



Clinical trial results:

An Open-label, Multicentre, Randomised, 3-arm Study to Investigate the Comparative Efficacy and Safety of Intravenous Ferric Carboxymaltose (Ferinject® High and Low Dosage Regimens) Versus Oral Iron for the Treatment of Iron Deficiency Anaemia in Subjects with Non-dialysis-dependent Chronic Kidney Disease

Summary

| | |
|--------------------------|--|
| EudraCT number | 2009-015579-28 |
| Trial protocol | GB BE SE FR DE DK ES IT CZ AT GR PT NL |
| Global end of trial date | 12 February 2013 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 04 December 2016 |
| First version publication date | 04 December 2016 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | FER-CKD-01 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00994318 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Vifor Pharma (International) Inc. |
| Sponsor organisation address | Rechenstrasse 37, St. Gallen, Switzerland, CH-9001 |
| Public contact | Medical Information, Vifor (International) Inc., medinfo@viforpharma.com |
| Scientific contact | Medical Information, 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 | 23 May 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 12 February 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 February 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term efficacy of ferric carboxymaltose (FCM) (using targeted ferritin levels to determine dosing) or oral iron to delay and/or reduce erythropoiesis stimulating agent (ESA) use and/or other anaemia management options in non-dialysis-dependent chronic kidney disease (NDD-CKD) subjects with iron deficiency anaemia (IDA).

Protection of trial subjects:

A Data Safety Monitoring Board (DSMB), governed by a charter which stipulated operation procedures, met periodically to analyse aggregate and individual subject safety data, data integrity, and overall study conduct, to assess study progress and make recommendations to continue, modify, or terminate the study.

Background therapy: -

Evidence for comparator:

The standard clinically relevant oral iron dose was used in the comparator group. The oral iron dose of 100 mg iron as ferrous sulphate twice daily was considered the most appropriate for a 1-year study, chosen so that subject compliance did not suffer due to adverse events (AEs), which would likely occur at higher doses or frequency.

| | |
|---|------------------|
| Actual start date of recruitment | 16 December 2009 |
| 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: 104 |
| Country: Number of subjects enrolled | Austria: 8 |
| Country: Number of subjects enrolled | Belgium: 10 |
| Country: Number of subjects enrolled | Denmark: 4 |
| Country: Number of subjects enrolled | France: 4 |
| Country: Number of subjects enrolled | Greece: 115 |
| Country: Number of subjects enrolled | Italy: 40 |
| Country: Number of subjects enrolled | Netherlands: 16 |
| Country: Number of subjects enrolled | Portugal: 9 |
| Country: Number of subjects enrolled | Spain: 18 |
| Country: Number of subjects enrolled | Sweden: 1 |
| Country: Number of subjects enrolled | United Kingdom: 71 |
| Country: Number of subjects enrolled | Norway: 5 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Czech Republic: 62 |
| Country: Number of subjects enrolled | Poland: 44 |
| Country: Number of subjects enrolled | Romania: 8 |
| Country: Number of subjects enrolled | United States: 14 |
| Country: Number of subjects enrolled | Turkey: 31 |
| Country: Number of subjects enrolled | Australia: 62 |
| Worldwide total number of subjects | 626 |
| EEA total number of subjects | 519 |

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) | 174 |
| From 65 to 84 years | 422 |
| 85 years and over | 30 |

Subject disposition

Recruitment

Recruitment details:

There were 938 subjects screened of which 626 were randomised, in 156 sites in 19 countries, and included in the study.

Pre-assignment

Screening details:

After an initial screening period of up to 4 weeks, eligible subjects were randomly allocated to receive 1 of 3 study drug regimens for a period of 52 weeks; FCM high-dose, FCM low-dose or oral iron in a 1:1:2 ratio.

Period 1 (pre-treatment): from informed consent to first study drug dose. For study results, only Periods 2 and 3 are described.

Period 1

| | |
|------------------------------|---------------------------|
| Period 1 title | Period 2 (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

NOTE: Period 2 (study treatment): from first study drug dose to reaching primary endpoint (treatment failure, i.e., application of additional or alternative anaemia management or hitting the Hb trigger) or end of study.

Arms

| | |
|--|-----------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Arm A: FCM high-dose |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | Ferric carboxymaltose (FCM) |
| Investigational medicinal product code | |
| Other name | Ferinject, FCM |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Day 0: 1,000 mg iron as FCM (subjects ≤66 kg dosed with 500 mg on Days 0 and 7).

Week 4 to 52 (dosing every 4 weeks ±3 days with last dose at Week 48): 1,000 mg iron as FCM (subjects ≤66 kg dosed with 500 mg on day of visit and 500 mg 1 week later) when ferritin was <200 mcg/L. If ferritin range was between 200 and <400 mcg/L, a dose of 500 mg iron as FCM was administered. No dose was administered if ferritin was ≥400 mcg/L.

FCM dosing was only initiated if transferrin saturation (TSAT) was <40%. For subjects with TSAT >35% from a prior assessment (completed >10 days prior to planned FCM administration day), dosing was withheld until TSAT was confirmed as <40%.

| | |
|--|-----------------------------|
| Arm title | Arm B: FCM low-dose |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | Ferric carboxymaltose (FCM) |
| Investigational medicinal product code | |
| Other name | Ferinject, FCM |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Day 0: 200 mg iron as FCM. No dose was administered if screening ferritin level (or value on day of randomisation, if available) was ≥100 mcg/L.

Week 4 to 52 (dosing every 4 weeks \pm 3 days with last dose at Week 48): 200 mg iron as FCM when ferritin was <100 mcg/L. No dose was administered if ferritin value was \geq 100 mcg/L. FCM dosing was only initiated if TSAT was <40%. For subjects with TSAT >35% from a prior assessment (completed >10 days prior to planned FCM administration day), dosing was withheld until TSAT was confirmed as <40%.

| | |
|--|--|
| Arm title | Arm C: daily oral iron |
| Arm description: - | |
| Arm type | Active comparator |
| Investigational medicinal product name | Oral iron |
| Investigational medicinal product code | |
| Other name | Plastufer® 100 mg capsules, ferrous sulphate |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Weeks 0 to 52: 200 mg iron/day (100 mg twice daily) orally. Oral iron was supplied as ferrous sulphate. Dosing was suspended if serum ferritin was \geq 200 mcg/L and resumed if values fell below <100 mcg/L.

| Number of subjects in period 1 | Arm A: FCM high-dose | Arm B: FCM low-dose | Arm C: daily oral iron |
|---------------------------------------|----------------------|---------------------|------------------------|
| Started | 155 | 154 | 317 |
| Completed | 133 | 136 | 250 |
| Not completed | 22 | 18 | 67 |
| Adverse event, serious fatal | 6 | 2 | 12 |
| Consent withdrawn by subject | 13 | 8 | 32 |
| Physician decision | - | 1 | 9 |
| Adverse event, non-fatal | - | 3 | 10 |
| Other | - | 1 | 1 |
| Lost to follow-up | 2 | 3 | 2 |
| Protocol deviation | 1 | - | 1 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|------------------------|
| Reporting group title | Arm A: FCM high-dose |
| Reporting group description: - | |
| Reporting group title | Arm B: FCM low-dose |
| Reporting group description: - | |
| Reporting group title | Arm C: daily oral iron |
| Reporting group description: - | |

| Reporting group values | Arm A: FCM high-dose | Arm B: FCM low-dose | Arm C: daily oral iron |
|--|----------------------|---------------------|------------------------|
| Number of subjects | 155 | 154 | 317 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 39 | 47 | 88 |
| From 65-84 years | 107 | 103 | 212 |
| 85 years and over | 9 | 4 | 17 |
| Age continuous Units: years | | | |
| arithmetic mean | 69.5 | 68.2 | 69.2 |
| standard deviation | ± 12.6 | ± 13.2 | ± 13.4 |
| Gender categorical Units: Subjects | | | |
| Female | 93 | 98 | 199 |
| Male | 62 | 56 | 118 |

| Reporting group values | Total | | |
|--|-------|--|--|
| Number of subjects | 626 | | |
| Age categorical Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 174 | | |
| From 65-84 years | 422 | | |
| 85 years and over | 30 | | |

| | | | |
|---|-----|--|--|
| Age continuous Units: years arithmetic mean standard deviation | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 390 | | |
| Male | 236 | | |

End points

End points reporting groups

| | |
|--------------------------------|------------------------|
| Reporting group title | Arm A: FCM high-dose |
| Reporting group description: - | |
| Reporting group title | Arm B: FCM low-dose |
| Reporting group description: - | |
| Reporting group title | Arm C: daily oral iron |
| Reporting group description: - | |

Primary: Time-to initiation of other anaemia management analysis, including Hb trigger based on central lab data

| | |
|------------------------|--|
| End point title | Time-to initiation of other anaemia management analysis, including Hb trigger based on central lab data |
| End point description: | <p>Subjects (FAS population) were considered as having met the primary endpoint if at last one of the following occurred:</p> <p>1- Additional or alternative anaemia management to the randomised treatment arm (including use of alternative iron product, or change to dosing schedule or total iron dose) was implemented by the treating physician to address lack of efficacy or subject treatment-related adverse events (AEs).</p> <p>2 - Subject had 2 consecutive haemoglobin (Hb) values <10 g/dL (and without an Hb increase of ≥ 0.5 g/dL between the 2 values). This was based on central laboratory assessments. Subjects were to continue on assigned treatment per protocol.</p> |
| End point type | Primary |
| End point timeframe: | From the first dose (either FCM high-dose, FCM low-dose or oral iron), until having met the primary endpoint after the 8-week period. |

| End point values | Arm A: FCM high-dose | Arm B: FCM low-dose | Arm C: daily oral iron | |
|----------------------------------|----------------------|----------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 153 | 152 | 308 | |
| Units: day | | | | |
| arithmetic mean (standard error) | 295.7 (± 7.65) | 283.8 (± 9.47) | 286.7 (± 7.71) | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Subjects requiring ESA |
| Comparison groups | Arm A: FCM high-dose v Arm C: daily oral iron |
| Number of subjects included in analysis | 461 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| P-value | = 0.57 |
| Method | Logrank |
| Parameter estimate | Log odds ratio |
| Point estimate | 0.85 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.48 |
| upper limit | 1.49 |

Notes:

[1] - There were 3 primary comparisons planned, using a hierarchical step-down procedure on the log-rank test to preserve the overall alpha level of 0.05. Analyses were performed in the following order:

1. FCM high-dose compared with oral iron
2. FCM high-dose compared with FCM low-dose
3. FCM low-dose compared with oral iron

| | |
|---|--|
| Statistical analysis title | Subjects requiring ESA |
| Comparison groups | Arm A: FCM high-dose v Arm B: FCM low-dose |
| Number of subjects included in analysis | 305 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.15 |
| Method | Logrank |
| Parameter estimate | Log odds ratio |
| Point estimate | 0.63 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.34 |
| upper limit | 1.18 |

| | |
|---|--|
| Statistical analysis title | Subjects requiring ESA |
| Comparison groups | Arm C: daily oral iron v Arm B: FCM low-dose |
| Number of subjects included in analysis | 460 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.27 |
| Method | Logrank |
| Parameter estimate | Log odds ratio |
| Point estimate | 1.34 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 2.27 |

Secondary: Time to first occurrence of Hb increase ≥ 1 g/dL prior to any other anaemia management

| | |
|-----------------|---|
| End point title | Time to first occurrence of Hb increase ≥ 1 g/dL prior to any other anaemia management |
|-----------------|---|

End point description:

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From the first dose (either FCM high-dose, FCM low-dose or oral iron), until having met the primary endpoint after the 8-week period. | |

| End point values | Arm A: FCM high-dose | Arm B: FCM low-dose | Arm C: daily oral iron | |
|----------------------------------|----------------------|----------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 153 | 152 | 308 | |
| Units: days | | | | |
| arithmetic mean (standard error) | 192.6 (\pm 12.84) | 268.2 (\pm 11.88) | 272 (\pm 8.74) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to discontinuation of study drug due to intolerance

| | |
|---|--|
| End point title | Time to discontinuation of study drug due to intolerance |
| End point description: | |
| Discontinuation of study drug due to intolerance was defined as subject experiencing a related AE for which the "action to study drug" was permanent discontinuation of study drug. | |
| Frequency counts and percentages were constructed for the number of subjects who had discontinued from the study drug due to intolerance. | |
| Time to first occurrence of discontinuation of study drug due to intolerance was defined as the earliest start date of AE meeting the above definition. If the start date was partial or missing, imputation rules were used. | |
| End point type | Secondary |
| End point timeframe: | |
| From the first dose (either FCM high-dose, FCM low-dose or oral iron), until having met the primary endpoint after the 8-week period. | |

| End point values | Arm A: FCM high-dose | Arm B: FCM low-dose | Arm C: daily oral iron | |
|--|----------------------|---------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 153 | 152 | 308 | |
| Units: days | | | | |
| arithmetic mean (full range (min-max)) | 242 (56 to 419) | 225.1 (44 to 437) | 329.4 (1 to 419) | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) reporting occurred from screening until Week 56.

Adverse event reporting additional description:

For reporting AEs, Periods 2 and 3 were considered.

Period 3: study treatment failure (from reaching primary endpoint to end of follow-up).

The results are described for safety set (SS).

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 15.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------|
| Reporting group title | Period 2: Arm A |
|-----------------------|-----------------|

Reporting group description: -

| | |
|-----------------------|-----------------|
| Reporting group title | Period 2: Arm B |
|-----------------------|-----------------|

Reporting group description: -

| | |
|-----------------------|-----------------|
| Reporting group title | Period 2: Arm C |
|-----------------------|-----------------|

Reporting group description: -

| | |
|-----------------------|-----------------|
| Reporting group title | Period 3: Arm A |
|-----------------------|-----------------|

Reporting group description: -

| | |
|-----------------------|-----------------|
| Reporting group title | Period 3: Arm B |
|-----------------------|-----------------|

Reporting group description: -

| | |
|-----------------------|-----------------|
| Reporting group title | Period 3: Arm C |
|-----------------------|-----------------|

Reporting group description: -

| | |
|-----------------------|---|
| Reporting group title | Period 3: Additional or Alternative Anaemia Management Only |
|-----------------------|---|

Reporting group description:

This reporting group includes all AEs that occurred from day of treatment failure until end of study.

These medications included all non-study drug therapies to treat anemia, including other intravenous or oral iron preparations, ESAs, or blood transfusions.

| Serious adverse events | Period 2: Arm A | Period 2: Arm B | Period 2: Arm C |
|---|-------------------|-------------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 39 / 154 (25.32%) | 36 / 150 (24.00%) | 59 / 312 (18.91%) |
| number of deaths (all causes) | 5 | 1 | 6 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Colon cancer | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 1 / 150 (0.67%) | 0 / 312 (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 |
| B-cell lymphoma | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Burkitt's lymphoma | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Cholesteatoma | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 312 (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 |
| Laryngeal cancer recurrent | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Lung carcinoma cell type unspecified recurrent | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Lung neoplasm | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Multiple myeloma | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Myelodysplastic syndrome | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Neuroendocrine carcinoma of the skin | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 312 (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 |
| Small cell lung cancer stage unspecified | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Thyroid cancer | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 312 (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 |
| Endometrial cancer | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Metastases to peritoneum | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Non-small cell lung cancer | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Ovarian neoplasm | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Vascular disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Hypertension | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 1 / 150 (0.67%) | 3 / 312 (0.96%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic stenosis | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 312 (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 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 312 (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 arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 312 (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 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Surgical and medical procedures | | | |
| Carotid artery stent insertion | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| General disorders and administration | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 1 / 150 (0.67%) | 0 / 312 (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 |
| Device failure | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hernia obstructive | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Sudden death | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 312 (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 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 2 / 150 (1.33%) | 2 / 312 (0.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| 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 failure | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Investigations | | | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 312 (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 |
| International normalised ratio increased | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Injury, poisoning and procedural complications | | | |
| Tibia fracture | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervical vertebral fracture | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Concussion | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laceration | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Ligament rupture | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple injuries | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Overdose | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 312 (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 |
| Pelvic fracture | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Perirenal haematoma | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 312 (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 |
| Renal haematoma | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 312 (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 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal fracture | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clavicle fracture | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Toxicity to various agents | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Transfusion reaction | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arteriovenous fistula site haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 2 / 154 (1.30%) | 0 / 150 (0.00%) | 4 / 312 (1.28%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 3 / 312 (0.96%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 2 / 154 (1.30%) | 1 / 150 (0.67%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 2 / 154 (1.30%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 1 / 150 (0.67%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina unstable | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 312 (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 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure acute | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 312 (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 |
| Extrasystoles | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive heart disease | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Myocardial ischaemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 312 (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 |
| Sinus arrhythmia | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 312 (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 |
| Atrioventricular block second degree | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Cardiogenic shock | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Mitral valve disease | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Angina pectoris | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 | | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 3 / 312 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 312 (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 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Hypoglycaemic coma | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotonia | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Loss of consciousness | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Orthostatic intolerance | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Vertebrobasilar insufficiency | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Cerebrovascular insufficiency | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Guillain-Barre syndrome | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 / 154 (0.65%) | 2 / 150 (1.33%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrogenic anaemia | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 312 (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 |
| Haemorrhagic anaemia | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 312 (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 |
| Duodenal ulcer | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 312 (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 |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenitis | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 312 (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 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 312 (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 |
| Enterocolitis | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 312 (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 |
| Gastric ulcer | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Pancreatic disorder | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 312 (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 |
| Umbilical hernia, obstructive | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Colonic polyp | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Inguinal hernia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Melaena | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Skin and subcutaneous tissue disorders | | | |
| Diabetic ulcer | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Drug eruption | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pemphigoid | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Rash | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal failure chronic | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 1 / 150 (0.67%) | 6 / 312 (1.92%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 2 / 312 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Azotaemia | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 1 / 150 (0.67%) | 0 / 312 (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 |
| Renal failure acute | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 2 / 312 (0.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis glandularis | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 artery stenosis | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 | | | |
| Hyperparathyroidism primary | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 2 / 154 (1.30%) | 1 / 150 (0.67%) | 0 / 312 (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 |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 312 (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 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoporotic fracture | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 4 / 312 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 2 / 312 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infective exacerbation of chronic obstructive airways disease | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 1 / 150 (0.67%) | 0 / 312 (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 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Abscess | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Endophthalmitis | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infected skin ulcer | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Infection | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| 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 tract infection | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 312 (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 sepsis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 312 (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 abscess | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound infection staphylococcal | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atypical pneumonia | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Lobar pneumonia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Pneumonia staphylococcal | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 1 / 150 (0.67%) | 5 / 312 (1.60%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 3 / 150 (2.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic foot | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 1 / 150 (0.67%) | 0 / 312 (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 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 312 (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 |
| Diabetic ketoacidosis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Fluid overload | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Fluid retention | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gout | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (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 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Period 3: Arm A | Period 3: Arm B | Period 3: Arm C |
|---|-----------------|-----------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 16 (50.00%) | 7 / 22 (31.82%) | 38 / 86 (44.19%) |
| number of deaths (all causes) | 0 | 0 | 8 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Colon cancer | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |

| | | | |
|---|----------------|----------------|----------------|
| B-cell lymphoma | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 22 (4.55%) | 0 / 86 (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 |
| Burkitt's lymphoma | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Cholesteatoma | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Laryngeal cancer recurrent | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Lung carcinoma cell type unspecified recurrent | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Lung neoplasm | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Multiple myeloma | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Myelodysplastic syndrome | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuroendocrine carcinoma of the skin | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Small cell lung cancer stage unspecified | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Thyroid cancer | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Endometrial cancer | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to peritoneum | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Non-small cell lung cancer | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Ovarian neoplasm | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| Hypertension | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Aortic stenosis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 2 / 86 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Carotid artery stent insertion | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| General disorders and administration | | | |

| | | | |
|---|----------------|----------------|----------------|
| site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device failure | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Hernia obstructive | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Death | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Sudden death | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| 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 failure | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 2 / 86 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Investigations | | | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| International normalised ratio increased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 creatinine increased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 22 (4.55%) | 0 / 86 (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 | | | |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Cervical vertebral fracture | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Concussion | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 22 (0.00%) | 0 / 86 (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 | 0 / 16 (0.00%) | 1 / 22 (4.55%) | 0 / 86 (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 |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laceration | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Ligament rupture | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Multiple injuries | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Overdose | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic fracture | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Perirenal haematoma | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Renal haematoma | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal fracture | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Clavicle fracture | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toxicity to various agents | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Transfusion reaction | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 22 (4.55%) | 0 / 86 (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 haemorrhage | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 2 / 86 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 2 / 86 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina unstable | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 2 / 86 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure acute | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 2 / 86 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Extrasystoles | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Hypertensive heart disease | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Myocardial ischaemia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Sinus arrhythmia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Atrioventricular block second degree | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiogenic shock | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Mitral valve disease | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Hypoglycaemic coma | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Hypotonia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Orthostatic intolerance | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Vertebrobasilar insufficiency | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular insufficiency | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 22 (4.55%) | 0 / 86 (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 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Guillain-Barre syndrome | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrogenic anaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Pancytopenia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Haemorrhagic anaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 2 / 86 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenal ulcer | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Duodenitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Enterocolitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Gastric ulcer | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 2 / 86 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Pancreatic disorder | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Umbilical hernia, obstructive | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Colonic polyp | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 22 (4.55%) | 0 / 86 (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 |
| Inguinal hernia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Melaena | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 22 (4.55%) | 0 / 86 (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 | | | |
| Diabetic ulcer | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Drug eruption | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Pemphigoid | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Rash | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Renal and urinary disorders | | | |
| Renal failure chronic | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 22 (0.00%) | 3 / 86 (3.49%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Azotaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 2 / 86 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis glandularis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal artery stenosis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Endocrine disorders | | | |
| Hyperparathyroidism primary | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Osteoporotic fracture | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 22 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 5 / 86 (5.81%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Infective exacerbation of chronic obstructive airways disease | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abscess | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |

| | | | |
|---|----------------|----------------|----------------|
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Endophthalmitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Infected skin ulcer | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Staphylococcal sepsis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Wound abscess | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Wound infection staphylococcal | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Atypical pneumonia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Lobar pneumonia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia staphylococcal | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 22 (4.55%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Diabetic foot | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Diabetic ketoacidosis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Fluid overload | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Fluid retention | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 2 / 86 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gout | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (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 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|--|--|
| Serious adverse events | Period 3: Additional or Alternative Anaemia Management Only | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 13 / 61 (21.31%) | | |
| number of deaths (all causes) | 5 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Colon cancer | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| B-cell lymphoma | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Basal cell carcinoma | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Burkitt's lymphoma | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cholesteatoma | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Laryngeal cancer recurrent | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lung carcinoma cell type unspecified recurrent | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lung neoplasm | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Multiple myeloma | | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myelodysplastic syndrome | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neuroendocrine carcinoma of the skin | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Small cell lung cancer stage unspecified | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Thyroid cancer | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Endometrial cancer | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Metastases to peritoneum | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Non-small cell lung cancer | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ovarian neoplasm | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 61 (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 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aortic stenosis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhage | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 61 (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 / 61 (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 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |

| | | | |
|--|----------------|--|--|
| Carotid artery stent insertion | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Device failure | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hernia obstructive | | | |
| subjects affected / exposed | 0 / 61 (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 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Death | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sudden death | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 61 (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 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Acute pulmonary oedema | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory distresss | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 61 (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 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cervical vertebral fracture | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|----------------|--|--|--|
| Concussion | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Femur fracture | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Humerus fracture | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Laceration | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ligament rupture | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Multiple injuries | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Overdose | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pelvic fracture | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Perirenal haematoma | | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Renal haematoma | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rib fracture | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Spinal fracture | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Upper limb fracture | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Clavicle fracture | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Toxicity to various agents | | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Transfusion reaction | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Femoral neck fracture | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arteriovenous fistula site haemorrhage | | | |
| subjects affected / exposed | 0 / 61 (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 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 61 (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 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Extrasystoles | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertensive heart disease | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Left ventricular dysfunction | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myocardial ischaemia | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sinus arrhythmia | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrioventricular block second degree | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac failure chronic | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiogenic shock | | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Mitral valve disease | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pericardial effusion | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pericarditis | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoglycaemic coma | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotonia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Orthostatic intolerance | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vertebrobasilar insufficiency | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebrovascular insufficiency | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Guillain-Barre syndrome | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephrogenic anaemia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhagic anaemia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Duodenal ulcer | | | |
| subjects affected / exposed | 0 / 61 (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 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Duodenitis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enterocolitis | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastric ulcer | | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal haemorrhage | | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haematemesis | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pancreatic disorder | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pancreatitis | | | | |
| subjects affected / exposed | 0 / 61 (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 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Colonic polyp | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemorrhoids | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Melaena | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Diabetic ulcer | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug eruption | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pemphigoid | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rash | | | |
| subjects affected / exposed | 0 / 61 (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 | 3 / 61 (4.92%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Azotaemia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cystitis glandularis | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal artery stenosis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Hyperparathyroidism primary | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|----------------|--|--|--|
| Osteoarthritis | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rheumatoid arthritis | | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Osteoporotic fracture | | | | |
| subjects affected / exposed | 0 / 61 (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 / 61 (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 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infective exacerbation of chronic obstructive airways disease | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pyelonephritis | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sepsis | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

| | | | | |
|---|----------------|--|--|--|
| Abscess | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bacteraemia | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bronchopneumonia | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cellulitis | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cystitis | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Endophthalmitis | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infected skin ulcer | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory tract infection | | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed | 2 / 61 (3.28%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Staphylococcal sepsis | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Upper respiratory tract infection | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urosepsis | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Viral upper respiratory tract infection | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Wound abscess | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Wound infection staphylococcal | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atypical pneumonia | | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastroenteritis | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lobar pneumonia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia staphylococcal | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetic foot | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dehydration | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fluid overload | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fluid retention | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gout | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |

Frequency threshold for reporting non-serious adverse events: 3 %

| Non-serious adverse events | Period 2: Arm A | Period 2: Arm B | Period 2: Arm C |
|---|-------------------------|-------------------------|------------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 122 / 154 (79.22%) | 125 / 150 (83.33%) | 248 / 312 (79.49%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) Basal cell carcinoma subjects affected / exposed occurrences (all) | 3 / 154 (1.95%) 3 | 0 / 150 (0.00%) 0 | 0 / 312 (0.00%) 0 |
| Endocrine neoplasm subjects affected / exposed occurrences (all) | 0 / 154 (0.00%) 0 | 0 / 150 (0.00%) 0 | 0 / 312 (0.00%) 0 |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 20 / 154 (12.99%) 22 | 14 / 150 (9.33%) 17 | 29 / 312 (9.29%) 31 |
| Hypotension subjects affected / exposed occurrences (all) | 8 / 154 (5.19%) 11 | 4 / 150 (2.67%) 5 | 5 / 312 (1.60%) 5 |
| Haemorrhage subjects affected / exposed occurrences (all) | 0 / 154 (0.00%) 0 | 0 / 150 (0.00%) 0 | 0 / 312 (0.00%) 0 |
| General disorders and administration site conditions Oedema peripheral subjects affected / exposed occurrences (all) | 21 / 154 (13.64%) 26 | 21 / 150 (14.00%) 22 | 29 / 312 (9.29%) 36 |
| Fatigue subjects affected / exposed occurrences (all) | 1 / 154 (0.65%) 1 | 6 / 150 (4.00%) 6 | 14 / 312 (4.49%) 15 |
| Asthenia subjects affected / exposed occurrences (all) | 3 / 154 (1.95%) 3 | 2 / 150 (1.33%) 2 | 6 / 312 (1.92%) 6 |
| Chest pain subjects affected / exposed occurrences (all) | 4 / 154 (2.60%) 4 | 0 / 150 (0.00%) 0 | 1 / 312 (0.32%) 1 |
| Oedema subjects affected / exposed occurrences (all) | 3 / 154 (1.95%) 4 | 2 / 150 (1.33%) 4 | 4 / 312 (1.28%) 4 |

| | | | |
|---|----------------------|------------------------|------------------------|
| Influenza like illness subjects affected / exposed occurrences (all) | 0 / 154 (0.00%) 0 | 2 / 150 (1.33%) 2 | 2 / 312 (0.64%) 3 |
| Medical device complication subjects affected / exposed occurrences (all) | 0 / 154 (0.00%) 0 | 0 / 150 (0.00%) 0 | 0 / 312 (0.00%) 0 |
| Reproductive system and breast disorders Breast pain subjects affected / exposed occurrences (all) | 0 / 154 (0.00%) 0 | 0 / 150 (0.00%) 0 | 0 / 312 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) | 7 / 154 (4.55%) 8 | 11 / 150 (7.33%) 11 | 11 / 312 (3.53%) 11 |
| Cough subjects affected / exposed occurrences (all) | 4 / 154 (2.60%) 5 | 6 / 150 (4.00%) 6 | 9 / 312 (2.88%) 9 |
| Rales subjects affected / exposed occurrences (all) | 2 / 154 (1.30%) 2 | 3 / 150 (2.00%) 3 | 5 / 312 (1.60%) 5 |
| Psychiatric disorders Sleep disorder subjects affected / exposed occurrences (all) | 1 / 154 (0.65%) 1 | 1 / 150 (0.67%) 1 | 2 / 312 (0.64%) 2 |
| Investigations Blood pressure increased subjects affected / exposed occurrences (all) | 3 / 154 (1.95%) 4 | 0 / 150 (0.00%) 0 | 5 / 312 (1.60%) 7 |
| Blood glucose increased subjects affected / exposed occurrences (all) | 1 / 154 (0.65%) 1 | 0 / 150 (0.00%) 0 | 4 / 312 (1.28%) 4 |
| Blood parathyroid hormone increased subjects affected / exposed occurrences (all) | 1 / 154 (0.65%) 2 | 1 / 150 (0.67%) 1 | 1 / 312 (0.32%) 1 |
| Blood urea increased | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 312 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cardiac murmur | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 1 / 312 (0.32%) |
| occurrences (all) | 0 | 1 | 1 |
| Glomerular filtration rate decreased | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 1 / 150 (0.67%) | 2 / 312 (0.64%) |
| occurrences (all) | 1 | 1 | 2 |
| Heart rate increased | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 1 / 150 (0.67%) | 1 / 312 (0.32%) |
| occurrences (all) | 1 | 1 | 1 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 4 / 154 (2.60%) | 6 / 150 (4.00%) | 6 / 312 (1.92%) |
| occurrences (all) | 4 | 7 | 6 |
| Fall | | | |
| subjects affected / exposed | 3 / 154 (1.95%) | 1 / 150 (0.67%) | 3 / 312 (0.96%) |
| occurrences (all) | 3 | 1 | 3 |
| Excoriation | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 2 / 150 (1.33%) | 2 / 312 (0.64%) |
| occurrences (all) | 0 | 2 | 2 |
| Joint dislocation | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle strain | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences (all) | 2 | 0 | 1 |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 3 / 154 (1.95%) | 5 / 150 (3.33%) | 2 / 312 (0.64%) |
| occurrences (all) | 3 | 6 | 2 |
| Atrial fibrillation | | | |

| | | | |
|---|-----------------------|------------------------|----------------------|
| subjects affected / exposed occurrences (all) | 1 / 154 (0.65%) 1 | 0 / 150 (0.00%) 0 | 3 / 312 (0.96%) 3 |
| Cardiac failure subjects affected / exposed occurrences (all) | 0 / 154 (0.00%) 0 | 0 / 150 (0.00%) 0 | 4 / 312 (1.28%) 4 |
| Tachyarrhythmia subjects affected / exposed occurrences (all) | 0 / 154 (0.00%) 0 | 0 / 150 (0.00%) 0 | 0 / 312 (0.00%) 0 |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 9 / 154 (5.84%) 10 | 8 / 150 (5.33%) 9 | 7 / 312 (2.24%) 8 |
| Headache subjects affected / exposed occurrences (all) | 6 / 154 (3.90%) 7 | 10 / 150 (6.67%) 12 | 7 / 312 (2.24%) 8 |
| Convulsion subjects affected / exposed occurrences (all) | 0 / 154 (0.00%) 0 | 0 / 150 (0.00%) 0 | 1 / 312 (0.32%) 1 |
| Guillain-Barre syndrome subjects affected / exposed occurrences (all) | 0 / 154 (0.00%) 0 | 0 / 150 (0.00%) 0 | 0 / 312 (0.00%) 0 |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 6 / 154 (3.90%) 6 | 6 / 150 (4.00%) 6 | 9 / 312 (2.88%) 9 |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 4 / 154 (2.60%) 4 | 5 / 150 (3.33%) 5 | 4 / 312 (1.28%) 5 |
| Eye disorders Eyelid oedema subjects affected / exposed occurrences (all) | 0 / 154 (0.00%) 0 | 0 / 150 (0.00%) 0 | 0 / 312 (0.00%) 0 |
| Scleral haemorrhage subjects affected / exposed occurrences (all) | 0 / 154 (0.00%) 0 | 0 / 150 (0.00%) 0 | 0 / 312 (0.00%) 0 |
| Gastrointestinal disorders | | | |

| | | | |
|--|------------------|------------------|-------------------|
| Diarrhoea | | | |
| subjects affected / exposed | 15 / 154 (9.74%) | 10 / 150 (6.67%) | 45 / 312 (14.42%) |
| occurrences (all) | 19 | 12 | 49 |
| Constipation | | | |
| subjects affected / exposed | 2 / 154 (1.30%) | 5 / 150 (3.33%) | 37 / 312 (11.86%) |
| occurrences (all) | 2 | 5 | 41 |
| Nausea | | | |
| subjects affected / exposed | 9 / 154 (5.84%) | 7 / 150 (4.67%) | 15 / 312 (4.81%) |
| occurrences (all) | 11 | 7 | 16 |
| Dyspepsia | | | |
| subjects affected / exposed | 2 / 154 (1.30%) | 2 / 150 (1.33%) | 17 / 312 (5.45%) |
| occurrences (all) | 2 | 2 | 17 |
| Vomiting | | | |
| subjects affected / exposed | 6 / 154 (3.90%) | 4 / 150 (2.67%) | 13 / 312 (4.17%) |
| occurrences (all) | 6 | 4 | 18 |
| Gastritis | | | |
| subjects affected / exposed | 2 / 154 (1.30%) | 1 / 150 (0.67%) | 4 / 312 (1.28%) |
| occurrences (all) | 2 | 1 | 4 |
| Gastritis haemorrhagic | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 1 / 150 (0.67%) | 2 / 312 (0.64%) |
| occurrences (all) | 1 | 1 | 2 |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 5 / 154 (3.25%) | 4 / 150 (2.67%) | 9 / 312 (2.88%) |
| occurrences (all) | 6 | 4 | 9 |
| Skin ulcer | | | |
| subjects affected / exposed | 2 / 154 (1.30%) | 1 / 150 (0.67%) | 4 / 312 (1.28%) |
| occurrences (all) | 4 | 1 | 4 |
| Dry skin | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 1 / 150 (0.67%) | 0 / 312 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Eczema | | | |

| | | | |
|---|------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 2 / 154 (1.30%) 3 | 1 / 150 (0.67%) 1 | 0 / 312 (0.00%) 0 |
| Scar subjects affected / exposed occurrences (all) | 0 / 154 (0.00%) 0 | 0 / 150 (0.00%) 0 | 0 / 312 (0.00%) 0 |
| Renal and urinary disorders | | | |
| Renal failure subjects affected / exposed occurrences (all) | 1 / 154 (0.65%) 1 | 3 / 150 (2.00%) 3 | 5 / 312 (1.60%) 5 |
| Renal impairment subjects affected / exposed occurrences (all) | 3 / 154 (1.95%) 3 | 2 / 150 (1.33%) 2 | 4 / 312 (1.28%) 4 |
| Renal failure chronic subjects affected / exposed occurrences (all) | 3 / 154 (1.95%) 3 | 1 / 150 (0.67%) 1 | 3 / 312 (0.96%) 3 |
| Endocrine disorders | | | |
| Hyperparathyroidism secondary subjects affected / exposed occurrences (all) | 1 / 154 (0.65%) 1 | 1 / 150 (0.67%) 1 | 4 / 312 (1.28%) 4 |
| Hyperparathyroidism subjects affected / exposed occurrences (all) | 0 / 154 (0.00%) 0 | 2 / 150 (1.33%) 2 | 0 / 312 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain subjects affected / exposed occurrences (all) | 15 / 154 (9.74%) 15 | 11 / 150 (7.33%) 12 | 11 / 312 (3.53%) 12 |
| Arthralgia subjects affected / exposed occurrences (all) | 10 / 154 (6.49%) 14 | 7 / 150 (4.67%) 7 | 15 / 312 (4.81%) 17 |
| Pain in extremity subjects affected / exposed occurrences (all) | 2 / 154 (1.30%) 2 | 8 / 150 (5.33%) 8 | 15 / 312 (4.81%) 17 |
| Muscle spasms subjects affected / exposed occurrences (all) | 1 / 154 (0.65%) 1 | 7 / 150 (4.67%) 7 | 3 / 312 (0.96%) 3 |
| Musculoskeletal pain | | | |

| | | | |
|-----------------------------------|-------------------|------------------|------------------|
| subjects affected / exposed | 0 / 154 (0.00%) | 5 / 150 (3.33%) | 4 / 312 (1.28%) |
| occurrences (all) | 0 | 5 | 4 |
| Myalgia | | | |
| subjects affected / exposed | 2 / 154 (1.30%) | 1 / 150 (0.67%) | 3 / 312 (0.96%) |
| occurrences (all) | 2 | 2 | 3 |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 17 / 154 (11.04%) | 10 / 150 (6.67%) | 15 / 312 (4.81%) |
| occurrences (all) | 21 | 12 | 16 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 13 / 154 (8.44%) | 10 / 150 (6.67%) | 16 / 312 (5.13%) |
| occurrences (all) | 18 | 10 | 20 |
| Influenza | | | |
| subjects affected / exposed | 4 / 154 (2.60%) | 8 / 150 (5.33%) | 7 / 312 (2.24%) |
| occurrences (all) | 5 | 9 | 7 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 6 / 154 (3.90%) | 4 / 150 (2.67%) | 9 / 312 (2.88%) |
| occurrences (all) | 8 | 4 | 10 |
| Bronchitis | | | |
| subjects affected / exposed | 4 / 154 (2.60%) | 1 / 150 (0.67%) | 11 / 312 (3.53%) |
| occurrences (all) | 4 | 1 | 11 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 5 / 154 (3.25%) | 4 / 150 (2.67%) | 5 / 312 (1.60%) |
| occurrences (all) | 5 | 4 | 7 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 4 / 150 (2.67%) | 5 / 312 (1.60%) |
| occurrences (all) | 1 | 4 | 6 |
| Wound infection | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cellulitis | | | |
| subjects affected / exposed | 3 / 154 (1.95%) | 2 / 150 (1.33%) | 4 / 312 (1.28%) |
| occurrences (all) | 3 | 2 | 7 |
| Vulvitis | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 312 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|------------------------------------|-----------------|-----------------|-----------------|
| Metabolism and nutrition disorders | | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 5 / 154 (3.25%) | 7 / 150 (4.67%) | 6 / 312 (1.92%) |
| occurrences (all) | 6 | 8 | 6 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 7 / 154 (4.55%) | 4 / 150 (2.67%) | 7 / 312 (2.24%) |
| occurrences (all) | 14 | 4 | 8 |
| Hyperuricaemia | | | |
| subjects affected / exposed | 2 / 154 (1.30%) | 5 / 150 (3.33%) | 6 / 312 (1.92%) |
| occurrences (all) | 3 | 5 | 8 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 7 / 154 (4.55%) | 0 / 150 (0.00%) | 5 / 312 (1.60%) |
| occurrences (all) | 9 | 0 | 6 |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 1 / 150 (0.67%) | 4 / 312 (1.28%) |
| occurrences (all) | 1 | 1 | 4 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 1 / 312 (0.32%) |
| occurrences (all) | 0 | 0 | 1 |
| Hyperphosphataemia | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 3 / 312 (0.96%) |
| occurrences (all) | 0 | 0 | 3 |

| Non-serious adverse events | Period 3: Arm A | Period 3: Arm B | Period 3: Arm C |
|---|-------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 16 / 16 (100.00%) | 16 / 22 (72.73%) | 65 / 86 (75.58%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 22 (4.55%) | 0 / 86 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Endocrine neoplasm | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 22 (0.00%) | 0 / 86 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 2 / 22 (9.09%) | 7 / 86 (8.14%) |
| occurrences (all) | 2 | 2 | 8 |

| | | | |
|---|----------------------|---------------------|---------------------|
| Hypotension subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 22 (4.55%) 2 | 0 / 86 (0.00%) 0 |
| Haemorrhage subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 22 (4.55%) 1 | 0 / 86 (0.00%) 0 |
| General disorders and administration site conditions | | | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 2 / 16 (12.50%) 2 | 1 / 22 (4.55%) 1 | 5 / 86 (5.81%) 6 |
| Fatigue subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 22 (0.00%) 0 | 4 / 86 (4.65%) 4 |
| Asthenia subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 22 (4.55%) 1 | 2 / 86 (2.33%) 2 |
| Chest pain subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 22 (0.00%) 0 | 3 / 86 (3.49%) 3 |
| Oedema subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 22 (0.00%) 0 | 1 / 86 (1.16%) 1 |
| Influenza like illness subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 22 (4.55%) 1 | 0 / 86 (0.00%) 0 |
| Medical device complication subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 22 (0.00%) 0 | 0 / 86 (0.00%) 0 |
| Reproductive system and breast disorders | | | |
| Breast pain subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 22 (0.00%) 0 | 0 / 86 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 22 (0.00%) 0 | 2 / 86 (2.33%) 2 |
| Cough subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 22 (0.00%) 0 | 1 / 86 (1.16%) 1 |
| Rales subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 22 (0.00%) 0 | 3 / 86 (3.49%) 4 |
| Psychiatric disorders Sleep disorder subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 22 (0.00%) 0 | 1 / 86 (1.16%) 1 |
| Investigations Blood pressure increased subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 1 / 22 (4.55%) 1 | 0 / 86 (0.00%) 0 |
| Blood glucose increased subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 22 (4.55%) 1 | 0 / 86 (0.00%) 0 |
| Blood parathyroid hormone increased subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 22 (0.00%) 0 | 0 / 86 (0.00%) 0 |
| Blood urea increased subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 22 (4.55%) 1 | 0 / 86 (0.00%) 0 |
| Cardiac murmur subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 22 (0.00%) 0 | 0 / 86 (0.00%) 0 |
| Glomerular filtration rate decreased subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 22 (4.55%) 1 | 0 / 86 (0.00%) 0 |
| Heart rate increased subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 22 (4.55%) 1 | 0 / 86 (0.00%) 0 |
| Weight decreased | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 22 (0.00%) 0 | 0 / 86 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fall | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 2 / 22 (9.09%) | 1 / 86 (1.16%) |
| occurrences (all) | 1 | 2 | 1 |
| Excoriation | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 22 (4.55%) | 0 / 86 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 22 (0.00%) | 0 / 86 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Muscle strain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 22 (4.55%) | 0 / 86 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 2 / 86 (2.33%) |
| occurrences (all) | 0 | 0 | 5 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences (all) | 0 | 0 | 1 |
| Cardiac failure | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences (all) | 2 | 0 | 1 |
| Tachyarrhythmia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 22 (4.55%) | 0 / 86 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences (all) | 0 | 0 | 1 |
| Headache | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 22 (0.00%) 0 | 3 / 86 (3.49%) 5 |
| Convulsion subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 22 (0.00%) 0 | 0 / 86 (0.00%) 0 |
| Guillain-Barre syndrome subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 22 (0.00%) 0 | 0 / 86 (0.00%) 0 |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 22 (4.55%) 1 | 2 / 86 (2.33%) 2 |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 22 (0.00%) 0 | 0 / 86 (0.00%) 0 |
| Eye disorders Eyelid oedema subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 22 (4.55%) 1 | 0 / 86 (0.00%) 0 |
| Scleral haemorrhage subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 22 (0.00%) 0 | 0 / 86 (0.00%) 0 |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 2 / 22 (9.09%) 2 | 7 / 86 (8.14%) 7 |
| Constipation subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 22 (0.00%) 0 | 4 / 86 (4.65%) 4 |
| Nausea subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 22 (0.00%) 0 | 5 / 86 (5.81%) 5 |
| Dyspepsia subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 22 (0.00%) 0 | 0 / 86 (0.00%) 0 |
| Vomiting | | | |

| | | | |
|--|----------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 22 (0.00%) 0 | 2 / 86 (2.33%) 3 |
| Gastritis subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 22 (0.00%) 0 | 0 / 86 (0.00%) 0 |
| Gastritis haemorrhagic subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 22 (4.55%) 1 | 0 / 86 (0.00%) 0 |
| Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 22 (0.00%) 0 | 0 / 86 (0.00%) 0 |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 22 (0.00%) 0 | 2 / 86 (2.33%) 2 |
| Skin ulcer subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 22 (0.00%) 0 | 4 / 86 (4.65%) 5 |
| Dry skin subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 22 (0.00%) 0 | 0 / 86 (0.00%) 0 |
| Eczema subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 22 (4.55%) 1 | 0 / 86 (0.00%) 0 |
| Scar subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 22 (4.55%) 1 | 0 / 86 (0.00%) 0 |
| Renal and urinary disorders | | | |
| Renal failure subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 22 (4.55%) 1 | 2 / 86 (2.33%) 2 |
| Renal impairment subjects affected / exposed occurrences (all) | 2 / 16 (12.50%) 2 | 0 / 22 (0.00%) 0 | 1 / 86 (1.16%) 1 |
| Renal failure chronic | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 22 (0.00%) 0 | 3 / 86 (3.49%) 3 |
| Endocrine disorders | | | |
| Hyperparathyroidism secondary subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 1 / 22 (4.55%) 1 | 0 / 86 (0.00%) 0 |
| Hyperparathyroidism subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 22 (0.00%) 0 | 1 / 86 (1.16%) 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 1 / 22 (4.55%) 1 | 2 / 86 (2.33%) 2 |
| Arthralgia subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 2 / 22 (9.09%) 5 | 5 / 86 (5.81%) 6 |
| Pain in extremity subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 22 (0.00%) 0 | 0 / 86 (0.00%) 0 |
| Muscle spasms subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 22 (0.00%) 0 | 2 / 86 (2.33%) 2 |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 22 (0.00%) 0 | 1 / 86 (1.16%) 1 |
| Myalgia subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 22 (4.55%) 1 | 2 / 86 (2.33%) 2 |
| Infections and infestations | | | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 2 / 22 (9.09%) 2 | 2 / 86 (2.33%) 2 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 22 (0.00%) 0 | 2 / 86 (2.33%) 2 |
| Influenza | | | |

| | | | |
|------------------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 2 / 86 (2.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Bronchitis | | | |
| subjects affected / exposed | 3 / 16 (18.75%) | 0 / 22 (0.00%) | 0 / 86 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 3 / 86 (3.49%) |
| occurrences (all) | 0 | 0 | 4 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 2 / 22 (9.09%) | 3 / 86 (3.49%) |
| occurrences (all) | 0 | 2 | 4 |
| Wound infection | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 22 (0.00%) | 2 / 86 (2.33%) |
| occurrences (all) | 1 | 0 | 2 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 22 (4.55%) | 1 / 86 (1.16%) |
| occurrences (all) | 0 | 1 | 1 |
| Vulvitis | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 22 (0.00%) | 0 / 86 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 22 (0.00%) | 2 / 86 (2.33%) |
| occurrences (all) | 3 | 0 | 2 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 0 / 86 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperuricaemia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences (all) | 1 | 0 | 1 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 22 (0.00%) | 1 / 86 (1.16%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|--|---------------------|---------------------|---------------------|
| Decreased appetite subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 22 (0.00%) 0 | 3 / 86 (3.49%) 3 |
| Diabetes mellitus subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 22 (4.55%) 1 | 1 / 86 (1.16%) 1 |
| Hyperphosphataemia subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 22 (4.55%) 1 | 0 / 86 (0.00%) 0 |

| | | | |
|--|--|--|--|
| Non-serious adverse events | Period 3: Additional or Alternative Anaemia Management Only | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 27 / 61 (44.26%) | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) Basal cell carcinoma subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | | |
| Endocrine neoplasm subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | | |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | | |
| Hypotension subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | | |
| Haemorrhage subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | | |
| General disorders and administration site conditions Oedema peripheral subjects affected / exposed occurrences (all) | 4 / 61 (6.56%) 4 | | |
| Fatigue | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences (all) | 2 | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oedema | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Medical device complication | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Reproductive system and breast disorders | | | |
| Breast pain | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences (all) | 1 | | |
| Cough | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rales | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Psychiatric disorders | | | |
| Sleep disorder | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Investigations | | | |

| | | | |
|--|---------------------|--|--|
| Blood pressure increased subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | | |
| Blood glucose increased subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | | |
| Blood parathyroid hormone increased subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | | |
| Blood urea increased subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | | |
| Cardiac murmur subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | | |
| Glomerular filtration rate decreased subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | | |
| Heart rate increased subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | | |
| Weight decreased subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | | |
| Injury, poisoning and procedural complications | | | |
| Contusion subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | | |
| Fall subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | | |
| Excoriation subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | | |
| Joint dislocation | | | |

| | | | |
|--------------------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Muscle strain | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | | |
| occurrences (all) | 2 | | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tachyarrhythmia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences (all) | 1 | | |
| Headache | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences (all) | 1 | | |
| Convulsion | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Guillain-Barre syndrome | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences (all) | 1 | | |
| Ear and labyrinth disorders | | | |

| | | | |
|---|--|--|--|
| Vertigo subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | | |
| Eye disorders Eyelid oedema subjects affected / exposed occurrences (all) Scleral haemorrhage subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 0 / 61 (0.00%) 0 | | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Gastritis subjects affected / exposed occurrences (all) Gastritis haemorrhagic subjects affected / exposed occurrences (all) Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 1 / 61 (1.64%) 1 0 / 61 (0.00%) 0 0 / 61 (0.00%) 0 0 / 61 (0.00%) 0 1 / 61 (1.64%) 1 0 / 61 (0.00%) 0 0 / 61 (0.00%) 0 | | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|----------------|--|--|
| Pruritus | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dry skin | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eczema | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Scar | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | | |
| occurrences (all) | 2 | | |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences (all) | 1 | | |
| Renal failure chronic | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Endocrine disorders | | | |
| Hyperparathyroidism secondary | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences (all) | 1 | | |
| Hyperparathyroidism | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences (all) | 1 | | |

| | | | |
|-----------------------------------|----------------|--|--|
| Arthralgia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences (all) | 1 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | | |
| occurrences (all) | 2 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | | |
| occurrences (all) | 2 | | |
| Influenza | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences (all) | 1 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences (all) | 1 | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastroenteritis | | | |

| | | | |
|------------------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Wound infection | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vulvitis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Metabolism and nutrition disorders | | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hyperphosphataemia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences (all) | 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 08 July 2010 | <p>Amendment 1:</p> <p>Included the following major changes:•ESA or additional or alternative anaemia management use not permitted in subjects with Hb ≥ 10 g/dL. •More specific details to state no change of iron product from the treatment assigned by randomisation (when Hb > 10 g/dL) was permitted except if "subject was not able to comply or tolerate the randomised treatment arm.". •Statement to advise that "After the 8-week period, subjects with 2 consecutive Hb values < 10 g/dL (and without an Hb increase of ≥ 0.5 g/dL rise in last 4 weeks) were considered to have met the primary endpoint but should continue on assigned treatment per protocol". •Within the oral arm, "Dosing may be suspended if serum ferritin ≥ 200 mcg/L and should be resumed if values fall below < 100 mcg/L". •Inclusion criterion 3: Updated to include clarification on 'previous eGFR loss'. •Inclusion criterion 4: Amended to permit a screening Hb average between 9 and 11 g/dL. The wording was also clarified. •Inclusion criterion 6: Amended to define ESA naïve subjects. •Inclusion criterion 7: Amended to ensure that the pregnancy test was completed 4 weeks prior to randomisation rather than screening. •Exclusion criterion 5: Amended to define the term 'active malignancy'. •Exclusion criterion 11: Amended to permit subjects on low doses of oral iron (or oral iron from multivitamin supplements) permitted for inclusion. •Exclusion criterion 12: Amended to define limited immunosuppressive therapies, i.e., those "that may lead to anaemia, such as cyclophosphamide, azathioprine, mycophenolate mofetil, etc. Steroid therapy was permitted". This clarified questions from several participating sites. •Exclusion criterion 13: Updated to state explicitly that renal dialysis refers to subjects "Currently requiring renal dialysis". •Exclusion criterion 17: More explicit in definition of poorly controlled hypertension – from $> 160/100$ mmHg to > 60 mmHg systolic pressure or > 100 mmHg diastolic pressure. •Dosing time updated for FCM arms.</p> |
| 16 December 2010 | <p>Amendment 2:</p> <p>Included the following major changes:•Inclusion criterion 4: Amended from "Screening Hb between 9 and 11 g/dL based on an average of at least 2 Hb readings taken in the 4 weeks prior to randomisation with a minimum of 2 days and a maximum of 4 weeks between values (with no single value ≥ 12 g/dL). At least 1 value had to be < 10.5 g/dL" to "Hb between 9 and 11 g/dL within 4 weeks of randomisation. A value taken as part of routine medical care could be used". •Inclusion criterion 5: Amended from "Screening ferritin < 100 mcg/L" to "Serum ferritin < 100 mcg/L or < 200 mcg/L with TSAT $< 20\%$ within 4 weeks of randomisation. Measurements taken as part of routine medical care may be used". The Arm B treatment section was also amended from "Day 0: 200 mg iron as FCM" to "Day 0: 200 mg iron as FCM. No dose administered if ferritin value is ≥ 100 mcg/L". •Inclusion criterion 7: Amended from "Females of childbearing potential must have a negative pregnancy test at within 4 weeks of randomisation" to "Females of childbearing potential must have a negative pregnancy test prior to randomisation". •Exclusion criterion 11: Amended from "Oral iron therapy at doses > 100 mg/day in previous 4 weeks prior to randomisation. Upon randomisation the oral iron therapy must be discontinued. Ongoing use of multivitamins containing iron are permitted" to "Oral iron therapy at doses > 100 mg/day in previous 1 week prior to randomisation and/or subjects who have been continuously treated with > 100 mg/day of oral iron for the last 3 months. Upon randomisation the oral iron therapy must be discontinued. Ongoing use of multivitamins containing iron was permitted". Exclusion criterion 3 (no changes in this amendment) excludes subjects that are intolerant to oral iron due to GI distress. •Schedule of Events: the following text added to footnote number 5 "Values collected as part of routine medical practice and prior to consent may be used to confirm eligibility". •Minor clarifying wording.</p> |

| | |
|-------------------|--|
| 01 September 2011 | <p>Amendment 3:</p> <p>Included the following major changes:</p> <ul style="list-style-type: none"> •Inclusion criterion 3: To provide more explicit instructions for obtaining the right number of eGFR measurements, their values and time intervals for obtaining them of eGFR measurements required for subjects' eligibility in the study. •Inclusion criterion 4: Language clarification for accepting of a(ny) single Hb value between 9 to 11 g/dL obtained as part of routine medical practice or study specific screening/randomisation visit procedures obtained within 4 weeks prior to the date of randomisation. •Inclusion criterion 5: Clarification for accepting a(ny) single serum ferritin value of <100 mcg/mL or <200 mcg/mL with TSAT of <20% that was obtained either as part of routine medical practice or study specific screening/randomisation visit procedures but within 4 weeks prior to the date of randomisation. •Inclusion criterion 7: Administrative change to clarify how pregnancy tests are accepted as medically valid in medical practice. •Exclusion criterion 8: Further guidance and clarification for using results from various serology tests. •Exclusion criterion 10: To clarify that IV iron administration or blood transfusions were prohibited at any time from 30 days prior to screening until randomisation. •Exclusion criterion 11: To further clarify language of oral iron therapy discontinuation in relation to randomisation time. •Procedures section: To clarify acceptance of central laboratory values when more convenient than local laboratory values. •Sample size section: Changed from "approximately 1,016 subjects." to "...a maximum of 1,016 subjects." •Statistical methods section: To calculate and confirm the study sample size based on the main comparison (FCM high-dose versus oral iron) within the primary endpoint and to clarify the recruitment end date if there was a reduced sample size. •Schema: Text addition of "last investigational product kit handed out at Week 48" at the end of Ferinject sentence. •Minor clarifying wording. |
| 14 August 2012 | <p>Amendment 4:</p> <p>Included the following major changes:</p> <ul style="list-style-type: none"> •Study design: Current protocol wording stipulated "2 consecutive Hb values <10 g/dL (and without an Hb increase of ≥ 0.5 g/dL rise in the last 4 weeks). •Laboratory procedures: Laboratory assessments could be performed before the study visit so the laboratory results were available at the time of visit. •Risks and precautions: Section 8 of the protocol was amended in accordance with the updated version of the Company Core Data Sheet from 12 December 2011, the revised Summary of Product Characteristics, approved by the Medicines and Healthcare products Regulatory Agency on 29 September 2011, and the changes implemented in the latest version of the product's Investigator's Brochure (Version 14.0, dated 14 March 2012). •There were other minor editorial changes to improve consistency and correct minor typographical errors in the overall protocol. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------------------|--|--------------|
| 31 December 2011 | Because of slow recruitment, the Sponsor decided to stop recruitment in December 2011 after sufficient subjects had been recruited to make the primary comparison between FCM high-dose and oral iron. | - |

Notes:

Limitations and caveats

None reported