



Clinical trial results:

A Phase 3, Randomized, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of Roxadustat for the Treatment of Anemia in Chronic Kidney Disease Patients not on Dialysis

Summary

| | |
|--------------------------|----------------------------|
| EudraCT number | 2012-005180-27 |
| Trial protocol | GB BE HU IT ES BG PL EE GR |
| Global end of trial date | 01 November 2017 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v3 (current) |
| This version publication date | 17 April 2021 |
| First version publication date | 16 November 2018 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | 1517-CL-0608 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01887600 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Astellas Pharma Europe B.V. (APEB) |
| Sponsor organisation address | Sylviusweg 62, Leiden, Netherlands, 2333 BE |
| Public contact | Clinical Trial Disclosure, Astellas Pharma Europe B.V. (APEB), 31 (0) 71 5455 050, astellas.resultsdisclosure@astellas.com |
| Scientific contact | Clinical Trial Disclosure, Astellas Pharma Europe B.V. (APEB), 31 (0) 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 | 01 November 2017 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 November 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of roxadustat in the treatment of anemia in non-dialysis chronic kidney disease (CKD) participants.

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: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 03 September 2013 |
| 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 | Belarus: 12 |
| Country: Number of subjects enrolled | Belgium: 9 |
| Country: Number of subjects enrolled | Bulgaria: 35 |
| Country: Number of subjects enrolled | Colombia: 3 |
| Country: Number of subjects enrolled | Dominican Republic: 12 |
| Country: Number of subjects enrolled | Estonia: 1 |
| Country: Number of subjects enrolled | Georgia: 17 |
| Country: Number of subjects enrolled | Greece: 6 |
| Country: Number of subjects enrolled | Guatemala: 27 |
| Country: Number of subjects enrolled | Hungary: 12 |
| Country: Number of subjects enrolled | Italy: 6 |
| Country: Number of subjects enrolled | Panama: 12 |
| Country: Number of subjects enrolled | Peru: 3 |
| Country: Number of subjects enrolled | Poland: 48 |
| Country: Number of subjects enrolled | Romania: 46 |
| Country: Number of subjects enrolled | Russian Federation: 98 |
| Country: Number of subjects enrolled | South Africa: 16 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Spain: 17 |
| Country: Number of subjects enrolled | Turkey: 19 |
| Country: Number of subjects enrolled | United Kingdom: 12 |
| Country: Number of subjects enrolled | Ukraine: 98 |
| Country: Number of subjects enrolled | Serbia: 85 |
| Worldwide total number of subjects | 594 |
| EEA total number of subjects | 180 |

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) | 335 |
| From 65 to 84 years | 249 |
| 85 years and over | 10 |

Subject disposition

Recruitment

Recruitment details:

Study population consisted of anemic participants with stages 3, 4 or 5 chronic kidney disease (CKD) (eGFR < 60 mL/min/1.73 m²) who are not on dialysis. Participants were recruited from 125 study centers located in 22 countries.

Pre-assignment

Screening details:

A total of 594 participants with CKD were randomized to receive one of the 2 treatment arms in a 2:1 ratio receiving roxadustat or placebo. Anemia was defined as a mean Hb ≤ 10.0 g/dL upon repeated measurements during the screening period. Participants needed a ferritin ≥ 30 ng/mL (≥ 67.4 pmol/L) and transferrin saturation (TSAT) ≥ 5%.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Overall Treatment Period (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Subject |

Arms

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

Arm description:

Participants received roxadustat according to the tiered weight-based approach, with starting doses of 70 mg given thrice weekly (TIW) to participants weighing up to 70 kg and 100 mg given TIW to participants weighing more than 70 kg. Dose-titration was performed based upon regular measurement of Hb levels until participants achieved central Hb value of ≥ 11.0 g/dL and Hb increase from baseline (BL) of ≥ 1.0 g/dL at two consecutive study visits, separated by at least 5 days. Once target Hb level was reached participants entered maintenance period during which roxadustat dosage was adjusted every 4 weeks to maintain participants Hb level within the target range of 10.0 g/dL and 12.0 g/dL. Participants received roxadustat for at least 52 weeks up to a maximum of 104 weeks.

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

Dosage and administration details:

Roxadustat was administered initially according to the tiered weight-based dosing, where participants with weight from ≥ 45 to ≤ 70 kg received 70 mg and participants with > 70 to ≤ 160 kg received 100 mg of roxadustat. Dose-titration based upon regular measurement of Hb levels was performed until participants achieved central Hb value of ≥ 11.0 g/dL and Hb increase from baseline (BL) of ≥ 1.0 g/dL at two consecutive study visits, separated by at least 5 days. Once target Hb level was reached participants entered maintenance period during which roxadustat dosage was adjusted every 4 weeks to maintain participants Hb level within the target range of 10.0 g/dL and 12.0 g/dL.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Participants received matching placebo according to the tiered weight-based approach, with starting doses of 70 mg given thrice weekly (TIW) to participants weighing up to 70 kg and 100 mg given TIW to participants weighing more than 70 kg. Dose-titration was performed based upon regular measurement of Hb levels until participants achieved central Hb value of ≥ 11.0 g/dL and Hb increase from baseline (BL) of ≥ 1.0 g/dL at two consecutive study visits, separated by at least 5 days. Once target Hb level was reached participants entered maintenance period during which roxadustat dosage was adjusted every 4 weeks to maintain participants Hb level within the target range of 10.0 g/dL and 12.0 g/dL. Participants received matching placebo for at least 52 weeks up to a maximum of 104 weeks.

| | |
|--|----------|
| Arm type | Placebo |
| Investigational medicinal product name | placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo was administered initially according to the tiered weight-based dosing, where participants with weight from ≥ 45 to ≤ 70 kg received 70 mg and participants with > 70 to ≤ 160 kg received 100 mg of roxadustat. Dose-titration based upon regular measurement of Hb levels was performed until participants achieved central Hb value of ≥ 11.0 g/dL and Hb increase from baseline (BL) of ≥ 1.0 g/dL at two consecutive study visits, separated by at least 5 days. Once target Hb level was reached participants entered maintenance period during which roxadustat dosage was adjusted every 4 weeks to maintain participants Hb level within the target range of 10.0 g/dL and 12.0 g/dL.

| Number of subjects in period 1 | Roxadustat | Placebo |
|---------------------------------------|------------|---------|
| Started | 391 | 203 |
| Treatment Received | 391 | 203 |
| Completed | 245 | 89 |
| Not completed | 146 | 114 |
| Physician decision | 7 | 8 |
| Consent withdrawn by subject | 58 | 52 |
| Adverse Event | 21 | 9 |
| Death | 39 | 16 |
| Miscellaneous | 6 | 2 |
| Non-compliance with study drug | 3 | - |
| Lost to follow-up | 5 | 1 |
| Progressive disease | 1 | - |
| Lack of efficacy | 3 | 26 |
| Protocol deviation | 3 | - |

Baseline characteristics

Reporting groups

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

Reporting group description:

Participants received roxadustat according to the tiered weight-based approach, with starting doses of 70 mg given thrice weekly (TIW) to participants weighing up to 70 kg and 100 mg given TIW to participants weighing more than 70 kg. Dose-titration was performed based upon regular measurement of Hb levels until participants achieved central Hb value of ≥ 11.0 g/dL and Hb increase from baseline (BL) of ≥ 1.0 g/dL at two consecutive study visits, separated by at least 5 days. Once target Hb level was reached participants entered maintenance period during which roxadustat dosage was adjusted every 4 weeks to maintain participants Hb level within the target range of 10.0 g/dL and 12.0 g/dL. Participants received roxadustat for at least 52 weeks up to a maximum of 104 weeks.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Participants received matching placebo according to the tiered weight-based approach, with starting doses of 70 mg given thrice weekly (TIW) to participants weighing up to 70 kg and 100 mg given TIW to participants weighing more than 70 kg. Dose-titration was performed based upon regular measurement of Hb levels until participants achieved central Hb value of ≥ 11.0 g/dL and Hb increase from baseline (BL) of ≥ 1.0 g/dL at two consecutive study visits, separated by at least 5 days. Once target Hb level was reached participants entered maintenance period during which roxadustat dosage was adjusted every 4 weeks to maintain participants Hb level within the target range of 10.0 g/dL and 12.0 g/dL. Participants received matching placebo for at least 52 weeks up to a maximum of 104 weeks.

| Reporting group values | Roxadustat | Placebo | Total |
|------------------------|------------|---------|-------|
| Number of subjects | 391 | 203 | 594 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|--|------------|------------|-----|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 60.6 | 61.7 | |
| standard deviation | ± 13.5 | ± 13.8 | - |
| Gender categorical | | | |
| Units: | | | |
| Male | 169 | 99 | 268 |
| Female | 222 | 104 | 326 |
| Race | | | |
| Units: Subjects | | | |
| White | 335 | 182 | 517 |
| Black or African American | 10 | 3 | 13 |
| Asian | 9 | 0 | 9 |
| Other | 37 | 18 | 55 |
| History of Diabetes | | | |
| Units: Subjects | | | |
| 1. Yes | 146 | 89 | 235 |
| 2. No | 245 | 114 | 359 |
| Iron Repletion at Baseline | | | |
| Units: Subjects | | | |
| TSAT $\geq 20\%$ and Ferritin ≥ 100 ng/mL | 204 | 109 | 313 |
| TSAT $< 20\%$ or Ferritin < 100 ng/mL | 187 | 94 | 281 |

| | | | |
|--|--------|--------|---|
| Baseline Hemoglobin (Baseline Hb) Value | | | |
| 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). | | | |
| Units: g/dL | | | |
| arithmetic mean | 9.08 | 9.10 | |
| standard deviation | ± 0.76 | ± 0.72 | - |
| Baseline Estimated Glomerular Filtration Rate (eGFR) | | | |
| Units: ml/min/1.73 m ² | | | |
| arithmetic mean | 16.5 | 17.2 | |
| standard deviation | ± 10.2 | ± 11.7 | - |
| Time From Chronic Kidney Disease (CKD) Diagnosis | | | |
| Units: Years | | | |
| arithmetic mean | 5.65 | 4.91 | |
| standard deviation | ± 7.02 | ± 5.99 | - |

End points

End points reporting groups

| | |
|---|------------|
| Reporting group title | Roxadustat |
| Reporting group description: | |
| Participants received roxadustat according to the tiered weight-based approach, with starting doses of 70 mg given thrice weekly (TIW) to participants weighing up to 70 kg and 100 mg given TIW to participants weighing more than 70 kg. Dose-titration was performed based upon regular measurement of Hb levels until participants achieved central Hb value of ≥ 11.0 g/dL and Hb increase from baseline (BL) of ≥ 1.0 g/dL at two consecutive study visits, separated by at least 5 days. Once target Hb level was reached participants entered maintenance period during which roxadustat dosage was adjusted every 4 weeks to maintain participants Hb level within the target range of 10.0 g/dL and 12.0 g/dL. Participants received roxadustat for at least 52 weeks up to a maximum of 104 weeks. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants received matching placebo according to the tiered weight-based approach, with starting doses of 70 mg given thrice weekly (TIW) to participants weighing up to 70 kg and 100 mg given TIW to participants weighing more than 70 kg. Dose-titration was performed based upon regular measurement of Hb levels until participants achieved central Hb value of ≥ 11.0 g/dL and Hb increase from baseline (BL) of ≥ 1.0 g/dL at two consecutive study visits, separated by at least 5 days. Once target Hb level was reached participants entered maintenance period during which roxadustat dosage was adjusted every 4 weeks to maintain participants Hb level within the target range of 10.0 g/dL and 12.0 g/dL. Participants received matching placebo for at least 52 weeks up to a maximum of 104 weeks. | |

Primary: Percentage of Participants With a Hemoglobin (Hb) Response to Treatment at Two Consecutive Visits During the First 24 Weeks of Treatment Without Rescue Therapy Prior to Hb Response

| | |
|--|--|
| End point title | Percentage of Participants With a Hemoglobin (Hb) Response to Treatment at Two Consecutive Visits During the First 24 Weeks of Treatment Without Rescue Therapy Prior to Hb Response |
| End point description: | |
| Hemoglobin (Hb) response was measured as Yes or No. Response Yes (responders) was defined as: Hb ≥ 11.0 g/dL and Hb increase from baseline by ≥ 1.0 g/dL, for participants with baseline Hb > 8.0 g/dL; or Hb increase from baseline by ≥ 2.0 g/dL, for participants with baseline Hb ≤ 8.0 g/dL at two consecutive visits with available data separated at least 5 days during the first 24 weeks of treatment without having received rescue therapy (red blood cell (RBC) transfusion, erythropoiesis-stimulating agent (ESA), or intravenous (IV) iron prior to Hb response. This was the primary efficacy endpoint for EU (EMA). The analysis population was the full analysis set (FAS), which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline to week 24 | |

| End point values | Roxadustat | Placebo | | |
|-----------------------------------|---------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | | | | |
| Responders | 79.2 (74.8 to 83.1) | 9.9 (6.1 to 14.8) | | |

Statistical analyses

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|---|--|
| Statistical analysis title | Hemoglobin (Hb) Response to Treatment (Yes/No) |
| Statistical analysis description: The Cochran-Mantel-Haenszel (CMH) test was adjusted by region, history of cardiovascular, cerebrovascular or thromboembolic (CV) disease, baseline Hb and baseline estimated glomerular filtration rate (eGFR). Superiority of roxadustat versus placebo was to be declared if the lower bound of the two-sided 95% confidence interval of the CMH odds ratio was higher than 1. | |
| Comparison groups | Placebo v Roxadustat |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 34.74 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 20.48 |
| upper limit | 58.93 |

Primary: Hb Change From Baseline (BL) to the Average Hb in Weeks 28-52 Regardless of Rescue Therapy

| | |
|--|--|
| End point title | Hb Change From Baseline (BL) to the Average Hb in Weeks 28-52 Regardless of Rescue Therapy |
| End point description: The change from baseline to the average Hb values across weeks 28 to 52 without having received rescue therapy. The Hb values from visit windows at weeks 28, 32, 36, 40, 44, 48 and 52 were used for the calculation of the average of weeks 28 to 52. This was the primary efficacy endpoint for US (FDA). The analysis population was All Randomized, and it consisted of all randomized participants with available data at all time points. | |
| End point type | Primary |
| End point timeframe: Baseline and weeks 28 to 52 | |

| | | | | |
|--|----------------------|----------------------|--|--|
| End point values | Roxadustat | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 312 | 146 | | |
| Units: g/dL | | | | |
| least squares mean (confidence interval 95%) | 1.992 (1.82 to 2.16) | 0.300 (0.09 to 0.51) | | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Change From BL to the Average Hb in Weeks 28-52 |
|-----------------------------------|---|

Statistical analysis description:

The Analysis of Covariance (ANCOVA) with Multiple Imputations (MI) model, adjusting for covariates was used for the analysis. The model included treatment as fixed factor, region and history of CV disease as class factors and baseline Hb, baseline eGFR as continuous covariates. Superiority of roxadustat versus placebo was considered successful if the lower bound of the two-sided 95% confidence interval of the difference between treatment arms (roxadustat minus placebo) was higher than 0.

| | |
|---|-------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 458 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.692 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.52 |
| upper limit | 1.86 |

Secondary: Hb Change From BL to the Average Hb in Weeks 28-36 Without Having Received Rescue Therapy Within 6 Weeks Prior to and During 8-Week Evaluation Period

| | |
|-----------------|---|
| End point title | Hb Change From BL to the Average Hb in Weeks 28-36 Without Having Received Rescue Therapy Within 6 Weeks Prior to and During 8-Week Evaluation Period |
|-----------------|---|

End point description:

The Hb values from visit windows at weeks 28, 32 and 36 were used for the calculation of the average of weeks 28 to 36. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment.

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

End point timeframe:

Baseline and weeks 28 to 36

| End point values | Roxadustat | Placebo | | |
|--|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 311 | 139 | | |
| Units: g/dL | | | | |
| least squares mean (confidence interval 95%) | 2.069 (1.94 to 2.20) | 0.470 (0.30 to 0.64) | | |

Statistical analyses

| Statistical analysis title | Change from BL to the Average Hb in weeks 28-36 |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

A Mixed Model of Repeated Measures (MMRM) has been applied using the visits up to week 36. The results were based on the estimated difference between the two treatment arms overall mean effects throughout the evaluation period (weeks 28 to 36). The model included treatment arm, region, CV History, visits and visit by treatment as categorical variables and baseline Hb, baseline eGFR and baseline Hb by visit as continuous variables.

| | |
|---|-------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 450 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[1] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.599 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.41 |
| upper limit | 1.78 |

Notes:

[1] - LSM Difference p-value is for test of differences. Tested using a fixed sequence testing procedure to maintain the overall two-sided type I error rate at 0.05.

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

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

End point description:

Analysis was completed on all values collected on day 1 and weeks 12, 20 and 28. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment.

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

End point timeframe:

Baseline and weeks 12 to 28

| End point values | Roxadustat | Placebo | | |
|--|-------------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 342 | 185 | | |
| Units: mmol/l | | | | |
| least squares mean (confidence interval 95%) | -0.650 (-0.76 to -0.54) | 0.051 (-0.08 to 0.18) | | |

Statistical analyses

| Statistical analysis title | LDL Change From BL |
|----------------------------|--------------------|
|----------------------------|--------------------|

Statistical analysis description:

A Mixed Model of Repeated Measures has been applied using the visits up to week 28. The results were based on the estimated difference between the two treatment arms and overall mean effects throughout the evaluation period (weeks 12 to 28). The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb, baseline eGFR and baseline LDL as continuous variables.

| | |
|---|-------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 527 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[2] |
| P-value | < 0.001 ^[3] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | -0.701 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.83 |
| upper limit | -0.57 |

Notes:

[2] - Superiority of roxadustat versus placebo was considered successful if the upper bound of the two-sided 95% confidence interval of the difference between treatment arms (roxadustat minus placebo) is below 0.

[3] - LSM Difference p-value is for test of differences. Tested using a fixed sequence testing procedure to maintain the overall two-sided type I error rate at 0.05.

Secondary: Time to First Use of Rescue Therapy (Composite of Red Blood Cell (RBC) Transfusions, Erythropoiesis-stimulating Agent (ESA) Use, and Intravenous (IV) Iron)

| | |
|-----------------|---|
| End point title | Time to First Use of Rescue Therapy (Composite of Red Blood Cell (RBC) Transfusions, Erythropoiesis-stimulating Agent (ESA) Use, and Intravenous (IV) Iron) |
|-----------------|---|

End point description:

The time to first use of rescue therapy was calculated (in years) as: (First event date – Analysis date of first dose intake + 1) / 365.25. The First event date was defined as Date of first dose of rescue medication during the efficacy emergent period and Analysis date of first dose intake was defined as date of first study drug dose intake collected on day 1. The Efficacy Emergent Period was defined as the evaluation period from the analysis date of first dose intake up to 7 days after the analysis date of last dose or the end of treatment (EOT) visit, whichever occurred first. Data reported was analysed by Kaplan-Meier estimate for cumulative proportion. Medication onset date was the date of the first use of rescue medication. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment.

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

End point timeframe:

Baseline to week 104 (End of Treatment)

| End point values | Roxadustat | Placebo | | |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Year 0.5 | 6.1 (3.6 to 8.7) | 33.3 (26.5 to 40.1) | | |
| Year 1 | 13.0 (9.3 to 16.7) | 50.1 (42.4 to 57.7) | | |
| Year 1.5 | 22.0 (16.6 to 27.3) | 52.5 (44.5 to 60.5) | | |
| Year 2 | 26.3 (20.2 to 32.4) | 57.8 (48.7 to 66.9) | | |

Statistical analyses

| Statistical analysis title | Time to First Use of Rescue Therapy |
|---|-------------------------------------|
| Statistical analysis description: | |
| Hazard ratio was calculated using stratified Cox Proportional Hazards Regression stratifying on CV history and region and adjusting on Hb and eGFR at baseline as continuous covariates. Superiority is declared if the upper bound of the 95% CI is below 1.0. | |
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[4] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.238 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.17 |
| upper limit | 0.33 |

Notes:

[4] - Tested using a fixed sequence testing procedure to maintain the overall two-sided type I error rate at 0.05.

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

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

End point description:

Change from BL in SF-36 VT sub-score to the average value in weeks 12-28 was calculated using the physical component scores (PCS) of SF-36. The multi-purpose, short-form health survey has 36 questions with an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures. The survey measures eight dimensions or scales: (1) physical functioning (PF) (10 items); (2) role limitations due to physical health problems (RP) (3 items); (3) bodily pain (BP) (2 items); (4) social functioning (SF) (2 items); (5) general health perceptions (GH) (5 items); (6) role limitations due to emotional problems (RE) (3 items); (7) vitality,

energy or fatigue (VT) (4 items); and (8) mental health (MH) (5 items). The SF-36 scores ranged from 0-100 with higher scores indicating better health status. The analysis population was the FAS.

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

| End point values | Roxadustat | Placebo | | |
|--|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 340 | 185 | | |
| Units: Units on a Scale | | | | |
| least squares mean (confidence interval 95%) | 2.788 (1.56 to 4.01) | 1.661 (0.23 to 3.10) | | |

Statistical analyses

| | |
|-----------------------------------|----------------------------------|
| Statistical analysis title | Change from BL in Vitality SF-36 |
|-----------------------------------|----------------------------------|

Statistical analysis description:

A Mixed Model of Repeated Measures has been applied using the visits up to week 28. The results were based on the estimated difference between the two treatment arms and overall mean effects throughout the evaluation period (weeks 12 to 28). The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline SF-36 VT, baseline Hb and baseline eGFR as continuous variables.

| | |
|---|-------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 525 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.093 ^[5] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.127 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.19 |
| upper limit | 2.44 |

Notes:

[5] - LSM Difference p-value is for test of differences. Tested using a fixed sequence testing procedure to maintain the overall two-sided type I error rate at 0.05.

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

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

End point description:

Change from baseline in SF-36 PF normalized sub-score compared to the average PF sub-score of weeks 12 to 28. The multi-purpose, short-form health survey has 36 questions with an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures. Change from baseline in PF subscore of SF-36 to the average of weeks 12–28 was compared by treatment arm for all participants (primary analysis) and in the subsets of participants with baseline PF subscore below 35 and equal or above 35. The SF-36 scores ranged from 0-100 with higher

scores indicating better health status. All available SF-36 PF values were used i.e., both scheduled and unscheduled for the calculation of the average PF sub-score of weeks 12 to 28. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment.

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

| End point values | Roxadustat | Placebo | | |
|--|----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 340 | 185 | | |
| Units: Units on a Scale | | | | |
| least squares mean (confidence interval 95%) | 1.344 (0.15 to 2.54) | 0.632 (-0.76 to 2.03) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Change from BL in Physical Functioning SF-36 |
|----------------------------|--|

Statistical analysis description:

A Mixed Model of Repeated Measures has been applied using the visits up to week 28. The results were based on the estimated difference between the two treatment arms and overall mean effects throughout the evaluation period (weeks 12 to 28). The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline SF-36 PF, baseline Hb and baseline eGFR as continuous variables.

| | |
|---|-------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 525 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.27 ^[6] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 0.713 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.56 |
| upper limit | 1.98 |

Notes:

[6] - LSM Difference p-value is for test of differences. Tested using a fixed sequence testing procedure to maintain the overall two-sided type I error rate at 0.05.

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

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

End point description:

The MAP was derived for each visit from the average systolic (SBP) and diastolic blood pressure (DBP) calculated for each visit using the three readings and the following equation: $MAP = (2/3) * DBP + (1/3) * SBP$. Baseline assessment was the assessment on day 1 (average of the three readings). If the baseline assessment was missing, then the latest available value prior to first drug administration was

used. The analysis population was the per protocol set (PPS), which consisted of all FAS participants who did not meet any reasons for exclusion from the PPS and had all available data at all time points.

| | |
|-----------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and weeks 20 to 28 | |

| End point values | Roxadustat | Placebo | | |
|--|------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 310 | 146 | | |
| Units: mmHg | | | | |
| least squares mean (confidence interval 95%) | -0.814 (-1.83 to 0.20) | -1.656 (-2.91 to -0.41) | | |

Statistical analyses

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Change From BL MAP to Average MAP |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

A Mixed Model of Repeated Measures was applied using the visits up to week 28. The results were based on the estimated difference between the two treatment arms with overall mean effects throughout the evaluation period (weeks 20 to 28). The model included treatment, visit, visit by treatment interaction, region and history of CV disease as fixed class factors and baseline MAP, baseline Hb, baseline eGFR as continuous covariates.

| | |
|---|--------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 456 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[7] |
| P-value | = 0.182 ^[8] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 0.842 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 2.08 |

Notes:

[7] - Non-inferiority can be concluded if the upper bound of the two-sided 95% CI of the difference between roxadustat and placebo (roxadustat minus placebo) is below 2 mmHg.

[8] - LSM Difference p-value is for test of differences.

Secondary: Time to First Occurrence of Hypertension

| | |
|-----------------|--|
| End point title | Time to First Occurrence of Hypertension |
|-----------------|--|

End point description:

Occurrence of hypertension was defined as SBP increase from BL ≥ 20 mmHg and SBP > 170 mmHg or DBP increase from BL ≥ 15 mmHg and DBP ≥ 110 mmHg. Time to first occurrence of hypertension was defined as first date where SBP criterion or DBP criterion is met, whichever occurred first. Data was analysed using Kaplan-Meier estimate for cumulative proportion. The analysis population was the PPS, which consisted of all FAS participants who did not meet any reasons for exclusion from the PPS and had all available data at all time points.

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

End point timeframe:

Baseline and year 0.5, year 1, year 1.5 and year 2

| End point values | Roxadustat | Placebo | | |
|-----------------------------------|---------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 359 | 183 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Year 0.5 | 11.4 (7.9 to 14.8) | 10.1 (5.5 to 14.7) | | |
| Year 1 | 14.8 (10.9 to 18.8) | 12.5 (7.3 to 17.7) | | |
| Year 1.5 | 17.5 (13.0 to 21.9) | 12.5 (7.3 to 17.7) | | |
| Year 2 | 18.5 (13.7 to 23.3) | 12.5 (7.3 to 17.7) | | |

Statistical analyses

| Statistical analysis title | Time to First Occurrence of Hypertension |
|--|--|
| Statistical analysis description: | |
| Hazard ratio was calculated using stratified Cox Proportional Hazards Regression stratifying on CV history and region and adjusting on Hb and eGFR at baseline as continuous covariates. | |
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 542 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[9] |
| P-value | = 0.334 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.29 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.77 |
| upper limit | 2.16 |

Notes:

[9] - Non-inferiority is declared if the upper bound of the 95% CI is below 1.3 (hazard ratio).

Secondary: Rate of Progression of CKD Measured by Annualized Estimated Glomerular Filtration Rate (eGFR) Slope Over Time

| | |
|-----------------|---|
| End point title | Rate of Progression of CKD Measured by Annualized Estimated Glomerular Filtration Rate (eGFR) Slope Over Time |
|-----------------|---|

End point description:

Annualized eGFR slope over time was estimated by a random slopes and intercepts model using all available eGFR values (one baseline and all post-treatment values up to EOT period or start of dialysis adjusted on baseline Hb, region, CV history at baseline and the interaction terms (baseline eGFR by timepoint and baseline Hb by timepoint). All assessments collected after initiation of chronic dialysis (acute or chronic) are excluded from the analysis. Baseline assessment was the assessment from day 1

visit. If this value was missing, the value from screening visit was used. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment.

| | |
|-------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to week 108 | |

| End point values | Roxadustat | Placebo | | |
|--|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: ml/min per 1.73 m ² per year | | | | |
| least squares mean (confidence interval 95%) | -2.65 (-3.29 to -2.02) | -3.24 (-4.21 to -2.28) | | |

Statistical analyses

| | |
|--|-------------------------------|
| Statistical analysis title | Annualized eGFR Slope |
| Statistical analysis description: | |
| Annualized eGFR slope over time was estimated by a random slopes and intercepts model using all available eGFR values adjusted on baseline Hb, region, CV history at Baseline and the interaction terms. | |
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.316 |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 0.59 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.57 |
| upper limit | 1.75 |

Secondary: Average Level of Hb Over Weeks 28 to 36 Without Use of Rescue Therapy Within 6 Weeks Prior to and During the Evaluation Period

| | |
|--|--|
| End point title | Average Level of Hb Over Weeks 28 to 36 Without Use of Rescue Therapy Within 6 Weeks Prior to and During the Evaluation Period |
| End point description: | |
| All scheduled and unscheduled hemoglobin values from weeks 28 to 36 were taken into account for calculating the average values. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment. | |
| End point type | Secondary |

End point timeframe:

Weeks 28 to 36

| End point values | Roxadustat | Placebo | | |
|--|-------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 311 | 139 | | |
| Units: g/dl | | | | |
| least squares mean (confidence interval 95%) | 11.106 (10.97 to 11.24) | 9.468 (9.29 to 9.65) | | |

Statistical analyses

| Statistical analysis title | Average Level of Hb Over Weeks 28 to 36 |
|---|---|
| Statistical analysis description: | |
| A Mixed Model of Repeated Measures was applied using the visits over weeks 28 to 36. The results were based on the estimated difference between the two treatment arms by visit based on this MMRM model. The model included treatment arm, region, CV History, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables. | |
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 450 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[10] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.638 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.44 |
| upper limit | 1.84 |

Notes:

[10] - LSM Difference p-value is for test of differences

Secondary: Average Level of Hb Over Weeks 44 to 52 Without Use of Rescue Therapy Within 6 Weeks Prior to and During the Evaluation Period

| | |
|-----------------|--|
| End point title | Average Level of Hb Over Weeks 44 to 52 Without Use of Rescue Therapy Within 6 Weeks Prior to and During the Evaluation Period |
|-----------------|--|

End point description:

All scheduled and unscheduled hemoglobin values from weeks 44 to 52 were taken into account for calculating the average values. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment.

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

End point timeframe:

Weeks 44 to 52

| End point values | Roxadustat | Placebo | | |
|--|-------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 287 | 118 | | |
| Units: g/dl | | | | |
| least squares mean (confidence interval 95%) | 10.984 (10.85 to 11.12) | 9.381 (9.19 to 9.58) | | |

Statistical analyses

| Statistical analysis title | Average Level of Hb Over Weeks 44 to 52 |
|--|---|
| Statistical analysis description: | |
| A Mixed Model of Repeated Measures was applied using the visits over weeks 44 to 52. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables. | |
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 405 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[11] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.604 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.39 |
| upper limit | 1.82 |

Notes:

[11] - LSM difference p-value is for test of differences.

Secondary: Average Level of Hb Over Weeks 96 to 104 Without Use of Rescue Therapy Within 6 Weeks Prior to and During the Evaluation Period

| | |
|---|---|
| End point title | Average Level of Hb Over Weeks 96 to 104 Without Use of Rescue Therapy Within 6 Weeks Prior to and During the Evaluation Period |
| End point description: | |
| All scheduled and unscheduled hemoglobin values from weeks 96 to 104 were taken into account for calculating the average values. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment. | |
| End point type | Secondary |
| End point timeframe: | |
| Weeks 96 to 104 | |

| End point values | Roxadustat | Placebo | | |
|--|-------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 120 | 32 | | |
| Units: g/dl | | | | |
| least squares mean (confidence interval 95%) | 10.816 (10.63 to 11.00) | 9.324 (9.01 to 9.64) | | |

Statistical analyses

| Statistical analysis title | Average Level of Hb Over Weeks 96 to 104 |
|---|--|
| Statistical analysis description: | |
| A Mixed Model of Repeated Measures was applied using the visits over weeks 96 to 104. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables. | |
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 152 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[12] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.492 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.14 |
| upper limit | 1.85 |

Notes:

[12] - LSM Difference p-value is for test of differences

Secondary: Time to Achieve the First Hb Response Without Rescue Therapy, as Defined by Primary Endpoint

| | |
|---|--|
| End point title | Time to Achieve the First Hb Response Without Rescue Therapy, as Defined by Primary Endpoint |
| End point description: | |
| For a participant without rescue therapy before Hb response (defined in 1 primary outcome), the time to achieve Hb response was calculated (in weeks) as: (First event date – Analysis date of first dose intake + 1) / 7 where First event date was defined as First date of both values that met the criteria for response. Participants who discontinued or received rescue therapy prior to the first Hb response or before the second consecutive Hb value defined as a response were classified as non- responders and were censored at week 24 or end of efficacy emergent period, whichever came first. Data analysis was completed using Kaplan-Meier estimate for cumulative proportion. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to week 24 | |

| End point values | Roxadustat | Placebo | | |
|-----------------------------------|---------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Week 4 | 26.0 (21.6 to 30.4) | 3.5 (0.9 to 6.0) | | |
| Week 8 | 59.8 (54.7 to 64.9) | 6.2 (2.8 to 9.7) | | |
| Week 16 | 83.4 (79.3 to 87.5) | 9.4 (5.1 to 13.7) | | |
| Week 24 | 89.1 (85.5 to 92.6) | 11.6 (6.8 to 16.5) | | |

Statistical analyses

| Statistical analysis title | Time to Achieve the First Hb Response |
|--|---------------------------------------|
| Statistical analysis description: | |
| Hazard ratio was calculated using stratified Cox Proportional Hazards Regression stratifying on CV history and region and adjusting on Hb and eGFR at baseline as continuous covariates. | |
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 19.001 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 11.98 |
| upper limit | 30.15 |

Secondary: Hb Change From BL to Each Post-Dosing Time Point

| End point title | Hb Change From BL to Each Post-Dosing Time Point |
|---|--|
| End point description: | |
| All scheduled and unscheduled hemoglobin values that belong to each visit window were taken into account using one value per analysis window. 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). N is the number of participants with available data at each time point. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline (day 1) and weeks 1,2,4,6,8,10,12,14,16,18,20,22,24,28,32,36,40,44,48,52,56,60,64,68,72,76,80,84,88,92,96,100,104 | |

| End point values | Roxadustat | Placebo | | |
|--|----------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: Number | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Hb Change From BL to Week 1 [N=372,193] | 0.390 (0.29 to 0.49) | -0.006 (-0.12 to 0.11) | | |
| Hb Change From BL to Week 2 [N=363,195] | 0.977 (0.87 to 1.08) | 0.039 (-0.09 to 0.17) | | |
| Hb Change From BL to Week 4 [N=360,189] | 1.591 (1.47 to 1.71) | 0.119 (-0.04 to 0.27) | | |
| Hb Change From BL to Week 6 [N=347,186] | 1.927 (1.79 to 2.06) | 0.100 (-0.07 to 0.27) | | |
| Hb Change From BL to Week 8 [N=346,188] | 2.236 (2.10 to 2.37) | 0.178 (0.01 to 0.35) | | |
| Hb Change From BL to Week 10 [N=335,184] | 2.129 (1.99 to 2.26) | 0.180 (0.01 to 0.35) | | |
| Hb Change From BL to Week 12 [N=337,179] | 2.412 (2.28 to 2.55) | 0.322 (0.15 to 0.49) | | |
| Hb Change From BL to Week 14 [N=332,174] | 2.214 (2.08 to 2.35) | 0.163 (0.00 to 0.33) | | |
| Hb Change From BL to Week 16 [N=321,173] | 2.365 (2.23 to 2.50) | 0.378 (0.20 to 0.56) | | |
| Hb Change From BL to Week 18 [N=317,161] | 2.087 (1.95 to 2.23) | 0.246 (0.06 to 0.43) | | |
| Hb Change From BL to Week 20 [N=310,151] | 2.191 (2.04 to 2.34) | 0.367 (0.18 to 0.56) | | |
| Hb Change From BL to Week 22 [N=312,149] | 1.873 (1.73 to 2.02) | 0.222 (0.03 to 0.41) | | |
| Hb Change From BL to Week 24 [N=307,142] | 1.802 (1.66 to 1.95) | 0.355 (0.16 to 0.55) | | |
| Hb Change From BL to Week 28 [N=301,145] | 1.996 (1.85 to 2.14) | 0.435 (0.24 to 0.63) | | |
| Hb Change From BL to Week 32 [N=300,137] | 1.911 (1.77 to 2.05) | 0.324 (0.13 to 0.52) | | |
| Hb Change From BL to Week 36 [N=290,131] | 2.100 (1.95 to 2.25) | 0.410 (0.21 to 0.61) | | |
| Hb Change From BL to Week 40 [N=290,125] | 1.887 (1.74 to 2.03) | 0.241 (0.04 to 0.45) | | |
| Hb Change From BL to Week 44 [N=275,122] | 1.977 (1.82 to 2.13) | 0.278 (0.06 to 0.49) | | |
| Hb Change From BL to Week 48 [N=282,114] | 1.695 (1.54 to 1.85) | 0.249 (0.03 to 0.46) | | |
| Hb Change From BL to Week 52 [N=267,111] | 1.939 (1.78 to 2.10) | 0.298 (0.07 to 0.52) | | |
| Hb Change From BL to Week 56 [N=217,74] | 1.725 (1.56 to 1.88) | 0.085 (-0.16 to 0.33) | | |
| Hb Change From BL to Week 60 [N=198,68] | 1.988 (1.81 to 2.16) | 0.354 (0.09 to 0.62) | | |
| Hb Change From BL to Week 64 [N=174,55] | 1.637 (1.45 to 1.82) | 0.233 (-0.06 to 0.52) | | |
| Hb Change From BL to Week 68 [N=173,49] | 1.913 (1.74 to 2.09) | 0.414 (0.13 to 0.70) | | |
| Hb Change From BL to Week 72 [N=158,50] | 1.765 (1.58 to 1.95) | 0.328 (0.03 to 0.63) | | |

| | | | | |
|---|----------------------|-----------------------|--|--|
| Hb Change From BL to Week 76 [N=156,47] | 1.859 (1.67 to 2.05) | 0.674 (0.36 to 0.99) | | |
| Hb Change From BL to Week 80 [N=145,43] | 1.752 (1.57 to 1.93) | 0.308 (0.01 to 0.61) | | |
| Hb Change From BL to Week 84 [N=143,37] | 1.854 (1.66 to 2.05) | 0.480 (0.14 to 0.82) | | |
| Hb Change From BL to Week 88 [N=132,31] | 1.570 (1.38 to 1.76) | 0.399 (0.06 to 0.74) | | |
| Hb Change From BL to Week 92 [N=125,32] | 1.800 (1.60 to 2.00) | 0.418 (0.06 to 0.78) | | |
| Hb Change From BL to Week 96 [N=122,32] | 1.701 (1.49 to 1.91) | 0.139 (-0.23 to 0.51) | | |
| Hb Change From BL to Week 100 [N=119,30] | 1.763 (1.57 to 1.96) | 0.315 (-0.03 to 0.66) | | |
| Hb Change From BL to Week 104 [N=102,26] | 1.857 (1.64 to 2.08) | 0.511 (0.11 to 0.91) | | |

Statistical analyses

| Statistical analysis title | Hb Change From BL to Week 1 |
|---|-------------------------------|
| Statistical analysis description: | |
| A Mixed Model of Repeated Measures was applied using the visits up to Week 104. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables. | |
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[13] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 0.396 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.29 |
| upper limit | 0.5 |

Notes:

[13] - LSM Difference p-value is for test of differences.

| Statistical analysis title | Hb Change From BL to Week 2 |
|---|-----------------------------|
| Statistical analysis description: | |
| A Mixed Model of Repeated Measures was applied using the visits up to Week 104. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables. | |
| Comparison groups | Roxadustat v Placebo |

| | |
|---|-------------------------------|
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[14] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 0.938 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.81 |
| upper limit | 1.07 |

Notes:

[14] - LSM Difference p-value is for test of differences.

| | |
|-----------------------------------|-----------------------------|
| Statistical analysis title | Hb Change From BL to Week 4 |
|-----------------------------------|-----------------------------|

Statistical analysis description:

A Mixed Model of Repeated Measures was applied using the visits up to Week 104. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables.

| | |
|---|-------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[15] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.471 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.3 |
| upper limit | 1.64 |

Notes:

[15] - LSM Difference p-value is for test of differences.

| | |
|-----------------------------------|-----------------------------|
| Statistical analysis title | Hb Change From BL to Week 6 |
|-----------------------------------|-----------------------------|

Statistical analysis description:

A Mixed Model of Repeated Measures was applied using the visits up to Week 104. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables.

| | |
|---|-------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[16] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.827 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.64 |
| upper limit | 2.02 |

Notes:

[16] - LSM Difference p-value is for test of differences.

| | |
|-----------------------------------|-----------------------------|
| Statistical analysis title | Hb Change From BL to Week 8 |
|-----------------------------------|-----------------------------|

Statistical analysis description:

A Mixed Model of Repeated Measures was applied using the visits up to Week 104. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables.

| | |
|---|-------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[17] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 2.058 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.87 |
| upper limit | 2.25 |

Notes:

[17] - LSM Difference p-value is for test of differences.

| | |
|-----------------------------------|------------------------------|
| Statistical analysis title | Hb Change From BL to Week 10 |
|-----------------------------------|------------------------------|

Statistical analysis description:

A Mixed Model of Repeated Measures was applied using the visits up to Week 104. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables.

| | |
|---|-------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[18] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.949 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.75 |
| upper limit | 2.14 |

Notes:

[18] - LSM Difference p-value is for test of differences.

| | |
|---|-------------------------------|
| Statistical analysis title | Hb Change From BL to Week 12 |
| Statistical analysis description: | |
| A Mixed Model of Repeated Measures was applied using the visits up to Week 104. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables. | |
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[19] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 2.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.9 |
| upper limit | 2.28 |

Notes:

[19] - LSM Difference p-value is for test of differences.

| | |
|---|-------------------------------|
| Statistical analysis title | Hb Change From BL to Week 14 |
| Statistical analysis description: | |
| A Mixed Model of Repeated Measures was applied using the visits up to Week 104. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables. | |
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[20] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 2.051 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.86 |
| upper limit | 2.24 |

Notes:

[20] - LSM Difference p-value is for test of differences.

| | |
|---|------------------------------|
| Statistical analysis title | Hb Change From BL to Week 16 |
| Statistical analysis description: | |
| A Mixed Model of Repeated Measures was applied. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables. | |
| Comparison groups | Roxadustat v Placebo |

| | |
|---|-------------------------------|
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[21] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.987 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.79 |
| upper limit | 2.19 |

Notes:

[21] - LSM Difference p-value is for test of differences.

| | |
|-----------------------------------|------------------------------|
| Statistical analysis title | Hb Change From BL to Week 18 |
|-----------------------------------|------------------------------|

Statistical analysis description:

A Mixed Model of Repeated Measures was applied. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables.

| | |
|---|-------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[22] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.841 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.64 |
| upper limit | 2.05 |

Notes:

[22] - LSM Difference p-value is for test of differences.

| | |
|-----------------------------------|------------------------------|
| Statistical analysis title | Hb Change From BL to Week 20 |
|-----------------------------------|------------------------------|

Statistical analysis description:

A Mixed Model of Repeated Measures was applied. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables.

| | |
|---|-------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[23] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.824 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.61 |
| upper limit | 2.04 |

Notes:

[23] - LSM Difference p-value is for test of differences.

| | |
|-----------------------------------|------------------------------|
| Statistical analysis title | Hb Change From BL to Week 22 |
|-----------------------------------|------------------------------|

Statistical analysis description:

A Mixed Model of Repeated Measures was applied. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables.

| | |
|---|-------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[24] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.651 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.43 |
| upper limit | 1.87 |

Notes:

[24] - LSM Difference p-value is for test of differences.

| | |
|-----------------------------------|------------------------------|
| Statistical analysis title | Hb Change From BL to Week 24 |
|-----------------------------------|------------------------------|

Statistical analysis description:

A Mixed Model of Repeated Measures was applied. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables.

| | |
|---|-------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[25] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.447 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.23 |
| upper limit | 1.67 |

Notes:

[25] - LSM Difference p-value is for test of differences.

| | |
|---|-------------------------------|
| Statistical analysis title | Hb Change From BL to Week 28 |
| Statistical analysis description: | |
| A Mixed Model of Repeated Measures was applied. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables. | |
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[26] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.561 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.34 |
| upper limit | 1.78 |

Notes:

[26] - LSM Difference p-value is for test of differences.

| | |
|---|-------------------------------|
| Statistical analysis title | Hb Change From BL to Week 32 |
| Statistical analysis description: | |
| A Mixed Model of Repeated Measures was applied. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables. | |
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[27] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.587 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.37 |
| upper limit | 1.81 |

Notes:

[27] - LSM Difference p-value is for test of differences.

| | |
|---|------------------------------|
| Statistical analysis title | Hb Change From BL to Week 36 |
| Statistical analysis description: | |
| A Mixed Model of Repeated Measures was applied. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables. | |
| Comparison groups | Roxadustat v Placebo |

| | |
|---|-------------------------------|
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[28] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.69 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.46 |
| upper limit | 1.92 |

Notes:

[28] - LSM Difference p-value is for test of differences.

| | |
|-----------------------------------|------------------------------|
| Statistical analysis title | Hb Change From BL to Week 40 |
|-----------------------------------|------------------------------|

Statistical analysis description:

A Mixed Model of Repeated Measures was applied. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables.

| | |
|---|-------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[29] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.645 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.41 |
| upper limit | 1.88 |

Notes:

[29] - LSM Difference p-value is for test of differences.

| | |
|-----------------------------------|------------------------------|
| Statistical analysis title | Hb Change From BL to Week 44 |
|-----------------------------------|------------------------------|

Statistical analysis description:

A Mixed Model of Repeated Measures was applied. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables.

| | |
|---|-------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[30] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.699 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.45 |
| upper limit | 1.94 |

Notes:

[30] - LSM Difference p-value is for test of differences.

| | |
|-----------------------------------|------------------------------|
| Statistical analysis title | Hb Change From BL to Week 48 |
|-----------------------------------|------------------------------|

Statistical analysis description:

A Mixed Model of Repeated Measures was applied. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables.

| | |
|---|-------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[31] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.446 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.2 |
| upper limit | 1.69 |

Notes:

[31] - LSM Difference p-value is for test of differences.

| | |
|-----------------------------------|------------------------------|
| Statistical analysis title | Hb Change From BL to Week 52 |
|-----------------------------------|------------------------------|

Statistical analysis description:

A Mixed Model of Repeated Measures was applied. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables.

| | |
|---|-------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[32] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.641 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.39 |
| upper limit | 1.89 |

Notes:

[32] - LSM Difference p-value is for test of differences.

| | |
|---|-------------------------------|
| Statistical analysis title | Hb Change From BL to Week 56 |
| Statistical analysis description: | |
| A Mixed Model of Repeated Measures was applied. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables. | |
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[33] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.64 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.37 |
| upper limit | 1.91 |

Notes:

[33] - LSM Difference p-value is for test of differences.

| | |
|---|-------------------------------|
| Statistical analysis title | Hb Change From BL to Week 60 |
| Statistical analysis description: | |
| A Mixed Model of Repeated Measures was applied. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables. | |
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[34] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.634 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.33 |
| upper limit | 1.94 |

Notes:

[34] - LSM Difference p-value is for test of differences.

| | |
|---|------------------------------|
| Statistical analysis title | Hb Change From BL to Week 64 |
| Statistical analysis description: | |
| A Mixed Model of Repeated Measures was applied. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables. | |
| Comparison groups | Roxadustat v Placebo |

| | |
|---|-------------------------------|
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[35] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.404 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.08 |
| upper limit | 1.73 |

Notes:

[35] - LSM Difference p-value is for test of differences.

| | |
|-----------------------------------|------------------------------|
| Statistical analysis title | Hb Change From BL to Week 68 |
|-----------------------------------|------------------------------|

Statistical analysis description:

A Mixed Model of Repeated Measures was applied. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables.

| | |
|---|-------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[36] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.499 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.18 |
| upper limit | 1.82 |

Notes:

[36] - LSM Difference p-value is for test of differences.

| | |
|-----------------------------------|------------------------------|
| Statistical analysis title | Hb Change From BL to Week 72 |
|-----------------------------------|------------------------------|

Statistical analysis description:

A Mixed Model of Repeated Measures was applied. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables.

| | |
|---|-------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[37] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.438 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.1 |
| upper limit | 1.78 |

Notes:

[37] - LSM Difference p-value is for test of differences.

| | |
|-----------------------------------|------------------------------|
| Statistical analysis title | Hb Change From BL to Week 76 |
|-----------------------------------|------------------------------|

Statistical analysis description:

A Mixed Model of Repeated Measures was applied. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables.

| | |
|---|-------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[38] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.185 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.83 |
| upper limit | 1.54 |

Notes:

[38] - LSM Difference p-value is for test of differences.

| | |
|-----------------------------------|------------------------------|
| Statistical analysis title | Hb Change From BL to Week 80 |
|-----------------------------------|------------------------------|

Statistical analysis description:

A Mixed Model of Repeated Measures was applied. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables.

| | |
|---|-------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[39] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.443 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.11 |
| upper limit | 1.78 |

Notes:

[39] - LSM Difference p-value is for test of differences.

| | |
|---|-------------------------------|
| Statistical analysis title | Hb Change From BL to Week 84 |
| Statistical analysis description: | |
| A Mixed Model of Repeated Measures was applied. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables. | |
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[40] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.374 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.99 |
| upper limit | 1.75 |

Notes:

[40] - LSM Difference p-value is for test of differences.

| | |
|---|-------------------------------|
| Statistical analysis title | Hb Change From BL to Week 88 |
| Statistical analysis description: | |
| A Mixed Model of Repeated Measures was applied. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables. | |
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[41] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.171 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.79 |
| upper limit | 1.55 |

Notes:

[41] - LSM Difference p-value is for test of differences.

| | |
|---|------------------------------|
| Statistical analysis title | Hb Change From BL to Week 92 |
| Statistical analysis description: | |
| A Mixed Model of Repeated Measures was applied. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables. | |
| Comparison groups | Roxadustat v Placebo |

| | |
|---|-------------------------------|
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[42] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.382 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.98 |
| upper limit | 1.78 |

Notes:

[42] - LSM Difference p-value is for test of differences.

| | |
|-----------------------------------|------------------------------|
| Statistical analysis title | Hb Change From BL to Week 96 |
|-----------------------------------|------------------------------|

Statistical analysis description:

A Mixed Model of Repeated Measures was applied. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables.

| | |
|---|-------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[43] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.563 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.15 |
| upper limit | 1.97 |

Notes:

[43] - LSM Difference p-value is for test of differences.

| | |
|-----------------------------------|-------------------------------|
| Statistical analysis title | Hb Change From BL to Week 100 |
|-----------------------------------|-------------------------------|

Statistical analysis description:

A Mixed Model of Repeated Measures was applied. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables.

| | |
|---|-------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[44] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.448 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.06 |
| upper limit | 1.83 |

Notes:

[44] - LSM Difference p-value is for test of differences.

| | |
|-----------------------------------|-------------------------------|
| Statistical analysis title | Hb Change From BL to Week 104 |
|-----------------------------------|-------------------------------|

Statistical analysis description:

A Mixed Model of Repeated Measures was applied. The results were based on the estimated difference between the two treatment arms by visit. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables.

| | |
|---|-------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[45] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.347 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9 |
| upper limit | 1.79 |

Notes:

[45] - LSM Difference p-value is for test of differences.

Secondary: Hb Change From BL to the Average Hb Value of Weeks 28-36 Regardless of the Use of Rescue Therapy

| | |
|-----------------|--|
| End point title | Hb Change From BL to the Average Hb Value of Weeks 28-36 Regardless of the Use of Rescue Therapy |
|-----------------|--|

End point description:

The Hb values from visit windows from weeks 28 to 36 were used for the calculation of the average regardless of rescue therapy. 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-dosing). The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment.

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

End point timeframe:

Baseline and week 28 to 36

| End point values | Roxadustat | Placebo | | |
|--|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 312 | 146 | | |
| Units: g/dl | | | | |
| least squares mean (confidence interval 95%) | 2.013 (1.88 to 2.15) | 0.399 (0.22 to 0.58) | | |

Statistical analyses

| Statistical analysis title | Change From Baseline to Average Hb Weeks 28-36 |
|--|--|
| Statistical analysis description: | |
| A Mixed Model of Repeated Measures was applied using the visits up to week 36. The results were based on the estimated difference between the two treatment arms overall mean effect during week 28 to 36 period based on this MMRM model. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables. | |
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 458 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[46] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.614 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.42 |
| upper limit | 1.81 |

Notes:

[46] - LSM difference p-value is for test of differences.

Secondary: Hb Change From BL to the Average Hb Value of Weeks 44-52 Regardless of the Use of Rescue Therapy

| End point title | Hb Change From BL to the Average Hb Value of Weeks 44-52 Regardless of the Use of Rescue Therapy |
|---|--|
| End point description: | |
| The Hb values from visit windows from weeks 44 to 52 were used for the calculation of the average regardless of rescue therapy. 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-dosing). The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and week 44 to 52 | |

| End point values | Roxadustat | Placebo | | |
|--|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 291 | 123 | | |
| Units: g/dl | | | | |
| least squares mean (confidence interval 95%) | 1.886 (1.75 to 2.03) | 0.292 (0.10 to 0.48) | | |

Statistical analyses

| Statistical analysis title | Change From Baseline to Average Hb Weeks 44-52 |
|--|--|
| Statistical analysis description: | |
| A Mixed Model of Repeated Measures was applied using the visits up to week 52. The results were based on the estimated difference between the two treatment arms overall mean effect during week 44 to 52 period based on this MMRM model. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables. | |
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.594 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.38 |
| upper limit | 1.81 |

Secondary: Hb Change From BL to the Average Hb Value of Weeks 96-104 Regardless of the Use of Rescue Therapy

| | |
|--|---|
| End point title | Hb Change From BL to the Average Hb Value of Weeks 96-104 Regardless of the Use of Rescue Therapy |
| End point description: | |
| The Hb values from visit windows from weeks 96 to 104 were used for the calculation of the average regardless of rescue therapy. 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-dosing). The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and week 96 to 104 | |

| End point values | Roxadustat | Placebo | | |
|--|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 124 | 32 | | |
| Units: g/dl | | | | |
| least squares mean (confidence interval 95%) | 1.779 (1.60 to 1.96) | 0.327 (0.01 to 0.64) | | |

Statistical analyses

| Statistical analysis title | Change From Baseline to Average Hb Weeks 96-104 |
|--|---|
| Statistical analysis description: | |
| A Mixed Model of Repeated Measures was applied using the visits up to week 104. The results were based on the estimated difference between the two treatment arms overall mean effect during week 96 to 104 period based on this MMRM model. The model included treatment arm, region, CV history, visits and visit by treatment as categorical variables and baseline Hb and baseline eGFR as continuous variables. | |
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 156 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[47] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.452 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.1 |
| upper limit | 1.8 |

Notes:

[47] - LSM difference p-value is for test of differences.

Secondary: Percentage of Hb Values Within 10.0-12.0 g/dL in Weeks 28-36 Without Use of Rescue Therapy

| End point title | Percentage of Hb Values Within 10.0-12.0 g/dL in Weeks 28-36 Without Use of Rescue Therapy |
|--|--|
| End point description: | |
| The percentage of Hb values measured during weeks 28-36 within 10.0 -12.0 g/dL, without having received rescue therapy within 6 weeks prior to and during the 8-week evaluation period is reported. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and week 28 to 36 | |

| End point values | Roxadustat | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 311 | 139 | | |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | 64.18 (± 32.90) | 34.20 (± 39.47) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Hb Values Within 10.0-12.0 g/dL in Weeks 44-52 Without Use of Rescue Therapy

| | |
|-----------------|--|
| End point title | Percentage of Hb Values Within 10.0-12.0 g/dL in Weeks 44-52 Without Use of Rescue Therapy |
|-----------------|--|

End point description:

The percentage of Hb values measured during weeks 44-52 with values within 10.0 - 12.0 g/dL, without having received rescue therapy within 6 weeks prior to and during the 8-week evaluation period is reported. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment.

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

End point timeframe:

Baseline and week 44 to 52

| End point values | Roxadustat | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 287 | 118 | | |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | 69.39 (± 32.47) | 35.45 (± 41.75) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Hb Values Within 10.0-12.0 g/dL in Weeks 96-104 Without Use of Rescue Therapy

| | |
|-----------------|---|
| End point title | Percentage of Hb Values Within 10.0-12.0 g/dL in Weeks 96-104 Without Use of Rescue Therapy |
|-----------------|---|

End point description:

The percentage of Hb values measured during weeks 96-104 within 10.0 -12.0 g/dL, without having received rescue therapy within 6 weeks prior to and during the 8-week evaluation period is reported. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment.

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

End point timeframe:
Baseline and week 96 to 104

| End point values | Roxadustat | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 120 | 32 | | |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | 64.65 (± 37.16) | 40.63 (± 44.39) | | |

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 was defined in years as the First event date during the Efficacy Emergent Period – (Analysis date of first dose intake +1)/365.25. The first event date was defined as the Date of first admission. The Efficacy Emergent Period was defined as the evaluation period from the analysis date of first dose intake up to 7 days after the analysis date of last dose or EOT visit, whichever occurred first. Analysis date of first dose intake was defined as the date of first study drug intake collected on day 1 visit. For participants who experienced more than one hospitalization, only their first event following study treatment was used. Data analysis was completed using Kaplan-Meier estimate for cumulative proportion. Data for Year 2 roxadustat could not be calculated and is denoted as "99999" as applicable. The analysis population was the FAS. | |
| End point type | Secondary |
| End point timeframe: Baseline up to week 104 | |

| End point values | Roxadustat | Placebo | | |
|-----------------------------------|------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Year 0.5 | 32.2 (27.3 to 37.0) | 39.8 (32.7 to 46.9) | | |
| Year 1 | 49.9 (44.6 to 55.2) | 49.3 (41.8 to 56.8) | | |
| Year 1.5 | 62.1 (56.3 to 67.9) | 64.0 (54.5 to 73.4) | | |
| Year 2 | 99999 (99999 to 99999) | 67.8 (57.9 to 77.7) | | |

Statistical analyses

| | |
|---|-------------------------------|
| Statistical analysis title | Time to First Hospitalization |
| Statistical analysis description: Hazard ratio was calculated using stratified Cox Proportional Hazards Regression stratifying on CV history and region and adjusting on Hb and eGFR at baseline as continuous covariates. | |
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.643 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.945 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.74 |
| upper limit | 1.2 |

Secondary: Number of Days of Hospitalization Per Patient Exposure Year (PEY)

| | |
|--|---|
| End point title | Number of Days of Hospitalization Per Patient Exposure Year (PEY) |
| End point description: The sum of the durations of all hospitalizations in days was adjusted for the duration of exposure. Derived only for participants with at least one hospitalization. The number of days of hospitalization per PEY was calculated as the sum of the durations of all hospitalizations in days [Minimum (Date of discharge, End of Efficacy Emergent Period) - Date of admission + 1] / [Duration of Efficacy Emergent Period in days / 365.25]. The analysis population was the FAS, which consisted of participants with hospitalizations. Participants can have more than one hospitalization. | |
| End point type | Secondary |
| End point timeframe: Baseline up to week 104 | |

| | | | | |
|--------------------------------------|-------------------|-------------------|--|--|
| End point values | Roxadustat | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 214 | 101 | | |
| Units: Number of days per year | | | | |
| arithmetic mean (standard deviation) | 26.479 (± 35.182) | 31.928 (± 36.441) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Use of Rescue Therapy (Composite of Red Blood Cell (RBC)

Transfusions, Erythropoiesis Stimulating Agent (ESA) Use, and Intravenous (IV) Iron) in the First 24 Weeks of Treatment

| | |
|-----------------|--|
| End point title | Time to First Use of Rescue Therapy (Composite of Red Blood Cell (RBC) Transfusions, Erythropoiesis Stimulating Agent (ESA) Use, and Intravenous (IV) Iron) in the First 24 Weeks of Treatment |
|-----------------|--|

End point description:

Time to first use of rescue therapy in years. Data analysis was completed using Kaplan-Meier estimate for cumulative proportion. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment.

| | |
|------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to week 24 | |

| End point values | Roxadustat | Placebo | | |
|-----------------------------------|------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Week 6 | 0.8 (0.0 to 1.7) | 6.0 (2.7 to 9.3) | | |
| Week 12 | 2.5 (0.9 to 4.1) | 15.8 (10.7 to 20.9) | | |
| Week 18 | 3.3 (1.5 to 5.2) | 25.3 (19.2 to 31.5) | | |
| Week 24 | 5.5 (3.1 to 7.9) | 32.1 (25.4 to 38.7) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Time to Start Rescue Therapy Within First 24 Weeks |
|----------------------------|--|

Statistical analysis description:

Hazard ratio was calculated using stratified Cox Proportional Hazards Regression stratifying on CV history and region and adjusting on Hb and eGFR at baseline as continuous covariates.

| | |
|---|----------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.139 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.08 |
| upper limit | 0.23 |

Secondary: Time to First Use of RBC Transfusions

| | |
|-----------------|---------------------------------------|
| End point title | Time to First Use of RBC Transfusions |
|-----------------|---------------------------------------|

End point description:

Time to First Use of RBC Transfusions during efficacy emergent period. For participants who have experienced more than one RBC transfusion, only their first event following study treatment was used. The efficacy emergent period was defined as the evaluation period from the analysis date of first dose intake up to 7 days after the analysis date of last dose or EOT visit, whichever occurred first. Data analysis was completed using Kaplan-Meier estimate for cumulative proportion. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment.

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

End point timeframe:

Baseline to week 104

| End point values | Roxadustat | Placebo | | |
|-----------------------------------|--------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Year 0.5 | 2.9 (1.1 to 4.7) | 15.2 (10.1 to 20.4) | | |
| Year 1 | 5.6 (3.0 to 8.1) | 20.2 (14.2 to 26.2) | | |
| Year 1.5 | 12.1 (7.7 to 16.5) | 21.8 (15.1 to 28.5) | | |
| Year 2 | 15.0 (9.9 to 20.1) | 27.0 (17.7 to 36.4) | | |

Statistical analyses

| | |
|----------------------------|---------------------------------------|
| Statistical analysis title | Time To First Use of RBS Transfusions |
|----------------------------|---------------------------------------|

Statistical analysis description:

Hazard ratio was calculated using stratified Cox Proportional Hazards Regression stratifying on CV history and region and adjusting on Hb and eGFR at baseline as continuous covariates.

| | |
|-------------------|----------------------|
| Comparison groups | Roxadustat v Placebo |
|-------------------|----------------------|

| | |
|---|-----|
| Number of subjects included in analysis | 592 |
|---|-----|

| | |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

| | |
|---------------|-------------|
| Analysis type | superiority |
|---------------|-------------|

| | |
|---------|---------|
| P-value | < 0.001 |
|---------|---------|

| | |
|--------|-----------------|
| Method | Regression, Cox |
|--------|-----------------|

| | |
|--------------------|-------------------|
| Parameter estimate | Hazard ratio (HR) |
|--------------------|-------------------|

| | |
|----------------|-------|
| Point estimate | 0.343 |
|----------------|-------|

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.21 |
| upper limit | 0.55 |

Secondary: Mean Monthly Number of RBC Packs

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

End point description:

During efficacy emergent period, the mean monthly number of RBC packs was calculated as the sum of 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 7 days after the analysis date of last dose or EOT visit, whichever occurred first. In case of missing number of packs, values were estimated based on 1 unit for packed cells = 250 mL or 1 unit for whole blood = 500 mL. Participants without RBC transfusion were included with a value of zero. No estimation if values were missing. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment.

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

End point timeframe:

Baseline to week 104

| End point values | Roxadustat | Placebo | | |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: RBC Packs per 28 days | | | | |
| arithmetic mean (standard deviation) | 0.041 (\pm 0.397) | 0.089 (\pm 0.243) | | |

Statistical analyses

| | |
|----------------------------|----------------------------------|
| Statistical analysis title | Mean Monthly Number of RBC Packs |
|----------------------------|----------------------------------|

Statistical analysis description:

The Analysis of Covariance (ANCOVA) model was applied including treatment as fixed factor, region and history of CV disease as class factors and baseline Hb, baseline eGFR as continuous covariates.

| | |
|---|-------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.128 |
| Method | ANCOVA |
| Parameter estimate | Least squares mean difference |
| Point estimate | -0.045 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.1 |
| upper limit | 0.01 |

Secondary: Mean Monthly Volume of Blood transfused

| | |
|-----------------|---|
| End point title | Mean Monthly Volume of Blood transfused |
|-----------------|---|

End point description:

During efficacy emergent period, the mean monthly volume of blood transfused was calculated as the sum of blood volume 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 7 days after the analysis date of last dose or EOT visit, whichever occurred first. The mean monthly volume transfused was calculated as the sum of the volume transfused between the first dose and up to the last dose in the period divided by duration (in days) and multiplied by 28 days. Participants without RBC transfusion were included with a value of zero. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment.

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

End point timeframe:

Baseline to week 104

| End point values | Roxadustat | Placebo | | |
|--------------------------------------|--------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: Milliliters (ml) per 28 days | | | | |
| arithmetic mean (standard deviation) | 11.331 (± 106.624) | 22.596 (± 60.666) | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Mean Monthly Volume of Blood Transfused |
|----------------------------|---|

Statistical analysis description:

The Analysis of Covariance (ANCOVA) model was applied including treatment arm, region, CV history as categorical variables and baseline Hb and baseline eGFR as continuous variables.

| | |
|---|-------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.183 |
| Method | ANCOVA |
| Parameter estimate | Least squares mean difference |
| Point estimate | -10.429 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -25.81 |
| upper limit | 4.95 |

Secondary: Time to First Use of ESA Rescue Therapy

| | |
|--|---|
| End point title | Time to First Use of ESA Rescue Therapy |
| End point description: | |
| Time to First Use of ESA Rescue Therapy during efficacy emergent period. For participants with use of ESA, the time to first use of ESA was calculated as (First event date – Analysis date of first dose intake + 1) / 365.25. The efficacy emergent period was defined as the evaluation period from the analysis date of first dose intake up to 7 days after the analysis date of last dose or EOT visit, whichever occurred first. Data analysis was completed using Kaplan-Meier estimate for cumulative proportion. Participants without ESA rescue were censored at the end of treatment. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to week 104 | |

| End point values | Roxadustat | Placebo | | |
|-----------------------------------|------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Year 0.5 | 1.8 (0.4 to 3.2) | 20.4 (14.5 to 26.3) | | |
| Year 1 | 4.8 (2.4 to 7.2) | 36.4 (28.9 to 43.9) | | |
| Year 1.5 | 6.0 (3.1 to 8.9) | 42.3 (33.9 to 50.8) | | |
| Year 2 | 6.7 (3.5 to 9.9) | 42.3 (33.9 to 50.8) | | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Time to First Use of ESA Rescue Therapy |
| Statistical analysis description: | |
| Hazard ratio was calculated using stratified Cox Proportional Hazards Regression stratifying on CV history and region and adjusting on Hb and eGFR at baseline as continuous covariates. | |
| Comparison groups | Roxadustat v Placebo |

| | |
|---|-------------------|
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.101 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.06 |
| upper limit | 0.17 |

Secondary: Time to First Use of IV Iron

| | |
|---|------------------------------|
| End point title | Time to First Use of IV Iron |
| End point description: | |
| Time to first use of IV iron during efficacy emergent period in years. For participants with use of IV iron, the time to first use of IV iron was calculated as (First event date – Analysis date of first dose intake + 1) / 365.25. The efficacy emergent period was defined as the evaluation period from the analysis date of first dose intake up to 7 days after the analysis date of last dose or EOT visit, whichever occurred first. Data analysis was completed using Kaplan-Meier estimate for cumulative proportion. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to week 104 | |

| End point values | Roxadustat | Placebo | | |
|-----------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Year 0.5 | 2.3 (0.7 to 3.9) | 6.2 (2.7 to 9.8) | | |
| Year 1 | 5.3 (2.8 to 7.8) | 9.4 (4.8 to 14.0) | | |
| Year 1.5 | 7.5 (4.3 to 10.7) | 10.7 (5.5 to 15.9) | | |
| Year 2 | 10.6 (6.3 to 14.8) | 19.1 (8.8 to 29.5) | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Time to First Use of IV Iron Supplementation |
| Statistical analysis description: | |
| Hazard Ratio was calculated using stratified Cox Proportional Hazards Regression stratifying on CV history and region and adjusting on Hb and eGFR at baseline as continuous covariates. | |

| | |
|---|----------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.045 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.538 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.29 |
| upper limit | 0.99 |

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

| | |
|---|---|
| End point title | Change From BL to Each Post-Dosing Visit in Total Cholesterol |
| End point description: | |
| Change from baseline to each planned assessment for total cholesterol is reported. Baseline was defined as the value on day 1. If the value was missing, the latest value prior to first study drug administration was used. N is the number of participants with available data at each time point. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and weeks 4,8,12,20,28,36,44,52,68,84,104 | |

| End point values | Roxadustat | Placebo | | |
|--------------------------------------|------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: mmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 [N=368,194] | -1.151 (± 1.058) | 0.108 (± 0.842) | | |
| Week 8 [N=348,191] | -1.066 (± 1.086) | 0.048 (± 0.932) | | |
| Week 12 [N=342,185] | -0.836 (± 1.173) | 0.088 (± 1.116) | | |
| Week 20 [N=323,167] | -0.747 (± 1.227) | 0.193 (± 1.129) | | |
| Week 28 [N=310,149] | -0.816 (± 1.284) | 0.201 (± 1.271) | | |
| Week 36 [N=295,133] | -0.803 (± 1.300) | 0.183 (± 1.174) | | |
| Week 44 [N=285,126] | -0.854 (± 1.238) | 0.077 (± 1.346) | | |
| Week 52 [N=278,120] | -0.815 (± 1.314) | 0.104 (± 1.304) | | |
| Week 68 [N=197,67] | -0.971 (± 1.382) | 0.188 (± 1.222) | | |

| | | | | |
|---------------------|------------------|-----------------|--|--|
| Week 84 [N=154,43] | -1.055 (± 1.554) | 0.102 (± 1.284) | | |
| Week 104 [N=123,32] | -0.944 (± 1.584) | 0.218 (± 1.067) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From BL to Each Post-Dosing Visit in Low Density Lipoprotein (LDL)/High-Density Lipoprotein (HDL) Ratio

| | |
|-----------------|--|
| End point title | Change From BL to Each Post-Dosing Visit in Low Density Lipoprotein (LDL)/High-Density Lipoprotein (HDL) Ratio |
|-----------------|--|

End point description:

Change from baseline to each planned assessment for LDL/HDL ratio is reported. Baseline was defined as the value on Day 1. If this value was missing, the latest value prior to first study drug administration was used. N is the number of participants with available data at each time point. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment.

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

End point timeframe:

Baseline and weeks 4,8,12,20,28,36,44,52,68,84,104

| End point values | Roxadustat | Placebo | | |
|--------------------------------------|------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: Ratio | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 [N=367,193] | -0.331 (± 0.777) | 0.076 (± 0.635) | | |
| Week 8 [N=347,190] | -0.374 (± 0.952) | 0.068 (± 0.685) | | |
| Week 12 [N=341,185] | -0.268 (± 0.905) | 0.081 (± 0.915) | | |
| Week 20 [N=322,166] | -0.250 (± 1.024) | 0.155 (± 0.788) | | |
| Week 28 [N=309,149] | -0.313 (± 1.057) | 0.156 (± 0.861) | | |
| Week 36 [N=293,133] | -0.349 (± 1.040) | 0.157 (± 1.053) | | |
| Week 44 [N=283,126] | -0.368 (± 1.099) | 0.099 (± 1.198) | | |
| Week 52 [N=277,120] | -0.429 (± 1.125) | 0.019 (± 1.076) | | |
| Week 68 [N=196,67] | -0.466 (± 1.219) | 0.052 (± 0.955) | | |
| Week 84 [N=154,43] | -0.509 (± 1.307) | 0.114 (± 1.113) | | |
| Week 104 [N=122,32] | -0.414 (± 1.306) | 0.105 (± 0.873) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From BL to Each Post-Dosing Visit in Non-HDL Cholesterol

| | |
|-----------------|---|
| End point title | Change From BL to Each Post-Dosing Visit in Non-HDL Cholesterol |
|-----------------|---|

End point description:

Change from baseline to each planned assessment for non-HDL is reported. Baseline was defined as the value on day 1. If this value was missing, the latest value prior to first study drug administration was used. N is the number of participants with available data at each time point. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment.

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

End point timeframe:

Baseline and weeks 4,8,12,20,28,36,44,52,68,84,104

| End point values | Roxadustat | Placebo | | |
|--------------------------------------|------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: mmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 [N=367,193] | -0.969 (± 0.989) | 0.118 (± 0.789) | | |
| Week 8 [N=347,190] | -0.909 (± 1.064) | 0.070 (± 0.864) | | |
| Week 12 [N=341,185] | -0.709 (± 1.107) | 0.078 (± 1.050) | | |
| Week 20 [N=322,166] | -0.638 (± 1.175) | 0.186 (± 1.072) | | |
| Week 28 [N=309,149] | -0.710 (± 1.227) | 0.206 (± 1.227) | | |
| Week 36 [N=293,133] | -0.711 (± 1.239) | 0.202 (± 1.133) | | |
| Week 44 [N=283,125] | -0.751 (± 1.190) | 0.106 (± 1.342) | | |
| Week 52 [N=277,120] | -0.751 (± 1.276) | 0.104 (± 1.299) | | |
| Week 68 [N=196,67] | -0.882 (± 1.325) | 0.174 (± 1.187) | | |
| Week 84 [N=154,43] | -0.939 (± 1.518) | 0.089 (± 1.343) | | |
| Week 104 [N=123,32] | -0.839 (± 1.554) | 0.174 (± 1.014) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From BL to Each Post-Dosing Visit in Apolipoproteins A1

| | |
|-----------------|--|
| End point title | Change From BL to Each Post-Dosing Visit in Apolipoproteins A1 |
|-----------------|--|

End point description:

Change from baseline to each planned assessment for apolipoproteins A1 is reported. N is the number of participants with available data at each time point. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment.

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

End point timeframe:

Baseline and weeks 4,8,12,20,28,36,44,52,68,84,104

| End point values | Roxadustat | Placebo | | |
|--------------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: g/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Apolipoprotein A1 Week 4 [N=183,102] | -0.168 (± 0.232) | 0.013 (± 0.190) | | |
| Apolipoprotein A1 Week 8 [N=174,102] | -0.148 (± 0.229) | 0.008 (± 0.227) | | |
| Apolipoprotein A1 Week 12 [N=170,97] | -0.072 (± 0.723) | 0.004 (± 0.203) | | |
| Apolipoprotein A1 Week 20 [N=158,90] | -0.114 (± 0.245) | 0.036 (± 0.222) | | |
| Apolipoprotein A1 Week 28 [N=134,67] | -0.104 (± 0.265) | 0.006 (± 0.233) | | |
| Apolipoprotein A1 Week 36 [N=149,77] | -0.101 (± 0.252) | 0.002 (± 0.223) | | |
| Apolipoprotein A1 Week 44 [N=140,72] | -0.135 (± 0.259) | -0.013 (± 0.268) | | |
| Apolipoprotein A1 Week 52 [N=139,71] | -0.090 (± 0.260) | -0.028 (± 0.248) | | |
| Apolipoprotein A1 Week 68 [N=63,28] | -0.157 (± 0.310) | 0.018 (± 0.204) | | |
| Apolipoprotein A1 Week 84 [N=30,12] | -0.132 (± 0.282) | 0.060 (± 0.196) | | |
| Apolipoprotein A1 Week 104 [N=12,4] | -0.098 (± 0.227) | 0.070 (± 0.136) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From BL to Each Post-Dosing Visit in Apolipoproteins B

| | |
|-----------------|---|
| End point title | Change From BL to Each Post-Dosing Visit in Apolipoproteins B |
|-----------------|---|

End point description:

Change from baseline to each planned assessment for apolipoproteins B is reported. N is the number of participants with available data at each time point. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment.

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

End point timeframe:

Baseline and weeks 4,8,12,20,28,36,44,52,68,84,104

| End point values | Roxadustat | Placebo | | |
|--------------------------------------|--------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Apolipoproteins B Week 4 [N=183,102] | -19.891 (± 20.669) | 2.059 (± 22.220) | | |
| Apolipoproteins B Week 8 [N=174,102] | -19.483 (± 21.009) | 2.059 (± 20.297) | | |
| Apolipoproteins B Week 12 [N=170,97] | -14.935 (± 24.613) | 0.278 (± 21.707) | | |
| Apolipoproteins B Week 20 [N=158,90] | -12.709 (± 24.424) | 5.711 (± 25.883) | | |
| Apolipoproteins B Week 28 [N=133,67] | -13.782 (± 28.634) | 9.746 (± 26.864) | | |
| Apolipoproteins B Week 36 [N=149,77] | -14.866 (± 25.469) | 6.623 (± 25.895) | | |
| Apolipoproteins B Week 44 [N=140,72] | -15.593 (± 26.594) | 3.222 (± 30.771) | | |
| Apolipoproteins B Week 52 [N=139,71] | -14.122 (± 27.503) | 4.676 (± 31.440) | | |
| Apolipoproteins B Week 68 [N=63,28] | -18.746 (± 28.633) | 2.786 (± 28.900) | | |
| Apolipoproteins B Week 84 [N=30,12] | -20.133 (± 28.134) | 12.500 (± 32.152) | | |
| Apolipoproteins B Week 104 [N=12,4] | -10.917 (± 22.885) | 14.750 (± 20.271) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From BL to Each Post-Dosing Visit in Ratio Apolipoprotein ApoB/ApoA1

| | |
|-----------------|---|
| End point title | Change From BL to Each Post-Dosing Visit in Ratio Apolipoprotein ApoB/ApoA1 |
|-----------------|---|

End point description:

Change from baseline to each planned assessment for ratio ApoB/ApoA1 is reported. Baseline was defined as the value on day 1. If this value was missing, the latest value prior to first study drug administration was used. N is the number of participants with available data at each time point. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment.

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

End point timeframe:

Baseline and weeks 4,8,12,20,28,36,44,52,68,84,104

| End point values | Roxadustat | Placebo | | |
|--------------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: Ratio | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 [N=183,101] | -0.073 (± 0.165) | 0.010 (± 0.169) | | |
| Week 8 [N=172,101] | -0.084 (± 0.202) | 0.000 (± 0.184) | | |
| Week 12 [N=169,96] | -0.059 (± 0.164) | -0.006 (± 0.201) | | |
| Week 20 [N=158,89] | -0.043 (± 0.189) | 0.009 (± 0.198) | | |
| Week 28 [N=133,66] | -0.066 (± 0.222) | 0.063 (± 0.205) | | |
| Week 36 [N=149,76] | -0.070 (± 0.200) | 0.045 (± 0.213) | | |
| Week 44 [N=140,71] | -0.053 (± 0.220) | 0.031 (± 0.265) | | |
| Week 52 [N=137,70] | -0.065 (± 0.207) | 0.047 (± 0.266) | | |
| Week 68 [N=63,28] | -0.086 (± 0.212) | 0.001 (± 0.184) | | |
| Week 84 [N=29,12] | -0.066 (± 0.210) | 0.058 (± 0.295) | | |
| Week 104 [N=12,4] | -0.024 (± 0.126) | 0.085 (± 0.132) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Mean LDL Cholesterol <100 mg/dL Calculated Over Weeks 12 to 28

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

End point description:

Mean LDL cholesterol <100 mg/dL over weeks 12 to 28 was defined as a binary variable (Yes/No), where Yes was defined as mean LDL cholesterol <100 mg/dL over weeks 12 to 28. Participants without any LDL value within this duration were excluded. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Weeks 12-28 | |

| End point values | Roxadustat | Placebo | | |
|------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Yes (Regardless of fasting status) | 62.9 | 41.1 | | |
| No (Regardless of fasting status) | 37.1 | 58.9 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Have Achieved Antihypertensive Treatment Goal in CKD Participants Over Weeks 12-28

| | |
|-----------------|---|
| End point title | Percentage of Participants Who Have Achieved Antihypertensive Treatment Goal in CKD Participants Over Weeks 12-28 |
|-----------------|---|

End point description:

Occurrence of achieved antihypertensive treatment goal was defined as the average SBP < 130 mmHg and the average DBP < 80 mmHg over the period of weeks 12-28. Participants without any blood pressure measurement were excluded. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Weeks 12-28 | |

| End point values | Roxadustat | Placebo | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Yes | 25.6 | 28.0 | | |
| No | 74.4 | 72.0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From BL to the Average Value of Weeks 12-28 in Quality of Life (QoL) SF-36 Physical Component Score (PCS)

| | |
|--|--|
| End point title | Change From BL to the Average Value of Weeks 12-28 in Quality of Life (QoL) SF-36 Physical Component Score (PCS) |
| End point description: The 36-Item short-form health survey (SF-36) is a multi-purpose survey with 36 questions. It provides an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures. For each scale scores range from 0-100. The physical component score was calculated based on the results of the SF-36 scores. Higher scores indicate better health status. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment. | |
| End point type | Secondary |
| End point timeframe: Baseline and weeks 12-28 | |

| | | | | |
|--|----------------------|----------------------|--|--|
| End point values | Roxadustat | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 340 | 185 | | |
| Units: Units on a Scale | | | | |
| least squares mean (confidence interval 95%) | 1.842 (0.88 to 2.80) | 1.468 (0.34 to 2.59) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Change from Baseline to Weeks 12-28 SF-36 PCS |
| Statistical analysis description: The Mixed Model of Repeated Measures included treatment, visit (week 8, week 12 and week 28), visit by treatment interaction, region and history of CV disease as fixed class factors and baseline SF-36 PCS, baseline Hb, baseline eGFR as continuous covariates. | |
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 525 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.475 |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 0.374 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.65 |
| upper limit | 1.4 |

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

| | |
|-----------------|---|
| End point title | Change From BL to the Average Value of Weeks 12-28 in |
|-----------------|---|

End point description:

Baseline FACT-An AnS was defined as the FACT-An AnS value on Day 1. Together with the Functional Assessment of Cancer Therapy - General (FACT-G), the Anemia Subscale (AnS) is referred to as the FACT-An Total. The AnS scale contains 13 fatigue specific items (the Fatigue Score) plus 7 items related to anemia. The Anemia AnS score range is 0 to 80. For the above score, a higher score indicates better QoL.

End point type Secondary

End point timeframe:

Baseline and weeks 12-28

| End point values | Roxadustat | Placebo | | |
|--|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 339 | 185 | | |
| Units: Units on a Scale | | | | |
| least squares mean (confidence interval 95%) | 4.470 (2.86 to 6.08) | 2.766 (0.91 to 4.62) | | |

Statistical analyses

Statistical analysis title FACT-An Ans Change from Baseline to Weeks 12-28

Statistical analysis description:

A Mixed Model of Repeated Measures was applied using the visits up to week 28. The model includes treatment, visit (week 8, week 12 and week 28), visit by treatment interaction, region and history of CV disease as fixed class factors and baseline FACT-An Ans, baseline Hb, baseline eGFR as continuous covariates. Baseline FACT-An Ans is defined as the FACT-An Ans value on day 1.

| | |
|---|-------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 524 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.047 ^[48] |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 1.704 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.02 |
| upper limit | 3.38 |

Notes:

[48] - LSM difference p-value is for test of differences

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

End point title Change From BL to the Average Value of Weeks 12-28 in Total FACT-An Score

End point description:

Baseline FACT-An Total Score was defined as the FACT-An Total score on Day 1. Total Fact-An score is

composed of FACT-G and Ans scales. FACT-G 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 AnS scale contains 13 fatigue specific items (the Fatigue Score) plus 7 items related to anemia. The total score is obtained by summation of the scores from PWB, SWB, EWB, FWB and AnS. The FACT-An Total Score scale range is 0-188. A higher score indicates better QoL.

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

| End point values | Roxadustat | Placebo | | |
|--|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 338 | 185 | | |
| Units: Units on a Scale | | | | |
| least squares mean (confidence interval 95%) | 5.777 (2.60 to 8.95) | 3.691 (0.01 to 7.37) | | |

Statistical analyses

| Statistical analysis title | Total FACT-An Score Change from BL to Average |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

A Mixed Model of Repeated Measures was applied using the visits up to week 28. The results were based on the estimated difference between the two treatment arms overall mean effect during week 12 to 28 period based on this MMRM model. The model includes treatment, visit (week8, week12 and week28), visit by treatment interaction, region and history of CV disease as fixed class factors and baseline FACT-An Total Score, baseline Hb, baseline eGFR as continuous covariates.

| | |
|---|-------------------------------|
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 523 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.225 |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | 2.086 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.29 |
| upper limit | 5.46 |

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

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

End point description:

The Euroqol Questionnaire – 5 Dimensions 5 Levels (EQ-5D 5L) is a self-reported questionnaire. The EQ-

5D is used as a measure of respondents' Health Related Quality of Life (HRQoL). The EQ- 5D consists of the EQ-5D descriptive system and the EQ visual analogue scale (VAS). The EQ-5D descriptive system comprises of 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 answers are labeled 'Best imaginable health state' and 'Worst imaginable health state' with higher scores for higher HRQoL. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment.

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

| End point values | Roxadustat | Placebo | | |
|--------------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 340 | 184 | | |
| Units: Units on a Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Average in week 12-28 | 5.390 (± 17.278) | 0.990 (± 15.859) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From BL to the Average Value of Weeks 12-28 in Overall Work Impairment Due to Anaemic Symptoms

| | |
|-----------------|---|
| End point title | Change From BL to the Average Value of Weeks 12-28 in Overall Work Impairment Due to Anaemic Symptoms |
|-----------------|---|

End point description:

Work productivity and activity impairment: anemic symptoms (WPAI:ANS) questionnaire version 2 was used to measure work and activity impairment during the last seven days due to anemia. It is self-assessed questionnaire which consists of 6 questions covering work and daily activities. Questions include asking if participant is working, how many hours the person missed work due to anemic symptoms, how many hours the person missed work due to other reasons, how many hours participant actually worked and how the anemic symptoms impacted their productivity and ability to do daily activities. For the last 2 questions, they were scored from 0-10 with 0 identifying no effect on work and 10 completely prevented from working. Overall work impairment due to ANS was calculated as $100 \times Q2 / (Q2 + Q4) + [(1 - Q2 / (Q2 + Q4)) \times (Q5 / 10)]$. Scores were calculated with the formula to derive the overall work impairment on each timepoints in percentage, and then changes of the percentage from baseline are reported.

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

| End point values | Roxadustat | Placebo | | |
|---|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: Percentage of work impairment arithmetic mean (standard deviation) | | | | |
| Average in week 12-28 | -5.965 (\pm 21.856) | -4.230 (\pm 23.679) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants in Each Category in Patients' Global Impression of Change (PGIC)

| | |
|-----------------|---|
| End point title | Percentage of Participants in Each Category in Patients' Global Impression of Change (PGIC) |
|-----------------|---|

End point description:

The Patients' Global Impression of Change (PGIC) is a participant rated instrument that measures change in participants overall status on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment.

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

End point timeframe:

Weeks 12 and 28

| End point values | Roxadustat | Placebo | | |
|---|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: Percentage of Participants number (not applicable) | | | | |
| Week 12 [Very much improved + Much improved] | 41.2 | 18.9 | | |
| Week 28 [Very much improved + Much improved] | 46.4 | 28.6 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From BL to Each Study Visit in Serum Hepcidin

| | |
|-----------------|--|
| End point title | Change From BL to Each Study Visit in Serum Hepcidin |
|-----------------|--|

End point description:

Baseline was assessed on 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. N is the number of participants with available data at each time point. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment.

| | |
|--------------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and weeks 4,12,20,36,52,104 | |

| End point values | Roxadustat | Placebo | | |
|--------------------------------------|--------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: ug/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 [N=345,182] | -19.835 (± 29.765) | 1.748 (± 35.368) | | |
| Week 12 [N=323,171] | -17.369 (± 31.572) | 0.971 (± 33.952) | | |
| Week 20 [N=303,148] | -10.684 (± 35.858) | -1.879 (± 30.661) | | |
| Week 36 [N=218,98] | -12.981 (± 32.351) | 0.803 (± 39.816) | | |
| Week 52 [N=268,114] | -12.274 (± 37.445) | 2.025 (± 40.678) | | |
| Week 104 [N=108,28] | -10.051 (± 33.671) | -7.436 (± 22.923) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From BL to Each Study Visit in Serum Ferritin

| | |
|---|--|
| End point title | Change From BL to Each Study Visit in Serum Ferritin |
| End point description: | |
| Baseline was assessed on 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. N is the number of participants with available data at each time point. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment. | |
| 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 | |

| End point values | Roxadustat | Placebo | | |
|--------------------------------------|----------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: pmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 [N=360,192] | -221.827 (± 248.902) | 11.564 (± 335.096) | | |
| Week 8 [N=346,191] | -247.955 (± 295.920) | -8.004 (± 252.615) | | |

| | | | | |
|---------------------|----------------------|---------------------|--|--|
| Week 12 [N=337,179] | -265.818 (± 318.445) | -31.548 (± 257.410) | | |
| Week 20 [N=318,154] | -198.349 (± 284.015) | -32.561 (± 320.382) | | |
| Week 28 [N=308,146] | -184.501 (± 341.114) | -5.123 (± 470.691) | | |
| Week 36 [N=295,132] | -142.876 (± 608.677) | 36.005 (± 538.357) | | |
| Week 44 [N=287,124] | -137.151 (± 352.715) | 57.373 (± 594.125) | | |
| Week 52 [N=276,118] | -164.009 (± 564.396) | 93.245 (± 640.998) | | |
| Week 60 [N=200,70] | -133.499 (± 467.931) | -18.833 (± 441.131) | | |
| Week 68 [N=177,50] | -159.906 (± 453.802) | 39.794 (± 581.616) | | |
| Week 76 [N=160,47] | -149.226 (± 408.126) | 25.291 (± 627.834) | | |
| Week 84 [N=149,38] | -103.284 (± 530.021) | 93.647 (± 753.265) | | |
| Week 92 [N=132,32] | -106.070 (± 464.192) | 1.011 (± 474.434) | | |
| Week 100 [N=127,30] | -119.647 (± 452.209) | 30.829 (± 514.823) | | |
| Week 104 [N=112,30] | -107.814 (± 458.702) | 4.524 (± 475.524) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From BL to Each Study Visit in Serum Transferrin Saturation (TSAT)

| | |
|-----------------|---|
| End point title | Change From BL to Each Study Visit in Serum Transferrin Saturation (TSAT) |
|-----------------|---|

End point description:

Baseline was assessed on 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. N is the number of participants with available data at each time point. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment.

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

| End point values | Roxadustat | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 [N=357,190] | -7.4 (± 11.7) | 0.7 (± 11.4) | | |
| Week 8 [N=344,191] | -5.7 (± 11.7) | -0.4 (± 13.0) | | |

| | | | | |
|---------------------|---------------|---------------|--|--|
| Week 12 [N=334,181] | -4.6 (± 13.5) | -0.7 (± 11.5) | | |
| Week 20 [N=317,152] | -1.1 (± 13.4) | -0.3 (± 11.5) | | |
| Week 28 [N=306,145] | -1.8 (± 13.8) | 0.8 (± 13.2) | | |
| Week 36 [N=292,127] | -1.6 (± 13.6) | 1.1 (± 14.6) | | |
| Week 44 [N=281,123] | -0.2 (± 14.0) | 1.0 (± 16.0) | | |
| Week 52 [N=275,115] | -0.7 (± 13.6) | 0.0 (± 16.3) | | |
| Week 60 [N=198,68] | -0.6 (± 14.1) | -2.7 (± 13.9) | | |
| Week 68 [N=177,49] | -2.2 (± 13.1) | -3.3 (± 12.3) | | |
| Week 76 [N=158,44] | -2.6 (± 13.8) | -1.7 (± 13.9) | | |
| Week 84 [N=148,35] | -3.4 (± 13.3) | -3.6 (± 13.8) | | |
| Week 92 [N=131,31] | -1.9 (± 13.2) | -1.8 (± 12.8) | | |
| Week 100 [N=125,29] | 0.0 (± 13.4) | 0.7 (± 12.0) | | |
| Week 104 [N=112,29] | -0.4 (± 12.6) | 0.0 (± 12.3) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From BL to Each Study Visit in Serum HbA1c Level

| | |
|--|---|
| End point title | Change From BL to Each Study Visit in Serum HbA1c Level |
| End point description: | |
| HbA1c was measured at each timepoint and presented in 'fraction of 1' unit by dividing the values in percentage by 100, in order to fit for CDISC (Clinical Data Interchange Standards Consortium) standard terminology. Changes from baseline to each timepoint were reported in unit 'fraction of 1'. Baseline was assessed on 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. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and weeks 12,28,36,44,60,84,104 | |

| End point values | Roxadustat | Placebo | | |
|--------------------------------------|-------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: Fraction of 1 | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 12 [N=338,182] | 0.0007 (± 0.0064) | -0.0001 (± 0.0061) | | |
| Week 28 [N=304,145] | 0.0006 (± 0.0086) | 0.0008 (± 0.0091) | | |
| Week 36 [N=225,108] | 0.0011 (± 0.0098) | 0.0007 (± 0.0075) | | |
| Week 44 [N=282,125] | 0.0018 (± 0.0081) | -0.0002 (± 0.0074) | | |
| Week 60 [N=200,70] | 0.0009 (± 0.0073) | 0.0012 (± 0.0080) | | |
| Week 84 [N=147,38] | 0.0028 (± 0.0085) | 0.0022 (± 0.0111) | | |
| Week 104 [N=111,29] | 0.0014 (± 0.0073) | 0.0004 (± 0.0059) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From BL to Each Study Visit in Fasting Blood Glucose

| | |
|-----------------|---|
| End point title | Change From BL to Each Study Visit in Fasting Blood Glucose |
|-----------------|---|

End point description:

Baseline was assessed on 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. N is the number of participants with available data at each time point. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment.

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

| End point values | Roxadustat | Placebo | | |
|--------------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: mmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 [N=241,134] | 0.107 (± 2.573) | -0.076 (± 2.730) | | |
| Week 8 [N=233,128] | -0.103 (± 3.179) | -0.162 (± 3.118) | | |
| Week 12 [N=223,118] | -0.100 (± 3.504) | -0.153 (± 4.629) | | |
| Week 20 [N=211,99] | -0.302 (± 4.052) | 0.523 (± 2.981) | | |
| Week 28 [N=199,95] | 0.160 (± 3.489) | 0.045 (± 3.281) | | |
| Week 36 [N=185,83] | 0.015 (± 2.991) | -0.117 (± 2.812) | | |
| Week 44 [N=167,76] | 0.073 (± 2.683) | 0.801 (± 3.416) | | |
| Week 52 [N=168,79] | 0.048 (± 4.348) | -0.086 (± 4.883) | | |
| Week 60 [N=116,47] | 0.130 (± 2.907) | 1.190 (± 3.946) | | |
| Week 68 [N=91,33] | 0.185 (± 2.831) | 0.698 (± 3.386) | | |
| Week 76 [N=81,28] | -0.015 (± 2.031) | -0.671 (± 5.148) | | |
| Week 84 [N=75,20] | 0.495 (± 3.117) | 0.435 (± 2.037) | | |
| Week 92 [N=65,19] | 0.612 (± 2.494) | -0.861 (± 3.298) | | |

| | | | | |
|--------------------|-----------------|------------------|--|--|
| Week 100 [N=58,19] | 0.405 (± 2.932) | -0.699 (± 2.161) | | |
| Week 104 [N=59,20] | 0.125 (± 2.633) | 0.237 (± 3.938) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From BL to Each Study Visit in Albumin/Creatinine Ratio in Urine

| | |
|-----------------|---|
| End point title | Change From BL to Each Study Visit in Albumin/Creatinine Ratio in Urine |
|-----------------|---|

End point description:

Baseline assessment was the assessment from day 1 visit. If baseline value was missing, value from screening visit was used. In case of missing data, no imputation rules were applied. To compute the geometric mean of albumin/creatinine ratio in urine and associated 95% CI, the mean of log-transformed albumin/creatinine ratio in urine values (ratio) and associated 95% CI are back-transformed to the raw scale. All assessments collected after initiation of dialysis (acute or chronic) were excluded from the analysis. N is the number of participants with available data at each time point. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment.

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

End point timeframe:

Baseline and weeks 12,24,36,52,64,76,88,104

| End point values | Roxadustat | Placebo | | |
|--|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: Ratio | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Week 12 [N=122,75] | 1.08 (0.96 to 1.20) | 1.06 (0.84 to 1.34) | | |
| Week 24 [N=103,53] | 1.19 (1.04 to 1.36) | 1.16 (0.89 to 1.53) | | |
| Week 36 [N=90,49] | 1.21 (1.04 to 1.41) | 1.04 (0.77 to 1.40) | | |
| Week 52 [N=74,38] | 1.28 (1.02 to 1.59) | 1.04 (0.72 to 1.51) | | |
| Week 64 [N=22,11] | 1.25 (0.84 to 1.87) | 0.96 (0.53 to 1.71) | | |
| Week 76 [N=14,10] | 1.12 (0.51 to 2.44) | 0.82 (0.41 to 1.65) | | |
| Week 88 [N=11,2] | 1.10 (0.38 to 3.17) | 0.51 (0.27 to 0.97) | | |
| Week 104 [N=4,2] | 1.92 (0.75 to 4.89) | 0.38 (0.08 to 1.88) | | |

Statistical analyses

Secondary: Change From BL to Each Study Visit in Serum Creatinine (Cr) Ratio

| | |
|-----------------|---|
| End point title | Change From BL to Each Study Visit in Serum Creatinine (Cr) Ratio |
|-----------------|---|

End point description:

Baseline assessment was the 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. To compute the geometric mean of serum Cr (ratio) and associated 95% CI, the mean of log-transformed serum Cr (ratio) values and associated 95% CI are back-transformed to the raw scale. All assessments collected after initiation of dialysis (acute or chronic) were excluded from the analysis. N is the number of participants with available data at each time point. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment.

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

| End point values | Roxadustat | Placebo | | |
|--|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: Ratio | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Week 4 [N=355,188] | 1.01 (1.00 to 1.03) | 1.05 (1.03 to 1.07) | | |
| Week 8 [N=338,184] | 1.03 (1.01 to 1.05) | 1.07 (1.04 to 1.09) | | |
| Week 12 [N=323,169] | 1.04 (1.02 to 1.06) | 1.07 (1.04 to 1.11) | | |
| Week 20 [N=289,135] | 1.08 (1.06 to 1.12) | 1.09 (1.05 to 1.13) | | |
| Week 28 [N=267,124] | 1.12 (1.08 to 1.16) | 1.13 (1.08 to 1.17) | | |
| Week 36 [N=238,108] | 1.12 (1.08 to 1.16) | 1.12 (1.07 to 1.18) | | |
| Week 44 [N=216,99] | 1.12 (1.07 to 1.16) | 1.16 (1.10 to 1.22) | | |
| Week 52 [N=201,90] | 1.12 (1.07 to 1.16) | 1.15 (1.09 to 1.22) | | |
| Week 60 [N=135,52] | 1.09 (1.05 to 1.14) | 1.15 (1.07 to 1.23) | | |
| Week 68 [N=117,36] | 1.11 (1.06 to 1.17) | 1.24 (1.13 to 1.37) | | |
| Week 76 [N=102,33] | 1.13 (1.07 to 1.20) | 1.23 (1.12 to 1.36) | | |
| Week 84 [N=94,26] | 1.13 (1.07 to 1.20) | 1.19 (1.05 to 1.35) | | |
| Week 92 [N=83,24] | 1.19 (1.12 to 1.27) | 1.22 (1.05 to 1.41) | | |
| Week 100 [N=75,22] | 1.16 (1.08 to 1.24) | 1.26 (1.06 to 1.50) | | |
| Week 104 [N=66,23] | 1.16 (1.05 to 1.27) | 1.28 (1.09 to 1.51) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Doubling of Serum Creatinine or Chronic Dialysis or Renal Transplant Compared to Baseline

| | |
|-----------------|---|
| End point title | Time to Doubling of Serum Creatinine or Chronic Dialysis or Renal Transplant Compared to Baseline |
|-----------------|---|

End point description:

The endpoint was defined as time to doubling serum creatinine or chronic dialysis or renal transplant what ever came first. Time to event was defined as (First event date – Analysis date of first dose intake + 1) / 365.25. First event date was defined as date of dialysis or date of renal transplant (whichever occurred first) and analysis date of first dose intake was defined as date of first study drug dose intake collected on day 1 visit. Data analysis was completed using Kaplan-Meier estimate for cumulative proportion. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment. The data evaluated until the safety emergent period, which was defined as the evaluation period from analysis date of first drug intake up to 28 days after the analysis last dose, and results were presented for every 6 months up to 2 years.

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

End point timeframe:

Baseline and year 0.5, year 1, year 1.5 and year 2

| End point values | Roxadustat | Placebo | | |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Years 0.5 | 17.4 (13.4 to 21.4) | 17.8 (12.3 to 23.4) | | |
| Years 1 | 36.8 (31.6 to 42.1) | 35.4 (27.9 to 42.9) | | |
| Years 1.5 | 47.3 (41.4 to 53.1) | 48.2 (38.6 to 57.8) | | |
| Years 2 | 55.0 (48.5 to 61.4) | 54.7 (43.8 to 65.6) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------------|
| Statistical analysis title | Time to Doubling of Serum Creatinine |
|----------------------------|--------------------------------------|

Statistical analysis description:

Hazard ratio was calculated using stratified Cox Proportional Hazards Regression stratifying on CV history and region and adjusting on Hb and eGFR at baseline as continuous covariates.

| | |
|-------------------|----------------------|
| Comparison groups | Roxadustat v Placebo |
|-------------------|----------------------|

| | |
|---|-------------------|
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.973 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.995 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.75 |
| upper limit | 1.32 |

Secondary: Time to Chronic Kidney Disease (CKD) Progression (Composite of Doubling Serum Creatinine, Chronic Dialysis or Renal Transplant, and Death)

| | |
|-----------------|--|
| End point title | Time to Chronic Kidney Disease (CKD) Progression (Composite of Doubling Serum Creatinine, Chronic Dialysis or Renal Transplant, and Death) |
|-----------------|--|

End point description:

CKD progression was defined as occurrence of chronic dialysis or renal transplant or doubled serum creatinine or death. The time to CKD progression was calculated (in years) as (First event date – Analysis date of first dose intake + 1) / 365.25. First event date was defined as first occurrence of any of the CKD progression, whichever occurred first. Analysis date of first dose intake was defined as date of first study drug dose intake collected on day 1 visit. Data analysis was completed using Kaplan-Meier estimate for cumulative proportion. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment. The data evaluated until the safety emergent period, which was defined as the evaluation period from analysis date of first drug intake up to 28 days after the analysis last dose, and results were presented for every 6 months up to 2 years.

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

End point timeframe:

Baseline and year 0.5, year 1, year 1.5 and year 2

| End point values | Roxadustat | Placebo | | |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Years 0.5 | 20.5 (16.3 to 24.7) | 20.0 (14.2 to 25.8) | | |
| Years 1 | 40.3 (35.1 to 45.5) | 38.3 (30.7 to 45.8) | | |
| Years 1.5 | 50.2 (44.5 to 55.9) | 50.5 (41.1 to 59.9) | | |
| Years 2 | 58.9 (52.7 to 65.1) | 61.1 (50.5 to 71.7) | | |

Statistical analyses

| Statistical analysis title | Time to CKD Progression |
|--|-------------------------|
| Statistical analysis description: | |
| Hazard ratio was calculated using stratified Cox Proportional Hazards Regression stratifying on CV history and region and adjusting on Hb and eGFR at baseline as continuous covariates. | |
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.972 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.995 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.76 |
| upper limit | 1.3 |

Secondary: Time to at Least 40% Decrease in eGFR From Baseline, Chronic Dialysis or Renal Transplant

| | |
|---|---|
| End point title | Time to at Least 40% Decrease in eGFR From Baseline, Chronic Dialysis or Renal Transplant |
| End point description: | |
| All eGFR values collected during the safety emergent period are considered, excluding those collected on or after initiation of dialysis (acute or chronic). The First event date was defined as First occurrence of 40% decrease in eGFR from baseline, first occurrence of chronic dialysis or renal transplant (whichever occurred first and Analysis date of first dose intake was defined as date of first study drug dose intake collected on day 1 visit. Data analysis was completed using Kaplan-Meier estimate for cumulative proportion. The analysis population was the FAS, which consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose Hb assessment. The data evaluated until the safety emergent period, which was defined as the evaluation period from analysis date of first drug intake up to 28 days after the analysis last dose, and results were presented for every 6 months up to 2 years. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and year 0.5, year 1, year 1.5 and year 2 | |

| End point values | Roxadustat | Placebo | | |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 389 | 203 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Years 0.5 | 20.7 (16.5 to 25.0) | 22.3 (16.2 to 28.4) | | |
| Years 1 | 44.4 (39.0 to 49.8) | 44.0 (36.2 to 51.7) | | |
| Years 1.5 | 54.6 (48.9 to 60.4) | 62.8 (53.2 to 72.5) | | |

| | | | | |
|---------|---------------------|---------------------|--|--|
| Years 2 | 64.5 (64.5 to 70.7) | 67.0 (56.8 to 77.1) | | |
|---------|---------------------|---------------------|--|--|

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Time to at Least 40% Decrease in eGFR from BL |
| Statistical analysis description: | |
| Hazard ratio was calculated using stratified Cox Proportional Hazards Regression stratifying on CV history and region and adjusting on Hb and eGFR at baseline as continuous covariates. | |
| Comparison groups | Roxadustat v Placebo |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.439 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.905 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 1.16 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 28 days after the last dose of study drug (up to 108 weeks), and up to 2.836 years at maximum for all-cause mortality

Adverse event reporting additional description:

The safety emergent period was defined as the period from date of first drug intake up to 28 days after the analysis last dose. All-cause mortality was monitored at any time after first administration of study drug to the end of the post-study follow-up, which includes deaths reported after the 28-day follow-up after the last dose.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 20.0 |

Reporting groups

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

Reporting group description:

Participants received roxadustat according to the tiered weight-based approach, with starting doses of 70 mg given thrice weekly (TIW) to participants weighing up to 70 kg and 100 mg given TIW to participants weighing more than 70 kg. Dose-titration was performed based upon regular measurement of Hb levels until participants achieved central Hb value of ≥ 11.0 g/dL and Hb increase from baseline (BL) of ≥ 1.0 g/dL at two consecutive study visits, separated by at least 5 days. Once target Hb level was reached participants entered maintenance period during which roxadustat dosage was adjusted every 4 weeks to maintain participants Hb level within the target range of 10.0 g/dL and 12.0 g/dL. Participants received roxadustat for at least 52 weeks up to a maximum of 104 weeks.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Participants received matching placebo according to the tiered weight-based approach, with starting doses of 70 mg given thrice weekly (TIW) to participants weighing up to 70 kg and 100 mg given TIW to participants weighing more than 70 kg. Dose-titration was performed based upon regular measurement of Hb levels until participants achieved central Hb value of ≥ 11.0 g/dL and Hb increase from baseline (BL) of ≥ 1.0 g/dL at two consecutive study visits, separated by at least 5 days. Once target Hb level was reached participants entered maintenance period during which roxadustat dosage was adjusted every 4 weeks to maintain participants Hb level within the target range of 10.0 g/dL and 12.0 g/dL. Participants received matching placebo for at least 52 weeks up to a maximum of 104 weeks.

| Serious adverse events | Roxadustat | Placebo | |
|---|--------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 241 / 391 (61.64%) | 115 / 203 (56.65%) | |
| number of deaths (all causes) | 45 | 20 | |
| number of deaths resulting from adverse events | 40 | 19 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Basal cell carcinoma | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 391 (0.26%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon cancer | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lipoma | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (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 | 1 / 391 (0.26%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Metastases to the mediastinum | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Metastatic carcinoma of the bladder | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Aortic stenosis | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Blood pressure inadequately controlled | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 4 / 391 (1.02%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic vascular disorder | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Extremity necrosis | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (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 | 4 / 391 (1.02%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 4 / 391 (1.02%) | 5 / 203 (2.46%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery stenosis | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral vascular disorder | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Hospitalisation | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leg amputation | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |

| | | | |
|---|-----------------|-----------------|--|
| Asthenia | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Catheter site haemorrhage | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 4 / 391 (1.02%) | 3 / 203 (1.48%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 1 / 4 | 0 / 3 | |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden cardiac death | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Immune system disorders | | | |
| Allergy to arthropod bite | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metrorrhagia | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ovarian cyst torsion | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydrothorax | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 3 / 391 (0.77%) | 3 / 203 (1.48%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 3 / 391 (0.77%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |

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|---|-----------------|-----------------|--|
| Pulmonary hypertension | | | |
| subjects affected / exposed | 3 / 391 (0.77%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 3 / 391 (0.77%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Respiratory disorder | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory distress | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory failure | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disorientation | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| Device dislocation | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (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 | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatic mass | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Steatohepatitis | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Blood urea increased | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Glomerular filtration rate decreased | | | |
| subjects affected / exposed | 21 / 391 (5.37%) | 11 / 203 (5.42%) | |
| occurrences causally related to treatment / all | 0 / 23 | 1 / 15 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Arterial injury | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (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 | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriovenous fistula thrombosis | | | |
| subjects affected / exposed | 14 / 391 (3.58%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 5 / 17 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Concussion | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Craniocerebral injury | | | |
| subjects affected / exposed | 3 / 391 (0.77%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Facial bones fracture | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fat embolism | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| 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 | 4 / 391 (1.02%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| 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 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative wound complication | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pubis fracture | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Congenital cystic kidney disease | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute left ventricular failure | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 6 / 391 (1.53%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 1 / 6 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriosclerosis coronary artery | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 3 / 391 (0.77%) | 3 / 203 (1.48%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block complete | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| 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 | 3 / 391 (0.77%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 3 / 391 (0.77%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 3 / 391 (0.77%) | 3 / 203 (1.48%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiogenic shock | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiopulmonary failure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left ventricular failure | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 8 / 391 (2.05%) | 3 / 203 (1.48%) | |
| occurrences causally related to treatment / all | 5 / 8 | 0 / 3 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 2 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 5 / 391 (1.28%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Dementia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic neuropathy | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (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 | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Headache | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive encephalopathy | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemic coma | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 4 / 391 (1.02%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Loss of consciousness | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myasthenic syndrome | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Partial seizures | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sciatica | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 3 / 391 (0.77%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular encephalopathy | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 8 / 391 (2.05%) | 7 / 203 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic anaemia | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Heparin-induced thrombocytopenia | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphadenopathy mediastinal | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrogenic anaemia | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Macular hole | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ulcerative keratitis | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic gastroparesis | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 391 (0.77%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gastric ulcer | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer perforation | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis erosive | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic erosive gastritis | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal perforation | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Large intestinal ulcer | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 3 / 391 (0.77%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophagitis | | | |
| subjects affected / exposed | 3 / 391 (0.77%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis chronic | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (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 | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 391 (0.77%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| 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 | 2 / 391 (0.51%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eczema nummular | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Panniculitis | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pruritus | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin ulcer | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toxic skin eruption | | | |

| | | | |
|---|--------------------|-------------------|--|
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute prerenal failure | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Azotaemia | | | |
| subjects affected / exposed | 10 / 391 (2.56%) | 8 / 203 (3.94%) | |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Calculus bladder | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (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 | 135 / 391 (34.53%) | 62 / 203 (30.54%) | |
| occurrences causally related to treatment / all | 1 / 135 | 0 / 63 | |
| deaths causally related to treatment / all | 0 / 8 | 0 / 4 | |
| Haematuria | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oliguria | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Renal colic | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urethral stenosis | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Endocrine disorders | | | |
| Goitre | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperparathyroidism primary | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperparathyroidism secondary | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (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 | | | |
| Gouty arthritis | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Joint contracture | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abscess limb | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal abscess | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis perforated | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis bacterial | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bursitis infective | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 3 / 391 (0.77%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (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 | 4 / 391 (1.02%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Diabetic foot infection | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterobacter bacteraemia | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epididymitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 3 / 391 (0.77%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye infection | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gangrene | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic echinococcosis | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis B | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (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 / 391 (0.26%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningoencephalitis herpetic | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orchitis | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (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 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Otitis media acute | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 5 / 391 (1.28%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 1 / 6 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 17 / 391 (4.35%) | 12 / 203 (5.91%) | |
| occurrences causally related to treatment / all | 1 / 21 | 0 / 14 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 3 | |
| Pneumonia staphylococcal | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (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 | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary sepsis | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis chronic | | | |
| subjects affected / exposed | 5 / 391 (1.28%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Pyonephrosis | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 6 / 391 (1.53%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Sinusitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tuberculosis | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (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 bacterial | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vulvovaginitis | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 1 / 203 (0.49%) | |
| 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 | 1 / 391 (0.26%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic metabolic decompensation | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 391 (0.26%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fluid overload | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gout | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 4 / 391 (1.02%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypervolaemia | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Roxadustat | Placebo | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 204 / 391 (52.17%) | 103 / 203 (50.74%) | |
| Investigations | | | |
| Glomerular filtration rate decreased | | | |
| subjects affected / exposed | 24 / 391 (6.14%) | 13 / 203 (6.40%) | |
| occurrences (all) | 25 | 13 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 85 / 391 (21.74%) | 27 / 203 (13.30%) | |
| occurrences (all) | 138 | 44 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 20 / 391 (5.12%) | 10 / 203 (4.93%) | |
| occurrences (all) | 21 | 11 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 16 / 391 (4.09%) | 31 / 203 (15.27%) | |
| occurrences (all) | 17 | 45 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 18 / 391 (4.60%) | 11 / 203 (5.42%) | |
| occurrences (all) | 22 | 13 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 44 / 391 (11.25%) | 21 / 203 (10.34%) | |
| occurrences (all) | 53 | 22 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 32 / 391 (8.18%) | 6 / 203 (2.96%) | |
| occurrences (all) | 38 | 9 | |
| Nausea | | | |

| | | | |
|--|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 34 / 391 (8.70%) 44 | 6 / 203 (2.96%) 6 | |
| Infections and infestations Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 38 / 391 (9.72%) 50 | 9 / 203 (4.43%) 15 | |
| Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all) | 36 / 391 (9.21%) 48 | 13 / 203 (6.40%) 19 | |
| Hyperuricaemia subjects affected / exposed occurrences (all) | 9 / 391 (2.30%) 9 | 11 / 203 (5.42%) 11 | |
| Iron deficiency subjects affected / exposed occurrences (all) | 26 / 391 (6.65%) 26 | 8 / 203 (3.94%) 10 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 17 December 2014 | The changes include: -Changes in the study dosing regimen as follows: Dosing frequency changed from thrice weekly (TIW), twice weekly (BIW) and once weekly (QW) to TIW only; Initial study drug dose changed from 70, 100 and 150 mg to 70 and 100 mg only; Maximum dose reduced from 3.5 mg/kg to 3.0 mg/kg and maximum absolute dose reduced from 400 mg to 300 mg. - Reduction in visit schedule by removal of 12 study visits, resulting in 39 visits. - Addition of a post-study follow-up period. - Addition of a primary efficacy endpoint to support submission of the data to the FDA |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported