



Clinical trial results:

An Open-label, Randomised, Active-controlled, Parallel Group, Multicentre, Phase 3 Study to Investigate the Safety and Efficacy of PA21 Compared with Sevelamer Carbonate Followed by a Randomised Comparison of PA21 Maintenance Dose Versus PA21 Low Dose in Dialysis Patients with Hyperphosphataemia

Summary

EudraCT number	2010-022011-19
Trial protocol	GB CZ LV LT SE AT DE BE
Global end of trial date	09 April 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-05A
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01324128
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 (International) Inc., medinfo@viforpharma.com
Scientific contact	MedInfo, Vifor (International) 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	14 October 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 April 2012
Global end of trial reached?	Yes
Global end of trial date	09 April 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Establish the superiority of PA21 maintenance dose (MD) versus PA21 low dose (LD) control in maintaining the phosphorus lowering effect in patients undergoing haemodialysis (HD), by comparing the change in serum phosphorus levels during a 3-week period (Stage 2) that follows 24 weeks of PA21 treatment (Stage 1). Assess the long-term safety and tolerability of PA21 in patients on dialysis.

Protection of trial subjects:

The study was conducted in accordance with the principles of the Declaration of Helsinki, 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 the Code of Federal Regulations 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) according to the regulatory and legal requirements of the participating country. No investigations specifically required for the study 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 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. The DSMB evaluated participant risk versus benefit of study participation and monitored external factors relevant to the trial, including scientific and therapeutic developments that may affect participant safety. Based on the observed benefits or adverse effects, the DSMB made recommendations to the Sponsor concerning continuation, termination or modifications of the trial.

Background therapy: -

Evidence for comparator:

Doses of PA21 were chosen based on the results of the Phase 2 study (PA-CL-03A) where it was shown that while the 1.25 g/day dose was not effective, PA21 at doses of 5.0 g/day to 12.5 g/day were effective in lowering elevated serum phosphorus in subjects undergoing maintenance HD. However, as there were no subject-reported, dose-limiting side effects seen with the highest PA21 dose (12.5 g/day), the maximum dose of PA21 allowed in this study was increased to 15.0 g/day.

For Stage 1, Sevelamer carbonate was chosen as the active comparator as its active ingredient (sevelamer) is considered a standard therapy for the treatment of hyperphosphataemia in patients undergoing dialysis. The sevelamer doses were based on its approved and commonly used doses.

Stage 2 used a dosing withdrawal design, with a LD of PA21 as the control treatment because it was shown to be ineffective in Study PA-CL-03A. This stage provided the opportunity to confirm the superiority of PA21 MD over the PA21 LD and demonstrate longer term maintenance of serum phosphorus control with the PA21 MD.

Actual start date of recruitment	07 March 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: 19
Country: Number of subjects enrolled	Austria: 14
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Czech Republic: 62
Country: Number of subjects enrolled	Latvia: 19
Country: Number of subjects enrolled	Lithuania: 24
Country: Number of subjects enrolled	Poland: 48
Country: Number of subjects enrolled	Romania: 33
Country: Number of subjects enrolled	Croatia: 27
Country: Number of subjects enrolled	Russian Federation: 151
Country: Number of subjects enrolled	Serbia: 71
Country: Number of subjects enrolled	South Africa: 7
Country: Number of subjects enrolled	Ukraine: 51
Country: Number of subjects enrolled	United States: 516
Worldwide total number of subjects	1059
EEA total number of subjects	263

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)	754
From 65 to 84 years	299
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

A total of 174 centres in 3 regions (United States, Europe and Rest Of the World) screened patients and 161 centres successfully randomised subjects.

Pre-assignment

Screening details:

In this study there was a screening period followed by a 2-4 week washout period, before the randomisation of the subjects into the study.

Period 1

Period 1 title	Stage 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Stage 1 - PA21 (2.5 g tablet)

Arm description:

PA21 chewable tablets containing 2.5 g PA21

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 starting dose was 5.0 g/day and the dose was titrated for efficacy and tolerability reasons. Dose increases or decreases of 2.5 g/day every 2 weeks were permitted. The maximum dose of PA21 was 15.0 g/day (6 tablets/day) and the minimum dose was 5.0 g/day (2 tablets/day). Stage 1 treatment ended on Week 24.

Arm title	Stage 1 - Sevelamer carbonate
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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	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Sevelamer carbonate (film-coated, compressed tablets) dose range of 2.4 g/day (3 tablets/day) to 14.4 g/day (18 tablets/day). The starting dose was 4.8 g/day and the dose was titrated for efficacy and tolerability reasons. Dose increases or decreases of 2.4 g/day (3 tablets/day (1 tablet per meal)) every 2 weeks were permitted. 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). Stage 1 treatment ended on Week 24.

Number of subjects in period 1	Stage 1 - PA21 (2.5 g tablet)	Stage 1 - Sevelamer carbonate
Started	710	349
Completed	515	293
Not completed	195	56
Adverse event, serious fatal	9	5
Consent withdrawn by subject	32	15
Physician decision	5	1
Adverse event, non-fatal	109	21
Other	10	3
Prohibited medication	2	-
Renal transplant	16	7
Sponsor decision	5	4
Protocol deviation	7	-

Period 2

Period 2 title	Stage 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Stage 2 - PA21 (2.5 g tablet) Maintenance Dose

Arm description:

PA21 chewable tablets containing 2.5 g PA21

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 first 100 subjects on HD who completed Stage 1 PA21 treatment group, and who had a controlled serum phosphorus level of <1.78 mmol/L (<5.5 mg/dL) at Week 20, were randomized in a 1:1 ratio to the PA21 MD group or the PA21-1 LD group. Subjects randomized to the PA21 MD group continued with the same dose they had been receiving at the end of Stage 1 (Week 24).

Arm title	Stage 2 - PA21-1 (1.25 g tablet) Low Dose
Arm description:	
PA21 chewable tablets containing 1.25 g PA21; dose was 1.25 g/day	
Arm type	Active comparator

Investigational medicinal product name	PA21-1
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 first 100 subjects on HD who completed Stage 1 PA21 treatment group, and who had a controlled serum phosphorus level of <1.78 mmol/L (<5.5 mg/dL) at Week 20, were randomized in a 1:1 ratio to the PA21 MD group or the PA21-1 LD group. Subjects randomized to the PA21 LD control group were switched from the dose they had been receiving at the end of Stage 1 (Week 24) to 1.25 g/day PA21-1 for the next 3 weeks. No dose adjustments were allowed until Stage 2 was complete.

Number of subjects in period 2^[1]	Stage 2 - PA21 (2.5 g tablet) Maintenance Dose	Stage 2 - PA21-1 (1.25 g tablet) Low Dose
Started	50	49
Completed	42	46
Not completed	8	3
Adverse event, serious fatal	-	1
Medication error	5	-
Predefined criteria within protocol	-	2
Noncompliance	3	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: In Stage 2, the first 100 subjects on HD who completed Stage 1 in the PA21 treatment group, and who had a controlled serum phosphorus level of <1.78 mmol/L (<5.5 mg/dL) at Week 20, were randomized in a 1:1 ratio to the PA21 MD group or the PA21 LD group. There was a single randomization error by the site and only 99 subjects were actually enrolled in Stage 2.

Baseline characteristics

Reporting groups

Reporting group title	Stage 1 - PA21 (2.5 g tablet)
Reporting group description: PA21 chewable tablets containing 2.5 g PA21	
Reporting group title	Stage 1 - Sevelamer carbonate
Reporting group description: Sevelamer carbonate, Renvela® tablets containing 800 mg of sevelamer carbonate	

Reporting group values	Stage 1 - PA21 (2.5 g tablet)	Stage 1 - Sevelamer carbonate	Total
Number of subjects	710	349	1059
Age categorical Units: Subjects			
Adults (18-64 years)	512	242	754
From 65-84 years	195	104	299
85 years and over	3	3	6
Age continuous Units: years			
arithmetic mean	56.4	55.9	
standard deviation	± 13.4	± 14.6	-
Gender categorical Units: Subjects			
Female	314	129	443
Male	396	220	616

End points

End points reporting groups

Reporting group title	Stage 1 - PA21 (2.5 g tablet)
Reporting group description: PA21 chewable tablets containing 2.5 g PA21	
Reporting group title	Stage 1 - Sevelamer carbonate
Reporting group description: Sevelamer carbonate, Renvela® tablets containing 800 mg of sevelamer carbonate	
Reporting group title	Stage 2 - PA21 (2.5 g tablet) Maintenance Dose
Reporting group description: PA21 chewable tablets containing 2.5 g PA21	
Reporting group title	Stage 2 - PA21-1 (1.25 g tablet) Low Dose
Reporting group description: PA21 chewable tablets containing 1.25 g PA21; dose was 1.25 g/day	

Primary: Serum phosphorus levels change from Baseline (Week 24) at Week 27

End point title	Serum phosphorus levels change from Baseline (Week 24) at Week 27
End point description: Change from Week 24, D1 (first dialysis session of the week) in serum phosphorus levels at Week 27, D1 – a superiority comparison between the PA21 MD group and the PA21 LD control group (fixed dose of 1.25 g/day) in the Primary Efficacy Set (PES) of subjects on HD. The PES consists of subjects who were randomized to Stage 2 and received at least 1 dose of study medication during Stage 2 and had at least 1 post-baseline (Stage 2) efficacy assessment in Stage 2.	
End point type	Primary
End point timeframe: 3 weeks. From Week 24 to Week 27.	

End point values	Stage 2 - PA21 (2.5 g tablet) Maintenance Dose	Stage 2 - PA21-1 (1.25 g tablet) Low Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	49		
Units: mg/dL				
least squares mean (standard error)	0.25 (± 0.23)	1.92 (± 0.23)		

Statistical analyses

Statistical analysis title	Change in serum phosphorus levels from Week 24-27
Statistical analysis description: ANCOVA-LOCF mixed model of change in serum phosphorus levels from Week 24 at Week 27. ANCOVA = Analysis of Covariance, LOCF = Last observation carried forward	

Comparison groups	Stage 2 - PA21 (2.5 g tablet) Maintenance Dose v Stage 2 - PA21-1 (1.25 g tablet) Low Dose
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	least squares mean
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.15
upper limit	2.19
Variability estimate	Standard error of the mean
Dispersion value	0.26

Notes:

[1] - The model included treatment, baseline serum phosphorus, and region (US/EU/ROW) as fixed effects.

Secondary: Serum phosphorus levels change from Baseline at Week 12

End point title	Serum phosphorus levels change from Baseline at Week 12
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End point description:

Change from baseline in serum phosphorus levels at Week 12 – a non-inferiority comparison between PA21 and sevelamer (Per-Protocol Set (PPS)).

The PPS consisted of all subjects who were randomised to treatment, received at least 1 dose of randomised study medication, had at least 1 post-baseline efficacy assessment, completed the analysis dose titration period (baseline to Week 12), had at least 1 evaluable serum phosphorus result at or after Week 12 and no major protocol deviations.

End point type	Secondary
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End point timeframe:

12 Weeks. Change from Baseline to Week 12.

End point values	Stage 1 - PA21 (2.5 g tablet)	Stage 1 - Sevelamer carbonate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	461	224		
Units: mg/dL				
least squares mean (standard error)	-2.19 (± 0.09)	-2.45 (± 0.11)		

Statistical analyses

Statistical analysis title	Change in serum phosphorus Baseline - Week 12-PPS
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Statistical analysis description:

ANCOVA (using a mixed model with the maximum likelihood estimation method) of the change in serum phosphorus levels from baseline at Week 12.

Comparison groups	Stage 1 - PA21 (2.5 g tablet) v Stage 1 - Sevelamer carbonate
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Number of subjects included in analysis	685
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[2]
Method	ANOVA
Parameter estimate	least square mean
Point estimate	0.26
Confidence interval	
level	Other: 97.5 %
sides	1-sided
upper limit	0.46
Variability estimate	Standard error of the mean
Dispersion value	0.1

Notes:

[2] - Data from the PPS was used. The model included treatment, dialysis status, region and baseline serum phosphorus level as fixed effects. Non-inferiority margin was 0.6 mg/dL.

Statistical analysis title	Change in serum phosphorus Baseline - Week 12-FAS
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Statistical analysis description:

ANCOVA (using a mixed model with the maximum likelihood estimation method) of the change in serum phosphorus levels from baseline at Week 12.

Comparison groups	Stage 1 - PA21 (2.5 g tablet) v Stage 1 - Sevelamer carbonate
Number of subjects included in analysis	685
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[3]
Method	ANOVA
Parameter estimate	least square mean
Point estimate	0.32
Confidence interval	
level	Other: 97.5 %
sides	1-sided
upper limit	0.5
Variability estimate	Standard error of the mean
Dispersion value	0.09

Notes:

[3] - Data from the FAS was used. The model included treatment, dialysis status, region and baseline serum phosphorus level as fixed effects. Non-inferiority margin was 0.6 mg/dL.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were recorded from the time the subject signed the informed consent form (ICF). The AE reporting period ended at the follow-up visit 14 days following the last intake of study medication.

Adverse event reporting additional description:

Serious AEs were recorded until 30 days following the last study visit or until 30 days after the last study drug administration, whichever was longer.

The safety population was considered for results regarding the AEs, which consisted of all randomised subjects who took at least 1 dose of study medication during the pertinent Stage.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	13.1
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Reporting groups

Reporting group title	Stage 1 - PA21 (2.5 g tablet)
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Reporting group description:

PA21 chewable tablets containing 2.5 g PA21. The starting dose was 5.0 g/day and the dose was titrated for efficacy and tolerability reasons. Dose increases or decreases of 2.5 g/day every 2 weeks were permitted. The maximum dose of PA21 was 15.0 g/day (6 tablets/day) and the minimum dose was 5.0 g/day (2 tablets/day). Stage 1 treatment ended on Week 24.

Reporting group title	Stage 1 - Sevelamer carbonate
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Reporting group description:

Sevelamer carbonate, Renvela® tablets containing 800 mg of sevelamer carbonate. Sevelamer carbonate, dose range of 2.4 g/day (3 tablets/day) to 14.4 g/day (18 tablets/day). The starting dose was 4.8 g/day and the dose was titrated for efficacy and tolerability reasons. Dose increases or decreases of 2.4 g/day (3 tablets/day (1 tablet per meal)) every 2 weeks were permitted. 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). Stage 1 treatment ended on Week 24.

Reporting group title	Stage 2 - PA21 (2.5 g tablet) Maintenance Dose
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Reporting group description:

PA21 chewable tablets containing 2.5 g PA21. The first 100 subjects on HD who completed Stage 1 PA21 treatment group, and who had a controlled serum phosphorus level of <1.78 mmol/L (<5.5 mg/dL) at Week 20, were randomized in a 1:1 ratio to the PA21 MD group or the PA21-1 LD group. Subjects randomized to the PA21 MD group continued with the same dose they had been receiving at the end of Stage 1 (Week 24).

Reporting group title	Stage 2 - PA21-1 (1.25 g tablet) Low Dose
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Reporting group description:

PA21 chewable tablets containing 1.25 g PA21; dose was 1.25 g/day. The first 100 subjects on HD who completed Stage 1 PA21 treatment group, and who had a controlled serum phosphorus level of <1.78 mmol/L (<5.5 mg/dL) at Week 20, were randomized in a 1:1 ratio to the PA21 MD group or the PA21-1 LD group. Subjects randomized to the PA21 LD control group were switched from the dose they had been receiving at the end of Stage 1 (Week 24) to 1.25 g/day PA21-1 for the next 3 weeks. No dose adjustments were allowed until Stage 2 was complete.

Serious adverse events	Stage 1 - PA21 (2.5 g tablet)	Stage 1 - Sevelamer carbonate	Stage 2 - PA21 (2.5 g tablet) Maintenance Dose
Total subjects affected by serious adverse events			
subjects affected / exposed	129 / 707 (18.25%)	69 / 348 (19.83%)	2 / 45 (4.44%)
number of deaths (all causes)	13	7	0
number of deaths resulting from	0	0	0

adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Myelofibrosis			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Prostate cancer recurrent			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Prostatic adenoma			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Renal cell carcinoma			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 707 (0.85%)	0 / 348 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	3 / 707 (0.42%)	1 / 348 (0.29%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic stenosis			
subjects affected / exposed	2 / 707 (0.28%)	0 / 348 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bleeding varicose vein			

subjects affected / exposed	2 / 707 (0.28%)	0 / 348 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	2 / 707 (0.28%)	0 / 348 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypertensive emergency			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Leriche syndrome			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 707 (0.14%)	1 / 348 (0.29%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral vascular disorder			
subjects affected / exposed	1 / 707 (0.14%)	3 / 348 (0.86%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aneurysm			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Arterial thrombosis limb			

subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Peripheral ischaemia			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Shock haemorrhagic			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Surgical and medical procedures			
Renal transplant			
subjects affected / exposed	1 / 707 (0.14%)	1 / 348 (0.29%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angioplasty			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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 fistula operation			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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 shunt operation			

subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Nephrectomy			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	8 / 707 (1.13%)	5 / 348 (1.44%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 9	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical device complication			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 707 (0.14%)	2 / 348 (0.57%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 707 (0.14%)	1 / 348 (0.29%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Thrombosis in device			
subjects affected / exposed	0 / 707 (0.00%)	2 / 348 (0.57%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic inflammatory response syndrome			

subjects affected / exposed	0 / 707 (0.00%)	0 / 348 (0.00%)	1 / 45 (2.22%)
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			
Dyspnoea			
subjects affected / exposed	4 / 707 (0.57%)	4 / 348 (1.15%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	3 / 707 (0.42%)	1 / 348 (0.29%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	3 / 707 (0.42%)	0 / 348 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 707 (0.28%)	0 / 348 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	1 / 707 (0.14%)	1 / 348 (0.29%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Pneumonia aspiration			
subjects affected / exposed	1 / 707 (0.14%)	1 / 348 (0.29%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary embolism			

subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 707 (0.14%)	1 / 348 (0.29%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pulmonary oedema			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Hypoxia			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood glucose abnormal			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Haemoglobin decreased			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
International normalised ratio decreased			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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

International normalised ratio increased			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Catheterisation cardiac			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Injury, poisoning and procedural complications			
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	3 / 707 (0.42%)	0 / 348 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Arteriovenous fistula thrombosis			
subjects affected / exposed	3 / 707 (0.42%)	2 / 348 (0.57%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular graft thrombosis			
subjects affected / exposed	3 / 707 (0.42%)	0 / 348 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Accidental overdose			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Contusion			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Fall			

subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Femur fracture			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Pelvic fracture			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Rib fracture			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Shunt occlusion			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Tibia fracture			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Traumatic brain injury			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Ankle fracture			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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 fistula aneurysm			

subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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 fistula site complication			
subjects affected / exposed	0 / 707 (0.00%)	2 / 348 (0.57%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous graft site haemorrhage			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Post concussion syndrome			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Shunt stenosis			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Shunt thrombosis			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Vascular access complication			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Wound complication			

subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Wrist fracture			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Congenital, familial and genetic disorders			
Arteriovenous malformation			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	9 / 707 (1.27%)	0 / 348 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 9	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	6 / 707 (0.85%)	1 / 348 (0.29%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	3 / 707 (0.42%)	1 / 348 (0.29%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 0
Angina pectoris			
subjects affected / exposed	2 / 707 (0.28%)	0 / 348 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	2 / 707 (0.28%)	2 / 348 (0.57%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Coronary artery disease			
subjects affected / exposed	2 / 707 (0.28%)	1 / 348 (0.29%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	2 / 707 (0.28%)	3 / 348 (0.86%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Ventricular tachycardia			
subjects affected / exposed	2 / 707 (0.28%)	0 / 348 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute left ventricular failure			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Angina unstable			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Atrial flutter			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Atrioventricular block complete			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Cardiac tamponade			
subjects affected / exposed	1 / 707 (0.14%)	1 / 348 (0.29%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardio-respiratory arrest			

subjects affected / exposed	1 / 707 (0.14%)	1 / 348 (0.29%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cardiogenic shock			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Congestive cardiomyopathy			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Pericardial effusion			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Aortic valve stenosis			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Bradycardia			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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 failure			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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 failure acute			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Cardiopulmonary failure			

subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Coronary artery stenosis			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Myocardial ischaemia			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Ventricular extrasystoles			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Acute coronary syndrome			
subjects affected / exposed	0 / 707 (0.00%)	0 / 348 (0.00%)	0 / 45 (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			
Cerebrovascular accident			
subjects affected / exposed	1 / 707 (0.14%)	1 / 348 (0.29%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Dementia			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Dizziness			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Dysarthria			

subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Embolitic stroke			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Hypertensive encephalopathy			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Syncope			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Transient ischaemic attack			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Cerebral haemorrhage			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Cervicobrachial syndrome			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Headache			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Toxic encephalopathy			

subjects affected / exposed	0 / 707 (0.00%)	0 / 348 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental impairment			
subjects affected / exposed	0 / 707 (0.00%)	0 / 348 (0.00%)	0 / 45 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 707 (0.14%)	3 / 348 (0.86%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 707 (0.28%)	0 / 348 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diabetic eye disease			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Vitreous haemorrhage			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Gastrointestinal disorders			
Peritonitis			

subjects affected / exposed	4 / 707 (0.57%)	0 / 348 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 707 (0.28%)	1 / 348 (0.29%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	2 / 707 (0.28%)	0 / 348 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall haematoma			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 707 (0.14%)	1 / 348 (0.29%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenitis haemorrhagic			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Faeces discoloured			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Oesophageal ulcer			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Pancreatitis chronic			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Umbilical hernia			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Umbilical hernia, obstructive			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Vomiting			
subjects affected / exposed	1 / 707 (0.14%)	1 / 348 (0.29%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal hernia obstructive			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Gastrointestinal necrosis			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Abdominal pain			

subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Hepatobiliary disorders			
Biliary dyskinesia			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Cholecystitis acute			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Cholecystitis			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Diabetic ulcer			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Skin ulcer			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Renal and urinary disorders			
Renal failure chronic			
subjects affected / exposed	2 / 707 (0.28%)	0 / 348 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0

Haemorrhage urinary tract subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Renal tubular necrosis subjects affected / exposed	0 / 707 (0.00%)	0 / 348 (0.00%)	0 / 45 (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
Endocrine disorders Thyroiditis subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Musculoskeletal and connective tissue disorders Joint swelling subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Myalgia subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Systemic lupus erythematosus subjects affected / exposed	0 / 707 (0.00%)	2 / 348 (0.57%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity subjects affected / exposed	0 / 707 (0.00%)	0 / 348 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations Pneumonia			

subjects affected / exposed	7 / 707 (0.99%)	2 / 348 (0.57%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	4 / 707 (0.57%)	1 / 348 (0.29%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	4 / 707 (0.57%)	3 / 348 (0.86%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sepsis syndrome			
subjects affected / exposed	3 / 707 (0.42%)	0 / 348 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess limb			
subjects affected / exposed	2 / 707 (0.28%)	0 / 348 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous graft site infection			
subjects affected / exposed	2 / 707 (0.28%)	0 / 348 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	2 / 707 (0.28%)	1 / 348 (0.29%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	2 / 707 (0.28%)	0 / 348 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			

subjects affected / exposed	2 / 707 (0.28%)	0 / 348 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 707 (0.28%)	1 / 348 (0.29%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute tonsillitis			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Bacterial sepsis			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Bronchopneumonia			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Clostridium difficile colitis			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Endocarditis			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Enterococcal bacteraemia			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Escherichia bacteraemia			

subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Escherichia sepsis			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Gangrene			
subjects affected / exposed	1 / 707 (0.14%)	2 / 348 (0.57%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 707 (0.14%)	1 / 348 (0.29%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Graft infection			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Groin abscess			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Hepatic cyst infection			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Necrotising fasciitis			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Osteomyelitis			

subjects affected / exposed	1 / 707 (0.14%)	1 / 348 (0.29%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis bacterial			
subjects affected / exposed	1 / 707 (0.14%)	1 / 348 (0.29%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Renal cyst infection			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Staphylococcal sepsis			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Appendicitis			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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 fistula site infection			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Bacteriuria			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Clostridial infection			

subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Device related infection			
subjects affected / exposed	0 / 707 (0.00%)	2 / 348 (0.57%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shunt infection			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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
Subcutaneous abscess			
subjects affected / exposed	0 / 707 (0.00%)	1 / 348 (0.29%)	0 / 45 (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	4 / 707 (0.57%)	4 / 348 (1.15%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	3 / 707 (0.42%)	0 / 348 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	2 / 707 (0.28%)	0 / 348 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calciophylaxis			

subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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
Hypoglycaemia			
subjects affected / exposed	1 / 707 (0.14%)	1 / 348 (0.29%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 707 (0.14%)	0 / 348 (0.00%)	0 / 45 (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

Serious adverse events	Stage 2 - PA21-1 (1.25 g tablet) Low Dose		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 49 (12.24%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Myelofibrosis			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Prostate cancer recurrent			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Prostatic adenoma			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal cell carcinoma			

subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aortic stenosis			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bleeding varicose vein			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhage			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertensive emergency			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Leriche syndrome			

subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral vascular disorder			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aneurysm			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arterial thrombosis limb			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral ischaemia			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Shock haemorrhagic			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Renal transplant			

subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Angioplasty			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arteriovenous fistula operation			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arteriovenous graft			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arteriovenous shunt operation			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephrectomy			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Medical device complication			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			

subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombosis in device			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary			

disease				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute respiratory failure				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute pulmonary oedema				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				

Bipolar disorder			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood glucose abnormal			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemoglobin decreased			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
International normalised ratio decreased			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
International normalised ratio increased			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Catheterisation cardiac			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arteriovenous fistula thrombosis			

subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular graft thrombosis				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Accidental overdose				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Contusion				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pelvic fracture				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Shunt occlusion				

subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Traumatic brain injury				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ankle fracture				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arteriovenous fistula aneurysm				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arteriovenous fistula site complication				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arteriovenous graft site haemorrhage				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post concussion syndrome				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Shunt stenosis				

subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Shunt thrombosis			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular access complication			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound complication			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wrist fracture			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Arteriovenous malformation			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Cardiac failure congestive subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angina pectoris subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular tachycardia subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute left ventricular failure subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angina unstable				

subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial flutter				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block complete				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac tamponade				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardio-respiratory arrest				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiogenic shock				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Congestive cardiomyopathy				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aortic valve stenosis				

subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bradycardia				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure acute				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiopulmonary failure				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery stenosis				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial ischaemia				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular extrasystoles				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute coronary syndrome				

subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dementia			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dysarthria			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Embolic stroke			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertensive encephalopathy			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			

subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebral haemorrhage			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cervicobrachial syndrome			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Toxic encephalopathy			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mental impairment			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Diabetic eye disease			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vitreous haemorrhage			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Peritonitis			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal wall haematoma			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Duodenitis haemorrhagic				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Faeces discoloured				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal ulcer				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis chronic				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Umbilical hernia				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Umbilical hernia, obstructive				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				

subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal hernia obstructive			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal necrosis			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Biliary dyskinesia			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis acute			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diabetic ulcer			

subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin ulcer			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure chronic			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhage urinary tract			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal tubular necrosis			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Endocrine disorders			
Thyroiditis			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Joint swelling			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myalgia			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Systemic lupus erythematosus subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pain in extremity subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis syndrome subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abscess limb subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arteriovenous graft site infection subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bacteraemia			

subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute tonsillitis				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bacterial sepsis				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchopneumonia				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endocarditis				

subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Enterococcal bacteraemia			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Escherichia bacteraemia			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Escherichia sepsis			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gangrene			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Graft infection			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Groin abscess			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic cyst infection			

subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Necrotising fasciitis				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonitis bacterial				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia viral				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal cyst infection				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Staphylococcal sepsis				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arteriovenous fistula site infection				

subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bacteriuria			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Clostridial infection			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Shunt infection			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subcutaneous abscess			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			

subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diabetic ketoacidosis			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Calciophylaxis			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Stage 1 - PA21 (2.5 g tablet)	Stage 1 - Sevelamer carbonate	Stage 2 - PA21 (2.5 g tablet) Maintenance Dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	574 / 707 (81.19%)	258 / 348 (74.14%)	8 / 45 (17.78%)
Vascular disorders			
Hypertension			
subjects affected / exposed	40 / 707 (5.66%)	26 / 348 (7.47%)	1 / 45 (2.22%)
occurrences (all)	48	39	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	141 / 707 (19.94%)	26 / 348 (7.47%)	1 / 45 (2.22%)
occurrences (all)	182	30	1
Faeces discoloured			

subjects affected / exposed occurrences (all)	109 / 707 (15.42%) 109	1 / 348 (0.29%) 1	0 / 45 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	51 / 707 (7.21%) 60	39 / 348 (11.21%) 41	1 / 45 (2.22%) 1
Vomiting subjects affected / exposed occurrences (all)	30 / 707 (4.24%) 35	18 / 348 (5.17%) 21	0 / 45 (0.00%) 0
Constipation subjects affected / exposed occurrences (all)	27 / 707 (3.82%) 33	25 / 348 (7.18%) 26	0 / 45 (0.00%) 0
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	23 / 707 (3.25%) 25	7 / 348 (2.01%) 7	0 / 45 (0.00%) 0
Metabolism and nutrition disorders Hyperphosphataemia subjects affected / exposed occurrences (all)	79 / 707 (11.17%) 114	27 / 348 (7.76%) 39	0 / 45 (0.00%) 0

Non-serious adverse events	Stage 2 - PA21-1 (1.25 g tablet) Low Dose		
Total subjects affected by non-serious adverse events subjects affected / exposed	19 / 49 (38.78%)		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	1 / 49 (2.04%) 1		
Faeces discoloured subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0		
Nausea			

subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Hyperphosphataemia			
subjects affected / exposed	7 / 49 (14.29%)		
occurrences (all)	7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 November 2010	<p>Protocol PA-CL-05A Amendment 1:</p> <p>Amendment 1 was implemented prior to screening and enrolment of subjects and introduced the following changes that impacted the conduct of the study:</p> <ul style="list-style-type: none">• Originally the protocol specified only serum total calcium for laboratory analysis; however, as laboratories commonly provide corrected and ionised calcium also, these were added to the protocol.• When creating the eCRF it was noted that there was a discrepancy in AE outcome options and wording; therefore these were amended for consistency. New wording: Outcome may be classified as recovered without sequelae; recovered with sequelae; improved; worsened; ongoing at end of study; or fatal.• SAEs were considered resolved if the seriousness criteria were no longer applicable; however this was missing from the protocol and was added. New wording: The resolution date of the SAE is defined as when the symptoms resolve, or the event is considered chronic (e.g., sequelae) or stable, and/or if the seriousness criteria are no longer applicable.• The wording of the first question in the patient satisfaction assessment was unclear with respect to which kind of tablets were referred to, so this was clarified to specify phosphate binder pills.
25 January 2011	<p>Protocol PA-CL-05A Amendment 2. Amendment 2 was implemented prior to screening and enrolment of subjects and introduced the following changes:</p> <ul style="list-style-type: none">• Nocturnal HD was specifically disallowed for eligibility criteria due to logistic issues. New wording: Subjects receiving maintenance HD 3 times/week with a Kt/V of ≥ 1.2 or PD with a Kt/V of ≥ 1.7 per week for at least 3 months prior to screening. No home HD or nocturnal HD (overnight stay at centre) will be allowed.• The washout procedure was clarified to indicate that a minimum of 2 weeks washout period is obligatory, to add a provision for a washout visit after 4 weeks if needed, and to recommend when subjects (PD and HD) should be randomised relative to their qualifying results.• Flexibility of timing of physical examination assessment was added so that physical examinations can be done at any time during the dialysis session/study visit, since the requirement for physical examination prior to HD was impractical for some centres.• The requirement for the ECG assessment to be done prior to the third dialysis session of the week was impractical at some centres and this was changed so that ECGs could be done prior to the second or third dialysis session of the week.• Specifications for follow-up telephone calls to subjects were added: if the Investigator has not seen the subject at a clinic visit at the end of the reporting period, the Investigator must attempt 2 telephone calls; and if there is no response, mail a registered letter with return receipt requested.• "Largest meal" was defined as the meal with highest phosphate content.• A DSMB was added to protect the safety of the study participants.• Drug storage requirements were clarified.• The requirement for axillary body temperature measurement was expanded to include oral or otic body measurement.• Dialysis and dietary data parameters to be collected were added.• Due to an IRB/EC request, follow-up requirements for SAE reporting after study completion were clarified.

20 June 2011	<p>Protocol PA-CL-05A Amendment 3:</p> <p>Amendment 3 was implemented during the conduct of Stage 1 and prior to initiation of Stage 2 and introduced the following changes:•For Exclusion Criterion 9, the upper allowed limit for serum ferritin was revised: SI units added, the relationship with C-reactive protein was removed and a new upper allowed limit (>2,000 mcg/L) was added. The level of serum ferritin in dialysis patients with iron overload is above 2,000 mcg/L. Levels below 2,000 mcg/L may be due to the inflammatory state of the patients and the common practice of administering intravenous iron preparations. C-reactive protein is rarely normal in patients undergoing dialysis; most have high levels due to their inflammatory state. Sample size was increased to ensure sufficient numbers to meet regulatory requirements for long-term safety. The sample size for the study was increased from 640 to 940 corresponding to a planned evaluable PPS of 507 and 752, respectively. However, because of the screening process and the washout period, 1,059 subjects were randomised. The hypothesis of a 20% loss of evaluable subjects between the randomised set and the PPS was underestimated and the final PPS was 685 subjects.•The maximum duration of the screening period has been increased to 3 weeks to allow for repeated laboratory samples to be obtained and results received where required.•Frequency of Kt/V calculation was changed, and parameters corrected for the Kt/V calculation.•Calcium-based antacids were added to the list of prohibited medications.•The requirement for trade names of concomitant medications in the eCRF was added.•The requirement for both differential (%) and absolute value for each white blood cell type had been omitted.•Total amount of blood taken during the study was modified due to the additional calcium and Kt/V measurements.</p> <p>Additional Changes: Clarification of the intent of the prohibited concomitant medications,Management of samples for bone markers and FGF-23.</p>
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported