CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205109Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	NDA20-5109/000
Drug Name:	PA21 (Velphoro Tablets)
Indication(s):	Control of Serum Phosphorus Levels in Patients with End-Stage Renal Disease (ESRD)
Applicant:	Vifor Fresenius Medical Care Renal Pharma
Date(s):	Date of Document: February 01, 2013 PDUFA Due Date: December 01, 2013
Review Priority:	Standard
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Keywords:	PA21, Serum phosphorus, Hyperphosphataemia, ESRD, Hemodialysis

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Two clinical studies (3a & 5a) were submitted to support the efficacy of PA21 in control of serum phosphorus levels in patients with end-stage renal disease (ESRD). Study 5a appears to demonstrate that PA21 maintenance dose (1000-3000 mg/day) is superior to the low dose (1.25 mg/day). Though a dose-response effect is suggested from Study 3a, the result of the study may be questionable due to post hoc manipulations of data.

1.2 Brief Overview of Clinical Studies

This NDA includes one supportive study (3a) and one pivotal study (5a) to support the effectiveness of PA21 in control of serum phosphorus levels in patients with ESRD. Study 3a was a phase II, randomized, open label, active-controlled, dose-ranging study to establish the dose-response of PA21; Study 5a was a confirmatory, phase III, 2-stage, re-randomization, withdrawal study to assess the superiority of PA21 comparing the maintenance dose (MD) to the low dose (LD). The detail of the studies is described as follows (Table 1):

Table 1 List of Study Included in Analysis

Study	Sample Size	Phase and Design	Treatment Period	# of Subjects Per Arm	Study Population
3a	154	Randomized, open label, active-controlled, dose-ranging, Phase II	6- week	250 mg/day: 26 1000 mg/day: 26 1500 mg/day: 25 2000 mg/day: 27 2500 mg/day: 24 Sevelamer: 26	ESRD
5a	93	Randomized, two-stage, open label, withdrawal, Phase III	3- week	Maintenance dose: 44 (1000-3000 mg/day) Low dose: 49 (250 mg/day)	ESRD

(Source: Sponsor's Table 1)

1.3 Statistical Issues and Findings

An active comparator of sevelamer was used in both studies [redacted] (b) (4)

Some issues were identified for Study 3a:

- The majority was non-US patients and the US population was under-represented.

- The result of Study 3a may be questionable for the following identified issues:

  - After final CSR has completed, some issues were discovered including inconsistencies between the original datasets and the final CSR, problems related to the programming and algorithm derivations.
  - Some post hoc manipulations were made including revising SAP, re-conducting analyses and updating CSR.

2. INTRODUCTION

2.1 Overview

Hyperphosphataemia is a common and serious complication in patients with chronic kidney disease (CKD), particularly those in ESRD requiring dialysis. Hyperphosphataemia has been shown to be an independent risk factor for cardiovascular mortality in dialysis patients.

Velphoro is a [redacted] (b) (4) phosphate binder to control serum phosphorus levels by absorbing the dietary phosphate in the GI tract, preventing its uptake into the blood, and thereby reducing the serum level of phosphorus in patients with ESRD.

2.2 Data Sources

The sponsor's SAS transport datasets were stored in the directory of \\cdsesub1\EVSPROD\NDA205109 of the Center's electronic document room.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

3.1.1 Study 3a

The sponsor stated that during the mapping of the raw and derived legacy datasets some issues were discovered. The issues included inconsistencies between the original datasets and the final CSR, problems related to the programming and algorithm derivations due to lack of clarity in documentation and insufficiently validation. At that time the final CSR has been completed (June 15, 2010).

An independent clinical research organization was requested to perform a review of the datasets, programming algorithm and analysis (March 30, 2012). A SAP addendum was then developed (May 29, 2012). Analyses affected by the issues were re-conducted and the final CSR was updated (October 21, 2012).

One of the identified issues related to efficacy was no visit windows pre-defined in the original SAP for any of the efficacy parameters and problems occurred in the identification of subjects in the FAS. Some subjects were identified as being treated, with returned post-baseline efficacy assessment and

still on treatment, but all values recorded in the follow-up visits. These data inconsistencies can mislead the principles of the ITT and the LOCF approach.

The statistical reviewer created a sample of subjects with the issue and asked the sponsor to verify the values of primary efficacy endpoint. The sponsor's responses to the identified issues seem to be acceptable. More discussions on the issues will be given in the section 3.2.1.

3.1.2 Study 5a

The quality of the data and analyses are acceptable. A consistent result of the primary efficacy analysis can be generated from both raw and derived data.

3.2 Evaluation of Efficacy

3.2.1 Study 3a

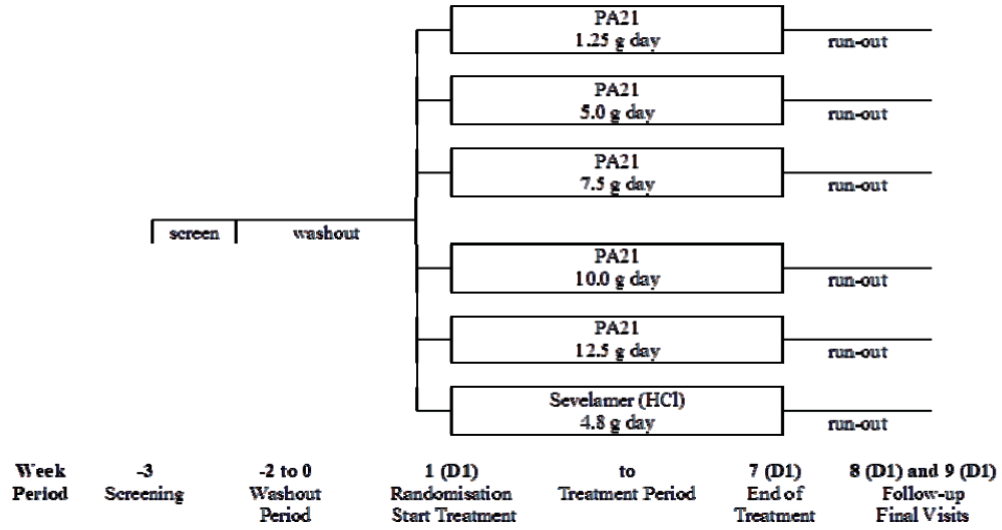
3.2.1.1 Study Objectives

The primary objective was to investigate the ability of different doses of PA21 to lower serum phosphorus levels in subjects with CKD.

3.2.1.2 Study Design

Study 3a was a parallel group, randomised, open-label, active-controlled, multicentre, dose-ranging study. The study consisted of a screening phase (up to 1 week), a washout phase of 2 weeks, a 6-week treatment phase, and a 2-week run-out phase. The detail of the study design is described as follows (Figure 1).

Figure 1 Study Design, Study 3a



(Source: Sponsor's Figure 1)

3.2.1.3 Efficacy Measures

1) Primary Efficacy Endpoint: Change from baseline in serum phosphorus levels at the end of treatment

2) Secondary Efficacy Endpoints:
- Change from baseline in serum phosphorus levels at each time point (apart from end of treatment)
- Percentage of patients achieving controlled serum phosphorus levels (i.e., ≥1.13 to 1.78 mmol/L (≥3.5 to ≤5.5 mg/dL)) after 1, 2, 3, 4, 5 and 6 weeks of treatment, separately
- Time to reach the first controlled serum phosphorus level
- Serum phosphorus level at each time point
- Serum calcium phosphorus product at each time point
- Change in serum calcium phosphorus products from baseline at each time point
- Serum iPTH levels at each time point
- Change in serum iPTH levels from baseline at each time point

3) Statistical Analysis Methodology:
- The primary efficacy analysis: The primary endpoint was analyzed with a single sample t-test within each treatment group. A hierarchical testing procedure was applied to preserve the overall alpha level of 0.05, testing from the highest PA21 dose (12.5 g/day) to the lowest dose (1.25 g/day) until all doses were tested or the first p-value above 0.05 was observed.

- The secondary primary efficacy analysis: The primary endpoint was also analyzed using an analysis of covariance (ANCOVA) model with dose group as fixed effect and baseline serum phosphorus levels as covariates. Pair-wise comparisons of the 4 higher-dose groups versus the lowest dose group were performed by means of the Dunnett procedure using the lowest dose group as the control group.

3.2.1.4 Patient Disposition, Demographic and Baseline Characteristics

1) Patient Disposition:

- Using the SAP addendum, of the 154 randomized subjects, 103 subjects (66.9%) completed the study and 51 subjects (33.1%) were withdrawn from the study (Table 2). The highest drop-out rate was in the 10.0 g/day group, and lowest in the 7.5 g/day group (Table 11). The most common reason for withdrawn was exceeding the upper safety limit (n=8, 6.3%) or decreasing below safety limit (n=20, 15.6%) of serum phosphorus level. The withdrawn criterion was pre-defined for patient safety purpose.

Table 2 Number of Subjects Randomized, Treated, Withdrawn and Completed, Study 3a
All Subjects Randomized, SAP Addendum

Reason	PA21					Sevelamer (HCl) (N=26) n (%)	Overall (N=154) n (%)
	1.25 g/Day (N=26) n (%)	5.0 g/Day (N=26) n (%)	7.5 g/Day (N=25) n (%)	10.0 g/Day (N=27) n (%)	12.5 g/Day (N=24) n (%)		
Subjects randomised	26 (100.0%)	26 (100.0%)	25 (100.0%)	27 (100.0%)	24 (100.0%)	26 (100.0%)	154 (100.0%)
Subjects randomised but not treated	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subjects treated	26 (100.0%)	26 (100.0%)	25 (100.0%)	27 (100.0%)	24 (100.0%)	26 (100.0%)	154 (100.0%)
Subjects who withdrew	8 (30.8%)	9 (34.6%)	5 (20.0%)	12 (44.4%)	9 (37.5%)	8 (30.8%)	51 (33.1%)
Subjects completed[(1)]	18 (69.2%)	17 (65.4%)	20 (80.0%)	15 (55.6%)	15 (62.5%)	18 (69.2%)	103 (66.9%)

(Source: Sponsor's Table 11, confirmed by the reviewer's analysis)

- Comparing to the original SAP, the numbers of patient disposition were similar to the numbers in SAP addendum (Table 3).

Table 3 Number of Patients Randomized, Treated, Withdrawn and Completed, Study 3a
All Patients Randomized, Original SAP

	PA21					Sevelamer (HCl)	Overall
	1.25 g/day (N=26)	5.0 g/day (N=26)	7.5 g/day (N=25)	10.0 g/day (N=27)	12.5 g/day (N=24)	(N=26)	(N=154)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Randomised but not treated	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)	1 (4.2)	0 (0.0)	2 (1.3)
Treated	26 (100.0)	26 (100.0)	25 (100.0)	26 (96.3)	23 (95.8)	26 (100.0)	152 (98.7)
Withdrawn[1]	7 (26.9)	9 (34.6)	5 (20.0)	12 (44.4)	9 (37.5)	8 (30.8)	50 (32.5)
Completed	19 (73.1)	17 (65.4)	20 (80.0)	15 (55.6)	15 (62.5)	18 (69.2)	104 (67.5)

(Source: Sponsor's Table 3)

2) Patient Demographic and Baseline Characteristics

The treatment groups appeared balanced with respect to demographic characteristics. More than 60% subjects were males, the majority was white. The following table summarizes patient disposition, demographic and baseline characteristics (Table 4).

Table 4 Patient disposition, demographic and baseline characteristics, Full ITT, Study 3a

Demographic Variable	PA21						Sevelamer (HCl) (N=24) n (%)
	1.25 g/Day (N=26) n (%)	5.0 g/Day (N=26) n (%)	7.5 g/Day (N=25) n (%)	10.0 g/Day (N=25) n (%)	12.5 g/Day (N=24) n (%)	Total PA21 (N=126) n (%)	
Age (yrs)							
Mean	60.1	59.7	61.9	60.8	59.3	60.4	61.6
SD	12.29	13.80	13.71	13.21	12.32	12.91	11.22
Median	63.0	57.5	63.0	62.0	62.0	62.0	63.0
Range	36-84	34-85	39-85	34-81	28-77	28-85	33-80
Height (cm)							
Mean	169.5	169.3	168.6	166.8	170.0	168.8	166.4
SD	10.93	8.97	11.65	7.29	9.45	9.69	9.70
Median	171.0	169.0	172.0	167.0	170.5	170.0	166.0
Range	152-193	153-182	139-188	152-178	152-185	139-193	151-185
Sex							
Male	17 (65.4%)	19 (73.1%)	16 (64.0%)	15 (60.0%)	13 (54.2%)	80 (63.5%)	14 (58.3%)
Female	9 (34.6%)	7 (26.9%)	9 (36.0%)	10 (40.0%)	11 (45.8%)	46 (36.5%)	10 (41.7%)
Race							
White	24 (92.3%)	26 (100.0%)	24 (96.0%)	22 (88.0%)	24 (100.0%)	120 (95.2%)	23 (95.8%)
Black	2 (7.7%)	0 (0.0%)	0 (0.0%)	2 (8.0%)	0 (0.0%)	4 (3.2%)	0 (0.0%)
Asian	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (4.2%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Serum Phosphorus Baseline Level (mg/dL)							
Mean	6.8	6.6	6.9	6.8	6.5	6.7	
SD	1.64	1.08	1.15	1.75	1.19	1.38	
Median	7.0	6.6	6.7	6.7	6.6	6.7	
Range	3.4-10.3	4.2-8.3	4.5-9.0	4.3-9.3	4.1- 9.2	3.4-10.3	
Reason for CKD							
Glomerulopathy	7 (26.9%)	4 (15.4%)	6 (24.0%)	8 (32.0%)	5 (20.8%)	30 (23.8%)	7 (29.2%)
Vascular nephropathy	7 (26.9%)	4 (15.4%)	5 (20.0%)	7 (28.0%)	3 (12.5%)	26 (20.6%)	3 (12.5%)
Interstitial nephropathy	2 (7.7%)	2 (7.7%)	4 (16.0%)	3 (12.0%)	4 (16.7%)	15 (11.9%)	3 (12.5%)
Other	9 (34.6%)	16 (61.5%)	9 (36.0%)	7 (28.0%)	12 (50.0%)	53 (42.1%)	11 (45.8%)
Missing	1 (3.8%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	2 (1.6%)	0 (0.0%)
Duration (months)							
n	25	26	24	24	24	123	24
Mean	59.1	64.6	87.2	90.7	85.2	77.0	118.3
SD	79.29	56.56	71.75	111.04	66.95	78.75	140.29
Median	40.8	47.3	63.6	48.9	74.0	54.2	65.0
Range	1-408	6-239	5-239	6-455	10-263	1-455	4-599

(Source: Sponsor's Tables 15 & 16, confirmed by the reviewer's analysis)

3.2.1.5 Sponsor's Primary Efficacy Results

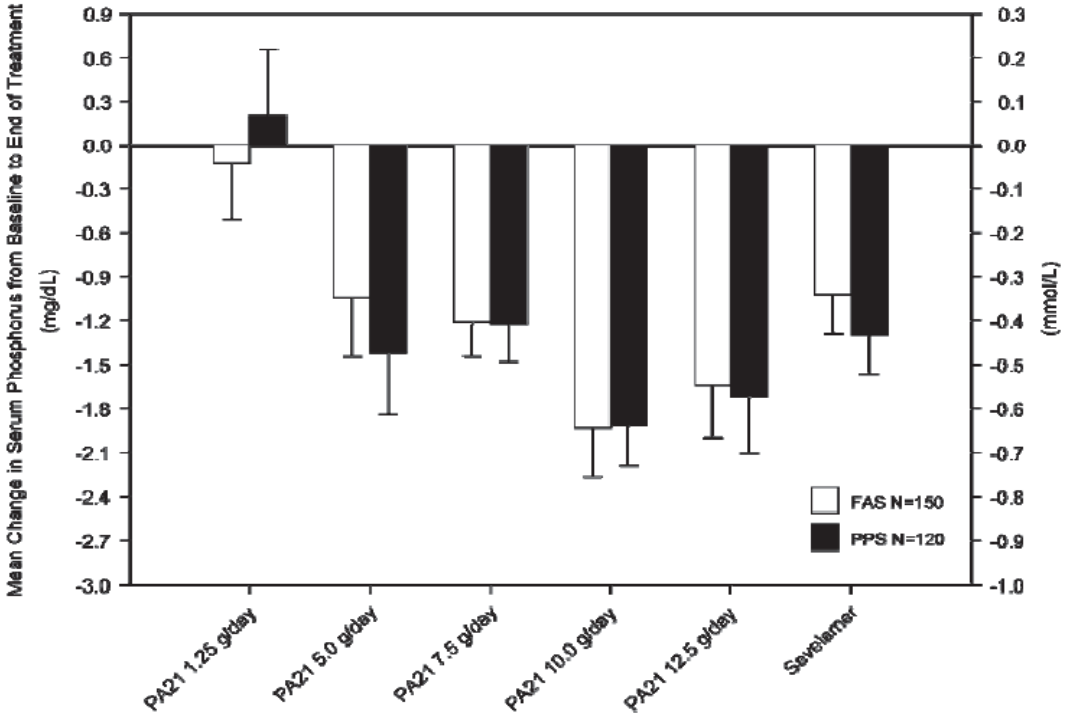
1) Primary efficacy analysis: Two SAPs produce a similar result. A statistically significant decrease ($p \leq 0.016$) in serum phosphorus levels from baseline to end of treatment was showed for all dose groups except for the dose of 1.25 g/day group (Table 5, Figure 2).

Table 5 Absolute Change in Serum Phosphorus from Baseline at End of Treatment (FAS), Study 3a

Variable	PA21					Sevelamer (HCL)
	1.25 g/day	5.0 g/day	7.5 g/day	10.0 g/day	12.5 g/day	
Using the Addendum of SAP						
	n=26	n=26	n=25	n=25	n=24	n=24
Mean	-0.042 (-0.130)	-0.348 (-1.076)	-0.404 (-1.250)	-0.644 (-1.995)	-0.547 (-1.692)	-0.341 (-1.055)
SD	0.650 (2.011)	0.684 (2.118)	0.391 (1.210)	0.551 (1.706)	0.584 (1.807)	0.436 (1.349)
Minimum	-1.66 (-5.14)	-2.07 (-6.41)	-1.26 (-3.90)	-1.85 (-5.73)	-1.85 (-5.73)	-1.22 (-3.78)
Median	-0.010 (-0.031)	-0.340 (-1.053)	-0.510 (-1.579)	-0.660 (-2.043)	-0.465 (-1.440)	-0.375 (-1.161)
Maximum	1.04 (3.22)	0.78 (2.41)	0.28 (0.87)	0.68 (2.11)	0.56 (1.73)	0.58 (1.80)
p-value(1)	0.7448	0.0157*	<0.001*	<0.001*	<0.001*	<0.001
Using the Original SAP						
	n=25	n=26	n=25	n=25	n=23	n=23
Mean	-0.01 (-0.02)	-0.42 (-1.30)	-0.41 (-1.26)	-0.53 (-1.64)	-0.59 (-1.81)	-0.41 (-1.27)
SD	0.72 (2.23)	0.71 (2.20)	0.39 (1.22)	0.60 (1.85)	0.55 (1.69)	0.43 (1.33)
Min	-1.66 (-5.14)	-2.07 (-6.41)	-1.26 (-3.90)	-1.85 (-5.73)	-1.85 (-5.73)	-1.22 (-3.78)
Median	0.02 (0.06)	-0.40 (-1.22)	-0.51 (-1.58)	-0.63 (-1.95)	-0.48 (-1.49)	-0.38 (-1.18)
Max	1.72 (5.33)	0.78 (2.42)	0.28 (0.87)	0.68 (2.11)	0.56 (1.73)	0.34 (1.05)
p-value[1]	0.971	0.006*	<0.001*	<0.001*	<0.001*	<0.001

(Source: Sponsor's Tables 10 & 20, confirmed by the reviewer's analysis)

Figure 2 Change from Baseline in Serum Phosphorus Levels at End of Treatment (FAS and PPS), Study 3a



Notes: p≤0.016 for change from baseline using a 2-sided single sample t-test for all dose groups except PA21 1.25 g/day, in both the FAS and PPS.
FAS = Full analysis set; PPS = Per-protocol set.

(Source: Sponsor's Figure 3, confirmed by the reviewer's analysis)

1) Secondary primary efficacy analysis: Using the addendum of SAP, a statistically significant larger decrease in serum phosphorus from baseline to end of treatment was showed in the two higher PA21 doses (12.5 and 10.0 g /day) when compared to the lowest dose (1.25 g/day) (Table 6). All PA21 doses of 5.0 g/day and above showed a statistically significantly greater reduction from baseline in serum phosphate when compared to the PA21 1.25 g/day group using the original SAP (Table 7).

Table 6 Absolute Change in Serum Phosphorus from Baseline at End of Treatment, ANCOVA (FAS), Study 3a

	Least Square Mean	p-value[(1)]
Pair-wise comparison of higher PA21 dose groups versus lowest PA21 dose group (FAS)		
PA21 12.5 g/day versus PA21 1.25 g/day	-0.564	0.001
PA21 10.0 g/day versus PA21 1.25 g/day	-0.612	<0.001
PA21 7.5 g/day versus PA21 1.25 g/day	-0.357	0.063
PA21 5.0 g/day versus PA21 1.25 g/day	-0.341	0.078

(Source: Sponsor's Table 21, confirmed by the reviewer's analysis)

Table 7 Serum Phosphate (mmol/L): Change from Baseline at End of Treatment, ANCOVA (FAS), Study 3a

	Least Square Mean	p-value[1]
Pair-wise comparison of higher PA21 dose groups versus lowest PA21 dose group		
PA21 12.5 g/day versus PA21 1.25 g/day	-0.656	<0.001
PA21 10.0 g/day versus PA21 1.25 g/day	-0.618	<0.001
PA21 7.5 g/day versus PA21 1.25 g/day	-0.422	0.030
PA21 5.0 g/day versus PA21 1.25 g/day	-0.477	0.010

1 p-value adjusted for multiple comparisons according to Dunnett.

(Source: Sponsor's Table 11)

3.2.1.6 Reviewer's Results

1) The reviewer verified the sponsor's primary and secondary primary efficacy analyses and concurred with their results.

2) The reviewer also conducted analyses to explore the dose response of PA21:

- Assessment of dose response: Analysis of ANCOVA is conducted, and linear and quadratic contrasts are tested. The result of analysis shows that a liner dose response seems appropriate to the data (P<.0001) (Table 8).

Table 8 Analysis Output

The GLM Procedure

Dependent Variable: CHG

Contrast	DF	Contrast SS	Mean Square	F Value	Pr > F
linear	1	49.50922891	49.50922891	17.99	<.0001
quadratic	1	3.08865849	3.08865849	1.12	0.2916

- Diagnosis of model fit: Data are fitted to linear, quadratic and Emax models. The goodness-fit of the model is assessed by AIC criteria and residual plot. The AIC criteria seem to indicate that a linear model fits data better (Table 9,). The residual plots appear to suggest that both linear and quadratic models are good fits for the data (Figure 3). Overall a linear model seems sufficient for the data. The Emax model has poor fit based on the residual plot and AIC value.

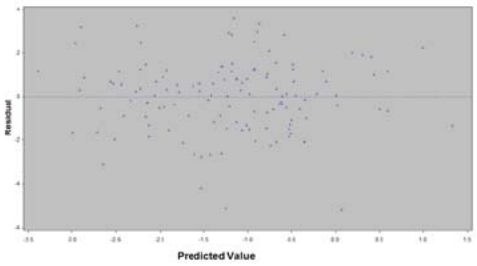
Table 9 Goodness-Fit of Model

Model		AIC
Linear Model:	Response= $\beta_0 + \beta_1 baseline + \beta_2 dose + e$	130.9
Quadratic Model:	Response= $\beta_0 + \beta_1 baseline + \beta_2 dose + \beta_3 dose^2 + e$	131.0

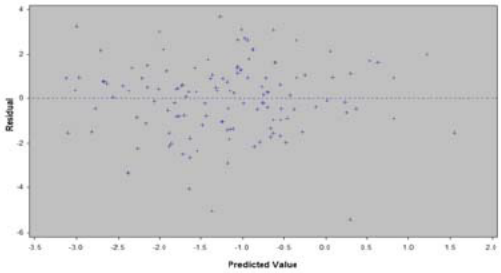
Emax Model: Response= $E_{baseline} + \frac{E_{max} dose^n}{ED50^n + dose^n}$	512.3

Figure 3 Residual Plots

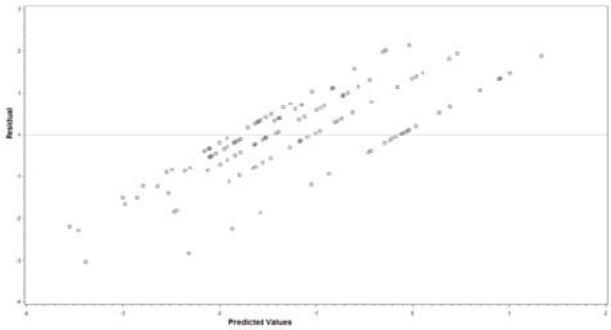
Linear Model



Quadratic Model



Emax Model



3.2.1.7 Conclusions

- A statistically significant decrease in serum phosphorus level from baseline to the end of treatment was shown for all PA21 doses (5.0, 7.5, 10.0, 12.5 g/day) except the lowest dose (1.25 g/day). A linear dose response seems appropriate for the data.

- A statistically significant larger decrease in serum phosphorus levels from baseline at end of treatment was shown in the two higher doses (10.0 and 12.5 g/day) compared to the lowest dose (1.25 g/day).

3.2.2 Study 5a

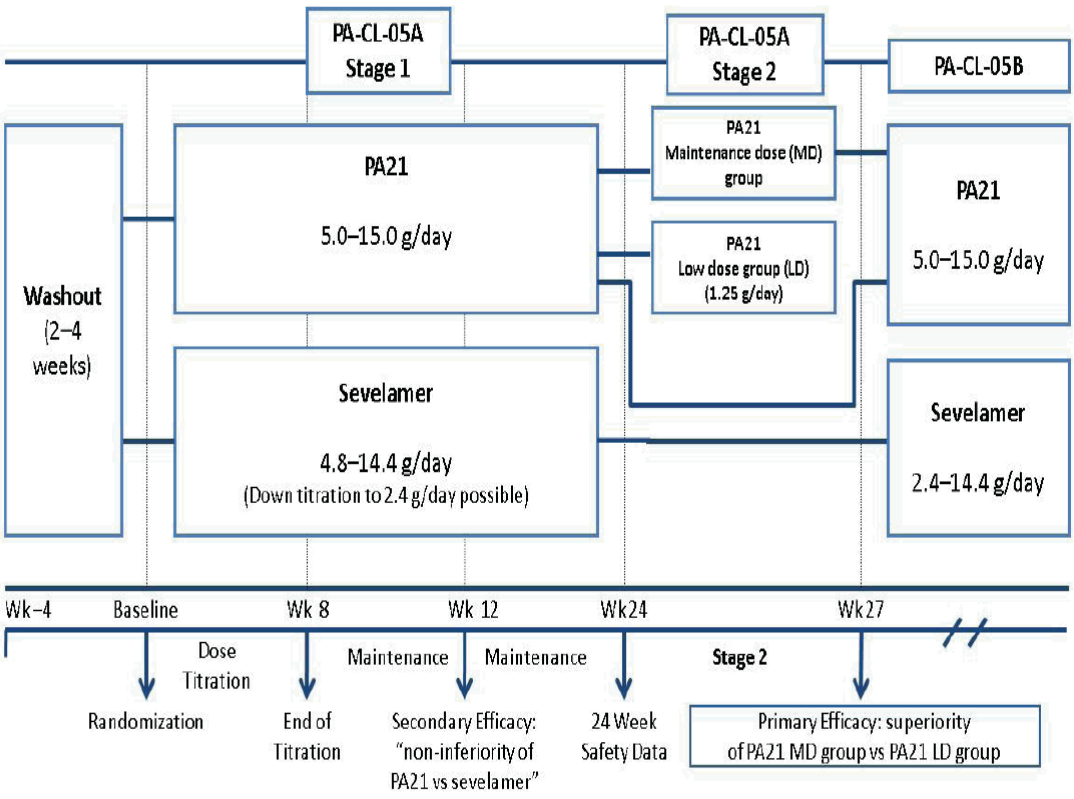
3.2.2.1 Study Objectives

The primary objective of this study was to establish the superiority of PA21 maintenance dose versus PA21 low dose in maintaining the phosphorus lowering effect in subjects undergoing haemodialysis (HD) in Stage 2.

3.2.2.2 Study Design

Study 5a consisted of two stages. Stage 1 was a prospective, randomised, parallel group, open-label, active controlled, 24-week study of PA21 compared to sevelamer to establish a non-inferiority at week 12; Stage 2 was a prospective, randomized, parallel group, open-label, 3-week study assessing the superiority of PA21 maintenance dose to PA21 low dose (Figure 4).

Figure 4 Study Design, Study 5a



(Source: Sponsor's Figure 1)

3.2.2.3 Efficacy Measures

1) Primary Efficacy Endpoint: Change from Week 24 in serum phosphorus levels at Week 27 (Stage 2).

2) Secondary Efficacy Endpoints:

- Change from baseline in serum phosphorus levels at Week 12 – a non-inferiority comparison between PA21 and sevelamer (per-protocol set (PPS) and full analysis set (FAS)).
- Change from baseline in serum phosphorus levels at Week 1 through to Week 8, Week 12, 16, 20, and 24 (PPS and FAS using a mixed model repeated measure analysis).
- Achievement of response (serum phosphorus control) at Week 12 and Week 24, defined as:
  - Percentage of subjects with serum phosphorus within the Kidney Disease Outcomes Quality Initiative (KDOQI) guideline target range of 1.13 to 1.78 mmol/L (3.5 to 5.5 mg/dL).
  - Percentage of subjects with serum phosphorus within the Kidney Disease Improving Global Outcomes (KDIGO) guideline normal range of 0.81 to 1.45 mmol/L (2.5 to 4.5 mg/dL).
- Duration of serum phosphorus levels in the KDIGO normal range 0.81 to 1.45 mmol/L (2.5 to 4.5 mg/dL).

- Duration of serum phosphorus levels in the KDOQI target range of 1.13 to 1.78 mmol/L (3.5 to 5.5 mg/dL).

3) Statistical Analysis Methodology:

The primary efficacy endpoint was analyzed using an analysis of covariance (ANCOVA) with treatment as a factor and baseline, region as covariates.

3.2.2.4 Patient Disposition, Demographic and Baseline Characteristics

1) Patient Disposition: Of the 99 subjects correctly randomized to Stage 2, 94 were treated and 88 (88.9%) completed in Stage 2 (Table 10). The drop-out rates were similar in both groups, approximately 6.0%. One subject (847-902) was randomized into stage 2 (MD), but not treated, and had no withdrawal date or reason for withdrawal. The subject was not included in the primary efficacy analysis in Stage 2 and the total number of subjects for the primary efficacy analysis is 93 (the reviewer verified).

Table 10 Subject Disposition in Stage 2, Study 5a

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

1 Includes the subjects in the MD group randomised but not treated. These subjects were dispensed PA-CL-05B drug in error.
2 The percentages of reasons for discontinuations were computed based on the total number of discontinuations.

(Source: Sponsor's Table14.1.2.2, confirmed by the reviewer's analysis)

2) Patient Demographic and Baseline Characteristics

PA21 maintenance dose and PA21 low dose treatment groups seemed balanced with respect to demographic characteristics; there were more white and non-Hispanic. The details of patient demographic and baseline characteristics are summarized below (Table 11).

Table 11 Summary of Demographic and Baseline Characteristics, Study 5a

Demographic Variable	PA21 MD (N=44)	PA21 LD (N=49)	Total (N=93)
Age (years)			
n	44	49	93
Mean (SD)	59.3 (13.60)	57.2 (11.40)	58.2 (12.46)
Median	58.0	58.0	58.0
Min/max	23.0/83.0	27.0/83.0	23.0/83.0
Sex (n (%))			
Female	24 (54.5%)	25 (51.0%)	49 (52.7%)
Male	20 (45.5%)	24 (49.0%)	44 (47.3%)
Race (n (%))			
White	28 (63.6%)	30 (61.2%)	58 (62.4%)
Black/African American	14 (31.8%)	18 (36.7%)	32 (34.4%)
Asian	0 (0.0%)	1 (2.0%)	1(1.1%)
American Indian/Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)
Native Hawaiian/Other Pacific Islander	1 (2.3%)	0 (0.0%)	1 (1.1%)
Other	1 (2.3%)	0 (0.0%)	1 (1.1%)
Ethnicity (n (%))			
Hispanic or Latino	9 (20.5%)	10 (20.4%)	19 (20.4)
Non-hispanic or Latino	35 (79.5%)	39 (79.6%)	74 (79.6%)
Weight (kg)			
n	44	48	92
Mean (SD)	84.1 (17.19)	85.1 (22.47)	84.6 (20.02)
Median	81.0	78.0	79.8
Min/max	50.8/123.9	44.1/167.3	44.1/167.3
Serum Phosphorus Level (mg/dL)			
n	44	45	93
Mean (SD)	4.7 (1.0)	5.0 (1.1)	4.9 (1.1)
Median	4.9	5.0	4.9
Min/Max	2.3/7.1	2.1/7.6	2.1/7.6

Time from start of ESRD (months)[1]			
n	44	49	93
Mean (SD)	73.8 (79.47)	59.9 (45.97)	66.5 (64.05)
Median	45.9	48.3	48.3
Min/max	6.4/381.6	6.7/243.8	6.4/381.6
Time from the first dialysis (months)[2]			
n	44	49	93
Mean (SD)	60.9 (63.66)	54.2 (40.40)	57.4 (52.51)
Median	37.8	47.2	43.3
Min/max	3.1/310.7	6.6/243.8	3.1/310.7
Baseline HD Kt/V value[3]			
n	44	49	93
Mean (SD)	1.6 (0.24)	1.7 (0.28)	1.7 (0.27)
Median	1.6	1.7	1.7
Min/max	1.2/2.2	1.3/2.4	1.2/2.4
Previous Renal Transplant (n (%))			
Yes	3 (6.8%)	5 (10.2%)	8 (8.6%)
No	41 (93.2%)	44 (89.8%)	85 (91.4%)
Previous parathyroidectomy (n (%))			
Yes	0 (0.0%)	2 (4.1%)	2 (2.2%)
No	44 (100%)	47 (95.9%)	91 (97.8%)

(Source: Sponsor's Tables 19 & 21, confirmed by the reviewer's analysis)

3.2.2.5 Sponsor's Primary Efficacy Results

1) The primary efficacy analysis showed that the PA 21 maintenance dose was superior to the PA 21 low dose ($p<0.001$) at Week 27 (Table 12).

Table 12 Chang in Serum Phosphorus Levels from Baseline (Week 24) at Week 27, LOCF, Study 5a

	PA21 MD	PA21 LD
N	44	49
LS Means (SE) (mmol/L)	0.08 (0.08)	0.62 (0.07)
Difference (95% CI)	0.54 (0.37, 0.71)	
P-value	<0.001	
LS Means (SE) (mg/dL)	0.25 (0.23)	1.92 (0.23)
Difference (95% CI)	1.67 (1.15, 2.19)	
P-value	<0.001	

(Source: Sponsor's Table 35, confirmed by the reviewer's analysis)

2) The MMRM-MAR analysis confirmed that the PA 21 maintenance dose is superior to

the PA 21 low dose at all time points (p<0.001) (Table 13).

Table 13 Analysis of Serum Phosphorus Change from Baseline (Week 24) (MMRM-MAR), Study 5a

Statistic	N	p-value	LS Mean	SE	95% CI
Serum phosphorus (mmol/L)					
Contrasts at Week 25					
PA21 LD vs. PA21 MD		<0.001	0.44	0.07	(0.30; 0.59)
Contrasts at Week 26					
PA21 LD vs. PA21 MD		<0.001	0.58	0.10	(0.38; 0.78)
Contrasts at Week 27					
PA21 LD vs. PA21 MD		<0.001	0.50	0.09	(0.33; 0.68)
Serum phosphorus (mg/dL)					
Contrasts at Week 25					
PA21 LD vs. PA21 MD		<0.001	1.37	0.22	(0.93; 1.82)
Contrasts at Week 26					
PA21 LD vs. PA21 MD		<0.001	1.79	0.31	(1.17; 2.41)
Contrasts at Week 27					
PA21 LD vs. PA21 MD		<0.001	1.56	0.27	(1.02; 2.10)

1 MMRM-MAR: mixed model analysis for repeated measures assuming the MAR missingness mechanism was used. The model includes subject as a random effect, fixed effects of week, treatment, baseline serum phosphorus, region (US/EU/ROW) and treatment*week, interactions. Type III analysis p-values were presented.

Notes: CI = Confidence interval; LD = Low dose; LS = Least square; MD = Maintenance dose; MMRM-MAR = Mixed effects model for repeated measures missing at random; SE = Standard error; PES = Primary efficacy set.

(Source: Sponsor's Table 36, confirmed by the reviewer's analysis)

3.2.2.6 Reviewer's Results

The reviewer verified the sponsor's primary efficacy analyses and concurred with their results.

3.2.2.7 Conclusions

PA 21 maintenance dose is superior to PA21 low dose in control of serum phosphorus level.

3.3 Evaluation of Safety

Please refer to Dr. Xiao's review for safety assessment.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Study 3a

Comparing to baseline, a statistically significant decrease (p≤0.0356) in serum phosphorus was shown in the three higher doses (7.5, 10.0 and 12.5 mmol/L) across age groups. The US population was under represented (13%) in the study, the majority of the subjects were from Europe (87%).

Serum phosphorus level was statistically significantly reduced ($p \leq 0.0081$) for all doses except the lowest dose (1.25 mmol/L) in European region; no statistical significant change in serum phosphorus level was observed in any dose in US region (Table 14).

Table 14 Subgroup Analysis of Primary Endpoint, Study 3a

	1.25 (mmol/L)		5.0 (mmol/L)		7.5 (mmol/L)		10.0 (mmol/L)		12.5 (mmol/L)	
	Mean Change (n)	95% CI o f Mean Change	Mean Change (n)	95% CI o f Mean Change	Mean Change (n)	95% CI of Mean Change	Mean Chang e (n)	95% CI of Mean Change	Mean Change (n)	95% CI o f Mean Change
Age										
<65 (N=75)	-0.0014 (14)	-0.4323, 0.4295	0.3628 (18)	-0.0125, 0.7381	0.4614 (14)	0.2635, 0.6594	0.5333 (15)	0.1899, 0.8768	0.4357 (14)	0.0636, 0.8079
=>65 (N=51)	0.0925 (12)	-0.2530, 0.4380	0.3138 (8)	-0.1340, 0.7615	0.330 (11)	0.0271, 0.6329	0.8110 (10)	0.5251, 1.0969	0.7020 (10)	0.3634, 1.0406
Region										
US (N=16)	0.2425 (4)	-0.1635, 0.6485	0.0475 (4)	-0.4191, 1.5141	0.2167 (3)	-0.2224, 0.6557	0.2567 (3)	-1.767, 2.2803	0.3750 (2)	-8.4558, 9.2058
Europe (N=110)	0.0055 (22)	-0.3030, 0.3139	0.4023 (22)	0.1164, 0.6881	0.4291 (22)	0.2485, 0.6097	0.6973 (22)	0.4715, 0.9230	0.5623 (22)	0.310, 0.8146

(Source: Reviewer's analysis)

4.2 Study 5a

The superiority of PA21 MD appears to be consistent across age, race, ethnicity and region (Table 15)

Table 15 Subgroup Analysis of Primary Endpoint, Study 5a

	PA21 MD		PA21 LD		
	N	LS Means (mmol/L)	N	LS Means (mmol/L)	Difference of LS Means (95% CI)
Age					
<65	38	0.0701	28	0.6532	-0.5831 (-0.8079, -0.3583)
>=65	11	0.074	16	0.4612	-0.3872 (-0.6094, -0.1651)
Sex					
Male	24	0.1109	20	0.6322	-0.5213 (-0.7083, -0.3342)
Female	25	0.0586	24	0.5697	-0.5111 (-0.7803, -0.2419)
Race					
Black	18	-0.0171	14	0.5229	-0.54 (-0.8535, -0.2265)
White	30	0.06462	28	0.6578	-0.5931 (-0.7928, -0.3934)

Others	1	-	2	-	-
Ethnicity					
Hispanic Latino	10	0.1092	9	0.8094	-0.7002 (-1.0510, -0.3493)
Non-Hispanic or Latino	39	0.0615	35	0.5593	-0.4978 (-0.6878, -0.3078)
Region					
US	37	0.0553	33	0.6229	-0.5676 (-0.7572, -0.3780)
Europe	8	0.1280	7	0.5630	-0.4349 (-0.7713, -0.0986)
Rest of World	4	0.1829	4	0.5096	-0.3267 (-1.8120, 1.1586)

(Source: Reviewer's analysis)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

An active comparator of sevelamer was used in both studies (b) (4) [redacted]

Some issues were identified for Study 3a:

- The majority was non-US patients and the US population was under-represented.
- The result of Study 3a may be questionable for the following identified issues:

  - After final CSR has completed, some issues were discovered including inconsistencies between the original datasets and the final CSR, problems related to the programming and algorithm derivations.
  - Some post hoc manipulations were made including revising SAP, re-conducting analyses and updating CSR.

5.2 Conclusions and Recommendations

Two clinical studies (3a & 5a) were submitted to support the efficacy of PA21 in control of serum phosphorus levels in patients with end-stage renal disease (ESRD). Study 5a appears to demonstrate that PA21 maintenance dose (1000-3000 mg/day) is superior to the low dose (1.25 mg/day). Though a dose-response effect is suggested from Study 3a, the result of the study may be questionable due to post hoc manipulations of data.

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/s/

QUQUAN LIU
09/20/2013

HSIEN MING J HUNG
09/21/2013

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 20-5109/SN0000 **Applicant: Vifor Fresenius Medical Care Renal Pharma** **Stamp Date: 02/01/2013**

Drug Name: PA21 (b) (4) **NDA/BLA Type: Standard**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			x	
Appropriate references for novel statistical methodology (if present) are included.			x	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	x			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	x			

Additional Comments:

Please provide statistical analysis programs for the analyses of primary and secondary endpoints.

File name: 5_Statistics Filing Checklist for a New NDA_BLA205109

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Ququan Liu	03/13/2013
Reviewing Statistician	Date
Supervisor/Team Leader	Date

File name: 5_Statistics Filing Checklist for a New NDA_BLA205109

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/s/

QUQUAN LIU
03/18/2013

HSIEN MING J HUNG
03/25/2013