



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 |
|-----------------------|-----------|

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 |
|------------------|-------------------------------|

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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|----------------------------|---|

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 ^[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 |
|-----------------------------------|---|

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 |
|-----------------|------------|

Dictionary used

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 13.1 |
|--------------------|------|

Reporting groups

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

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 |
|-----------------------|-------------------------------|

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 |
|-----------------------|--|

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 |
|-----------------------|---|

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

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| 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