, i.e. 139 millimetres. In case no kit/bottle is returned or all kits/bottles are declared as lost, the compliance will be considered as missing.

For patients with all dispensed tablets/sachets or bottles unused, reported as lost and no tablets/sachets or bottles returned dates, all exposure variables listed above excluding exposure durations and prescribed daily dose variables (maximum, average); and compliance will be set to missing.

For subjects who did not enter into Stage 2: all the records from the "Dispensation/Compliance" CRF Form will be assigned into Stage 1.

For subjects who entered into Stage 2: all the records from the "Dispensation/Compliance" CRF Form with a dispensed date < End of Stage 1 date -3 days will be assigned into Stage 1; the other records will be assigned into Stage 2.

Table 7 Approximate transformation from millimetres to millilitres to be used for Phoslyra compliance derivation

Phoslyra Bottle	
Millimetres (mm)	**Millilitres (mL)**
139	473
130	448
120	411
110	375
100	339
90	303
80	268
70	234
60	200
50	166
40	130
30	94
20	59
10	24
1	1

Linear interpolation will be used for millimetres not listed in table 7. The following formula will be applied:

$mL = mL_0 + (mm - mm_0) * [(mL_1 - mL_0)/(mm_1 - mm_0)]$

Where

- mm is the observed value in millimetres for which approximate transformation in millilitres needs to be derived
- mL is the approximate transformation of mm in millilitres
- mm_0 is the lower value in millimetres from table 7 compared to mm
- mm_1 is the upper value in millimetres from table 7 compared to mm
- mL_0 is the known value in millilitres (from table 7) for mm_0
- mL_1 is the known value in millilitres (from table 7) for mm_1

Compliance (%) will be derived based on the sachets/tablets/bottles returned, reported as lost and dispensed and total prescribed dose during the stage considered.

All exposure data will be listed including the overall maximum dose prescribed (unit/day), overall maximum dose prescribed (unit/kg/day) and overall maximum dose received (unit/kg/day). In case subjects received both PA21 and Phoslyra during the study, one listing will be generated to display the list of subjects in that situation.

4.7. Efficacy Evaluation

Efficacy analysis will be conducted using the FAS and PPS Populations as outlined below.

All results related to serum phosphorus will be expressed in both mmol/L and mg/dL units.

Standard units (mmol/L) from the laboratory file sent by the external vendor will be used to derive the unit in mg/dL using the following conversion factor: ×3.096, starting from the standardized result.

4.7.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change in serum phosphorus levels from baseline to the end of Stage 1 (i.e. considering the last available value in stage 1) in PA21 group. It is based on central laboratory data; in case of missing data regarding central laboratory data, local laboratory measurements are used (please refer to Section 4.2.8.1 for the imputation to be applied).

The change from baseline in the PA21 group will be analysed using a linear mixed model with treatment, baseline serum phosphorus, age (in categories) at randomisation, region and gender as fixed effects. Summary statistics with the estimate of the adjusted mean change from baseline and its 95%CI as well as the corresponding p-value from the t-test will also be provided.

The SAS code used for the linear mixed model will be as below:

```
proc mixed data=input method=type3;
        class treatment age region gender;
        model chg_end_stage1=treatment age region gender baseline / ddfm=KENWARDROGER solution;
        lsmeans treatment / CL alpha=0.05;
        where treatment='PA21';
        ods output lsmeans=lsm1;
run;
```

The primary efficacy analysis will be repeated on the FAS by the following subgroups:

- Formulation (tablets only/sachets only/both)
- Serum phosphorus at baseline according to the age related normal range (above, within + below; see Table 5)
- Age group at randomisation (0-<2, 2-<6, 6-<12, 12-<=18) * Serum phosphorus at baseline according to the age related normal range (above, within + below; see Table 5). In case of no subject in an age group, this category will not be displayed.

Sensitivity analyses will include a repeat of the primary analysis on the FAS population based on observed data from the central laboratory only (with no imputation by local laboratory data).

Homogeneity of the results of the primary endpoint will be investigated on the FAS population by displaying summary statistics of change from baseline with the estimate of the adjusted mean change from baseline and its 95%CI for the following subgroups using the same linear mixed model as above:

- By age group at randomisation
- By gender
- By region

4.7.2. Secondary Efficacy Endpoints

For the following secondary endpoints, summary statistics with 95%CIs for the mean change will be provided by treatment group using the same linear mixed model as for the primary efficacy endpoint:

- Change in serum phosphorus levels from baseline to the end of Stage 1 in Phoslyra group
- Change in serum phosphorus levels from baseline to the end of Stage 2 in both groups

The above secondary endpoints are based on central laboratory data; in case of missing data regarding central laboratory data, local laboratory measurements are used (please refer to Sections 4.2.8.1 and 4.2.8.2 for the imputation to be applied).

Serum phosphorus values over time will be summarised by treatment group using descriptive statistics based both on central and on local laboratory measurements, separately.

Box plots will be generated for the change in serum phosphorus levels from baseline for each treatment arm to the end of Stage 1 and to the end of Stage 2 on the FAS and PPS Populations.

In addition, plots will be provided with one curve for each treatment arm representing the mean change (±standard error of the mean (SEM)) from baseline in serum phosphorus levels at each time point to the end of Stage 1 and to the end of Stage 2 for the FAS and PPS Populations.

For the following secondary endpoints based on both central and local laboratory measurements, number and percentage calculated using the number of subjects with non-missing serum phosphorus level as denominators with corresponding exact 95%CIs will be provided by treatment group:

- Subjects with serum phosphorus level within the age related target range at each visit
- Subjects with serum phosphorus level within the age related normal range at each visit.

4.8. Pharmacokinetic Evaluations

Not applicable.

4.9. Safety Analyses

Safety analyses will be conducted using the Safety Population.

4.9.1. Primary Safety Endpoint: Adverse Events

Adverse events will be coded using MedDRA and displayed in tables and listings using System Organ Class (SOC) and Preferred Term.

Analyses of adverse events will be performed for those events that are considered treatment emergent, where treatment emergent is defined as any adverse event with onset after the administration of study medication through the end of the study or any event that was present at baseline but worsened in intensity.

Adverse events are summarised by subject incidence rates, therefore, in any tabulation, a subject contributes only once to the count for a given adverse event (SOC or preferred term using the worst severity and the strongest relationship). The number of events will be reported as well in the summary tables. Multiple occurrences of the same TEAE in one subject during the same treatment in the trial will be counted as multiple events in the frequency counts for adverse events.

All TEAE summaries will be generated by treatment group and for both periods cumulatively, i.e. until end of stage 1 and until end of stage 2.

An overview of adverse events will be presented and will include the number and percentage of patients as well as the number of events with at least one:

- Treatment-emergent adverse events
- Treatment-related treatment-emergent adverse events
- Serious treatment-emergent adverse events
- Treatment-emergent adverse events leading to study drug discontinuation
- Treatment-emergent adverse events leading to Death
- Severe treatment-emergent adverse events

This table will be also repeated for any treatment-emergent adverse event of special interest (listed in Table 8 below). The overall summary of TEAEs will be also repeated by treatment group and overall maximum dose prescribed (see Table 9) during the trial. Results of the TEAE analysis by overall maximum dose prescribed may be confounded as the dose prescribed depends on the age. Therefore, a summary table with descriptive statistics for age will be provided for each overall maximum dose prescribed category by treatment.

The number and percentage of subjects as well as the number of events with the following adverse events will be presented by SOC and PT:

- with any treatment-emergent adverse event,
- with any treatment-emergent adverse events by causality assessed by the Investigator (related, unrelated),
- with any treatment-emergent adverse events by intensity assessed by investigator (mild, moderate, severe),
- with any treatment-emergent adverse events by age at randomisation (0-<2, 2-<6, 6-<12, 12-<=18). The denominator will be the number of patients in each age group category,
- with any treatment-emergent adverse event of special interest (listed in Table 8 below),
- with any serious treatment-emergent adverse event,
- with any serious treatment-related treatment-emergent adverse event,
- with any serious treatment-emergent adverse event that led to death,
- with any non-serious treatment-emergent adverse event,
- with any treatment-emergent adverse events that led to study drug discontinuation,
- and with any treatment-emergent adverse events started <4 weeks (<1 weeks, 1-<2 weeks and 2-<4 weeks will also be presented for more granularity), 4 to <12 weeks, 12 to <24 weeks, ≥24 weeks. The denominator is the number of patients at risk at the beginning of

the period (excluding those who have withdrawn or completed); i.e. in the category 2-<4 weeks, the denominator will include patients at risk/active at week 2.

Related events include Events with Certain or Probably/Likely or Possible as causality assessed by the investigator. Unrelated events include unlikely or unrelated as causality assessed by the investigator.

Table 8 Adverse Event of special interest definition

Events of special interest	MedDRA
Diarrhoea	MedDRA PT: -Diarrhoea
Potential of iron accumulation	MedDRA PT: -Cardiac iron overload -Haemochromatosis -Haemosiderosis -Hereditary haemochromatosis -Hepatic siderosis -Iron overload -Pulmonary haemosiderosis -Superficial siderosis of central nervous system
Masking of GI bleeding due to discoloured stool	MedDRA PT: -Faeces discoloured MedDRA SMQs: -SMQ GI haemorrhage
Events, which could be linked to (deficiencies in) growth and skeletal development and review of bone markers	SOC: Musculoskeletal and connective tissue disorder -HLT: Bone disorders NEC (from HLGT Bone disorders (excl congenital and fractures)) -HLT: Metabolic bone disorders NEC (from HLGT Bone disorders (excl congenital and fractures)) -HLGT: Fractures SOC: Metabolism and nutrition disorders -HLT: Bone metabolism disorders (HLGT: Bone, calcium, magnesium and phosphorus metabolism disorders) -HLT: Calcium metabolism disorders (HLGT: Bone, calcium, magnesium and phosphorus metabolism disorders)

The maximum dose prescribed during the trial to be considered for each treatment is listed below:

Table 9 List of Maximum daily dose prescribed by treatment

PA21 (g PA21/day)	Phoslyra (mL/day)
≤2.5	<15
]2.5-5.0]	[15-25[

]5.0-7.5]	[25-35[
]7.5-10.0]	[35-44[
]10.0-12.5]	≥44
]12.5-15.0]	

Conversion between both units for PA21 (mg Iron and g PA21) will be obtained using the below table:

PA21 Dose (Units)		
mg iron	**g PA21**	**Number of Tablets (using 1 tablet=2.5g PA21)**
250	1.25	0.5
500	2.5	1
750	3.75	1.5
1000	5.0	2
1500	7.5	3
1750	8.75	3.5
2000	10.0	4
2250	11.25	4.5
2500	12.5	5
3000	15.0	6

In these tabulations, each subject will contribute only once (i.e., the most related occurrence or the most severe occurrence) to each of the incidence rates in the descriptive analysis, regardless of the number of episodes.

No formal hypothesis-testing analysis of adverse events incidence rates will be performed.

If a subject switches from a treatment to the other by mistake, then further summary tables will be generated to display for each treatment the adverse events reported under each received treatment.

All adverse events (treatment-emergent adverse events or non-treatment-emergent adverse events) occurring on study will be listed in subject data listings.

By-subject listings also will be provided for the following: subject deaths; serious adverse events; adverse events leading to study drug withdrawal; most common SOC based on PA21 total; adverse events of special interest.

If a subject switches from a treatment to the other by mistake, then further by-subject listings for adverse events will be provided, one by treatment.

4.9.2. Secondary Safety Endpoints

For serum total corrected calcium and serum total corrected calcium-phosphorus product expressed in mmol/L and $mmol^2/L^2$ respectively, absolute value and change from baseline value

based on both central and local laboratory data, separately, will be described at each time point by treatment group.

For serum intact parathyroid hormone (iPTH) levels, absolute value and change from baseline value based on central laboratory data will be described at each time point by treatment group and will be expressed in both pmol/L and ng/mL units.

Percentage of subjects who develop at least 1 episode of sustained hypercalcaemia (defined as total calcium value>upper safety limit from Table 6 confirmed by repeat sample 1 week later) after start of treatment will be provided by treatment group. All the records from the local and central laboratories including scheduled and unscheduled visits will be taken into account. Patient will be considered as having an episode of sustained hypercalcaemia if two consecutive assessments separated by 6 days or more have calcium value greater than the upper limit of safety.

4.9.3. Laboratory Data

Clinical laboratory values will be expressed using SI units.

The actual value and change from baseline will be summarised for each clinical laboratory parameter at each time point by treatment group based on central laboratory measurements. For serum phosphorus, calcium (total and corrected) and albumin chemistry parameters, both central and local laboratory summary tables will be provided.

Shift tables from baseline to each post-baseline visit will be produced using the low/normal/high classification based on laboratory reference ranges.

The normal ranges of some parameters from the central laboratory data are only available for the age group above or equal to 18 years and not from 0 to 17yrs; therefore shift tables will not produce for the below parameters due to missing normal ranges. Only Actual Values and Changes Over Time tables and listings will be presented.

- Ferritin
- Osteocalcin
- Transferrin
- Vitamin A
- Vitamin E
- Vitamin K
- Intact parathyroid hormone
- Fibroblast growth factor 23
- Tartrate-resistant acid phosphatase 5b
- Atypical lymphocytes and Lymphocytes atypical/leukocytes

All laboratory data will be provided in data listings.

A subset listing will be presented for all abnormal laboratory values.

Table 10 List of Laboratory Parameters

Category	Parameters
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
Chemistry	Calcium (total, corrected), Intact parathyroid hormone (only shift tables as already summarised as part of the secondary safety endpoints), Creatinine, Glucose, Triglycerides, Total protein, Albumin, Urea, Uric acid, Total bilirubin, Total cholesterol (differential in high density lipoproteins and low density lipoproteins), Creatine phosphokinase, C-reactive protein, Bicarbonate, Sodium, Potassium, Chloride
Chemistry – Liver Enzymes	Alkaline phosphatase, Aspartate transaminase, Alanine transaminase, Lactate dehydrogenase, Gamma-glutamyl transpeptidase
Iron Status Parameters	Iron, Ferritin, Transferrin, Unsaturated Iron Binding Capacity, Transferrin saturation
Vitamins	A, 25(OH)D, 1,25(OH)2D, E, K
Bone Markers	Carboxyterminal cross-linking telopeptide of bone collagen, Tartrate-resistant acid phosphatase 5b, Bone-specific alkaline phosphatase, Osteocalcin, Fibroblast growth factor 23

In addition, the actual value will be summarised for eGFR (estimated Glomerular Filtration Rate) at each time point by treatment group based on central laboratory measurements for subjects not on dialysis at screening. For subjects not on dialysis at screening but requiring dialysis for the first time during the study, only eGFR values before dialysis will be part of the summary table.

All eGFR values will be listed and for subjects on dialysis, values of glomerular filtration rate will not be deemed interpretable and therefore will be flagged. For subjects on dialysis at screening, all eGFR values will be flagged. For subjects not on dialysis at screening but requiring dialysis for the first time during the study, eGFR values after dialysis will be flagged.

Glomerular Filtration Rate will be estimated through creatinine clearance paediatric Schwartz (2009) formula and it will be available at each timepoint it is possible to derive it as depending on height and serum creatinine. Age at each timepoint from Central Laboratory file will be used. If not available, age from CRF data at the same visit will be used, and in case of missing data, imputation will be done as follows:

- If visit date is missing, age will be left as missing, so eGFR will not be calculated
- If visit date is available, then calculate the duration in days between the last visit with an available age and the visit with a missing age (visit y date – visit x date + 1), and if this duration <= 365 days then imputed age will be the age at the previous visit, else impute with age (years) at previous visit + 1.

Please refer to Table 11 for the formula to be used.

Table 11 eGFR formula by age and gender categories

Category	eGFR Formula	Unit
< 1 year	(0.45 * Height (cm))/ (serum creatinine (umol/L) * 0.01131)	mL/min/1.73m^2
1 - <13 years	(0.55 * Height (cm))/ (serum creatinine (umol/L) * 0.01131)	mL/min/1.73m^2
Females 13- ≤18 years	(0.55 * Height (cm))/ (serum creatinine (umol/L) * 0.01131)	mL/min/1.73m^2
Males 13- ≤18 years	(0.70 * Height (cm))/ (serum creatinine (umol/L) * 0.01131)	mL/min/1.73m^2

4.9.4. Vital Signs and Physical Examinations

The actual value and change from baseline will be summarised for each vital signs (height, weight, BMI, resting blood pressure, resting heart rate and temperature) parameter at each time point by treatment group. The vital signs will also be summarised by age categories at randomisation within treatment group.

As the temperature can be taken using different modes (Oral, Otic or Axillary), then it will not be presented in the summary statistics when the mode at Week x is different from the mode at Baseline and then the change from baseline will not be derived in that case. All values will be presented in the listing.

So for the temperature, summary by mode will be presented.

By-subject listings of vital sign measurements will be presented in data listings.

For physical examination, shift table from baseline to each time point will be presented. All physical examination findings will be presented in a data listing.

4.9.5. Electrocardiogram

Not applicable.

4.9.6. Prior and Concomitant Medications

A concomitant medication is defined as any medication/therapy with an end date on or after the date of the first drug administration of study drug or missing (medication assumed to be ongoing).

A prior medication is defined as any medication with an end date prior to the date of the first administration of study drug.

Prior and concomitant medications will be coded using the WHO Drug Dictionary. Results will be tabulated by Anatomic Therapeutic Chemical (ATC) Level 2, Level 4) and Preferred Term.

All medications will be presented in a data listing, with a flag identifying them as prior or concomitant medications.

Type of dialysis (haemodialysis, peritoneal dialysis, none) will be summarised at each visit. All data related to dialysis will be listed.

4.9.7. Subject Reported Palatability and Acceptability

Subject reported palatability and acceptability results will be summarised at each time point. By-subject listings of visual analogue scale measurements will be presented in a data listing.

5. CHANGES TO PLANNED ANALYSES

To take into consideration covariate factors for the evaluation of the primary endpoint, baseline serum phosphorus, age (in categories) at randomisation, region and gender, a mixed model will be used in replacement to the paired t-test mentioned in the protocol.

Following discussions and agreements with PDCO and FDA, the following new age classification at randomisation will be used for the outputs: 0 to <1 year/ ≥1 year to <6 years/ ≥6 years to <12 years/ ≥12 years to <18 years.

Due to difficulties in the recruitment of patients below 9 years of age, PDCO agreed to reduce required minimum numbers of recruited patients as follows:

At least 60 subjects must be randomised into PA21 group and the following number of subjects from each age group as detailed below:

- Less than 1 year: no minimum number of randomised patients
- From 1 to less than 6 years: at least 5 patients on PA21
- From 6 to less than 12 years: at least 10 patients on PA21
- From 12 to less than 18 years: at least 10 patients on PA21
- Phoslyra arm: no minimum number of randomised patients.

Furthermore, FDA agreed that a partial waiver of PREA study requirements in patients less than 2 years of age can be justified on the basis that necessary studies are impossible or highly impracticable. The Agency also believes that it may be possible to generalize the findings in older paediatric patients down to younger patients greater than 2 years of age, indicating that the study can be completed without the need to recruit originally required minimum numbers of patients below 9 years of age.

Following PDCO advice from the Modification Summary Report Day 30 (EMA/170421/2018), the Sponsor plans to include additional comparison with an external control from paediatric study SVCARB07609 (EudraCT No. 2011-002329-23), conducted with sevelamer carbonate [Fathallah-Shaykh S. et al, 2018] where appropriate. This Phase II study is a 2-week, randomized, placebo-controlled, fixed dose period followed by a 6-month, single-arm, open-label, dose titration period study to investigate the efficacy and safety of sevelamer carbonate in hyperphosphatemic paediatric patients with CKD. The Sponsor selected this external control from available studies on the hyperphosphatemic paediatric patients with CKD due to the large sample size and the results of this paediatric study supported the extension of the indication for sevelamer to paediatric patients in the EU [EMA/271022/2016 and EMA/352101/2017]. However, due to differences in the design of the studies, there will be limitations to this comparison approach.
Descriptive comparison of safety endpoints, including AE profile, using publicly available data from the SVCARB07609 trial is foreseen and will be summarised in a separate report supporting the main conclusions from the PA-CL-PED-01 study.

According to the clinical study protocol the following iron status parameters have to be assessed: Iron, Ferritin, Transferrin and Transferrin saturation (TSAT). The iron parameters assessed during the conduct of study PA-CL-PED-01 are: Iron, Ferritin, Transferrin and Unsaturated Iron Binding Capacity (UIBC).
Unsaturated iron binding capacity (UIBC) is a surrogate marker of TSAT and has been reported to identify 100% of iron overloaded patients and 95% of patients with normal iron stores. The UIBC is therefore a reliable method.

The use of UIBC instead of TSAT is estimated to have no impact on the reliability of safety assessments in this clinical study and on the conclusions of the analysis. Therefore, TSAT will not be derived and presented. A Note to File at Vifor was created.

6. REFERENCES

EMA/271022/2016: Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006, 1 April 2016.

EMA/352101/2017: EPAR - Assessment report – Variation Type II, 18 May 2017.

Fathallah-Shaykh S, Drozdz D, Flynn J, Jenkins R, Wesseling-Perry K, et al. Efficacy and safety of sevelamer carbonate in hyperphosphatemic pediatric patients with chronic kidney disease. Pediatr Nephrol (2018) 33: 325.

International Conference on Harmonisation (ICH) E3. (ICH E3: Structure and content of Clinical Study Reports, dated 30 November 1995)

Schwartz GJ and Work DF. Measurement and estimation of GFR in children and adolescents. J Am Soc Nephrol. 2009; Nov; 4(11): 1832–1843

7. CLINICAL STUDY REPORT APPENDICES

7.1. Statistical Tables to be generated

Table 14.1.1 Subject Enrolment (Safety Population)

Table 14.1.2 Study Population (Safety Population)

Table 14.1.3.1 Subject Disposition (All Enrolled Subjects)

Table 14.1.3.2 Early Termination and Reason (Safety Population)

Table 14.1.3.2.1 Early Termination and Reason, by Age (Safety Population)

Table 14.1.3.3 Major Protocol Deviations (FAS Population)

Table 14.1.4.1 Demographic Characteristics (Safety Population)

Table 14.1.4.2 Demographic Characteristics (Stage 2 Safety Population)

Table 14.1.4.3 Demographic Characteristics (FAS Population)

Table 14.1.4.4 Demographic Characteristics (PPS Population)

Table 14.1.4.5 Demographic Characteristics, by Age (Safety Population)

Table 14.1.4.6 Demographic Characteristics, by Age (Stage 2 Safety Population)

Table 14.1.4.7 Demographic Characteristics, by Age (FAS Population)

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Table 14.1.4.9 Demographic Characteristics, by Gender (Safety Population)

Table 14.1.4.10 Demographic Characteristics, by Gender (Stage 2 Safety Population)

Table 14.1.4.11 Demographic Characteristics, by Gender (FAS Population)

Table 14.1.4.12 Demographic Characteristics, by Gender (PPS Population)

Table 14.1.4.13 Demographic Characteristics, by Region (Safety Population)

Table 14.1.4.14 Demographic Characteristics, by Region (Stage 2 Safety Population)

Table 14.1.4.15 Demographic Characteristics, by Region (FAS Population)

Table 14.1.4.16 Demographic Characteristics, by Region (PPS Population)

Table 14.1.5.1 Baseline Disease Characteristics (Safety Population)

Table 14.4.8.3	Clinical Laboratories – Chemistry - Liver Enzymes: Shift Table from Baseline to each Post-Baseline Value by timepoint (Safety Population)
Table 14.4.8.4	Clinical Laboratories – Iron Status Parameters: Shift Table from Baseline to each Post-Baseline Value by timepoint (Safety Population)
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Table 14.4.10	Physical Examination (Safety Population)
Table 14.4.11	Concomitant Medications (Safety Population)
Table 14.4.12	Dialysis Type over Time (Safety Population)
Table 14.4.13	Subject Reported Palatability and Acceptability over Time (Safety Population)

7.2. Data Listings to be Generated

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Listing 16.1.6.1.B	Investigational Product(s) Received for Phoslyra Dosing (Safety Population)
Listing 16.1.6.2	Listing of Patients Receiving Test Drug(s)/Investigational Product(s) From Specific Batches, Where More Than One Batch Was Used
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Listing 16.2.2.2	Protocol Deviations (Safety Population)
Listing 16.2.3	Subjects Excluded from Efficacy Analysis (Safety Population)
Listing 16.2.4.1	Demographic Data (Safety Population)
Listing 16.2.4.2	Baseline Disease Characteristics (Safety Population)
Listing 16.2.4.3	Medical History (Safety Population)
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Listing 16.2.8.7	Laboratory Results: Bone Markers (Safety Population)
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Listing 16.2.9.6	Subject Reported Palatability and Acceptability(Safety Population)

7.3. Figures to be Generated

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Figure 14.2.1.2	Change in Serum Phosphorus Levels from Baseline to End of Stage 1 (PPS Population)
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Figure 14.2.1.4	Change in Serum Phosphorus Levels from Baseline to End of Stage 2 (PPS Population)
Figure 14.2.2.1	Mean Change (±SEM) from Baseline in Serum Phosphorus Levels to End of Stage 1 (FAS Population)
Figure 14.2.2.2	Mean Change (±SEM) from Baseline in Serum Phosphorus Levels to End of Stage 1 (PPS Population)