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

Summary

EudraCT number	2008-004748-36
Trial protocol	DE CZ BG
Global end of trial date	13 October 2009

Results information

Result version number	v1 (current)
This version publication date	09 December 2016
First version publication date	09 December 2016

Trial information

Trial identification

Sponsor protocol code	PA-CL-03A

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00824460
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vifor (International) Inc.
Sponsor organisation address	Rechenstrasse 37, St. Gallen, Switzerland, CH-9001
Public contact	MedInfo , Vifor (Internationa) Inc. , medinfo@viforpharma.com
Scientific contact	MedInfo , Vifor (Internationa) Inc. , medinfo@viforpharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 October 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 October 2009
Global end of trial reached?	Yes
Global end of trial date	13 October 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator:

A sevelamer hydrochloride (HCl) group was added to assess assay sensitivity and to provide an active control group for comparability of efficacy and tolerability. The dose of sevelamer HCl used in this study was 4.8 g/day; this dose was chosen as it is an approved dose for this product and is commonly used.

Actual start date of recruitment	28 January 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	Poland: 15
Country: Number of subjects enrolled	Bulgaria: 23
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Romania: 12
Country: Number of subjects enrolled	United States: 21
Country: Number of subjects enrolled	Croatia: 40
Country: Number of subjects enrolled	Russian Federation: 28
Country: Number of subjects enrolled	Switzerland: 5
Worldwide total number of subjects	154
EEA total number of subjects	100

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	93
From 65 to 84 years	59
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

417 subjects were screened at 60 centres and 154 of them were randomised at 50 centres, in 9 countries.

Pre-assignment

Screening details:

After a washout period from their previous phosphate binder treatment, suitable subjects were randomised to receive either PA21 or sevelamer (HCl) for 6 weeks. The phases of 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.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	1.25 g PA21

Arm description:

Daily dose of 1.25 g PA21 (1 tablet taken with the largest meal of the day).
All randomized subjects were considered.

Arm type	Experimental
Investigational medicinal product name	PA21
Investigational medicinal product code	
Other name	Mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches; Stabilised polynuclear iron oxyhydroxide
Pharmaceutical forms	Chewable tablet
Routes of administration	Oral use

Dosage and administration details:

Daily dose of 1.25 g PA21 (1 tablet taken with the largest meal of the day).

Arm title	5.0 g PA21

Arm description:

Daily dose of 5.0 g PA21 (4 tablets of 1.25 g: 2 tablets with the largest meal of the day and 1 tablet each with the 2 smaller meals of the day).
All randomized subjects were considered.

Arm type	Experimental
Investigational medicinal product name	PA21
Investigational medicinal product code	
Other name	Mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches; Stabilised polynuclear iron oxyhydroxide
Pharmaceutical forms	Chewable tablet
Routes of administration	Oral use

Dosage and administration details:

Daily dose of 5.0 g PA21 (4 tablets of 1.25 g: 2 tablets with the largest meal of the day and 1 tablet each with the 2 smaller meals of the day).

Arm title	7.5 g PA21

Arm description:

Daily dose of 7.5 g PA21 (6 tablets of 1.25 g: 2 tablets with each meal of the day).

All randomized subjects were considered.

Arm type	Experimental
Investigational medicinal product name	PA21
Investigational medicinal product code	
Other name	Mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches; Stabilised polynuclear iron oxyhydroxide
Pharmaceutical forms	Chewable tablet
Routes of administration	Oral use

Dosage and administration details:

Daily dose of 7.5 g PA21 (6 tablets of 1.25 g: 2 tablets with each meal of the day).

Arm title	10.0 g PA21

Arm description:

Daily dose of 10.0 g PA21 (8 tablets of 1.25 g: 4 tablets with the largest meal of the day and 2 tablets each with the 2 smaller meals of the day).
All randomized subjects were considered.

Arm type	Experimental
Investigational medicinal product name	PA21
Investigational medicinal product code	
Other name	Mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches; Stabilised polynuclear iron oxyhydroxide
Pharmaceutical forms	Chewable tablet
Routes of administration	Oral use

Dosage and administration details:

Daily dose of 10.0 g PA21 (8 tablets of 1.25 g: 4 tablets with the largest meal of the day and 2 tablets each with the 2 smaller meals of the day).

Arm title	12.5 g PA21

Arm description:

Daily dose of 12.5 g PA21 (10 tablets of 1.25 g: 4 tablets with the largest meal of the day and 3 tablets each with the 2 smaller meals of the day).
All randomized subjects were considered.

Arm type	Experimental
Investigational medicinal product name	PA21
Investigational medicinal product code	
Other name	Mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches; Stabilised polynuclear iron oxyhydroxide
Pharmaceutical forms	Chewable tablet
Routes of administration	Oral use

Dosage and administration details:

Daily dose of 12.5 g PA21 (10 tablets of 1.25 g: 4 tablets with the largest meal of the day and 3 tablets each with the 2 smaller meals of the day).

Arm title	Sevelamer HCl

Arm description:

Daily dose of 4.8 g sevelamer HCl (6 tablets of 800 mg: divided in 3 doses with meals).
All randomized subjects were considered.

Arm type	Active comparator
Investigational medicinal product name	Sevelamer HCl
Investigational medicinal product code	
Other name	Renagel®; Poly(allylamine-co-N,N’-diallyl-1,3-diamino-2-hydroxypropane) hydrochloride
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Daily dose of 4.8 g sevelamer HCl (6 tablets of 800 mg: divided in 3 doses with meals).

Number of subjects in period 1	1.25 g PA21	5.0 g PA21	7.5 g PA21
Started	26	26	25
Completed	18	17	20
Not completed	8	9	5
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	1	-	1
Adverse event, non-fatal	-	-	-
Subject protocol noncompliance	-	-	-
Kidney Transplant	-	-	-
Prohibited medication	-	-	-
Predefined criteria within protocol	7	7	3
Refusal of Treatment	-	-	1
Protocol deviation	-	1	-

Number of subjects in period 1	10.0 g PA21	12.5 g PA21	Sevelamer HCl
Started	27	24	26
Completed	15	15	18
Not completed	12	9	8
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	2	1	-
Adverse event, non-fatal	1	1	2
Subject protocol noncompliance	-	1	-
Kidney Transplant	-	-	1
Prohibited medication	-	-	2
Predefined criteria within protocol	9	6	3
Refusal of Treatment	-	-	-
Protocol deviation	-	-	-

Baseline characteristics

Reporting groups	
Reporting group title	1.25 g PA21
Reporting group description:	
Daily dose of 1.25 g PA21 (1 tablet taken with the largest meal of the day). All randomized subjects were considered.	
Reporting group title	5.0 g PA21
Reporting group description:	
Daily dose of 5.0 g PA21 (4 tablets of 1.25 g: 2 tablets with the largest meal of the day and 1 tablet each with the 2 smaller meals of the day). All randomized subjects were considered.	
Reporting group title	7.5 g PA21
Reporting group description:	
Daily dose of 7.5 g PA21 (6 tablets of 1.25 g: 2 tablets with each meal of the day). All randomized subjects were considered.	
Reporting group title	10.0 g PA21
Reporting group description:	
Daily dose of 10.0 g PA21 (8 tablets of 1.25 g: 4 tablets with the largest meal of the day and 2 tablets each with the 2 smaller meals of the day). All randomized subjects were considered.	
Reporting group title	12.5 g PA21
Reporting group description:	
Daily dose of 12.5 g PA21 (10 tablets of 1.25 g: 4 tablets with the largest meal of the day and 3 tablets each with the 2 smaller meals of the day). All randomized subjects were considered.	
Reporting group title	Sevelamer HCl
Reporting group description:	
Daily dose of 4.8 g sevelamer HCl (6 tablets of 800 mg: divided in 3 doses with meals). All randomized subjects were considered.	

Reporting group values	1.25 g PA21	5.0 g PA21	7.5 g PA21
Number of subjects	26	26	25
Age categorical			
All randomised patients were considered.			
Units: Subjects			
Adults (18-64 years)	14	18	14
From 65-84 years	12	7	10
85 years and over	0	1	1
Age continuous			
The safety set was considered: all randomised subjects who received at least 1 dose of study treatment. Subjects were included in the analysis according to the treatment received. N=154.			
Units: years			
arithmetic mean	60.1	59.7	61.9
standard deviation	± 12.29	± 13.8	± 13.71
Gender categorical			
All randomised patients were considered.			
Units: Subjects			
Female	9	7	9
Male	17	19	16

Reporting group values	10.0 g PA21	12.5 g PA21	Sevelamer HCl
Number of subjects	27	24	26
Age categorical			
All randomised patients were considered.			
Units: Subjects			
Adults (18-64 years)	17	14	16
From 65-84 years	10	10	10
85 years and over	0	0	0
Age continuous			
The safety set was considered: all randomised subjects who received at least 1 dose of study treatment. Subjects were included in the analysis according to the treatment received. N=154.			
Units: years			
arithmetic mean	60.6	59.3	61.1
standard deviation	± 12.74	± 12.32	± 11
Gender categorical			
All randomised patients were considered.			
Units: Subjects			
Female	10	11	11
Male	17	13	15

Reporting group values	Total		
Number of subjects	154		
Age categorical			
All randomised patients were considered.			
Units: Subjects			
Adults (18-64 years)	93		
From 65-84 years	59		
85 years and over	2		
Age continuous			
The safety set was considered: all randomised subjects who received at least 1 dose of study treatment. Subjects were included in the analysis according to the treatment received. N=154.			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
All randomised patients were considered.			
Units: Subjects			
Female	57		
Male	97		

End points

End points reporting groups

Reporting group title	1.25 g PA21
Reporting group description:	
Daily dose of 1.25 g PA21 (1 tablet taken with the largest meal of the day). All randomized subjects were considered.	
Reporting group title	5.0 g PA21
Reporting group description:	
Daily dose of 5.0 g PA21 (4 tablets of 1.25 g: 2 tablets with the largest meal of the day and 1 tablet each with the 2 smaller meals of the day). All randomized subjects were considered.	
Reporting group title	7.5 g PA21
Reporting group description:	
Daily dose of 7.5 g PA21 (6 tablets of 1.25 g: 2 tablets with each meal of the day). All randomized subjects were considered.	
Reporting group title	10.0 g PA21
Reporting group description:	
Daily dose of 10.0 g PA21 (8 tablets of 1.25 g: 4 tablets with the largest meal of the day and 2 tablets each with the 2 smaller meals of the day). All randomized subjects were considered.	
Reporting group title	12.5 g PA21
Reporting group description:	
Daily dose of 12.5 g PA21 (10 tablets of 1.25 g: 4 tablets with the largest meal of the day and 3 tablets each with the 2 smaller meals of the day). All randomized subjects were considered.	
Reporting group title	Sevelamer HCl
Reporting group description:	
Daily dose of 4.8 g sevelamer HCl (6 tablets of 800 mg: divided in 3 doses with meals). All randomized subjects were considered.	

Primary: Change from baseline in serum phosphorus levels at the end of treatment

End point title	Change from baseline in serum phosphorus levels at the end of treatment
End point description:	
For this primary endpoint, data from the full analysis set (FAS) was used. The FAS consisted of all randomised subjects who received at least 1 dose of study treatment and had at least 1 post-baseline efficacy evaluation (while on treatment).	
End point type	Primary
End point timeframe:	
Baseline and End of Treatment six weeks after.	

End point values	1.25 g PA21	5.0 g PA21	7.5 g PA21	10.0 g PA21
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	26	25	25
Units: mmol/L				
arithmetic mean (standard deviation)	-0.042 (± 0.65)	-0.348 (± 0.684)	-0.404 (± 0.391)	-0.644 (± 0.551)

End point values	12.5 g PA21	Sevelamer HCl		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: mmol/L				
arithmetic mean (standard deviation)	-0.547 (± 0.584)	-0.341 (± 0.436)		

Statistical analyses

Statistical analysis title	Analysis of serum phosphorus -5.0 g

Statistical analysis description:

Analysis of serum phosphorus (mmol/L): absolute change from baseline at end of treatment.
The absolute change from baseline in serum phosphorus levels at the end of treatment (i.e., value at Week 7, D1, or last observation carried forward (LOCF) for missing values (where a subject was withdrawn prior to Week 7)) was analysed within each of the 5 PA21 dose groups using a single sample paired t-test.

Comparison groups	5.0 g PA21 v 1.25 g PA21
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.078
Method	t-test, 2-sided
Parameter estimate	least squares mean
Point estimate	-0.341
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.07
upper limit	0.78
Variability estimate	Standard deviation
Dispersion value	0.684

Notes:

[1] - To preserve the overall alpha, a hierarchical testing procedure was applied, testing from the highest PA21
dose (12.5 g/day) to the lowest dose (1.25 g/day) until all doses are tested or the first p-value above 0.05 is observed.

Statistical analysis title	Analysis of serum phosphorus - 7.5 g

Statistical analysis description:

Analysis of serum phosphorus (mmol/L): absolute change from baseline at end of treatment.
The absolute change from baseline in serum phosphorus levels at the end of treatment (i.e., value at Week 7, D1, or last observation carried forward (LOCF) for missing values (where a subject was withdrawn prior to Week 7)) was analysed within each of the 5 PA21 dose groups using a single sample paired t-test.

Comparison groups	7.5 g PA21 v 1.25 g PA21

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.063
Method	t-test, 2-sided
Parameter estimate	least squares mean
Point estimate	-0.357
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.26
upper limit	0.28
Variability estimate	Standard deviation
Dispersion value	0.391

Notes:

[2] - To preserve the overall alpha, a hierarchical testing procedure was applied, testing from the highest PA21
dose (12.5 g/day) to the lowest dose (1.25 g/day) until all doses are tested or the first p-value above 0.05 is observed.

Statistical analysis title	Analysis of serum phosphorus - 10.0 g

Statistical analysis description:

Analysis of serum phosphorus (mmol/L): absolute change from baseline at end of treatment.
The absolute change from baseline in serum phosphorus levels at the end of treatment (i.e., value at Week 7, D1, or last observation carried forward (LOCF) for missing values (where a subject was withdrawn prior to Week 7)) was analysed within each of the 5 PA21 dose groups using a single sample paired t-test.

Comparison groups	10.0 g PA21 v 1.25 g PA21
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.001
Method	t-test, 2-sided
Parameter estimate	least squares mean
Point estimate	-0.612
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.85
upper limit	0.68
Variability estimate	Standard deviation
Dispersion value	0.551

Notes:

[3] - To preserve the overall alpha, a hierarchical testing procedure was applied, testing from the highest PA21
dose (12.5 g/day) to the lowest dose (1.25 g/day) until all doses are tested or the first p-value above 0.05 is observed.

Statistical analysis title	Analysis of serum phosphorus - 12.5 g

Statistical analysis description:

Analysis of serum phosphorus (mmol/L): absolute change from baseline at end of treatment.
The absolute change from baseline in serum phosphorus levels at the end of treatment (i.e., value at Week 7, D1, or last observation carried forward (LOCF) for missing values (where a subject was withdrawn prior to Week 7)) was analysed within each of the 5 PA21 dose groups using a single sample paired t-test.

Comparison groups	12.5 g PA21 v 1.25 g PA21

Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.001
Method	t-test, 2-sided
Parameter estimate	least squares mean
Point estimate	-0.564
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.85
upper limit	0.56
Variability estimate	Standard deviation
Dispersion value	0.584

Notes:

[4] - To preserve the overall alpha, a hierarchical testing procedure was applied, testing from the highest PA21
dose (12.5 g/day) to the lowest dose (1.25 g/day) until all doses are tested or the first p-value above 0.05 is observed.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From screening to the end of trial.	
Adverse event reporting additional description:	
The safety set was considered.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups	
Reporting group title	1.25 g PA21
Reporting group description:	
Daily dose of 1.25 g PA21 (1 tablet)	
Reporting group title	5.0 g PA21
Reporting group description:	
Daily dose of 5.0 g PA21 (4 tablets)	
Reporting group title	7.5 g PA21
Reporting group description:	
Daily dose of 7.5 g PA21 (6 tablets)	
Reporting group title	10.0 g PA21
Reporting group description:	
Daily dose of 10.0 g PA21 (8 tablets)	
Reporting group title	12.5 g PA21
Reporting group description:	
Daily dose of 12.5 g PA21 (10 tablets)	
Reporting group title	Sevelamer HCl
Reporting group description:	
Daily dose of 4.8 g Sevelamer hydrochloride (6 tablets)	

Serious adverse events	1.25 g PA21	5.0 g PA21	7.5 g PA21
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 26 (7.69%)	2 / 26 (7.69%)	1 / 25 (4.00%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous graft site haematoma			

subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diabetic retinopathy			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diverticular perforation			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pancreatitis			

subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Staphylococcal sepsis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous graft site abscess			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal infection			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	10.0 g PA21	12.5 g PA21	Sevelamer HCl
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 27 (3.70%)	2 / 24 (8.33%)	2 / 26 (7.69%)

number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous graft site haematoma			
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 27 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 27 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 27 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diabetic retinopathy			
subjects affected / exposed	0 / 27 (0.00%)	0 / 24 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diverticular perforation			
subjects affected / exposed	0 / 27 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 24 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 24 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 27 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Staphylococcal sepsis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous graft site abscess			
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal infection			
subjects affected / exposed	0 / 27 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Fluid overload			

subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	1.25 g PA21	5.0 g PA21	7.5 g PA21
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 26 (50.00%)	15 / 26 (57.69%)	13 / 25 (52.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	2 / 25 (8.00%)
occurrences (all)	1	0	2
Hypotension			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	3 / 25 (12.00%)
occurrences (all)	0	0	4
Gastrointestinal disorders			
Faeces discoloured			
subjects affected / exposed	2 / 26 (7.69%)	3 / 26 (11.54%)	3 / 25 (12.00%)
occurrences (all)	2	3	3
Diarrhoea			
subjects affected / exposed	1 / 26 (3.85%)	2 / 26 (7.69%)	2 / 25 (8.00%)
occurrences (all)	1	8	5
Constipation			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	1 / 25 (4.00%)
occurrences (all)	0	5	1
Vomiting			
subjects affected / exposed	0 / 26 (0.00%)	2 / 26 (7.69%)	0 / 25 (0.00%)
occurrences (all)	0	6	0
Musculoskeletal and connective tissue disorders			
Muscle spasms			

subjects affected / exposed	1 / 26 (3.85%)	1 / 26 (3.85%)	2 / 25 (8.00%)
occurrences (all)	5	1	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	2 / 26 (7.69%)	4 / 26 (15.38%)	2 / 25 (8.00%)
occurrences (all)	2	6	2
Hyperphosphataemia			
subjects affected / exposed	5 / 26 (19.23%)	3 / 26 (11.54%)	1 / 25 (4.00%)
occurrences (all)	6	3	1
Hypercalcaemia			
subjects affected / exposed	2 / 26 (7.69%)	2 / 26 (7.69%)	1 / 25 (4.00%)
occurrences (all)	2	2	1

Non-serious adverse events	10.0 g PA21	12.5 g PA21	Sevelamer HCl
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 27 (66.67%)	17 / 24 (70.83%)	14 / 26 (53.85%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 27 (0.00%)	2 / 24 (8.33%)	1 / 26 (3.85%)
occurrences (all)	0	3	1
Hypotension			
subjects affected / exposed	0 / 27 (0.00%)	0 / 24 (0.00%)	3 / 26 (11.54%)
occurrences (all)	0	0	7
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 27 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Faeces discoloured			
subjects affected / exposed	4 / 27 (14.81%)	3 / 24 (12.50%)	0 / 26 (0.00%)
occurrences (all)	4	3	0
Diarrhoea			

subjects affected / exposed	1 / 27 (3.70%)	1 / 24 (4.17%)	3 / 26 (11.54%)
occurrences (all)	1	1	3
Constipation			
subjects affected / exposed	2 / 27 (7.41%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences (all)	2	0	0
Vomiting			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	1 / 26 (3.85%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	1 / 27 (3.70%)	3 / 24 (12.50%)	0 / 26 (0.00%)
occurrences (all)	1	3	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 27 (0.00%)	2 / 24 (8.33%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	8 / 27 (29.63%)	7 / 24 (29.17%)	3 / 26 (11.54%)
occurrences (all)	8	8	3
Hyperphosphataemia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	2 / 26 (7.69%)
occurrences (all)	1	0	2
Hypercalcaemia			
subjects affected / exposed	1 / 27 (3.70%)	1 / 24 (4.17%)	2 / 26 (7.69%)
occurrences (all)	1	1	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 November 2008	Amendment 1 was implemented before the first patient was randomised and included the following changes pertaining to conduct and interpretation of the study: • Clarification of the AE reporting procedures (eliciting and recording of AEs) • Addition of 2 bone markers (carboxyterminal cross-linking telopeptide of bone collagen (beta-CTX) and tartrate-resistant acid phosphatase 5b) • Clarification that the study treatment must not be taken on an empty stomach • The assessment of calcium and iPTH was made consistent with the risk-benefit analysis (measurement of calcium added to Visits Week -2, D1, and Week -1, D2, and D3, and clarification that the iPTH exclusion criterion applied only at screening) • Exclusion criteria 4, 10 and 13 were clarified to confirm that they referred to screening
17 March 2009	Amendment 2 included the following changes pertaining to conduct and interpretation of the study: • Text modified in risk-benefit assessment section on AEs seen with sevelamer (HCl) • Clarification that patients' serum phosphate level assessed twice during Week -1 and patients could be randomised based on their serum phosphate level at either Week -1, D2 or Week -1, D3 • Inclusion criterion 9 modified to allow for small dose adjustments of erythropoietin therapy before and during the study • Exclusion criterion 10 modified to include a history of other iron storage disorders and removal of reference to ferritin level (>800mcg/L at screening) • Exclusion criterion 12 modified (split into 2 separate criteria) to allow for Investigator's judgment (criterion 12) and to add the time window (5 years) for major gastrointestinal surgery (criterion 13) • Exclusion criterion 13 clarified (now exclusion criterion 14) to exclude patients with active hepatitis B or C infection • Exclusion criterion 24 modified (now exclusion criterion 25) to exclude patients taking medication specifically for moderate to severe arrhythmic and seizure disorders • Planned number of EU study centres and countries reduced from 65 to 60 and 10 to 8, respectively. Planned number of US centres increased from 10 to 15 • Permitted and prohibited medications was clarified that IV iron preparations were permitted until end of screening, and anti-arrhythmic and anti-seizure medications were not permitted during the study if prescribed for moderate to severe arrhythmic and seizure disorders • General considerations section of statistical methods was clarified that no adjustments for multiplicity unless specified otherwise in subsequent sections • Clarified that comparisons between PA21 and sevelamer (HCl) were not based on statistical tests • Text modified for determination of sample size • Protocol updated to reference Declaration of Helsinki, dated 2008 instead of 1996
10 June 2009	Amendment 3 included the following changes pertaining to conduct and interpretation of the study: • The sample size was reduced from 252 randomised patients to up to 132 randomised patients to obtain about 114 evaluable patients (i.e., who have at least 1 post-baseline efficacy measurement)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/23124782