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	v1
This version publication date	16 November 2018
First version publication date	16 November 2018

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
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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	192

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 m^2) 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 pm ol/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	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Roxadustat

Arm description:

Participants were treated with roxadustat three times a week (TIW) for at least 52 weeks up to a maximum of 104 weeks. Treatment dosage was adjusted based on the predefined targeted hemoglobin (Hb) values.

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 were treated with placebo three times a week (TIW) for at least 52 weeks up to a maximum of 104 weeks. Treatment dosage was adjusted based on the predefined targeted hemoglobin (Hb) values.

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	277	116
Not completed	114	87
Subject unable to come to the site for procedures	1	-
Physician decision	6	7
Consent withdrawn by subject	47	43
Adverse Event	17	6
EOT done by mistake instead of week 48 visit	1	-
Death	27	9
Non-compliance with study drug	2	-
Subject's lack in compliance	1	-
Lost to follow-up	5	1
Lack of efficacy	3	20
Protocol deviation	2	-
Sponsor request to withdraw subject	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Roxadustat
Reporting group description:	
Participants were treated with roxadustat three times a week (TIW) for at least 52 weeks up to a maximum of 104 weeks. Treatment dosage was adjusted based on the predefined targeted hemoglobin (Hb) values.	
Reporting group title	Placebo
Reporting group description:	
Participants were treated with placebo three times a week (TIW) for at least 52 weeks up to a maximum of 104 weeks. Treatment dosage was adjusted based on the predefined targeted hemoglobin (Hb) values.	

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			
Yes	146	89	235
No	245	114	359
Iron Repletion at Baseline Units: Subjects			
TSAT >= 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 were treated with roxadustat three times a week (TIW) for at least 52 weeks up to a maximum of 104 weeks. Treatment dosage was adjusted based on the predefined targeted hemoglobin (Hb) values.

Reporting group title	Placebo

Reporting group description:

Participants were treated with placebo three times a week (TIW) for at least 52 weeks up to a maximum of 104 weeks. Treatment dosage was adjusted based on the predefined targeted hemoglobin (Hb) values.

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

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 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	Roxadustat v Placebo
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.

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 participants with available data at all time points.

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.

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 participants with available data at all time points.

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
P-value	< 0.001 [2]
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] - LSM Difference p-value is for test of differences.

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.

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				
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
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

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 baseline 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, which consisted of participants with available data at all time points.

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, overall mean effects throughout the evaluation period (weeks 12 to 28) based on the MMRM model. The model includes treatment, visit, visit by treatment interaction, region and history of CV disease as fixed class factors and baseline SF-36 VT, 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	= 0.093 [3]
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:

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

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 physical functioning (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 participants with available data at all time points.

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 overall mean effects throughout the evaluation period (weeks 12 to 28) based on this MMRM model. The model included treatment, visit, visit by treatment interaction, region and history of CV disease as fixed class factors and baseline SF-36 PF, 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	= 0.27 [4]
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:

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

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	superiority
P-value	= 0.182 [5]
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:

[5] - 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 PPS, which consisted of participants with available data at all time points.

End point type	Secondary

End point timeframe:

Baseline to week 108

End point values	Roxadustat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	359	183		
Units: Percentage				
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	superiority
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

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.	
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				
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 participants with available data at all time points.

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%)	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 [6]
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:

[6] - 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 participants with available data at all time points.

End point type	Secondary

End point timeframe:

Baseline and 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 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	405
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [7]
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:

[7] - 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 participants with available data at all time points.

End point type	Secondary

End point timeframe:

Baseline and 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 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	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [8]
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:

[8] - 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:

Hb response was measured as Yes or No; Yes 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. For a participant without rescue therapy before Hb response, 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 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.

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				
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.

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 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	592
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [9]
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:

[9] - 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 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	592
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [10]
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:

[10] - 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 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	592
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [11]
Method	Mixed models analysis
Parameter estimate	Least squares mean difference
Point estimate	1.471
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.3
upper limit	1.64

Notes:

[11] - 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 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	592
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [12]
Method	Mixed models analysis
Parameter estimate	Least squares mean difference
Point estimate	1.827
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.64
upper limit	2.02

Notes:

[12] - 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 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	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	2.058
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.87
upper limit	2.25

Notes:

[13] - 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 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	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	1.949
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.75
upper limit	2.14

Notes:

[14] - 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 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	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	2.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.9
upper limit	2.28

Notes:

[15] - 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 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	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	2.051
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.86
upper limit	2.24

Notes:

[16] - 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 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	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	1.987

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.79
upper limit	2.19

Notes:

[17] - 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 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	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	1.841
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.64
upper limit	2.05

Notes:

[18] - 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 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	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	1.824
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.61
upper limit	2.04

Notes:

[19] - 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 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	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	1.651
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.43
upper limit	1.87

Notes:

[20] - 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 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	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	1.447
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.23
upper limit	1.67

Notes:

[21] - 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 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	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	1.561
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.34
upper limit	1.78

Notes:

[22] - 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 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	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	1.587
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.37
upper limit	1.81

Notes:

[23] - 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 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	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	1.69

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.46
upper limit	1.92

Notes:

[24] - 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 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	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	1.645
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.41
upper limit	1.88

Notes:

[25] - 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 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	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	1.699
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.45
upper limit	1.94

Notes:

[26] - 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 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	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	1.446
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	1.69

Notes:

[27] - 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 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	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	1.641
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.39
upper limit	1.89

Notes:

[28] - 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 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	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	1.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.37
upper limit	1.91

Notes:

[29] - 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 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	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	1.634
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.33
upper limit	1.94

Notes:

[30] - 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 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	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	1.404

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	1.73

Notes:

[31] - 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 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	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	1.499
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.18
upper limit	1.82

Notes:

[32] - 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 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	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	1.438
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	1.78

Notes:

[33] - 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 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	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	1.185
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.54

Notes:

[34] - 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 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	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	1.443
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.11
upper limit	1.78

Notes:

[35] - 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 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	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	1.374
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	1.75

Notes:

[36] - 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 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	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	1.171
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.55

Notes:

[37] - 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 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	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	1.382

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.78

Notes:

[38] - 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 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	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	1.563
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.15
upper limit	1.97

Notes:

[39] - 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 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	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	1.448
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	1.83

Notes:

[40] - 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 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	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	1.347
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.79

Notes:

[41] - 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 participants with available data at all time points.

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 [42]
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:

[42] - 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 participants with available data at all time points.

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 participants with available data at all time points.

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 [43]
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:

[43] - 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 -12.00 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 participants with at least one non-missing Hb assessed during the period.

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 participants with at least one non-missing Hb assessed during the period.

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 participants with at least one non-missing Hb assessed during the period.

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 occured 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				
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 patient-exposure-year (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.

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				
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:	
For participants who have experienced more than one RBC transfusion, only their first event following study treatment was used. Data analysis was completed using Kaplan-Meier estimate for cumulative proportion. The analysis population was the FAS.	
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				
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 Per Participant Per Month

End point title	Mean Monthly Number of RBC Packs Per Participant Per Month

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 occured 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.

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 (± 0.397)	0.089 (± 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 RBC Transfusions Per Month

End point title	Mean Monthly Volume of RBC Transfusions Per Month

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.

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 included 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:

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 First event date was defined as Date of first ESA and Analysis date of first dose intake was defined as the first study drug dose intake collected in the day 1 visit. 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.

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				
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 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 first event date was defined as date of first IV iron during the efficacy emergent period and analysis date of first dose intake was defined as the date of first study drug dose intake collected on Day 1 visit. 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.

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				
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.

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.

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.

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.

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.

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.

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 region were excluded. The analysis population was the FAS.

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.

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 included participants with available data.

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 Anemia Subscale (Ans) of Functional Assessment of Cancer Therapy (FACT-An) Score

End point description:

The functional assessment of cancer therapy general (FACT-G) Version 4 contains 27 items that cover four dimensions of well-being: physical (PWB)—7 items, functional (FWB)—7 items, social/family (SWB)—7 items each, and emotional (EWB)—6 items. A subscale of 13 fatigue specific items (the Fatigue Subscale) plus seven additional items related to anemia were developed for use in conjunction with the FACT-G. The 13 fatigue items plus the seven additional items related to anemia comprise the Anemia Subscale (AnS). Administration of the FACT-G plus the AnS is referred to as the FACT-An. Respondents are asked to provide responses, (i.e., 'Not at all', 'A little bit', 'Somewhat', 'Quite a bit' and 'Very much'), to a list of statements which are either positively or negatively phrased. For all FACT-An scales, a higher score indicates better QoL. The analysis population was the FAS, which included participants with available data.

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%)	4.324 (2.71 to 5.93)	2.652 (0.79 to 4.51)		

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	= 0.051 [44]
Method	Mixed models analysis
Parameter estimate	Least squares mean difference
Point estimate	1.672
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	3.35

Notes:

[44] - 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:

FACT-An Total Score consist of 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 and Anemia Subscale (AnS). Respondents were asked to provide responses, (Not at all, A little bit, Somewhat, Quite a bit and Very much), to a list of statements which were either positively or negatively phrased. Each individual item was scored from 0 (Not at all) to 4 (Very much), and then the total score was obtained by summation of the resulted scores. A final higher score indicates better QoL. The analysis population was the FAS, which included participants with available data.

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%)	5.641 (2.47 to 8.81)	3.593 (-0.08 to 7.27)		

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	= 0.233
Method	Mixed models analysis
Parameter estimate	Least squares mean difference
Point estimate	2.049
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.32
upper limit	5.42

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.

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 Work Productivity and Activity Impairment:Anemic Symptoms (WPAI:ANS)

End point title	Change From BL to the Average Value of Weeks 12-28 in Work Productivity and Activity Impairment:Anemic Symptoms (WPAI:ANS)

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 2 domains and 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 participant actually worked and how the anemic symptoms impacted their productivity and ability to do daily activities. WPAI:ANS was scored from 0-10 with 0 identifying low impact and 10 highest impact on the work activities. Work time missed due to anaemic symptoms was calculated as 100 x Q2/(Q2+Q4). Overall work impairment due to anaemic symptoms was calculated as 100 x Q2/(Q2+Q4)+[(1-Q2/(Q2+Q4))x(Q5/10)]. N is the number of participants with available data at each time point. The analysis population was the FAS.

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: Units on a Scale				
arithmetic mean (standard deviation)				
Work time missed due to ANS [N=49,27]	-4.688 (± 23.927)	-0.431 (± 30.738)		
Impairment at work due to ANS [N=51,27]	-4.359 (± 25.964)	7.963 (± 28.998)		

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.

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:

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.

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:

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.

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:

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.

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:

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.

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:

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.

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 (Cr) Ratio in Urine

End point title	Change From BL to Each Study Visit in Albumin/Creatinine (Cr) 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.

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

No statistical analyses for this end point

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.

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.

End point type	Secondary

End point timeframe:

Baseline and up to week 108

End point values	Roxadustat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	389	203		
Units: Percentage				
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 date of occurrence of chronic dialysis or date of renal transplant or doubled serum creatinine or date of death, whichever came first. 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 serum creatinine being doubled compared with baseline, first occurrence of chronic dialysis or renal transplant, occurrence of participants who died (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.

End point type	Secondary

End point timeframe:

Baseline and up to week 108

End point values	Roxadustat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	389	203		
Units: Percentage				
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. The safety emergent period was defined as the evaluation period from the analysis date of first drug intake up to 28 days after the analysis date of last dose or end of study (EOS), whichever occurred first. Data analysis was completed using Kaplan-Meier estimate for cumulative proportion. The analysis population was the FAS.

End point type	Secondary

End point timeframe:

Baseline and up to week 108

End point values	Roxadustat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	389	203		
Units: Percentage				
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)

Adverse event reporting additional description:

Total number of deaths (all causes) includes deaths reported after the time frame above.The mortality rate during the safety emergent period was 7.4 per 100-yr in roxadustat and 7.6 in placebo.Rate for Acute myocardial infraction was 1.2 per 100-yr in roxadustat and 1.0 in placebo,Pulmonary embolism was 0.6 per 100-yr in roxadustat and 0.5 placebo.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants were treated with placebo three times a week (TIW) for at least 52 weeks up to a maximum of 104 weeks. Treatment dosage was adjusted based on the predefined targeted hemoglobin (Hb) values.

Reporting group title	Roxadustat

Reporting group description:

Participants were treated with roxadustat three times a week (TIW) for at least 52 weeks up to a maximum of 104 weeks. Treatment dosage was adjusted based on the predefined targeted hemoglobin (Hb) values.

Serious adverse events	Placebo	Roxadustat	
Total subjects affected by serious adverse events			
subjects affected / exposed	115 / 203 (56.65%)	241 / 391 (61.64%)	
number of deaths (all causes)	20	45	
number of deaths resulting from adverse events	19	40	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma			
subjects affected / exposed	1 / 203 (0.49%)	0 / 391 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 203 (0.49%)	1 / 391 (0.26%)	
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	1 / 203 (0.49%)	0 / 391 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 203 (0.49%)	0 / 391 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipoma			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 203 (0.49%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to the mediastinum			
subjects affected / exposed	1 / 203 (0.49%)	0 / 391 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastatic carcinoma of the bladder			
subjects affected / exposed	1 / 203 (0.49%)	0 / 391 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	1 / 203 (0.49%)	0 / 391 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 203 (0.49%)	0 / 391 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic stenosis			

subjects affected / exposed	1 / 203 (0.49%)	2 / 391 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood pressure inadequately controlled			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 203 (0.00%)	4 / 391 (1.02%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic vascular disorder			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extremity necrosis			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 203 (0.49%)	4 / 391 (1.02%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypertensive crisis			
subjects affected / exposed	5 / 203 (2.46%)	4 / 391 (1.02%)	
occurrences causally related to treatment / all	1 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 203 (0.49%)	0 / 391 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			

subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	0 / 203 (0.00%)	2 / 391 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 203 (0.00%)	2 / 391 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hospitalisation			
subjects affected / exposed	1 / 203 (0.49%)	0 / 391 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leg amputation			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 203 (0.99%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

subjects affected / exposed	2 / 203 (0.99%)	0 / 391 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sudden death			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	1 / 203 (0.49%)	0 / 391 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metrorrhagia			
subjects affected / exposed	1 / 203 (0.49%)	0 / 391 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst torsion			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			

subjects affected / exposed	1 / 203 (0.49%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	1 / 203 (0.49%)	2 / 391 (0.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 203 (0.49%)	2 / 391 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 203 (0.49%)	0 / 391 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	2 / 203 (0.99%)	0 / 391 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	3 / 203 (1.48%)	3 / 391 (0.77%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 203 (0.49%)	3 / 391 (0.77%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pulmonary hypertension			

subjects affected / exposed	1 / 203 (0.49%)	3 / 391 (0.77%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	2 / 203 (0.99%)	3 / 391 (0.77%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory disorder			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 203 (0.49%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 203 (0.00%)	2 / 391 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			

subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic mass			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Steatohepatitis			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood urea increased			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerular filtration rate decreased			
subjects affected / exposed	11 / 203 (5.42%)	21 / 391 (5.37%)	
occurrences causally related to treatment / all	1 / 15	0 / 23	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Arterial injury			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

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

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

subjects affected / exposed	1 / 203 (0.49%)	3 / 391 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Cardiac failure			
subjects affected / exposed	1 / 203 (0.49%)	3 / 391 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure chronic			
subjects affected / exposed	3 / 203 (1.48%)	3 / 391 (0.77%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 203 (0.49%)	1 / 391 (0.26%)	
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	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiogenic shock			
subjects affected / exposed	1 / 203 (0.49%)	0 / 391 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery disease			

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

subjects affected / exposed	2 / 203 (0.99%)	0 / 391 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 203 (0.49%)	2 / 391 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Headache			
subjects affected / exposed	1 / 203 (0.49%)	1 / 391 (0.26%)	
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	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic coma			
subjects affected / exposed	1 / 203 (0.49%)	0 / 391 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 203 (0.49%)	4 / 391 (1.02%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			

subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenic syndrome			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 203 (0.49%)	0 / 391 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 203 (0.49%)	3 / 391 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular encephalopathy			
subjects affected / exposed	0 / 203 (0.00%)	2 / 391 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 203 (3.45%)	8 / 391 (2.05%)	
occurrences causally related to treatment / all	0 / 9	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic anaemia			

subjects affected / exposed	1 / 203 (0.49%)	1 / 391 (0.26%)	
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	1 / 203 (0.49%)	0 / 391 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy mediastinal			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrogenic anaemia			
subjects affected / exposed	1 / 203 (0.49%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 203 (0.49%)	0 / 391 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 203 (0.49%)	0 / 391 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 203 (0.49%)	0 / 391 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Macular hole			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			

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

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

subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 203 (0.00%)	3 / 391 (0.77%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 203 (0.00%)	3 / 391 (0.77%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis chronic			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 203 (0.49%)	3 / 391 (0.77%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis			

subjects affected / exposed	1 / 203 (0.49%)	0 / 391 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot			
subjects affected / exposed	0 / 203 (0.00%)	2 / 391 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema nummular			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panniculitis			
subjects affected / exposed	1 / 203 (0.49%)	0 / 391 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			
subjects affected / exposed	0 / 203 (0.00%)	2 / 391 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 203 (0.00%)	2 / 391 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	2 / 203 (0.99%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute prerenal failure			
subjects affected / exposed	1 / 203 (0.49%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Azotaemia			
subjects affected / exposed	8 / 203 (3.94%)	10 / 391 (2.56%)	
occurrences causally related to treatment / all	0 / 10	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus bladder			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
End stage renal disease			
subjects affected / exposed	62 / 203 (30.54%)	135 / 391 (34.53%)	
occurrences causally related to treatment / all	0 / 63	1 / 135	
deaths causally related to treatment / all	0 / 4	0 / 8	
Haematuria			
subjects affected / exposed	0 / 203 (0.00%)	2 / 391 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oliguria			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal colic			

subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 203 (0.00%)	2 / 391 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperparathyroidism primary			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperparathyroidism secondary			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Gouty arthritis			
subjects affected / exposed	0 / 203 (0.00%)	2 / 391 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint contracture			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

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

subjects affected / exposed	0 / 203 (0.00%)	3 / 391 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 203 (0.00%)	2 / 391 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye infection			
subjects affected / exposed	1 / 203 (0.49%)	0 / 391 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic echinococciasis			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	1 / 203 (0.49%)	1 / 391 (0.26%)	
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	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningoencephalitis herpetic			

subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media acute			
subjects affected / exposed	1 / 203 (0.49%)	0 / 391 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 203 (0.49%)	5 / 391 (1.28%)	
occurrences causally related to treatment / all	0 / 1	1 / 6	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonia			
subjects affected / exposed	12 / 203 (5.91%)	17 / 391 (4.35%)	
occurrences causally related to treatment / all	0 / 14	1 / 21	
deaths causally related to treatment / all	0 / 3	0 / 4	
Pneumonia staphylococcal			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 203 (0.49%)	0 / 391 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			

subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 203 (0.00%)	2 / 391 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis chronic			
subjects affected / exposed	2 / 203 (0.99%)	5 / 391 (1.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pyonephrosis			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 203 (0.00%)	6 / 391 (1.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 2	
Septic shock			
subjects affected / exposed	0 / 203 (0.00%)	2 / 391 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Sinusitis			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			

subjects affected / exposed	1 / 203 (0.49%)	0 / 391 (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			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 203 (0.49%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulvovaginitis			
subjects affected / exposed	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 203 (0.49%)	1 / 391 (0.26%)	
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 / 203 (0.49%)	1 / 391 (0.26%)	
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	0 / 203 (0.00%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic metabolic decompensation			
subjects affected / exposed	2 / 203 (0.99%)	1 / 391 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			

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

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

Non-serious adverse events	Placebo	Roxadustat	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	103 / 203 (50.74%)	204 / 391 (52.17%)	
Investigations			
Glomerular filtration rate decreased			
subjects affected / exposed	13 / 203 (6.40%)	24 / 391 (6.14%)	
occurrences (all)	13	25	
Vascular disorders			
Hypertension			
subjects affected / exposed	27 / 203 (13.30%)	85 / 391 (21.74%)	
occurrences (all)	44	138	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 203 (4.93%)	20 / 391 (5.12%)	
occurrences (all)	11	21	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	31 / 203 (15.27%)	16 / 391 (4.09%)	
occurrences (all)	45	17	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	11 / 203 (5.42%)	18 / 391 (4.60%)	
occurrences (all)	13	22	
Oedema peripheral			
subjects affected / exposed	21 / 203 (10.34%)	44 / 391 (11.25%)	
occurrences (all)	22	53	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 203 (2.96%)	32 / 391 (8.18%)	
occurrences (all)	9	38	
Nausea			
subjects affected / exposed	6 / 203 (2.96%)	34 / 391 (8.70%)	
occurrences (all)	6	44	
Infections and infestations			

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

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