



Clinical trial results:

A Phase 3, Randomized, Open-Label, Active-Controlled Study to Evaluate the Efficacy and Safety of Roxadustat in the Maintenance Treatment of Anemia in End Stage Renal Disease Patients on Stable Dialysis

Summary

| | |
|--------------------------|----------------------------------|
| EudraCT number | 2013-001497-16 |
| Trial protocol | GB DE IT BE PT HU ES BG HR SK CZ |
| Global end of trial date | 06 July 2018 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 |
| This version publication date | 18 July 2019 |
| First version publication date | 18 July 2019 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | 1517-CL-0613 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02278341 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Astellas Pharma Europe B.V. |
| Sponsor organisation address | Sylviusweg 62, Leiden, Netherlands, 2333 BE |
| Public contact | Clinical Trial Disclosure, Astellas Pharma Europe B.V., 31 71 5455 050, astellas.resultsdisclosure@astellas.com |
| Scientific contact | Clinical Trial Disclosure, Astellas Pharma Europe B.V., 31 71 5455 050, astellas.resultsdisclosure@astellas.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 | 06 July 2018 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 July 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the efficacy of roxadustat compared to epoetin alfa and darbepoetin alfa in the maintenance treatment of anemia in end stage renal disease (ESRD) participants on stable dialysis.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy:

Oral iron treatment was recommended for supplementation to support erythropoiesis and as first-line treatment for iron deficiency, unless participant was intolerant to this treatment. For participants receiving roxadustat the recommended daily dose was 200 mg of elemental iron. Participants were advised to take roxadustat at least 1 hour before or 1 hour after oral iron. Intravenous iron supplementation for participants receiving roxadustat was allowed if all of the following criteria were met: The participant's Hb level had not responded adequately to roxadustat following two consecutive dose increases or reached the maximum dose limit, and participant's ferritin was < 100 ng/mL (< 220 pmol/L) or TSAT < 20%, or the participant was intolerant of oral iron therapy. For participants treated with epoetin alfa or darbepoetin alfa, IV iron supplementation was given according to standard of care.

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 21 November 2014 |
| 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 | Belgium: 31 |
| Country: Number of subjects enrolled | Bulgaria: 156 |
| Country: Number of subjects enrolled | Croatia: 59 |
| Country: Number of subjects enrolled | Czech Republic: 16 |
| Country: Number of subjects enrolled | France: 12 |
| Country: Number of subjects enrolled | Georgia: 6 |
| Country: Number of subjects enrolled | Germany: 35 |
| Country: Number of subjects enrolled | Hungary: 136 |
| Country: Number of subjects enrolled | Italy: 40 |
| Country: Number of subjects enrolled | Poland: 29 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Portugal: 17 |
| Country: Number of subjects enrolled | Romania: 40 |
| Country: Number of subjects enrolled | Russian Federation: 98 |
| Country: Number of subjects enrolled | Serbia: 86 |
| Country: Number of subjects enrolled | Slovakia: 32 |
| Country: Number of subjects enrolled | Spain: 29 |
| Country: Number of subjects enrolled | United Kingdom: 14 |
| Worldwide total number of subjects | 836 |
| EEA total number of subjects | 646 |

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) | 452 |
| From 65 to 84 years | 361 |
| 85 years and over | 23 |

Subject disposition

Recruitment

Recruitment details:

Study population consisted of participants with end-stage renal disease (ESRD) who were on stable hemodialysis (HD) or peritoneal dialysis (PD, and were also on stable treatment with epoetin (i.e. epoetin alfa, beta, theta, zeta, delta or omega) or darbepoetin alfa for anemia.

Pre-assignment

Screening details:

Participants were randomized in a 1:1 ratio, receiving roxadustat or ESA (epoetin alfa or darbepoetin alfa). Randomization was stratified by 5 factors: previous ESA treatment, region, history of cardiovascular, cerebrovascular or thromboembolic diseases, average weekly ESA dose 4 weeks prior to randomization and the screening hemoglobin (Hb) value.

Period 1

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

Arms

| | |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Roxadustat |

Arm description:

Participants received roxadustat three times a week (TIW) for at least 52 weeks up to a maximum of 104 weeks. Treatment dosage was adjusted according to the pre-specified rule of keeping the participant's Hb levels between 10.0 to 12.0 g/dL.

| | |
|--|------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Roxadustat |
| Investigational medicinal product code | ASP1517, FG-4592 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received initial dose of roxadustat in doses of 100 mg, 150 mg or 200 mg, according to the average weekly dose of epoetin or darbepoetin alfa prior to randomization. Participants' roxadustat dosage was adjusted every 4 weeks to maintain Hb level within the target range 10.0 to 12.0 g/dL. Dose adjustment steps were as follows: 20, 40, 50, 70, 100, 150, 200, 250, 300, and 400 mg. Oral iron treatment of 200 mg was allowed for supplementation to support erythropoiesis. Treatment with intravenous iron was allowed only if certain protocol criteria were met.

| | |
|------------------|--|
| Arm title | ESA (Erythropoiesis-Stimulating Agent) |
|------------------|--|

Arm description:

Participants received epoetin alfa once weekly, twice weekly or TIW and darbepoetin alfa once a week or once every other week. Participants were treated for at least 52 weeks up to a maximum of 104 weeks. Treatment dosage was adjusted according to the pre-specified rule of keeping the participant's Hb levels between 10.0 to 12.0 g/dL. Participants were not allowed to switch from epoetin alfa to darbepoetin alfa or vice versa.

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | Epoetin alfa |
| Investigational medicinal product code | |
| Other name | Eprex® |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Intravenous use, Subcutaneous use |

Dosage and administration details:

Participants received epoetin alfa once a week, twice a week, or three times a week (TIW). Epoetin alfa

dosage was adjusted to maintain Hb level within the target range. Dosing of epoetin alfa was per UK SmPC of Eprex®. Participants received IV iron supplementation according to the standard of care.

| | |
|--|--|
| Investigational medicinal product name | Darbepoetin alfa |
| Investigational medicinal product code | |
| Other name | Aranesp® |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Intravenous use, Subcutaneous use |

Dosage and administration details:

Participants received darbepoetin alfa once a week or once every other week. Darbepoetin alfa dosage was adjusted to maintain Hb level within the target range. Dosing of darbepoetin alfa was per EU SmPC of Aranesp®. Participants received IV iron supplementation according to the standard of care.

| Number of subjects in period 1 | Roxadustat | ESA (Erythropoiesis-Stimulating Agent) |
|--|------------|--|
| Started | 415 | 421 |
| Received Treatment | 414 | 420 |
| Completed | 297 | 329 |
| Not completed | 118 | 92 |
| Randomized but never received study drug | 1 | 1 |
| Physician decision | 1 | 1 |
| Adverse event, non-fatal | 3 | - |
| Death | 68 | 56 |
| Micellaneous | 15 | 14 |
| Withdrawal by Subject | 30 | 19 |
| Lost to follow-up | - | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | Roxadustat |
|-----------------------|------------|

Reporting group description:

Participants received roxadustat three times a week (TIW) for at least 52 weeks up to a maximum of 104 weeks. Treatment dosage was adjusted according to the pre-specified rule of keeping the participant's Hb levels between 10.0 to 12.0 g/dL.

| | |
|-----------------------|--|
| Reporting group title | ESA (Erythropoiesis-Stimulating Agent) |
|-----------------------|--|

Reporting group description:

Participants received epoetin alfa once weekly, twice weekly or TIW and darbepoetin alfa once a week or once every other week. Participants were treated for at least 52 weeks up to a maximum of 104 weeks. Treatment dosage was adjusted according to the pre-specified rule of keeping the participant's Hb levels between 10.0 to 12.0 g/dL. Participants were not allowed to switch from epoetin alfa to darbepoetin alfa or vice versa.

| Reporting group values | Roxadustat | ESA (Erythropoiesis-Stimulating Agent) | Total |
|------------------------|------------|--|-------|
| Number of subjects | 415 | 421 | 836 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|--|--------|--------|-----|
| Age continuous | | | |
| The analysis population was the All randomized population, which consisted of participants who were randomized into the study. | | | |
| Units: years | | | |
| arithmetic mean | 61 | 61.8 | |
| standard deviation | ± 13.8 | ± 13.4 | - |
| Gender categorical | | | |
| The analysis population was the All randomized population, which consisted of participants who were randomized into the study. | | | |
| Units: Subjects | | | |
| Male | 246 | 236 | 482 |
| Female | 169 | 185 | 354 |
| Race | | | |
| The analysis population was the All randomized, which consisted of participants who were randomized into the study. | | | |
| Units: Subjects | | | |
| WHITE | 405 | 408 | 813 |
| BLACK OR AFRICAN AMERICAN | 6 | 6 | 12 |
| ASIAN | 2 | 3 | 5 |
| OTHER | 2 | 4 | 6 |
| Baseline Hemoglobin (Hb) Value | | | |
| The analysis population was the All randomized, which consisted of participants who were randomized into the study. | | | |
| Units: Subjects | | | |
| ≤11.0 g/dL | 267 | 266 | 533 |
| >11.0 g/dL | 148 | 155 | 303 |
| Baseline Mean Hb | | | |
| Baseline Hb was defined as the mean of four latest central laboratory Hb values prior or on the same date as first study drug intake (pre-dose). The analysis population was the All randomized, which consisted of participants who were randomized into the study. | | | |

| | | | |
|--------------------|--------|--------|---|
| Units: g/dL | | | |
| arithmetic mean | 10.75 | 10.77 | |
| standard deviation | ± 0.62 | ± 0.62 | - |

End points

End points reporting groups

| | |
|---|--|
| Reporting group title | Roxadustat |
| Reporting group description: Participants received roxadustat three times a week (TIW) for at least 52 weeks up to a maximum of 104 weeks. Treatment dosage was adjusted according to the pre-specified rule of keeping the participant's Hb levels between 10.0 to 12.0 g/dL. | |
| Reporting group title | ESA (Erythropoiesis-Stimulating Agent) |
| Reporting group description: Participants received epoetin alfa once weekly, twice weekly or TIW and darbepoetin alfa once a week or once every other week. Participants were treated for at least 52 weeks up to a maximum of 104 weeks. Treatment dosage was adjusted according to the pre-specified rule of keeping the participant's Hb levels between 10.0 to 12.0 g/dL. Participants were not allowed to switch from epoetin alfa to darbepoetin alfa or vice versa. | |

Primary: Change From Baseline (BL) to the Average Hemoglobin (Hb) in Weeks 28-36 Without Rescue Therapy [EU (EMA)]

| | |
|---|---|
| End point title | Change From Baseline (BL) to the Average Hemoglobin (Hb) in Weeks 28-36 Without Rescue Therapy [EU (EMA)] |
| End point description: Baseline Hb was defined as the mean of four central laboratory Hb values: four latest Hb values prior or on the same date as the first study drug intake. For participants who did not have an available Hb value during the week 28-36 period, imputation rules were applied. For analyses without rescue therapy, participants who used rescue therapy after the initiation of rescue therapy were set to missing for 6 weeks from the start date of rescue therapy. If no Hb value was available, an imputation technique was used, with the mean of all available values from Day 1 to minimum (End of Efficacy Emergent Period) carried forward. The analysis population was the Per Protocol Set (PPS) which consisted of all Full Analysis Set (FAS) participants who did not meet any of exclusion criteria from the PPS. The FAS consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose valid Hb assessment. | |
| End point type | Primary |
| End point timeframe: Baseline and weeks 28 to 36 | |

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|--|------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 354 | 381 | | |
| Units: g/dL | | | | |
| least squares mean (confidence interval 95%) | 0.428 (0.350 to 0.506) | 0.193 (0.117 to 0.268) | | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

The model includes treatment arm, region, CV History, previous ESA treatment, visits and visit by treatment as categorical variables and baseline Hb and baseline Hb by visit as continuous variable.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 735 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[1] |
| P-value | < 0.001 ^[2] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.235 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.132 |
| upper limit | 0.339 |

Notes:

[1] - Non Inferiority, Margin = -0.75

[2] - p-value for non-inferiority test based on 1-sided significance level.

Primary: Change From BL to the Average Hb in Weeks 28 to 52 Regardless of Rescue Therapy [US (FDA)]

| | |
|-----------------|--|
| End point title | Change From BL to the Average Hb in Weeks 28 to 52 Regardless of Rescue Therapy [US (FDA)] |
|-----------------|--|

End point description:

Baseline Hb was defined as the mean of four central laboratory Hb values: four latest Hb values prior or on the same date as first study drug intake. Change from baseline to the average Hb are observed values. Missing hemoglobin data was imputed for each treatment relying on non-missing data from all participants within each treatment group using the Monte Carlo Markov Chain (MCMC) imputation model with treatment, baseline hemoglobin, randomization stratification factors and the available non missing hemoglobin for each scheduled week. The analysis population was the All Randomized, which consisted of participants who received at least one dose of study drug, and who had available data.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline and weeks 28 to 52

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|--|------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 420 | | |
| Units: g/dL | | | | |
| least squares mean (confidence interval 95%) | 0.363 (0.288 to 0.438) | 0.192 (0.121 to 0.262) | | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

The model includes treatment arm, region, CV History, previous ESA treatment as categorical variables and baseline Hb as continuous variable. Statistical analysis used was ANCOVA model with multiple imputations (MI). Missing hemoglobin data was imputed for each treatment relying on non-missing data from all participants within each treatment group using the MCMC imputation model.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[3] |
| P-value | < 0.001 ^[4] |
| Method | ANCOVA |
| Parameter estimate | LSM Difference |
| Point estimate | 0.171 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.082 |
| upper limit | 0.261 |

Notes:

[3] - Non-Inferiority, Margin = -0.75

[4] - p-value for non-inferiority test based on 1-sided significance level.

Secondary: Percentage of Participants with Hb Response During Weeks 28 to 36

| | |
|-----------------|---|
| End point title | Percentage of Participants with Hb Response During Weeks 28 to 36 |
|-----------------|---|

End point description:

Hb response during weeks 28–36, was defined as mean Hb from 10–12 g/dL without receiving rescue therapy in the 6 weeks prior to, or during, the evaluation period. The percentages and 95% CI were unadjusted, the exact method of Clopper-Pearson was used for 95% CI. The Efficacy Emergent Period was defined as the evaluation period from the Analysis date of first dose intake up to end of treatment (EOT) Visit or last non-missing Hb assessment (for participants who died during the treatment period). The analysis population was the PPS.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 28 to 36

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|-----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 386 | 397 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 84.2 (80.2 to 87.7) | 82.4 (78.3 to 86.0) | | |

Statistical analyses

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|-----------------------------------|------------------------|

Statistical analysis description:

A generalized linear model was used to estimate the difference in response rates between the arms, as an approximation for the Miettinen and Nurminen method, adjusting for following covariates: region, previous ESA treatment, cardiovascular history and baseline Hb as categorical variables.

| | |
|---|---|
| Comparison groups | ESA (Erythropoiesis-Stimulating Agent) v Roxadustat |
| Number of subjects included in analysis | 783 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[5] |
| P-value | < 0.05 ^[6] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Difference of Percentages |
| Point estimate | 2.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.9 |
| upper limit | 7.6 |

Notes:

[5] - Non-inferiority of roxadustat versus ESA (the non-inferiority margin for the difference between groups is -15%).

[6] - p-value for non-inferiority test based on 1-sided significance level

Secondary: Change From BL in Low Density Lipoprotein Cholesterol (LDL-C) to the Average LDL-C of Weeks 12 to 28

| | |
|-----------------|--|
| End point title | Change From BL in Low Density Lipoprotein Cholesterol (LDL-C) to the Average LDL-C of Weeks 12 to 28 |
|-----------------|--|

End point description:

Baseline LDL was defined as the LDL value on Day 1. If this value was missing, the latest value prior to first study drug administration was used. The analysis population was the FAS, with participants who had available data.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and weeks 12 to 28

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|--|---------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 394 | 412 | | |
| Units: mmol/L | | | | |
| least squares mean (confidence interval 95%) | -0.459 (-0.517 to -0.401) | -0.082 (-0.138 to -0.026) | | |

Statistical analyses

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|-----------------------------------|------------------------|

Statistical analysis description:

The model includes treatment arm, region, CV History, previous ESA treatment, visits and visit by treatment as categorical variables and baseline LDL, baseline Hb as continuous variables.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 806 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[7] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | -0.377 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.451 |
| upper limit | -0.304 |

Notes:

[7] - p-value for superiority test based on 2-sided significance level

Secondary: Mean Monthly Intravenous (IV) Iron Use

| | |
|------------------------|---|
| End point title | Mean Monthly Intravenous (IV) Iron Use |
| End point description: | Participants with no or missing medication records of IV Iron have their monthly IV Iron use set to 0 mg. For participants who took IV Iron, but without a dosing frequency, the average values were set to missing. The analysis population was the FAS, with participants who had available data. |
| End point type | Secondary |
| End point timeframe: | Day 1 to week 36 |

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|--|---------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 419 | | |
| Units: mg | | | | |
| least squares mean (confidence interval 95%) | 21.6 (14.0 to 29.3) | 53.5 (46.0 to 61.1) | | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | The model includes treatment arm, region, CV History, previous ESA treatment as categorical variables and baseline Hb as continuous variable. |
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |

| | |
|---|------------------------|
| Number of subjects included in analysis | 832 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[8] |
| Method | ANCOVA |
| Parameter estimate | LSM Difference |
| Point estimate | -31.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -41.4 |
| upper limit | -22.4 |

Notes:

[8] - p-value for superiority test based on 2-sided significance level

Secondary: Change From BL in Short Form-36 (SF-36) Health Survey Physical Functioning (PF) Sub-score to the Average of Weeks 12 to 28

| | |
|-----------------|--|
| End point title | Change From BL in Short Form-36 (SF-36) Health Survey Physical Functioning (PF) Sub-score to the Average of Weeks 12 to 28 |
|-----------------|--|

End point description:

Baseline SF-36 PF was defined as the SF-36 PF value on Day 1. The SF-36 is a Quality of Life (QoL) instrument designed to assess generic health concepts relevant across age, disease, and treatment groups. The SF-36 contains 36 items that measure eight scales: (1) physical functioning (PF); (2) role limitations due to physical health problems (RP); (3) bodily pain (BP); (4) social functioning (SF); (5) general health perceptions (GH); (6) role limitations due to emotional problems (RE); (7) vitality, energy or fatigue (VT); and (8) mental health (MH). Each scale is transformed into 0-100 score, with higher scores indicating better health status. The SF-36 PF consists of 11 questions focused on health and ability to do usual activities, with higher scores indicating better health status. The analysis population was the PPS, with participants who had available data.

| | |
|-----------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and weeks 12 to 28 | |

| End point values | Roxadustat | ESA (Erythropoiesis-Stimulating Agent) | | |
|--|-------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 376 | 391 | | |
| Units: Units on a scale | | | | |
| least squares mean (confidence interval 95%) | 0.050 (-0.640 to 0.740) | -0.155 (-0.825 to 0.514) | | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

The model includes treatment arm, region, CV History, previous ESA treatment, visits (week 8, week 12, week 28) and visit by treatment as categorical variables, and baseline SF-36 PF, baseline Hb as

continuous variables.

| | |
|---|---|
| Comparison groups | ESA (Erythropoiesis-Stimulating Agent) v Roxadustat |
| Number of subjects included in analysis | 767 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[9] |
| P-value | < 0.05 ^[10] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.205 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.649 |
| upper limit | 1.059 |

Notes:

[9] - The margin for non-inferiority was -3.

[10] - p-value for non-inferiority test based on 1-sided significance level

Secondary: Change From BL in SF-36 Vitality (VT) Sub-score to the Average of Weeks 12 to 28

| | |
|-----------------|--|
| End point title | Change From BL in SF-36 Vitality (VT) Sub-score to the Average of Weeks 12 to 28 |
|-----------------|--|

End point description:

Baseline VT Subscore was defined as the VT value on Day 1. The SF-36 is a QoL instrument designed to assess generic health concepts relevant across age, disease, and treatment groups. The SF-36 vitality has four questions with score range from 0-100 with higher scores indicating better vitality status. The analysis population was the PPS, with participants who had available data.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and weeks 12 to 28

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|--|-------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 377 | 391 | | |
| Units: Units on a scale | | | | |
| least squares mean (confidence interval 95%) | 0.460 (-0.329 to 1.249) | -0.396 (-1.165 to 0.373) | | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

The model includes treatment arm, region, CV History, previous ESA treatment, visits (week 8, week 12, week 28) and visit by treatment as categorical variables, and baseline SF-36 VT, baseline Hb as continuous variables.

| | |
|-------------------|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
|-------------------|---|

| | |
|---|---------------------------------|
| Number of subjects included in analysis | 768 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[11] |
| P-value | < 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.856 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.115 |
| upper limit | 1.828 |

Notes:

[11] - The margin for non-inferiority was -3.

Secondary: Change From BL in Mean Arterial Pressure (MAP) to the Average of Weeks 20 to 28

| | |
|-----------------|---|
| End point title | Change From BL in Mean Arterial Pressure (MAP) to the Average of Weeks 20 to 28 |
|-----------------|---|

End point description:

Baseline MAP was defined as the MAP value on Day 1. If this value was missing, the latest value prior to first study drug administration was used. Mean Arterial Pressure (MAP) is derived as: $MAP = (2/3) \times DBP + (1/3) \times SBP$. The analysis population was the PPS, with participants who had available data.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and weeks 20 to 28

| End point values | Roxadustat | ESA (Erythropoiesis-Stimulating Agent) | | |
|--|---------------------------|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 373 | 388 | | |
| Units: mmHg | | | | |
| least squares mean (confidence interval 95%) | -0.969 (-1.838 to -0.099) | -0.120 (-0.972 to 0.732) | | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

The model includes treatment arm, region, CV History, previous ESA treatment, visits and visit by treatment as categorical variables, and baseline MAP, baseline Hb as continuous variables.

| | |
|-------------------|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
|-------------------|---|

| | |
|---|------------------------|
| Number of subjects included in analysis | 761 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | < 0.05 ^[12] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | -0.849 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.971 |
| upper limit | 0.273 |

Notes:

[12] - p-value for non-inferiority test based on 1-sided significance level

Secondary: Time to First Occurrence of an Increase in Blood Pressure

| | |
|---|---|
| End point title | Time to First Occurrence of an Increase in Blood Pressure |
| End point description: | |
| Increase in Blood Pressure was defined as either: Systolic Blood Pressure (SBP) \geq 170 mmHg and an increase from BL \geq 20 mmHg, or as: Diastolic Blood Pressure (DBP) \geq 100 mmHg and an increase from BL \geq 15 mmHg. For participants who have experienced more than one event, only their first event following study treatment was used. Data reported was analyzed by Kaplan-Meier estimate for cumulative proportion and the 95% confidence interval was calculated with Greenwood's formula. The analysis population was the PPS, with participants who had available data. | |
| End point type | Secondary |
| End point timeframe: | |
| Weeks 1 to 36 | |

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|-----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 386 | 397 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Week 12 | 11.7 (8.5 to 14.9) | 11.1 (8.0 to 14.2) | | |
| Week 24 | 15.9 (12.2 to 19.6) | 15.4 (11.9 to 19.0) | | |
| Week 36 | 21.1 (14.0 to 28.2) | 23.5 (16 to 30.9) | | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Hazard Ratio was calculated using stratified Cox Proportional Hazards regression stratifying on region, CV history, previous ESA treatment, and adjusting on Hb at baseline as continuous covariate. Non-inferiority was declared if the upper bound of the 95% CI is below 1.3.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 783 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[13] |
| P-value | < 0.05 ^[14] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.924 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.669 |
| upper limit | 1.276 |

Notes:

[13] - Non-inferiority (hazard ratio margin of 1.3).

[14] - p-value for non-inferiority test based on 1-sided significance level

Secondary: Change From BL in Mean Arterial Pressure (MAP) to the Average MAP Value of Weeks 20 to 28

| | |
|---|---|
| End point title | Change From BL in Mean Arterial Pressure (MAP) to the Average MAP Value of Weeks 20 to 28 |
| End point description: | |
| Baseline MAP was defined as the MAP value on day 1. If this value was missing, the latest value prior to first study drug administration was used. Mean Arterial Pressure (MAP) is derived as: $MAP = (2/3)*DBP + (1/3)*SBP$. The analysis population was the FAS, with participants who had available data. | |
| End point type | Secondary |
| End point timeframe: | |
| Weeks 20 to 28 | |

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|--|--------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 381 | 401 | | |
| Units: mmHg | | | | |
| least squares mean (confidence interval 95%) | -0.739 (-1.600 to 0.123) | -0.160 (-0.997 to 0.678) | | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | |
| The model includes treatment arm, region, CV History, previous ESA treatment, visits and visit by treatment as categorical variables, and baseline MAP, baseline Hb as continuous variables. | |
| Comparison groups | ESA (Erythropoiesis-Stimulating Agent) v Roxadustat |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 782 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.308 ^[15] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | -0.579 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.694 |
| upper limit | 0.536 |

Notes:

[15] - p-value for superiority test based on 2-sided significance level

Secondary: Time to First Occurrence of an Increase in Blood Pressure

| | |
|--|---|
| End point title | Time to First Occurrence of an Increase in Blood Pressure |
| End point description: | |
| Increase in Blood Pressure was defined as either: SBP \geq 170 mmHg and an increase from BL \geq 20 mmHg, or as: DBP \geq 100 mmHg and an increase from BL \geq 15 mmHg. Data reported was analyzed by Kaplan-Meier estimate for cumulative proportion and the 95% confidence interval was calculated with Greenwood's formula. The analysis population was the FAS, with participants who had available data. | |
| End point type | Secondary |
| End point timeframe: | |
| Weeks 1 to 36 | |

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|-----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 420 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Week 12 | 11.6 (8.5 to 14.8) | 12.0 (8.9 to 15.1) | | |
| Week 24 | 16.1 (12.5 to 19.7) | 16.2 (12.6 to 19.7) | | |
| Week 36 | 21.2 (14.1 to 28.3) | 24.1 (16.7 to 31.4) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | |
| Hazard Ratio was calculated using stratified Cox Proportional Hazards regression stratifying on region, CV history, previous ESA treatment, and adjusting on Hb at baseline as continuous covariate. Superiority was declared if the upper bound of the 95% CI is lower than 1. | |
| Comparison groups | ESA (Erythropoiesis-Stimulating Agent) v Roxadustat |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.582 ^[16] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.915 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.668 |
| upper limit | 1.254 |

Notes:

[16] - p-value for superiority test based on 2-sided significance level

Secondary: Percentage of Participants with a Hb Response During Weeks 28 and 36 Regardless of Use of Rescue Therapy

| | |
|-----------------|--|
| End point title | Percentage of Participants with a Hb Response During Weeks 28 and 36 Regardless of Use of Rescue Therapy |
|-----------------|--|

End point description:

Hb response was defined as mean Hb during weeks 28 to 36 within the target range of 10.0 to 12.0 g/dL. The percentages and 95% CI are unadjusted, the exact method of Clopper-Pearson was used for 95% CI. The analysis population was the FAS, with participants who had available data.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 28 to 36

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|-----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 420 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 83.1 (79.1 to 86.5) | 82.1 (78.1 to 85.7) | | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

A generalized linear model was used to estimate the difference in response rates between the arms, as an approximation for the Miettinen and Nurminen method, adjusting for following covariates: region, previous ESA treatment, cardiovascular history and baseline Hb as categorical variables.

| | |
|-------------------|---|
| Comparison groups | ESA (Erythropoiesis-Stimulating Agent) v Roxadustat |
|-------------------|---|

| | |
|---|-------------------------------|
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.609 ^[17] |
| Method | Miettinen and Nurminen method |
| Parameter estimate | Difference of Percentages |
| Point estimate | 1.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.8 |
| upper limit | 6.5 |

Notes:

[17] - p-value for superiority test based on 2-sided significance level

Secondary: Change From BL in Hb to Each Postdosing Time Point

| | |
|---|--|
| End point title | Change From BL in Hb to Each Postdosing Time Point |
| End point description: | |
| Baseline Hb was defined as the mean of four latest central laboratory Hb values prior or on the same date as first study drug intake (pre-dose). The analysis population was the FAS, with participants who had available data. N is the number of participants with available data at each time point. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and weeks 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, and 104 | |

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|--|---------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 420 | | |
| Units: g/dL | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Hb Change From BL to Week 1 [N=407,411] | 0.232 (0.164 to 0.300) | 0.068 (0.000 to 0.135) | | |
| Hb Change From BL to Week 2 [N=401,411] | 0.496 (0.420 to 0.572) | 0.054 (-0.022 to 0.129) | | |
| Hb Change From BL to Week 3 [N=394,408] | 0.633 (0.552 to 0.714) | 0.071 (-0.008 to 0.151) | | |
| Hb Change From BL to Week 4 [N=399,413] | 0.803 (0.715 to 0.891) | 0.095 (0.009 to 0.181) | | |
| Hb Change From BL to Week 5 [N=399,407] | 0.723 (0.633 to 0.812) | -0.045 (-0.133 to 0.043) | | |
| Hb Change From BL to Week 6 [N=391,405] | 0.868 (0.776 to 0.959) | 0.138 (0.048 to 0.228) | | |
| Hb Change From BL to Week 7 [N=389,404] | 0.698 (0.606 to 0.791) | -0.031 (-0.122 to 0.060) | | |
| Hb Change From BL to Week 8 [N=393,402] | 0.816 (0.724 to 0.907) | 0.116 (0.026 to 0.206) | | |

| | | | | |
|--|----------------------------|-----------------------------|--|--|
| Hb Change From BL to Week 10 [N=396,409] | 0.640 (0.546 to 0.734) | -0.019 (-0.111 to 0.073) | | |
| Hb Change From BL to Week 12 [N=384,399] | 0.732 (0.634 to 0.830) | 0.139 (0.043 to 0.235) | | |
| Hb Change From BL to Week 14 [N=383,400] | 0.508 (0.409 to 0.608) | 0.005 (-0.093 to 0.103) | | |
| Hb Change From BL to Week 16 [N=381,401] | 0.613 (0.511 to 0.716) | 0.244 (0.144 to 0.344) | | |
| Hb Change From BL to Week 18 [N=378,395] | 0.380 (0.283 to 0.477) | 0.017 (-0.078 to 0.112) | | |
| Hb Change From BL to Week 20 [N=376,394] | 0.501 (0.405 to 0.596) | 0.217 (0.124 to 0.309) | | |
| Hb Change From BL to Week 22 [N=370,395] | 0.266 (0.170 to 0.363) | 0.069 (-0.025 to 0.163) | | |
| Hb Change From BL to Week 24 [N=362,387] | 0.262 (0.168 to 0.356) | 0.075 (-0.017 to 0.166) | | |
| Hb Change From BL to Week 26 [N=359,387] | 0.316 (0.220 to 0.412) | 0.073 (-0.020 to 0.165) | | |
| Hb Change From BL to Week 28 [N=360,388] | 0.549 (0.452 to 0.647) | 0.342 (0.248 to 0.437) | | |
| Hb Change From BL to Week 30 [N=351,380] | 0.333 (0.236 to 0.429) | 0.106 (0.013 to 0.198) | | |
| Hb Change From BL to Week 32 [N=345,376] | 0.310 (0.211 to 0.409) | 0.111 (0.016 to 0.207) | | |
| Hb Change From BL to Week 34 [N=342,374] | 0.364 (0.268 to 0.460) | 0.084 (-0.007 to 0.176) | | |
| Hb Change From BL to Week 36 [N=339,373] | 0.482 (0.382 to 0.581) | 0.225 (0.130 to 0.321) | | |
| Hb Change From BL to Week 40 [N=336,373] | 0.199 (0.095 to 0.304) | 0.064 (-0.036 to 0.163) | | |
| Hb Change From BL to Week 44 [N=328,367] | 0.335 (0.221 to 0.448) | 0.252 (0.145 to 0.360) | | |
| Hb Change From BL to Week 48 [N=323,365] | 0.158 (0.047 to 0.270) | 0.131 (0.027 to 0.236) | | |
| Hb Change From BL to Week 52 [N=308,363] | 0.385 (0.273 to 0.496) | 0.186 (0.082 to 0.290) | | |
| Hb Change From BL to Week 56 [N=311,360] | 0.217 (0.104 to 0.329) | 0.069 (-0.035 to 0.174) | | |
| Hb Change From BL to Week 60 [N=299,353] | 0.368 (0.256 to 0.479) | 0.171 (0.067 to 0.275) | | |
| Hb Change From BL to Week 64 [N=289,344] | 0.181 (0.067 to 0.295) | -0.093 (-0.198 to 0.012) | | |
| Hb Change From BL to Week 68 [N=290,349] | 0.306 (0.195 to 0.416) | 0.100 (-0.002 to 0.202) | | |
| Hb Change From BL to Week 72 [N=284,339] | 0.109 (-0.005 to 0.222) | -0.009 (-0.113 to 0.095) | | |
| Hb Change From BL to Week 76 [N=278,338] | 0.401 (0.280 to 0.521) | 0.189 (0.079 to 0.299) | | |
| Hb Change From BL to Week 80 [N=274,327] | 0.087 (-0.028 to 0.203) | -0.015 (-0.120 to 0.091) | | |
| Hb Change From BL to Week 84 [N=270,328] | 0.318 (0.199 to 0.438) | 0.126 (0.017 to 0.235) | | |
| Hb Change From BL to Week 88 [N=258,326] | 0.026 (-0.091 to 0.144) | -0.018 (-0.124 to 0.088) | | |
| Hb Change From BL to Week 92 [N=255,313] | 0.357 (0.232 to 0.483) | 0.154 (0.041 to 0.267) | | |
| Hb Change From BL to Week 96 [N=253,312] | 0.126 (0.010 to 0.242) | -0.058 (-0.163 to 0.046) | | |
| Hb Change From BL to Week 100 [N=248,311] | 0.302 (0.175 to 0.430) | 0.138 (0.024 to 0.253) | | |
| Hb Change From BL to Week 104 [N=240,299] | 0.232 (0.100 to 0.363) | 0.133 (0.014 to 0.251) | | |

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|--|---|
| Statistical analysis description: | |
| Week 1- The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates. | |
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[18] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.164 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.072 |
| upper limit | 0.256 |

Notes:

[18] - p-value for superiority test based on 2-sided significance level

| Statistical analysis title | Statistical analysis 2 |
|--|---|
| Statistical analysis description: | |
| Week 2- The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates. | |
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[19] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.443 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.339 |
| upper limit | 0.546 |

Notes:

[19] - p-value for superiority test based on 2-sided significance level

| Statistical analysis title | Statistical analysis 3 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

Week 3 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment,

region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[20] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.561 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.451 |
| upper limit | 0.672 |

Notes:

[20] - p-value for superiority test based on 2-sided significance level

| | |
|---|---|
| Statistical analysis title | Statistical analysis 4 |
| Statistical analysis description: | |
| Week 4 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates. | |
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[21] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.708 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.588 |
| upper limit | 0.828 |

Notes:

[21] - p-value for superiority test based on 2-sided significance level

| | |
|---|---|
| Statistical analysis title | Statistical analysis 5 |
| Statistical analysis description: | |
| Week 5 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates. | |
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[22] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.768 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.645 |
| upper limit | 0.89 |

Notes:

[22] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 6 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 6 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[23] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.729 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.604 |
| upper limit | 0.855 |

Notes:

[23] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 7 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 7 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[24] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.729 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.603 |
| upper limit | 0.856 |

Notes:

[24] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 8 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 8 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[25] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.574 |
| upper limit | 0.826 |

Notes:

[25] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 9 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 10 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[26] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.659 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.53 |
| upper limit | 0.788 |

Notes:

[26] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 10 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 12 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[27] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.593 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.459 |
| upper limit | 0.727 |

Notes:

[27] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 11 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 14 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[28] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.503 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.366 |
| upper limit | 0.64 |

Notes:

[28] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 12 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 16 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[29] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.369 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.229 |
| upper limit | 0.51 |

Notes:

[29] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 13 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 18 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[30] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.363 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.23 |
| upper limit | 0.496 |

Notes:

[30] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 14 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 20 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[31] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.284 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.154 |
| upper limit | 0.414 |

Notes:

[31] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 15 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 22 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.003 ^[32] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.197 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.065 |
| upper limit | 0.329 |

Notes:

[32] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 16 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 24 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.004 ^[33] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.187 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.059 |
| upper limit | 0.316 |

Notes:

[33] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 17 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 26 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[34] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.243 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.113 |
| upper limit | 0.373 |

Notes:

[34] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 18 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 28 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.002 ^[35] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.207 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.074 |
| upper limit | 0.34 |

Notes:

[35] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 19 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 30 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[36] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.227 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.096 |
| upper limit | 0.358 |

Notes:

[36] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 20 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 32 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.004 ^[37] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.199 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.064 |
| upper limit | 0.334 |

Notes:

[37] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 21 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 34 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[38] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.279 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.15 |
| upper limit | 0.409 |

Notes:

[38] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 22 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 36- The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[39] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.256 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.121 |
| upper limit | 0.391 |

Notes:

[39] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 23 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 40 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.06 ^[40] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.136 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.006 |
| upper limit | 0.277 |

Notes:

[40] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 24 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 44 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.293 ^[41] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.082 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.071 |
| upper limit | 0.236 |

Notes:

[41] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 25 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 48 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.723 ^[42] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.027 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.123 |
| upper limit | 0.177 |

Notes:

[42] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 26 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 52 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.009 ^[43] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.199 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.049 |
| upper limit | 0.348 |

Notes:

[43] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 27 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 56 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.056 ^[44] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.147 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.004 |
| upper limit | 0.298 |

Notes:

[44] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 28 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 60 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.01 ^[45] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.196 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.047 |
| upper limit | 0.346 |

Notes:

[45] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 29 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 64 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[46] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.275 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.122 |
| upper limit | 0.427 |

Notes:

[46] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 30 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 68 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.006 ^[47] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.206 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.059 |
| upper limit | 0.353 |

Notes:

[47] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 31 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 72 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.127 ^[48] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.118 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.033 |
| upper limit | 0.269 |

Notes:

[48] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 32 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 76 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.01 ^[49] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.211 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.051 |
| upper limit | 0.371 |

Notes:

[49] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 33 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 80 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.191 ^[50] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.102 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.051 |
| upper limit | 0.255 |

Notes:

[50] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 34 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 84 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.018 ^[51] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.192 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.033 |
| upper limit | 0.351 |

Notes:

[51] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 35 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 88 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.576 ^[52] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.044 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.111 |
| upper limit | 0.2 |

Notes:

[52] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 36 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 92 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.017 ^[53] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.203 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.037 |
| upper limit | 0.369 |

Notes:

[53] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 37 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 96 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.019 ^[54] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.184 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.031 |
| upper limit | 0.338 |

Notes:

[54] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 38 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 100 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.056 ^[55] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.164 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.004 |
| upper limit | 0.333 |

Notes:

[55] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 39 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 104 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.267 ^[56] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.099 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.076 |
| upper limit | 0.273 |

Notes:

[56] - p-value for superiority test based on 2-sided significance level

Secondary: Hb Level Averaged Over Weeks 28 to 36, 44 to 52, and 96 to 104 Without Use of Rescue Therapy

| | |
|-----------------|--|
| End point title | Hb Level Averaged Over Weeks 28 to 36, 44 to 52, and 96 to 104 Without Use of Rescue Therapy |
|-----------------|--|

End point description:

Baseline Hb was defined as the mean of four latest central laboratory Hb values prior or on the same date as first study drug intake (pre-dose). Averaged Hb values over weeks 28-36, weeks 44-52 and weeks 96-104 are observed values. The analysis population was the FAS, with participants who had available data. N is the number of participants with available data at each time point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 28 to 36, 44 to 52, and 96 to 104

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|--|------------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 420 | | |
| Units: g/dL | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Average Hb Over Weeks 28-36 N=[362,393] | 11.183 (11.100 to 11.265) | 10.946 (10.867 to 11.025) | | |
| Average Hb Over Weeks 44-52 N=[330,370] | 11.099 (11.009 to 11.189) | 10.994 (10.909 to 11.079) | | |
| Average Hb Over Weeks 96-104 N=[252,317] | 11.007 (10.904 to 11.110) | 10.858 (10.766 to 10.950) | | |

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|--|---|
| Statistical analysis description: | |
| Weeks 28-36 - The model includes treatment arm, region, CV History, previous ESA treatment, visits and visit by treatment as categorical variables and baseline Hb as continuous variable. | |
| Comparison groups | ESA (Erythropoiesis-Stimulating Agent) v Roxadustat |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[57] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.237 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.127 |
| upper limit | 0.347 |

Notes:

[57] - p-value for superiority test based on 2-sided significance level

| Statistical analysis title | Statistical analysis 2 |
|--|---|
| Statistical analysis description: | |
| Weeks 44-52 - The model includes treatment arm, region, CV History, previous ESA treatment, visits and visit by treatment as categorical variables and baseline Hb as continuous variable. | |
| Comparison groups | ESA (Erythropoiesis-Stimulating Agent) v Roxadustat |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.086 ^[58] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.105 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.015 |
| upper limit | 0.225 |

Notes:

[58] - p-value for superiority test based on 2-sided significance level

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

Weeks 96-104 - The model includes treatment arm, region, CV History, previous ESA treatment, visits and visit by treatment as categorical variables and baseline Hb as continuous variable.

| | |
|---|---|
| Comparison groups | ESA (Erythropoiesis-Stimulating Agent) v Roxadustat |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.031 ^[59] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.149 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.014 |
| upper limit | 0.284 |

Notes:

[59] - p-value for superiority test based on 2-sided significance level

Secondary: Change From BL in Hb to the Average of Weeks 28 to 36, 44 to 52, and 96 to 104 Regardless of the Use of Rescue Therapy

| | |
|-----------------|--|
| End point title | Change From BL in Hb to the Average of Weeks 28 to 36, 44 to 52, and 96 to 104 Regardless of the Use of Rescue Therapy |
|-----------------|--|

End point description:

Change from baseline to the average Hb are observed values. Baseline Hb was defined as the mean of four latest central laboratory Hb values prior or on the same date as first study drug intake (pre-dose). The analysis population was the FAS, with participants who had available data. N is the number of participants with available data at each time point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and weeks 28 to 36, 44 to 52, and 96 to 104

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|--|---------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 420 | | |
| Units: g/dL | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Hb Change From BL to Weeks 28-36 [N=364,393] | 0.408 (0.325 to 0.491) | 0.173 (0.093 to 0.252) | | |
| Hb Change From BL to Weeks 44-52 [N=331,371] | 0.298 (0.203 to 0.394) | 0.194 (0.104 to 0.284) | | |
| Hb Change From BL to Weeks 96-104 [N=254,318] | 0.225 (0.119 to 0.331) | 0.076 (-0.020 to 0.171) | | |

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|--|---|
| Statistical analysis description: | |
| Weeks 28-36 - The model includes treatment arm, region, CV History, previous ESA treatment, visits and visit by treatment as categorical variables and baseline Hb as continuous variable. | |
| Comparison groups | ESA (Erythropoiesis-Stimulating Agent) v Roxadustat |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.235 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.125 |
| upper limit | 0.346 |

| Statistical analysis title | Statistical analysis 2 |
|--|---|
| Statistical analysis description: | |
| Weeks 44-52 - The model includes treatment arm, region, CV History, previous ESA treatment, visits and visit by treatment as categorical variables and baseline Hb as continuous variable. | |
| Comparison groups | ESA (Erythropoiesis-Stimulating Agent) v Roxadustat |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.11 |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.104 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.024 |
| upper limit | 0.232 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

Weeks 96-104 - The model includes treatment arm, region, CV History, previous ESA treatment, visits and visit by treatment as categorical variables and baseline Hb as continuous variable.

| | |
|---|---|
| Comparison groups | ESA (Erythropoiesis-Stimulating Agent) v Roxadustat |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.036 |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.149 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.01 |
| upper limit | 0.288 |

Secondary: Percentage of Hb Values ≥ 10 g/dL and Within 10.0 to 12.0 g/dL in Weeks 28 to 36, 44 to 52, and 96 to 104 Without Use of Rescue Therapy

| | |
|-----------------|--|
| End point title | Percentage of Hb Values ≥ 10 g/dL and Within 10.0 to 12.0 g/dL in Weeks 28 to 36, 44 to 52, and 96 to 104 Without Use of Rescue Therapy |
|-----------------|--|

End point description:

Percentage for each participant was calculated from the Number of Hb values within 10.0-12.0 g/dL / Total number of Hb values*100 in weeks 28 to 36, 44 to 52 and 96 to 104 without use of rescue therapy within 6 weeks prior to and during the 8 week evaluation period. The analysis population was the FAS, with participants who had available data. N is the number of participants with available data at each time point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 28-36, 44-52 and 96-104

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|---|---------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 420 | | |
| Units: g/dL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Weeks 28-36 (≥ 10 g/dL) [N=364,393] | 93.002 (\pm 18.320) | 87.286 (\pm 25.114) | | |
| Weeks 28-36 (Within 10-12 g/dL) [N=364,393] | 76.326 (\pm 28.175) | 76.098 (\pm 28.991) | | |
| Weeks 44-52 (≥ 10 g/dL) [N=331,371] | 89.421 (\pm 24.267) | 86.914 (\pm 25.366) | | |
| Weeks 44-52 (Within 10-12 g/dL) [N=331,371] | 75.891 (\pm 31.047) | 74.634 (\pm 30.589) | | |
| Weeks 96-104 (≥ 10 g/dL) [N=254,318] | 88.858 (\pm 24.708) | 83.543 (\pm 30.296) | | |
| Weeks 96-104 (Within 10-12 g/dL) [N=254,318] | 76.522 (\pm 30.378) | 73.690 (\pm 33.040) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Hospitalizations

| | |
|--|----------------------------|
| End point title | Number of Hospitalizations |
| End point description: | |
| The number of hospitalizations per participant were calculated during the Efficacy Emergent Period. The Efficacy Emergent Period was defined as the evaluation period from the Analysis date of first dose intake up to EOT Visit or last non-missing Hb assessment (for participants who died during the treatment period). It included all Non-Hemodialysis (HD) hospitalizations. The HD days were not counted as hospitalizations, even when performed overnight. The analysis population was the FAS, with participants who had available data. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to End of Treatment (EOT) (Up to week 104) | |

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|--------------------------------------|------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 420 | | |
| Units: Hospitalizations | | | | |
| arithmetic mean (standard deviation) | 0.9 (\pm 1.3) | 0.9 (\pm 1.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Days of Hospitalization per Year

| | |
|--|--|
| End point title | Number of Days of Hospitalization per Year |
| End point description: The number of days of hospitalizations per year was calculated as the sum of the durations of all non-HD hospitalizations in days (Date of discharge – Date of admission + 1) / (duration of efficacy emergent period in days / 365.25). In case of missing dates, the hospitalization duration was imputed by the average duration per stay derived from the participants with non-missing duration within the same treatment group. The analysis population was the FAS, with participants who had available data. | |
| End point type | Secondary |
| End point timeframe: Baseline to EOT (Up to week 104) | |

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 420 | | |
| Units: Days per year | | | | |
| arithmetic mean (standard deviation) | 12.186 (± 34.121) | 7.868 (± 22.948) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Hospitalization

| | |
|--|-------------------------------|
| End point title | Time to First Hospitalization |
| End point description: Time to first hospitalization in years was defined in years as: (First event date during the Efficacy Emergent Period – Analysis date of First dose intake + 1)/365.25, and the 'First event date' was defined as 'Date of first Admission and 'Analysis Date of first dose intake. For participants without hospitalization, the time to censoring was calculated as: (Date of End of Efficacy Emergent Period – Analysis Date of first dose intake + 1) / 365.25. Date of End of Efficacy Emergent Period was defined as as the treatment period up to the EOT visit. For participants who have experienced more than one hospitalization, only their first event following study treatment was used. Data reported was analyzed by Kaplan-Meier estimate for cumulative proportion and the 95% confidence interval was calculated with Greenwood's formula. The analysis population was the FAS | |
| End point type | Secondary |
| End point timeframe: Baseline to EOT (Up to week 104) | |

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|-----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 420 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Year 0.5 | 19.4 (15.5 to 23.3) | 18.3 (14.6 to 22.0) | | |
| Year 1 | 32.0 (27.3 to 36.6) | 32.7 (28.2 to 37.3) | | |
| Year 1.5 | 43.5 (38.5 to 48.6) | 41.9 (37.0 to 46.7) | | |
| Year 2 | 52.6 (47.5 to 57.8) | 48.3 (43.3 to 53.3) | | |

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|--|---|
| Statistical analysis description: | |
| Hazard Ratio was calculated using stratified Cox Proportional Hazards regression stratifying on region, CV history, previous ESA treatment and adjusting on Hb at baseline as continuous covariate. Superiority was declared if the upper bound of the 95% CI was below 1.0. | |
| Comparison groups | ESA (Erythropoiesis-Stimulating Agent) v Roxadustat |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.164 ^[60] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.154 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.943 |
| upper limit | 1.411 |

Notes:

[60] - p-value for superiority test based on 2-sided significance level

Secondary: Time to First Use of Rescue Therapy

| End point title | Time to First Use of Rescue Therapy |
|---|-------------------------------------|
| End point description: | |
| Rescue therapy was defined as red blood cell (RBC) transfusion for both treatment groups and ESA for roxadustat participants. Only rescue medication that was started during the study treatment and up to end of efficacy emergent period was taken into account and considered as use of rescue medication. For participants who have experienced more than one use of rescue therapy, only their first event following study treatment was used. Data reported was analyzed by Kaplan-Meier estimate for cumulative proportion and the 95% confidence interval was calculated with Greenwood's formula. The analysis population was the FAS. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to EOT (Up to week 104) | |

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|-----------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 420 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Year 0.5 | 3.9 (2.0 to 5.8) | 3.2 (1.5 to 4.8) | | |
| Year 1 | 8.2 (5.4 to 11.1) | 8.4 (5.6 to 11.1) | | |
| Year 1.5 | 11.4 (8.1 to 14.8) | 10.9 (7.8 to 14.0) | | |
| Year 2 | 12.8 (9.3 to 16.4) | 14.4 (10.8 to 18.0) | | |

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|--|---|
| Statistical analysis description: | |
| Hazard Ratio was calculated using stratified Cox Proportional Hazards regression stratifying on region, CV history, previous ESA treatment and adjusting on Hb at baseline as continuous covariate. Superiority was declared if the upper bound of the 95% CI was below 1.0. | |
| Comparison groups | ESA (Erythropoiesis-Stimulating Agent) v Roxadustat |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.917 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.979 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.656 |
| upper limit | 1.462 |

Secondary: Time to First RBC Transfusion

| End point title | Time to First RBC Transfusion |
|--|-------------------------------|
| End point description: | |
| For participants who have experienced more than one RBC transfusion, only their first event following study treatment was used. For RBC transfusions, when the number of units was not given but the volume transfused was, the number of units were estimated by volume transfused/250 mL (for transfusion of packed cell units) or volume transfused/500 mL (for transfusion of full blood). Data reported was analyzed by Kaplan-Meier estimate for cumulative proportion and the 95% confidence interval was calculated with Greenwood's formula. The analysis population was the FAS. | |
| End point type | Secondary |

End point timeframe:
Baseline to EOT (Up to week 104)

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|-----------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 420 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Year 0.5 | 3.6 (1.8 to 5.5) | 3.2 (1.5 to 4.8) | | |
| Year 1 | 7.4 (4.7 to 10.1) | 8.4 (5.6 to 11.1) | | |
| Year 1.5 | 10.0 (6.9 to 13.2) | 10.9 (7.8 to 14.0) | | |
| Year 2 | 11.4 (8.0 to 14.9) | 14.4 (10.8 to 18.0) | | |

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|---|
| Statistical analysis description: | |
| Hazard Ratio was calculated using stratified Cox Proportional Hazards regression stratifying on region, CV history, previous ESA treatment, and adjusting on Hb at baseline as continuous covariate. Superiority was declared if the upper bound of the 95% CI was below 1.0. | |
| Comparison groups | ESA (Erythropoiesis-Stimulating Agent) v Roxadustat |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.501 ^[61] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.867 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.573 |
| upper limit | 1.313 |

Notes:

[61] - p-value for superiority test based on 2-sided significance level

Secondary: Mean Monthly Number of RBC Packs Per Participant

| | |
|-----------------|--|
| End point title | Mean Monthly Number of RBC Packs Per Participant |
|-----------------|--|

End point description:

During efficacy emergent period, the mean monthly number of RBC packs were calculated as the sum of blood volume and units transfused between the first dose and up to the last dose in the period divided by duration of efficacy emergent period (in days) divided by 28 days. Participants without medication records of RBC have their number of RBC packs and volume set to 0. The analysis population was the

FAS.

| | |
|----------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline to EOT (Up to week 104) | |

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|--|----------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 420 | | |
| Units: RBC Packs | | | | |
| least squares mean (confidence interval 95%) | 0.026 (0.01 to 0.04) | 0.032 (0.02 to 0.05) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | |
| The model included treatment arm, region, CV History, previous ESA treatment as categorical variables and baseline Hb as continuous variable. | |
| Comparison groups | ESA (Erythropoiesis-Stimulating Agent) v Roxadustat |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.507 ^[62] |
| Method | ANCOVA |
| Parameter estimate | LSM Difference |
| Point estimate | -0.006 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.02 |
| upper limit | 0.01 |

Notes:

[62] - p-value for superiority test based on 2-sided significance level

Secondary: Mean Monthly Volume of RBC Transfusion Per Participant

| | |
|--|--|
| End point title | Mean Monthly Volume of RBC Transfusion Per Participant |
| End point description: | |
| During Efficacy Emergent Period, the mean monthly volume of blood transfused are calculated as the sum of blood volume and units transfused between the first dose and up to the last dose in the period divided by duration of efficacy emergent period (in days) divided by 28 days. The Efficacy Emergent Period was defined as the evaluation period from the Analysis date of first dose intake up to EOT Visit or last non-missing Hb assessment (for participants who died during the treatment period). The analysis population was the FAS. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to EOT (Up to week 104) | |

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|--|----------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 420 | | |
| Units: milliliter (mL) | | | | |
| least squares mean (confidence interval 95%) | 6.061 (2.82 to 9.30) | 5.929 (2.74 to 9.12) | | |

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|---|
| Statistical analysis description: | |
| The model included treatment arm, region, CV History, previous ESA treatment as categorical variables and baseline Hb as continuous variable. | |
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.949 |
| Method | ANCOVA |
| Parameter estimate | LSM Difference |
| Point estimate | 0.132 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.9 |
| upper limit | 4.16 |

Secondary: Time to First Use of IV Iron Supplementation

| End point title | Time to First Use of IV Iron Supplementation |
|--|--|
| End point description: | |
| For participants who have received more than one IV iron, only their first event following study treatment was used. Data reported was analyzed by Kaplan-Meier estimate for cumulative proportion and the 95% confidence interval was calculated with Greenwood's formula. The analysis population was the FAS. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to EOT (Up to week 104) | |

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|-----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 420 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Year 0.5 | 11.2 (8.1 to 14.3) | 33.5 (29.0 to 38.1) | | |
| Year 1 | 17.4 (13.5 to 21.2) | 44.1 (39.3 to 49.0) | | |
| Year 1.5 | 23.6 (19.1 to 28.1) | 55.0 (50.1 to 59.9) | | |
| Year 2 | 33.3 (26.0 to 40.7) | 59.3 (54.4 to 64.3) | | |

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|--|---|
| Statistical analysis description: | |
| Hazard Ratio was calculated using stratified Cox Proportional Hazards regression stratifying on region, CV history, previous ESA treatment and adjusting on Hb at baseline as continuous covariate. Superiority was declared if the upper bound of the 95% CI was below 1.0. | |
| Comparison groups | ESA (Erythropoiesis-Stimulating Agent) v Roxadustat |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.368 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.291 |
| upper limit | 0.465 |

Secondary: Mean Monthly Intravenous (IV) Iron per Participant During Weeks 37-52 and Weeks 53-104

| | |
|---|--|
| End point title | Mean Monthly Intravenous (IV) Iron per Participant During Weeks 37-52 and Weeks 53-104 |
| End point description: | |
| Participants with no or missing medication records of IV Iron had their monthly IV Iron use set to 0 mg. The analysis population was the FAS. | |
| End point type | Secondary |
| End point timeframe: | |
| Weeks 37-52 and weeks 53-104 | |

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|--|---------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 420 | | |
| Units: milligrams (mg) | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Weeks 37-52 | 34.9 (20.9 to 48.9) | 70.0 (56.9 to 83.2) | | |
| Weeks 53-104 | 49.5 (31.0 to 67.9) | 98.1 (81.1 to 115.2) | | |

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|--|---|
| Statistical analysis description: | |
| Weeks 37-52 - Participants with no or missing medication records of IV Iron had their monthly IV Iron use set to 0 mg. The model includes treatment arm, region, CV History, previous ESA treatment as categorical variables and baseline Hb as continuous variable. | |
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | LSM Difference |
| Point estimate | -35.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -51.8 |
| upper limit | -18.4 |

| Statistical analysis title | Statistical analysis 2 |
|---|---|
| Statistical analysis description: | |
| Weeks 53-104 - Participants with no or missing medication records of IV Iron had their monthly IV Iron use set to 0 mg. The model includes treatment arm, region, CV History, previous ESA treatment as categorical variables and baseline Hb as continuous variable. | |
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |

| | |
|---|----------------|
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | LSM Difference |
| Point estimate | -48.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -70.3 |
| upper limit | -27 |

Secondary: Percentage of Participants with Oral Iron Use Only

| | |
|----------------------------------|---|
| End point title | Percentage of Participants with Oral Iron Use Only |
| End point description: | Percentage of participants with/without IV iron was calculated based on total number of participants within the efficacy emergent period. The Efficacy Emergent Period is defined as the evaluation period from the Analysis date of first dose intake up to EOT Visit or last non-missing Hb assessment (for participants who died during the treatment period).The analysis population was the FAS. |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to EOT (Up to week 104) | |

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|-----------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 420 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 31.0 | 11.7 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From BL to Each Post-dosing Study Visit in Total Cholesterol

| | |
|------------------------|---|
| End point title | Change From BL to Each Post-dosing Study Visit in Total Cholesterol |
| End point description: | Baseline assessment was the assessment from Day 1 visit. If baseline value was missing, then the latest screening period value was used as the baseline regardless of fasting status. The analysis population was the FAS, with participants who had available data at all time points. N is the number of participants with available data at each time point. |
| End point type | Secondary |

End point timeframe:

Baseline and week 8, 28, 52, 104

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|---|---------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 420 | | |
| Units: mmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change from BL to Week 8 [N=392,411] | -0.608 (± 0.889) | -0.105 (± 0.712) | | |
| Change from BL to Week 28 [N=364,393] | -0.641 (± 0.960) | -0.135 (± 0.805) | | |
| Change from BL to Week 52 [N=318,362] | -0.803 (± 1.027) | -0.241 (± 0.906) | | |
| Change from BL to Week 104 [N=247,307] | -0.904 (± 1.053) | -0.277 (± 1.002) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From BL to Each Post-dosing Study Visit in LDL-C/High-density Lipoprotein cholesterol (HDL-C) Ratio

| | |
|-----------------|--|
| End point title | Change From BL to Each Post-dosing Study Visit in LDL-C/High-density Lipoprotein cholesterol (HDL-C) Ratio |
|-----------------|--|

End point description:

Baseline was defined as the value on Day 1. If baseline value was missing, the latest value prior to first study drug administration was used regardless of fasting. The analysis population was the FAS, with participants who had available data at all time points. N is the number of participants with available data at each time point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and week 8, 28, 52, 104

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|--|---------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 420 | | |
| Units: Ratio | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change from BL to Week 8 [N=390,411] | -0.245 (± 0.818) | -0.060 (± 0.726) | | |
| Change from BL to Week 28 [N=362,393] | -0.155 (± 1.046) | -0.057 (± 0.922) | | |

| | | | | |
|---|---------------------|---------------------|--|--|
| Change from BL to Week 52 [N=317,361] | -0.345 (± 0.904) | -0.078 (± 0.886) | | |
| Change from BL to Week 104 [N=246,307] | -0.261 (± 1.167) | -0.013 (± 1.048) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From BL to Each Postdosing Study Visit in Non-HDL Cholesterol

| | |
|-----------------|--|
| End point title | Change From BL to Each Postdosing Study Visit in Non-HDL Cholesterol |
|-----------------|--|

End point description:

Baseline was defined as the value on Day 1. If baseline value was missing, the latest value prior to first study drug administration was used regardless of fasting. The analysis population was the FAS, with participants who had available data at all time points. N is the number of participants with available data at each time point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and week 8, 28, 52, 104

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|---|---------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 420 | | |
| Units: mmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change from BL to Week 8 [N=388,404] | -0.518 (± 0.823) | -0.107 (± 0.701) | | |
| Change from BL to Week 28 [N=360,391] | -0.540 (± 0.907) | -0.127 (± 0.789) | | |
| Change from BL to Week 52 [N=314,360] | -0.700 (± 0.965) | -0.229 (± 0.886) | | |
| Change from BL to Week 104 [N=245,304] | -0.788 (± 1.024) | -0.240 (± 1.010) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From BL to Each Postdosing Study Visit in Apolipoproteins A1 (ApoA1)

| | |
|-----------------|---|
| End point title | Change From BL to Each Postdosing Study Visit in Apolipoproteins A1 (ApoA1) |
|-----------------|---|

End point description:

Baseline was defined as the value on Day 1. If baseline value was missing, the latest value prior to first study drug administration was used regardless of fasting. The analysis population was the FAS, with

participants who had available data at all time points. N is the number of participants with available data at each time point.

| | |
|----------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and week 8, 28, 52, 104 | |

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|---|---------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 420 | | |
| Units: g/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change from BL to Week 8 [N=394,415] | -0.114 (± 0.197) | -0.006 (± 0.172) | | |
| Change from BL to Week 28 [N=367,393] | -0.113 (± 0.217) | -0.012 (± 0.193) | | |
| Change from BL to Week 52 [N=320,366] | -0.097 (± 0.230) | -0.013 (± 0.195) | | |
| Change from BL to Week 104 [N=246,309] | -0.097 (± 0.220) | -0.012 (± 0.196) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From BL to Each Postdosing Study Visit in Apolipoproteins B (ApoB)

| | |
|-----------------|---|
| End point title | Change From BL to Each Postdosing Study Visit in Apolipoproteins B (ApoB) |
|-----------------|---|

End point description:

Baseline was defined as the value on Day 1. If baseline value was missing, the latest value prior to first study drug administration was used regardless of fasting. The analysis population was the FAS, with participants who had available data at all time points. N is the number of participants with available data at each time point.

| | |
|----------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and week 8, 28, 52, 104 | |

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 420 | | |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | | | | |

| | | | | |
|--|------------------|-----------------|--|--|
| Change from BL to Week 8 [N=394,415] | -11.03 (± 18.49) | 1.00 (± 14.34) | | |
| Change from BL to Week 28 [N=366,393] | -11.18 (± 20.39) | -0.12 (± 16.91) | | |
| Change from BL to Week 52 [N=320,366] | -13.18 (± 20.67) | -0.01 (± 18.88) | | |
| Change from BL to Week 104 [N=246,309] | -13.50 (± 24.94) | -0.01 (± 20.00) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From BL to Each Postdosing Study Visit in ApoB/ApoA1 Ratio

| | |
|-----------------|---|
| End point title | Change From BL to Each Postdosing Study Visit in ApoB/ApoA1 Ratio |
|-----------------|---|

End point description:

Baseline was defined as the value on Day 1. If baseline value was missing, the latest value prior to first study drug administration was used. The analysis population was the FAS, with participants who had available data at all time points. N is the number of participants with available data at each time point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and week 8, 28, 52, 104

| End point values | Roxadustat | ESA (Erythropoiesis-Stimulating Agent) | | |
|--|------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 420 | | |
| Units: Ratio | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change from BL to Week 8 [N=393,415] | -0.037 (± 0.147) | 0.013 (± 0.141) | | |
| Change from BL to Week 28 [N=365,392] | -0.034 (± 0.177) | 0.002 (± 0.148) | | |
| Change from BL to Week 52 [N=318,365] | -0.051 (± 0.191) | 0.007 (± 0.164) | | |
| Change from BL to Week 104 [N=246,309] | -0.062 (± 0.210) | 0.007 (± 0.201) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Mean LDL Cholesterol < 100 mg/dL Over Weeks 12 to 28

| | |
|-----------------|--|
| End point title | Number of Participants with Mean LDL Cholesterol < 100 mg/dL Over Weeks 12 to 28 |
|-----------------|--|

End point description:

Missing category for Fasting Only includes non-fasting participants and the participants with missing values. The analysis population was the FAS.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 12 to 28

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|--|-----------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 420 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Yes [Regardless of Fasting Status] | 275 | 231 | | |
| No [Regardless of Fasting Status] | 119 | 181 | | |
| Missing [Regardless of Fasting Status] | 19 | 8 | | |
| Yes [Fasting Only] | 111 | 85 | | |
| No [Fasting Only] | 61 | 80 | | |
| Missing [Fasting Only] | 241 | 255 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with CKD Who Achieved Antihypertensive Treatment Goal

| | |
|-----------------|--|
| End point title | Number of Participants with CKD Who Achieved Antihypertensive Treatment Goal |
|-----------------|--|

End point description:

Achieved antihypertensive treatment goal was defined as SBP < 140 mmHg and DBP < 90 mmHg over an evaluation period based on the average of available values in weeks 12-28 (pre-dialysis). The analysis population was the FAS.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 12 to 28

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|---------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 420 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Antihypertensive Treatment Goal - Yes | 264 | 261 | | |

| | | | | |
|---|-----|-----|--|--|
| Antihypertensive Treatment Goal - No | 130 | 149 | | |
| Antihypertensive Treatment Goal - Missing | 19 | 10 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From BL to the Average of Weeks 12 to 28 in SF-36 Physical Component Score

| | |
|---|---|
| End point title | Change From BL to the Average of Weeks 12 to 28 in SF-36 Physical Component Score |
| End point description: | |
| Baseline SF-36 PCS was defined as the SF-36 PCS value on Day 1. The SF-36 is a QoL instrument designed to assess generic health concepts relevant across age, disease, and treatment groups. The SF-36 contains 36 items that measures eight scales: (1) physical functioning (PF); (2) role limitations due to physical health problems (RP); (3) bodily pain (BP); (4) social functioning (SF); (5) general health perceptions (GH); (6) role limitations due to emotional problems (RE); (7) vitality, energy or fatigue (VT); and (8) mental health (MH). The physical component summary was calculated based on all 8 scales of health. Each scale is transformed into 0-100 score, with higher scores indicating better health status. The analysis population was the FAS, with participants who had available data at all time point. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and weeks 12 to 28 | |

| End point values | Roxadustat | ESA (Erythropoiesis-Stimulating Agent) | | |
|--|-------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 384 | 404 | | |
| Units: Units on a scale | | | | |
| least squares mean (confidence interval 95%) | 0.560 (-0.029 to 1.148) | 0.039 (-0.528 to 0.605) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | |
| The model includes treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline SF-36 PCS, baseline Hb, as continuous covariates. | |
| Comparison groups | ESA (Erythropoiesis-Stimulating Agent) v Roxadustat |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 788 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.161 ^[63] |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.521 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.208 |
| upper limit | 1.25 |

Notes:

[63] - p-value for superiority test based on 2-sided significance level

Secondary: Change From BL to the Average of Weeks 12 to 28 in Anemia Subscale (AnS) ("Additional Concerns") of Functional Assessment of Cancer Therapy-Anemia (FACT-An) Score

| | |
|-----------------|--|
| End point title | Change From BL to the Average of Weeks 12 to 28 in Anemia Subscale (AnS) ("Additional Concerns") of Functional Assessment of Cancer Therapy-Anemia (FACT-An) Score |
|-----------------|--|

End point description:

Baseline FACT-An AnS was defined as the FACT-An Ans value on Day 1. The Functional Assessment of Cancer Therapy – General (FACT-G; version 4) contains 27 items that cover four dimensions of well-being: physical (PWB) – 7 items, functional (FWB) – 7 items, social/family (SWB) – 7 items, and emotional (EWB) – 6 items. The 'additional concerns' section contains 20 items: 13 fatigue specific items plus 7 additional items related to anemia. The 13 fatigue items plus the seven additional items related to anemia comprise the Anemia Subscale (AnS). Each individual item is scored from 0 (Not at all) to 4 (Very much), and then the total score is obtained by summation of the scores, with final higher score indicating better QoL. The analysis population was the FAS, with participants who had available data at all time point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and weeks 12 to 28

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|--|-------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 384 | 403 | | |
| Units: Units on a scale | | | | |
| least squares mean (confidence interval 95%) | 0.534 (-0.486 to 1.554) | 0.363 (-0.617 to 1.342) | | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

The model includes treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and

history of CV disease as fixed class factors and baseline FACT-An Ans, baseline Hb, as continuous covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 787 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.788 |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | 0.172 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.083 |
| upper limit | 1.426 |

Secondary: Change From BL to the Average Value of Weeks 12 to 28 in Total FACT-An Score

| | |
|--|--|
| End point title | Change From BL to the Average Value of Weeks 12 to 28 in Total FACT-An Score |
| End point description: | |
| Baseline Total FACT-An Score was defined as the FACT-An Total Score value on Day 1. Administration of the FACT-G plus the Anemia Subscale (AnS) is referred to as the FACT-An. The Functional Assessment of Cancer Therapy- General (FACT-G) Version 4 contains 27 items that cover 4 dimensions of physical well-being (PWB)—7 items, functional (FWB)—7 items, social/family (SWB)—7 items each, and emotional (EWB)—6 items. Each individual item is scored from 0 (Not at all) to 4 (Very much), and then the total score is obtained by summation of the scores, with final higher score indicating better QoL. The analysis population was the FAS, with participants who had available data at all time points. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and weeks 12 to 28 | |

| End point values | Roxadustat | ESA (Erythropoiesis-Stimulating Agent) | | |
|--|--------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 383 | 403 | | |
| Units: Units on a scale | | | | |
| least squares mean (confidence interval 95%) | -0.392 (-2.466 to 1.681) | -0.287 (-2.276 to 1.701) | | |

Statistical analyses

| | |
|---|------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | |
| The model includes treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline FACT-An Ans, baseline Hb, as continuous | |

covariates.

| | |
|---|---|
| Comparison groups | Roxadustat v ESA (Erythropoiesis-Stimulating Agent) |
| Number of subjects included in analysis | 786 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.936 |
| Method | Mixed models analysis |
| Parameter estimate | LSM Difference |
| Point estimate | -0.105 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.672 |
| upper limit | 2.462 |

Secondary: Change From BL to the Average of Weeks 12 to 28 in Euroqol Questionnaire-5 Dimensions 5 levels (EQ-5D 5L) Visual Analogue Scale (VAS) Score

| | |
|-----------------|---|
| End point title | Change From BL to the Average of Weeks 12 to 28 in Euroqol Questionnaire-5 Dimensions 5 levels (EQ-5D 5L) Visual Analogue Scale (VAS) Score |
|-----------------|---|

End point description:

Baseline assessment was defined as the value on Day 1. The EuroQol Questionnaire -5 Dimensions -5 Levels (EQ-5D-5L) is a self-reported questionnaire, used as a measure of respondents' Health Related Quality of Life (HRQoL) and utility values. The EQ-5D consists of the descriptive system and the visual analogue scale (VAS). The EQ-5D descriptive system comprises 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, extreme problems. The VAS records the respondent's self rated health status on a graduated (0–100) scale, where the endpoints are labeled 'Best imaginable health state' and 'Worst imaginable health state' with higher scores for higher HRQoL. The analysis population was the FAS, with participants who had available data at all time points.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and weeks 12 to 28

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|--------------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 385 | 401 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | 3.041 (± 14.910) | 2.735 (± 14.477) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Improvements Measured by Patients' Global Impression of Change (PGIC)

| | |
|-----------------|---|
| End point title | Percentage of Participants with Improvements Measured by Patients' Global Impression of Change (PGIC) |
|-----------------|---|

End point description:

The PGIC is a patient-rated instrument that measures change in participant's overall status on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse), when compared to the start of treatment. The percentage of participants presented includes very much improved, much improved and minimally improved. The analysis population was the FAS, with participants who had available data at all time points.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and weeks 8, 12, 28, 36, 52, 76, 104

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|-----------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 420 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Week 8 | 59.6 | 49.5 | | |
| Week 12 | 65.5 | 49.5 | | |
| Week 28 | 62.3 | 57.1 | | |
| Week 36 | 60.4 | 56.3 | | |
| Week 52 | 57.1 | 55.3 | | |
| Week 76 | 61.2 | 51.9 | | |
| Week 104 | 61.6 | 51.3 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From BL in Serum Hepcidin

| | |
|-----------------|----------------------------------|
| End point title | Change From BL in Serum Hepcidin |
|-----------------|----------------------------------|

End point description:

Baseline assessment was assessment from Day 1 visit. If baseline value was missing, the value from screening visit was used. In case of missing data, no imputation rules were applied. The analysis population was the FAS, with participants who had available data at baseline. N is the number of participants with available data at each time point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and weeks 4, 12, 20, 36, 52, 104, and End of Study (EOS - up to 108 weeks)

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|--------------------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 420 | | |
| Units: µg/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 [N=387,400] | -14.265 (± 42.393) | -4.265 (± 33.518) | | |
| Week 12 [N=375,391] | -12.298 (± 41.335) | -6.741 (± 38.507) | | |
| Week 20 [N=361,382] | -15.149 (± 43.152) | -11.818 (± 41.596) | | |
| Week 36 [N=332,366] | -23.405 (± 43.033) | -14.530 (± 43.449) | | |
| Week 52 [N=310,357] | -32.709 (± 42.342) | -17.522 (± 47.307) | | |
| Week 104 [N=242,298] | -40.101 (± 48.611) | -18.735 (± 51.632) | | |
| EOS (up to 108 weeks) [N=280,320] | -27.192 (± 52.169) | -17.664 (± 51.688) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From BL in Serum Ferritin

| | |
|--|----------------------------------|
| End point title | Change From BL in Serum Ferritin |
| End point description: | |
| Baseline assessment was assessment from Day 1 visit. If baseline value was missing, the value from screening visit was used. In case of missing data, no imputation rules were applied. The analysis population was the FAS, with participants who had available data at baseline. N is the number of participants with available data at each time point. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and weeks 4, 8, 12, 20, 28, 36, 44, 52, 60, 68, 76,84, 92, 100, 104, and EOS (up to 108 weeks) | |

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|--------------------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 420 | | |
| Units: pmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 [N=400,408] | -214.64 (± 824.96) | -141.78 (± 456.15) | | |
| Week 8 [N=394,405] | -245.37 (± 668.51) | -160.75 (± 607.39) | | |

| | | | | |
|-----------------------------------|---------------------|---------------------|--|--|
| Week 12 [N=389,404] | -269.76 (± 761.24) | -179.47 (± 586.95) | | |
| Week 20 [N=379,396] | -337.94 (± 645.73) | -246.89 (± 727.64) | | |
| Week 28 [N=363,392] | -427.46 (± 699.95) | -265.21 (± 816.64) | | |
| Week 36 [N=343,379] | -507.34 (± 726.61) | -269.26 (± 855.01) | | |
| Week 44 [N=328,371] | -545.14 (± 668.02) | -323.30 (± 986.38) | | |
| Week 52 [N=318,365] | -615.19 (± 677.97) | -347.58 (± 1058.87) | | |
| Week 60 [N=304,359] | -622.55 (± 675.22) | -394.40 (± 837.81) | | |
| Week 68 [N=293,349] | -604.47 (± 773.19) | -456.16 (± 1039.18) | | |
| Week 76 [N=283,339] | -646.76 (± 838.76) | -447.70 (± 967.63) | | |
| Week 84 [N=274,333] | -629.31 (± 1060.24) | -454.44 (± 1193.43) | | |
| Week 92 [N=258,326] | -749.58 (± 828.32) | -371.64 (± 1157.18) | | |
| Week 100 [N=250,313] | -746.86 (± 796.74) | -364.78 (± 1802.37) | | |
| Week 104 [N=248,308] | -753.82 (± 791.12) | -348.70 (± 1292.49) | | |
| EOS (up to 108 weeks) [N=290,323] | -554.53 (± 910.01) | -166.94 (± 2035.26) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From BL in Transferrin Saturation (TSAT)

| | |
|--|---|
| End point title | Change From BL in Transferrin Saturation (TSAT) |
| End point description: | |
| Baseline assessment was assessment from Day 1 visit. If baseline value was missing, the value from screening visit was used. In case of missing data, no imputation rules were applied. The analysis population was the FAS, with participants who had available data at baseline. N is the number of participants with available data at each time point. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and weeks 4, 8, 12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, 100, 104 and EOS (up to 108 weeks) | |

| End point values | Roxadustat | ESA (Erythropoiesis-Stimulating Agent) | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 412 | 420 | | |
| Units: Percentage of saturation | | | | |
| arithmetic mean (standard deviation) | | | | |

| | | | | |
|-----------------------------------|-------------------|-------------------|--|--|
| Week 4 [N=392,402] | -4.151 (± 16.147) | -2.331 (± 13.178) | | |
| Week 8 [N=383,399] | -3.681 (± 17.062) | -3.128 (± 14.461) | | |
| Week 12 [N=381,397] | -2.643 (± 17.551) | -3.189 (± 13.912) | | |
| Week 20 [N=363,387] | -3.782 (± 16.634) | -4.398 (± 14.444) | | |
| Week 28 [N=356,385] | -5.463 (± 17.798) | -3.829 (± 15.216) | | |
| Week 36 [N=336,372] | -5.351 (± 17.803) | -4.022 (± 15.471) | | |
| Week 44 [N=320,358] | -6.069 (± 16.349) | -5.254 (± 15.144) | | |
| Week 52 [N=313,353] | -7.278 (± 17.244) | -5.788 (± 14.666) | | |
| Week 60 [N=295,348] | -6.997 (± 16.774) | -5.187 (± 16.097) | | |
| Week 68 [N=287,338] | -7.279 (± 17.809) | -6.237 (± 15.934) | | |
| Week 76 [N=275,332] | -7.156 (± 17.682) | -6.623 (± 16.395) | | |
| Week 84 [N=270,331] | -7.867 (± 17.654) | -5.378 (± 17.771) | | |
| Week 92 [N=251,320] | -6.996 (± 19.850) | -6.259 (± 16.605) | | |
| Week 100 [N=248,308] | -8.379 (± 17.809) | -6.354 (± 17.147) | | |
| Week 104 [N=243,299] | -7.650 (± 17.842) | -5.054 (± 17.195) | | |
| EOS (up to 108 weeks) [N=283,321] | -5.466 (± 16.626) | -3.763 (± 17.813) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From BL in Glycated Hemoglobin (HbA1c) Level

| | |
|-----------------|---|
| End point title | Change From BL in Glycated Hemoglobin (HbA1c) Level |
|-----------------|---|

End point description:

Baseline assessment was assessment from Day 1 visit. If baseline value was missing, the value from screening visit was used. In case of missing data, no imputation rules were applied. The analysis population was the FAS, with participants who had available data at baseline. N is the number of participants with available data at each time point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and weeks 12, 28, 36, 44, 52, 60, 84, 104 and EOS (up to 108 weeks)

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|--------------------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 413 | 419 | | |
| Units: Fraction of 1 | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 12 [N=385,401] | 0.0009 (± 0.0071) | -0.0005 (± 0.0057) | | |
| Week 28 [N=360,389] | -0.0004 (± 0.0067) | -0.0006 (± 0.0064) | | |
| Week 36 [N=342,378] | -0.0001 (± 0.0065) | -0.0004 (± 0.0067) | | |
| Week 44 [N=327,370] | -0.0001 (± 0.0069) | -0.0006 (± 0.0067) | | |
| Week 52 [N=317,363] | -0.0001 (± 0.0070) | -0.0007 (± 0.0068) | | |
| Week 60 [N=303,355] | 0.0000 (± 0.0080) | -0.0004 (± 0.0070) | | |
| Week 84 [N=269,331] | 0.0003 (± 0.0072) | 0.0001 (± 0.0078) | | |
| Week 104 [N=242,305] | 0.0000 (± 0.0075) | -0.0003 (± 0.0082) | | |
| EOS (up to 108 weeks) [N=286,319] | 0.0011 (± 0.0076) | 0.0001 (± 0.0080) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment-Emergent Adverse Events (TEAEs)

| | |
|--|---|
| End point title | Number of Participants with Treatment-Emergent Adverse Events (TEAEs) |
| End point description: | |
| Safety was assessed by evaluation of the following variables: (TEAEs; frequency, severity, seriousness, and relationship to study drug), Vital signs (systolic and diastolic blood pressure, pulse, respiratory rate and weight), Clinical laboratory variables (hematology, biochemistry including liver enzymes and total bilirubin, and urinalysis), Physical examination, 12-lead electrocardiogram (ECG) and Vascular Access Thrombosis. All AEs collected during the Safety Emergent Period were counted as TEAE. The TEAE was defined as an adverse event (AE) if it was observed after starting administration of the roxadustat or ESA. Any clinically significant abnormalities were reported as an AE. All reported deaths after the first study drug administration and up to 28 days after the Analysis Date of Last Dose and considering last dosing frequency. The analysis population was the Safety Analysis Set (SAF) which consisted of all randomized participants who received at least one dose of study drug. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to EOS (Up to week 108) | |

| End point values | Roxadustat | ESA (Erythropoiesis -Stimulating Agent) | | |
|---|-----------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 414 | 420 | | |
| Units: Participants | | | | |
| TEAE | 359 | 361 | | |
| Drug-Related TEAE | 77 | 35 | | |
| Serious TEAE | 210 | 189 | | |
| Drug-Related Serious TEAE | 33 | 10 | | |
| TEAE Leading to Death | 67 | 55 | | |
| Drug-Related TEAE Leading to Death | 5 | 2 | | |
| TEAE Leading to Withdrawal of Treatment | 35 | 16 | | |
| Drug-Related TEAE Leading to Withdraw of Treatment | 9 | 1 | | |
| TEAE NCI CTC Grades 3 or Higher | 181 | 149 | | |
| Death During the Safety Emergent Period | 64 | 51 | | |
| Death | 78 | 59 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to End of Study (EOS) (Up to week 108)

Adverse event reporting additional description:

The Safety Emergent Period was defined as the evaluation period from the Analysis date of first drug intake up to 28 days after the end of treatment taking into account the different dosing frequencies of the study treatments.

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

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 20 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | Roxadustat |
|-----------------------|------------|

Reporting group description:

Participants received roxadustat three times a week (TIW) for at least 40 weeks up to a maximum of 104 weeks. Treatment dosage was adjusted according to the pre-specified rule of keeping the participant's Hb levels between 10.0 to 12.0 g/dL.

| | |
|-----------------------|--|
| Reporting group title | ESA (Erythropoiesis-Stimulating Agent) |
|-----------------------|--|

Reporting group description:

Participants received epoetin alfa once weekly, twice weekly or TIW and darbepoetin alfa once a week or once every other week. Treatment dosage was adjusted according to the pre-specified rule of keeping the participant's Hb levels between 10.0 to 12.0 g/dL.

| Serious adverse events | Roxadustat | ESA (Erythropoiesis-Stimulating Agent) | |
|---|--------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 210 / 414 (50.72%) | 189 / 420 (45.00%) | |
| number of deaths (all causes) | 78 | 59 | |
| number of deaths resulting from adverse events | 67 | 55 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute myeloid leukaemia | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adenocarcinoma gastric | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adenocarcinoma of colon | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Benign lung neoplasm | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Benign renal neoplasm | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder cancer | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bowen's disease | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carcinoid tumour pulmonary | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon adenoma | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon cancer | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colorectal adenocarcinoma | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colorectal cancer metastatic | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endometrial adenocarcinoma | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemangioma of bone | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypopharyngeal neoplasm | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Kidney angiomyolipoma | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung neoplasm | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 3 / 414 (0.72%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Malignant neoplasm of choroid | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to liver | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastatic neoplasm | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ovarian neoplasm | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Papillary thyroid cancer | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Parathyroid tumour benign | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Penile cancer | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Refractory anaemia with an excess of blasts | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal cell carcinoma | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin cancer | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small cell lung cancer | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Squamous cell carcinoma of lung | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Aortic dissection | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic stenosis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arterial disorder | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Circulatory collapse | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 4 / 414 (0.97%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic vascular disorder | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dry gangrene | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 3 / 420 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 10 / 414 (2.42%) | 5 / 420 (1.19%) | |
| occurrences causally related to treatment / all | 3 / 10 | 2 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 3 / 414 (0.72%) | 3 / 420 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 4 / 414 (0.97%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Intermittent claudication | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphoedema | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant hypertension | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 4 / 420 (0.95%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Peripheral artery occlusion | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 3 / 420 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery stenosis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery thrombosis | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 4 / 420 (0.95%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral vascular disorder | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Steal syndrome | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subclavian artery thrombosis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subclavian vein thrombosis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vasculitis necrotising | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Venous stenosis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Catheter placement | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Therapy cessation | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| General disorders and administration site conditions | | | |

| | | | |
|---|-----------------|-----------------|--|
| Asthenia | | | |
| subjects affected / exposed | 3 / 414 (0.72%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Catheter site haematoma | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Catheter site inflammation | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Chills | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Complication associated with device | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 6 / 414 (1.45%) | 3 / 420 (0.71%) | |
| occurrences causally related to treatment / all | 1 / 6 | 0 / 3 | |
| deaths causally related to treatment / all | 1 / 6 | 0 / 3 | |
| Device related thrombosis | | | |
| subjects affected / exposed | 3 / 414 (0.72%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperthermia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Impaired healing | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malaise | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Medical device site phlebitis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 4 / 414 (0.97%) | 4 / 420 (0.95%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden cardiac death | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Sudden death | | | |
| subjects affected / exposed | 7 / 414 (1.69%) | 3 / 420 (0.71%) | |
| occurrences causally related to treatment / all | 1 / 7 | 0 / 3 | |
| deaths causally related to treatment / all | 1 / 7 | 0 / 3 | |
| Vascular stent stenosis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Anti-neutrophil cytoplasmic antibody positive vasculitis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal transplant failure | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Ovarian disorder | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine polyp | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Bronchitis chronic | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic respiratory failure | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Dyspnoea | | | |
| subjects affected / exposed | 4 / 414 (0.97%) | 4 / 420 (0.95%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Eosinophilic pneumonia | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 6 / 414 (1.45%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural thickening | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleurisy | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary alveolar haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 4 / 414 (0.97%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 3 | 0 / 1 | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pulmonary infarction | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 6 / 414 (1.45%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 1 / 6 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory arrest | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory failure | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Delirium | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disorientation | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fear of falling | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mental disorder due to a general medical condition | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Organic brain syndrome | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| Device dislocation | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device failure | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device malfunction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 4 / 414 (0.97%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Blood potassium increased | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrocardiogram abnormal | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriovenous fistula aneurysm | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriovenous fistula occlusion | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriovenous fistula site complication | | | |
| subjects affected / exposed | 6 / 414 (1.45%) | 5 / 420 (1.19%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriovenous fistula site haemorrhage | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 2 / 414 (0.48%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriovenous fistula thrombosis | | | |
| subjects affected / exposed | 29 / 414 (7.00%) | 15 / 420 (3.57%) | |
| occurrences causally related to treatment / all | 6 / 37 | 4 / 18 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriovenous graft site haemorrhage | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriovenous graft site stenosis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriovenous graft thrombosis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back injury | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Comminuted fracture | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Concussion | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Facial bones fracture | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 6 / 420 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 5 / 420 (1.19%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Graft thrombosis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Head injury | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ligament rupture | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Limb injury | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 414 (0.00%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lip injury | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower limb fracture | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Poisoning | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Post procedural haematoma | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural inflammation | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural complication | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pubis fracture | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shunt aneurysm | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shunt malfunction | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shunt occlusion | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shunt stenosis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shunt thrombosis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 4 / 420 (0.95%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin injury | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin wound | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal fracture | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thermal burn | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thoracic vertebral fracture | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tibia fracture | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ulna fracture | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper limb fracture | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular access malfunction | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular access site haemorrhage | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular pseudoaneurysm | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 3 / 414 (0.72%) | 3 / 420 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 1 | |
| Acute left ventricular failure | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 2 / 414 (0.48%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 9 / 414 (2.17%) | 11 / 420 (2.62%) | |
| occurrences causally related to treatment / all | 0 / 9 | 1 / 13 | |
| deaths causally related to treatment / all | 0 / 4 | 1 / 6 | |
| Angina pectoris | | | |
| subjects affected / exposed | 5 / 414 (1.21%) | 6 / 420 (1.43%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic valve stenosis | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Arteriosclerosis coronary artery | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 12 / 414 (2.90%) | 8 / 420 (1.90%) | |
| occurrences causally related to treatment / all | 1 / 14 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial tachycardia | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block second degree | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 4 / 414 (0.97%) | 8 / 420 (1.90%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 6 | |
| Cardiac failure | | | |
| subjects affected / exposed | 8 / 414 (1.93%) | 9 / 420 (2.14%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 5 | 0 / 3 | |
| Cardiac failure acute | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 414 (0.72%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 5 / 414 (1.21%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac fibrillation | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | |
| Cardiogenic shock | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 3 / 414 (0.72%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 1 | |
| Cardiovascular insufficiency | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Coronary artery disease | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 414 (0.48%) | 3 / 420 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diastolic dysfunction | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive heart disease | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left ventricular failure | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mitral valve stenosis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Myocardial infarction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 6 / 420 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 4 / 414 (0.97%) | 4 / 420 (0.95%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pericarditis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus node dysfunction | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 5 / 420 (1.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachyarrhythmia | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tricuspid valve incompetence | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular arrhythmia | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular fibrillation | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Nervous system disorders | | | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carpal tunnel syndrome | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebellar infarction | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral arteriosclerosis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral artery occlusion | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 4 / 420 (0.95%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral ischaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 3 / 414 (0.72%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Cerebrovascular disorder | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cognitive disorder | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coma | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Disturbance in attention | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolic cerebral infarction | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalopathy | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epileptic encephalopathy | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Generalised tonic-clonic seizure | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hypoxic-ischaemic encephalopathy | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Idiopathic partial epilepsy | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lethargy | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Loss of consciousness | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular dementia | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertigo CNS origin | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 5 / 414 (1.21%) | 7 / 420 (1.67%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hypocoagulable state | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Hypoacusis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Angle closure glaucoma | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cataract | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye haemorrhage | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal adhesions | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal wall haematoma | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute abdomen | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal fissure | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal fistula | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal incontinence | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic gastritis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis ischaemic | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 3 / 420 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulum | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulum intestinal | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer | | | |
| subjects affected / exposed | 4 / 414 (0.97%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erosive duodenitis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Faecaloma | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis erosive | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 6 / 420 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal ischaemia | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gastrointestinal necrosis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus paralytic | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal ischaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal ulcer perforation | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intra-abdominal haematoma | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine perforation | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mechanical ileus | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Melaena | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 414 (0.48%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal ulcer | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophagitis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 3 / 420 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ulcerative gastritis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Bile duct obstruction | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bile duct stone | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholangitis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 3 / 420 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatotoxicity | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaundice | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Cutaneous vasculitis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic foot | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 414 (0.00%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ingrowing nail | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neurodermatitis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash vesicular | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin lesion | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Skin necrosis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin ulcer | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toxic epidermal necrolysis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Urticaria | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Calculus urinary | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| End stage renal disease | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal cyst ruptured | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tubulointerstitial nephritis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urethral perforation | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinoma | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Hyperparathyroidism secondary | | | |
| subjects affected / exposed | 3 / 414 (0.72%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toxic goitre | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fistula discharge | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Joint contracture | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mobility decreased | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteitis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sarcopenia | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |

| | | | |
|---|-----------------|-----------------|--|
| Abdominal abscess | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Abdominal infection | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abscess neck | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute hepatitis B | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriovenous fistula site infection | | | |
| subjects affected / exposed | 3 / 414 (0.72%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthritis bacterial | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacterial sepsis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Biliary sepsis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 5 / 414 (1.21%) | 3 / 420 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis infective | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 3 / 420 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related sepsis | | | |
| subjects affected / exposed | 3 / 414 (0.72%) | 3 / 420 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Diabetic gangrene | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalomyelitis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocarditis | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Enterobacter bacteraemia | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterococcal sepsis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 3 / 420 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia bacteraemia | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fungal oesophagitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gangrene | | | |
| subjects affected / exposed | 5 / 414 (1.21%) | 4 / 420 (0.95%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer helicobacter | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 6 / 420 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal candidiasis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematoma infection | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Incision site infection | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infected skin ulcer | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infectious colitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 414 (0.00%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral discitis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver abscess | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised infection | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung abscess | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Medical device site joint infection | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis bacterial | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis bacterial | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Penile abscess | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Periodontitis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 10 / 414 (2.42%) | 3 / 420 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 15 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Peritonitis bacterial | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 15 / 414 (3.62%) | 21 / 420 (5.00%) | |
| occurrences causally related to treatment / all | 0 / 15 | 0 / 22 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 6 | |
| Pneumonia pneumococcal | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pseudomonal sepsis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pyelonephritis chronic | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyonephrosis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal abscess | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal cyst infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection bacterial | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 8 / 414 (1.93%) | 9 / 420 (2.14%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 3 | |
| Sepsis syndrome | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin infection | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Soft tissue infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 3 / 414 (0.72%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Streptococcal sepsis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic infection | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Tracheobronchitis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 4 / 414 (0.97%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection enterococcal | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection pseudomonal | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection staphylococcal | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Cachexia | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Dehydration | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fluid overload | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 2 / 420 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fluid retention | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 4 / 414 (0.97%) | 3 / 420 (0.71%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hypervolaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 420 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 420 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Roxadustat | ESA (Erythropoiesis-Stimulating Agent) | |
|---|--------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 210 / 414 (50.72%) | 209 / 420 (49.76%) | |
| Injury, poisoning and procedural complications | | | |
| Arteriovenous fistula thrombosis | | | |
| subjects affected / exposed | 27 / 414 (6.52%) | 18 / 420 (4.29%) | |
| occurrences (all) | 34 | 21 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 66 / 414 (15.94%) | 75 / 420 (17.86%) | |
| occurrences (all) | 101 | 116 | |
| Hypotension | | | |
| subjects affected / exposed | 30 / 414 (7.25%) | 26 / 420 (6.19%) | |
| occurrences (all) | 40 | 40 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 36 / 414 (8.70%) | 29 / 420 (6.90%) | |
| occurrences (all) | 41 | 39 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |

| | | | |
|--|------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 33 / 414 (7.97%) 51 | 32 / 420 (7.62%) 60 | |
| Nausea subjects affected / exposed occurrences (all) | 27 / 414 (6.52%) 29 | 8 / 420 (1.90%) 10 | |
| Endocrine disorders Hyperparathyroidism secondary subjects affected / exposed occurrences (all) | 21 / 414 (5.07%) 21 | 16 / 420 (3.81%) 17 | |
| Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all) | 15 / 414 (3.62%) 21 | 33 / 420 (7.86%) 48 | |
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) | 29 / 414 (7.00%) 38 | 27 / 420 (6.43%) 34 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 14 / 414 (3.38%) 19 | 21 / 420 (5.00%) 29 | |
| Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 28 / 414 (6.76%) 61 | 39 / 420 (9.29%) 68 | |
| Metabolism and nutrition disorders Iron deficiency subjects affected / exposed occurrences (all) | 30 / 414 (7.25%) 39 | 51 / 420 (12.14%) 64 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------|---|
| 13 May 2015 | <p>The changes include:</p> <ul style="list-style-type: none">-For patients randomized to roxadustat, maximum dose was reduced from 3.5 mg/kg to 3.0 mg/kg.-For patients randomized to receive ESA, (i.e., epoetin alfa or darbepoetin alfa), dosing frequencies were converted to the protocol pre-specified frequencies irrespective of their frequency of administration prior to randomization.-Another primary efficacy endpoint added to support submission of the data to the US health authority (FDA). Existing primary efficacy endpoint was made specific for the EU submission. An additional secondary endpoint (Patients' Global Impression of Change) was added. None of these changes were driven by safety concerns. |
| 13 May 2015 | <p>The changes include:</p> <ul style="list-style-type: none">-Substantial changes included collection of serious adverse events (SAEs) and cardiovascular and thromboembolic adverse events (AEs) instead of hospitalizations during the follow-up period; requirement for female and male patients that, if required by local law, two highly effective methods of birth control be used, one of which must be a barrier method; the change in Hb over the past 4 weeks which was used for decisions on dose adjustments, was increased from ± 0.8 g/dL to ± 1.0 g/dL; the roxadustat dosing rules for excessive hematopoiesis were consolidated into one rule: "If Hb increased by > 2.0 g/dL within 4 weeks, the dose was to be reduced by one dose step."; the text of ESA rescue therapy was updated; the text on the use of supplemental iron was updated and clarified; the statistical section was updated: a sensitivity analysis was added to check for homogeneity of the treatment difference before and after the protocol amendment; optional additional assessments at unscheduled visits were added; guidance text on the concomitant use of statins and other drugs that are substrates for Organic anion transporting polypeptide 1B1 was updated; information was added regarding the potential interaction between roxadustat and phosphate binders; lower strengths were added to the ESA study treatments and relevant medical conditions was clarified. |
| 13 May 2015 | <p>The changes include:</p> <ul style="list-style-type: none">-The treatment period was 104 weeks and is being changed to a variable treatment period with a minimum of 52 weeks and maximum of 104 weeks.-A planned interim analysis was to be performed when all patients had completed 52 weeks of treatment; this interim analysis was removed. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Overall 838 were randomized to receive treatment. Two participants randomized to the pooled ESA treatment group were excluded due to GCP violations and their data was excluded. Total of 836 were considered randomized.

Notes:

