Clinical trial results:
An Open-label, Randomised, Active-controlled, Parallel Group, Multicentre Phase 3 Study to Investigate the Long-term Safety, Tolerability and Efficacy of PA21 compared with Sevelamer Carbonate in Dialysis Patients with Hyperphosphataemia. Extension Study for Protocol PA-CL-05A.

Summary

EudraCT number	2010-022012-40
Trial protocol	GB CZ LV LT SE AT DE BE
Global end of trial date	25 October 2012

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-05B

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01464190
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	03 May 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 October 2012
Global end of trial reached?	Yes
Global end of trial date	25 October 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of the trial are to assess the long-term safety and tolerability of PA21, compare the long-term serum phosphorus control of PA21 versus sevelamer and compare the safety and tolerability of PA21 versus sevelamer.

Protection of trial subjects:

The study was conducted in accordance with the principles of the Declaration of Helsinki and in compliance with the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), the Committee for Proprietary Medicinal Products Guideline (CPMP/ICH/135/95), and the EU Clinical Trial Directive (Directive 2001/20/EC) and/or the Code of Federal Regulations (CFR) for informed consent and protection of patient rights (21 CFR, Parts 50 and 56).
Before each subject was admitted to the study, a signed and dated informed consent was obtained from the subject (or his/her legally authorised representative). A copy of the document was provided to the subject. No investigations specifically required for the studies were conducted until valid consent was obtained. Subjects were informed that their participation in the study was entirely voluntary and would have no effect on clinical care otherwise available, and that they could withdraw consent to participate at any time without penalty or loss of further medical treatment. Subjects were told that competent authorities and authorised persons could examine their records but that personal information would be treated as strictly confidential and would not be publicly available.
A Data and Safety Monitoring Board (DSMB) was formed to assess the progress, safety data and, if needed, critical efficacy endpoints of the study. The DSMB was composed of clinicians with expertise in relevant clinical specialties and at least 1 biostatistician knowledgeable about statistical methods for clinical trials and sequential analysis of trial data.

Background therapy: -

Evidence for comparator:

Sevelamer carbonate was chosen as the active comparator as its active ingredient (sevelamer) is considered a standard treatment for hyperphosphataemia in patients undergoing dialysis. The sevelamer doses were based on its approved and commonly used doses.

Actual start date of recruitment	20 September 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Austria: 11
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Czech Republic: 39
Country: Number of subjects enrolled	Latvia: 9
Country: Number of subjects enrolled	Lithuania: 5

Country: Number of subjects enrolled	Poland: 31
Country: Number of subjects enrolled	United States: 287
Country: Number of subjects enrolled	Romania: 22
Country: Number of subjects enrolled	Croatia: 24
Country: Number of subjects enrolled	Russian Federation: 109
Country: Number of subjects enrolled	Serbia: 55
Country: Number of subjects enrolled	Ukraine: 47
Country: Number of subjects enrolled	South Africa: 3
Worldwide total number of subjects	659
EEA total number of subjects	158

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)	486
From 65 to 84 years	168
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 143 of the centres that conducted the PA-CL-05A study and these centres enrolled 659 subjects.

Pre-assignment

Screening details:

Subjects who had completed treatment in PA-CL-05A (Stage 1 or Stage 2, except subjects randomised to the PA21 low dose (LD) group of Stage 2) were eligible for the 28-week extension study. All eligible subjects continued to receive either PA21 or sevelamer according to their randomisation into PA-CL-05A and started at the dose being administered.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	PA21

Arm description:

PA21 chewable tablets containing 2.5 g of PA21. Dose range from 5.0 g/day (2 tablets/day) to 15.0 g/day (6 tablets/day).

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:

The maximum dose was 15.0 g/day (6 tablets/day) and the minimum dose was 5.0 g/day (2 tablets/day). Dose adjustments for efficacy or tolerability reasons were permitted. Dose adjustments of 2.5 g/day (one 2.5 g tablet/day) were allowed.

Arm title	Sevelamer carbonate

Arm description:

Sevelamer carbonate, Renvela® tablets containing 800 mg of sevelamer carbonate.

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

Dosage and administration details:

The maximum dose of sevelamer was 14.4 g/day (18 tablets/day) and the minimum dose was 2.4 g/day (3 tablets/day). Dose adjustments for efficacy or tolerability reasons were permitted. Dose adjustments of 2.4 g/day (three 800 mg tablets/day (1 tablet/meal)) were allowed.

Number of subjects in period 1	PA21	Sevelamer carbonate
Started	391	268
Completed	322	227
Not completed	69	41
Adverse event, serious fatal	6	5
Consent withdrawn by subject	9	8
Physician decision	6	3
Renal Transplant	11	7
Adverse event, non-fatal	17	4
Transferred to another facility	1	1
Predefined criteria within protocol	14	7
Sponsor decision	-	3
Protocol deviation	5	3

Baseline characteristics

Reporting groups	
Reporting group title	PA21
Reporting group description:	
PA21 chewable tablets containing 2.5 g of PA21. Dose range from 5.0 g/day (2 tablets/day) to 15.0 g/day (6 tablets/day).	
Reporting group title	Sevelamer carbonate
Reporting group description:	
Sevelamer carbonate, Renvela® tablets containing 800 mg of sevelamer carbonate.	

Reporting group values	PA21	Sevelamer carbonate	Total
Number of subjects	391	268	659
Age categorical Units: Subjects			
Adults (18-64 years)	296	190	486
From 65-84 years	93	75	168
85 years and over	2	3	5
Age continuous Units: years			
arithmetic mean	55.2	55.6	
standard deviation	± 13.2	± 14.6	-
Gender categorical Units: Subjects			
Female	171	103	274
Male	220	165	385

End points

End points reporting groups

Reporting group title	PA21
Reporting group description:	
PA21 chewable tablets containing 2.5 g of PA21. Dose range from 5.0 g/day (2 tablets/day) to 15.0 g/day (6 tablets/day).	
Reporting group title	Sevelamer carbonate
Reporting group description:	
Sevelamer carbonate, Renvela® tablets containing 800 mg of sevelamer carbonate.	
Subject analysis set title	Full analysis set for PA-CL-05B (FAS5B)
Subject analysis set type	Full analysis
Subject analysis set description:	
FAS5B included subjects who received at least 1 dose of PA-CL-05B study medication and had at least 1 evaluable efficacy assessment during PA-CL-05B.	

Primary: Serum Phosphorus Change from PA-CL-05B Baseline at Key Time Points

End point title	Serum Phosphorus Change from PA-CL-05B Baseline at Key Time Points
End point description:	
The changes from PA-CL-05B baseline in serum phosphorus levels at each PA-CL-05B visit (observed cases) and at endpoint (last observation on treatment) were also compared between the PA21 and sevelamer groups with an analysis of covariance (ANCOVA) using baseline phosphorus level, region and dialysis status as covariates. All tests were at the alpha 0.05 level with no adjustments made for the multiplicity of tests. 95% confidence intervals of the difference in the serum phosphorus levels between the PA21 and sevelamer groups were calculated. The FAS5B set was considered (N=644; PA21:384 and sevelamer:260).	
End point type	Primary
End point timeframe:	
Extension baseline (Week 0), and Weeks 4, 8, 12, 16, 20, 24 and 28. They correspond to Weeks 24, 28, 32, 36, 40, 44, 48 and 52 of the integrated studies PA-CL-05A and PA-CL-05B.	

End point values	PA21	Sevelamer carbonate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	391	268		
Units: mg/dL				
least squares mean (standard error)				
Extension Week 4 (Week 28), N=582	-0.25 (± 0.1)	-0.27 (± 0.11)		
Extension Week 8 (Week 32), N=563	-0.21 (± 0.1)	0.04 (± 0.12)		
Extension Week 12 (Week 36), N=564	-0.1 (± 0.11)	0.09 (± 0.12)		
Extension Week 16 (Week 40), N=541	0.01 (± 0.12)	0.16 (± 0.14)		
Extension Week 20 (Week 44), N=521	-0.05 (± 0.11)	0.1 (± 0.13)		
Extension Week 24 (Week 48), N=494	0.03 (± 0.12)	0.12 (± 0.14)		
Extension Week 28 (Week 52), N=497	0.13 (± 0.12)	0.08 (± 0.14)		
Endpoint, N=644	0.01 (± 0.11)	0.14 (± 0.13)		

Statistical analyses

Statistical analysis title	Contrast ANCOVA - Extension Week 4 (Week 28)
Statistical analysis description:	
Comparison: PA21 v Sevelamer carbonate	
Comparison groups	PA21 v Sevelamer carbonate
Number of subjects included in analysis	659
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.878
Method	ANCOVA
Parameter estimate	least squares mean
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	0.23
Variability estimate	Standard error of the mean
Dispersion value	0.11

Notes:

[1] - Exploratory analysis. N for this analysis was 582.
A mixed-effect model for repeated measures/missing at random (MMRM-MAR) assumption model was run for sensitivity purpose and similar results were obtained.

Statistical analysis title	Contrast ANCOVA - Extension Week 8 (Week 32)
Comparison groups	PA21 v Sevelamer carbonate
Number of subjects included in analysis	659
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.026
Method	ANCOVA
Parameter estimate	least squares mean
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.46
upper limit	-0.03
Variability estimate	Standard error of the mean
Dispersion value	0.11

Notes:

[2] - Exploratory analysis. N for this analysis was 563.
A MMRM-MAR assumption model was run for sensitivity purpose and similar results were obtained.

Statistical analysis title	Contrast ANCOVA - Extension Week 12 (Week 36)
Comparison groups	PA21 v Sevelamer carbonate

Number of subjects included in analysis	659
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.092
Method	ANCOVA
Parameter estimate	least squares mean
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	0.03
Variability estimate	Standard error of the mean
Dispersion value	0.11

Notes:

[3] - Exploratory analysis. N for this analysis was 564.
A MMRM-MAR assumption model was run for sensitivity purpose and similar results were obtained.

Statistical analysis title	Contrast ANCOVA - Extension Week 16 (Week 40)
Comparison groups	PA21 v Sevelamer carbonate
Number of subjects included in analysis	659
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.231
Method	ANCOVA
Parameter estimate	least squares mean
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.13

Notes:

[4] - Exploratory analysis. N for this analysis was 541.
A MMRM-MAR assumption model was run for sensitivity purpose and similar results were obtained.

Statistical analysis title	Contrast ANCOVA - Extension Week 20 (Week 44)
Comparison groups	PA21 v Sevelamer carbonate
Number of subjects included in analysis	659
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.182
Method	ANCOVA
Parameter estimate	least squares mean
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	0.07

Variability estimate	Standard error of the mean
Dispersion value	0.11

Notes:

[5] - Exploratory analysis. N for this analysis was 521.
A MMRM-MAR assumption model was run for sensitivity purpose and similar results were obtained.

Statistical analysis title	Contrast ANCOVA - Extension Week 24 (Week 48)
Comparison groups	PA21 v Sevelamer carbonate
Number of subjects included in analysis	659
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.47
Method	ANCOVA
Parameter estimate	least squares mean
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	0.16
Variability estimate	Standard error of the mean
Dispersion value	0.13

Notes:

[6] - Exploratory analysis. N for this analysis was 494.
A MMRM-MAR assumption model was run for sensitivity purpose and similar results were obtained.

Statistical analysis title	Contrast ANCOVA - Extension Week 28 (Week 52)
Comparison groups	PA21 v Sevelamer carbonate
Number of subjects included in analysis	659
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.705
Method	ANCOVA
Parameter estimate	least squares mean
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.13

Notes:

[7] - Exploratory analysis. N for this analysis was 497.
A MMRM-MAR assumption model was run for sensitivity purpose and similar results were obtained.

Statistical analysis title	Contrast ANCOVA - Endpoint
Comparison groups	PA21 v Sevelamer carbonate

Number of subjects included in analysis	659
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.293
Method	ANCOVA
Parameter estimate	least squares mean
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	0.11
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[8] - Exploratory analysis. N for this analysis was 644.
A MMRM-MAR assumption model was run for sensitivity purpose and similar results were obtained.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from the signing of informed consent. The AE reporting period ended at the study follow-up visit, 14 days following the last intake of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	PA21

Reporting group description:

PA21 (2.5 g tablet). Dose range of 5.0 g/day (2tablets/day) to 15.0 g/day (6 tablets/day).

Reporting group title	Sevelamer carbonate

Reporting group description: -

Serious adverse events	PA21	Sevelamer carbonate	
Total subjects affected by serious adverse events			
subjects affected / exposed	78 / 391 (19.95%)	52 / 267 (19.48%)	
number of deaths (all causes)	7	7	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung squamous cell carcinoma stage unspecified			
subjects affected / exposed	1 / 391 (0.26%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			

subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma stage IV			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haematoma			
subjects affected / exposed	4 / 391 (1.02%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial stenosis			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial thrombosis			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis			
subjects affected / exposed	1 / 391 (0.26%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Circulatory collapse			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemorrhage			

subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemia			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 391 (0.26%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aneurysm ruptured			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aortic aneurysm			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			

subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 391 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermittent claudication			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian artery stenosis			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Arteriovenous graft			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal operation			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	3 / 391 (0.77%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Device occlusion			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device complication			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis in device			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary oedema			
subjects affected / exposed	2 / 391 (0.51%)	3 / 267 (1.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			

subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 391 (0.26%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 391 (0.26%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary alveolar haemorrhage			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
International normalised ratio increased			

subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Vascular graft thrombosis			
subjects affected / exposed	3 / 391 (0.77%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula thrombosis			
subjects affected / exposed	2 / 391 (0.51%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental overdose			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Operative haemorrhage			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural hypotension			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			

subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt malfunction			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft complication			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft occlusion			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	0 / 391 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arteriovenous graft site haemorrhage			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			

subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirenal haematoma			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 391 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt thrombosis			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant failure			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	3 / 391 (0.77%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			

subjects affected / exposed	2 / 391 (0.51%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 391 (0.26%)	3 / 267 (1.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 391 (0.26%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 391 (0.26%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery disease			
subjects affected / exposed	1 / 391 (0.26%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiomyopathy			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	3 / 391 (0.77%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular disorder			

subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypertensive encephalopathy			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 391 (0.26%)	3 / 267 (1.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolysis			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocoagulable state			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vestibular disorder			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye haemorrhage			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Peritonitis			
subjects affected / exposed	3 / 391 (0.77%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 391 (0.51%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diarrhoea			
subjects affected / exposed	1 / 391 (0.26%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric disorder			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mallory-Weiss syndrome			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 391 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	3 / 391 (0.77%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 391 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder perforation			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal cyst ruptured			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal mass			

subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperparathyroidism secondary			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	6 / 391 (1.53%)	6 / 267 (2.25%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	3 / 391 (0.77%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 391 (0.51%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gangrene			
subjects affected / exposed	2 / 391 (0.51%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	2 / 391 (0.51%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	2 / 391 (0.51%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	2 / 391 (0.51%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	1 / 391 (0.26%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			

subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 391 (0.26%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft infection			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia haemophilus			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdiaphragmatic abscess			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	1 / 391 (0.26%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint abscess			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			

subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 391 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Thrombophlebitis septic			
subjects affected / exposed	0 / 391 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	4 / 391 (1.02%)	6 / 267 (2.25%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	2 / 391 (0.51%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diabetic foot			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid retention			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			

subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 391 (0.26%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	PA21	Sevelamer carbonate	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	280 / 391 (71.61%)	197 / 267 (73.78%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	38 / 391 (9.72%)	20 / 267 (7.49%)	
occurrences (all)	53	29	
Hypotension			
subjects affected / exposed	19 / 391 (4.86%)	20 / 267 (7.49%)	
occurrences (all)	37	36	
Nervous system disorders			
Headache			
subjects affected / exposed	20 / 391 (5.12%)	8 / 267 (3.00%)	
occurrences (all)	28	19	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	14 / 391 (3.58%)	14 / 267 (5.24%)	
occurrences (all)	15	14	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	31 / 391 (7.93%)	14 / 267 (5.24%)	
occurrences (all)	42	18	
Nausea			
subjects affected / exposed	23 / 391 (5.88%)	11 / 267 (4.12%)	
occurrences (all)	26	12	
Endocrine disorders			

Hyperparathyroidism secondary			
subjects affected / exposed	15 / 391 (3.84%)	23 / 267 (8.61%)	
occurrences (all)	15	24	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	26 / 391 (6.65%)	16 / 267 (5.99%)	
occurrences (all)	39	20	
Metabolism and nutrition disorders			
Hyperphosphataemia			
subjects affected / exposed	47 / 391 (12.02%)	29 / 267 (10.86%)	
occurrences (all)	73	47	
Hypophosphataemia			
subjects affected / exposed	22 / 391 (5.63%)	14 / 267 (5.24%)	
occurrences (all)	26	14	
Hyperkalaemia			
subjects affected / exposed	15 / 391 (3.84%)	16 / 267 (5.99%)	
occurrences (all)	29	27	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 February 2011	Protocol Amendment 1: Amendment 1 was implemented prior to enrolment of subjects into PA-CL-05B and introduced the following changes that impacted the conduct of the study or data analyses: • Corrected and ionised calcium were added to the laboratory parameters reported. • Flexibility of timing of physical examination assessment was added. • Flexibility of timing of ECG assessment was added. • Specifications for follow-up telephone calls to subjects were added. • "Largest meal" was defined. • A DSMB was added. • Drug storage requirements were clarified. • Requirement for daily recording of drug storage temperature was added. • Flexibility of method of body temperature measurement was added. • Dialysis and dietary data parameters were added. • AE outcome options and wording were amended for consistency with the case report form. • Follow-up requirements for SAE reporting after study completion were clarified. • The definition of SAE resolution was clarified. • The SAE form template was revised to make it specific and consistent with the protocol and case report form.
04 July 2011	Protocol Amendment 2: Amendment 2 was implemented prior to enrolment of subjects into PA-CL-05B and introduced the following changes that impacted the conduct of the study or data analyses: • Exclusion criteria 7, serum ferritin levels were amended to exclude subjects with serum ferritin >2,000 mcg/L, raised from >1,500 mcg/L. • Sample size was increased and enrolment of subjects was to be continued to ensure a sufficient number of subjects to meet regulatory requirements for long-term safety. • Statistical testing of demographic, baseline characteristics and safety data was removed. • Frequency of Kt/V calculation was changed, and parameters for Kt/V calculation were corrected. • Calcium-based antacids were added to the list of prohibited medications. • The requirement for trade names of concomitant medications to be recorded in the eCRF was added. • White blood cell differential was amended to include percentage and absolute values.
12 August 2011	Protocol Amendment 3: Amendment 3 was implemented prior to subject enrolment into PA-CL-05B and introduced the following change that impacted the conduct of the study or data analyses: • The HD parameters to be recorded at each study visit were clarified.
31 January 2012	Protocol Amendment 4: Amendment 4 was implemented after subjects had enrolled, however, the amendment did not impact the conduct of the study or data analyses as it involved only the change of a signatory and a correction of a typographical error.

04 September 2012	Protocol Amendment 5: Amendment 5 was implemented after subjects had enrolled and introduced the following changes that impacted the conduct of the study or data analyses: • Clarification of withdrawal of non-eligible subjects. • Revision of study drug storage conditions. • Clarification of prohibited oral iron preparations. • Clarification of ECG reporting instructions. • Addition of guidance on unscheduled visits. • Clarification of SAE recording of kidney transplants. • Revision to reference the latest version of the PA21 Investigator's Brochure (Version 12), and update the AEs for the comparator medicinal product (sevelamer carbonate) to be in line with the Renvela Summary of Product Characteristics. • Inclusion of a planned interim safety analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported