Clinical trial results:
A Phase 3, Randomized, Open-Label, Active-Controlled Study to Evaluate the Efficacy and Safety of Roxadustat in the Treatment of Anemia in Chronic Kidney Disease Patients Not on Dialysis

Summary

EudraCT number	2013-000951-42
Trial protocol	GB DE ES NL CZ SK SI PT AT IE DK FI LV SE FR HR HU BG
Global end of trial date	15 November 2019

Results information

Result version number	v1 (current)
This version publication date	04 November 2020
First version publication date	04 November 2020

Trial information

Trial identification

Sponsor protocol code	1517-CL-0610

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02021318
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Europe B.V.
Sponsor organisation address	Sylviusweg 62, Leiden, Netherlands, 2333 BE
Public contact	Clinical Trial Disclosure, Astellas Pharma Europe B.V., 31 71 5455 050, astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Europe B.V., 31 71 5455 050, astellas.resultsdisclosure@astellas.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 November 2019
Is this the analysis of the primary	No

completion data?	
Global end of trial reached?	Yes
Global end of trial date	15 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the efficacy of roxadustat compared to darbepoetin alfa in the treatment of anemia in nondialysis-dependent chronic kidney disease 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	12 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belarus: 17
Country: Number of subjects enrolled	Bulgaria: 19
Country: Number of subjects enrolled	Croatia: 73
Country: Number of subjects enrolled	Czech Republic: 33
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	France: 18
Country: Number of subjects enrolled	Georgia: 19
Country: Number of subjects enrolled	Germany: 37
Country: Number of subjects enrolled	Hungary: 32
Country: Number of subjects enrolled	Ireland: 8
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Latvia: 4
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 12
Country: Number of subjects enrolled	Montenegro: 4
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Poland: 30
Country: Number of subjects enrolled	Portugal: 17
Country: Number of subjects enrolled	Romania: 16
Country: Number of subjects enrolled	Russian Federation: 48
Country: Number of subjects enrolled	Serbia: 48
Country: Number of subjects enrolled	Slovakia: 26
Country: Number of subjects enrolled	Slovenia: 15

Country: Number of subjects enrolled	Spain: 33
Country: Number of subjects enrolled	Ukraine: 36
Country: Number of subjects enrolled	United Kingdom: 61
Worldwide total number of subjects	616
EEA total number of subjects	429

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)	237
From 65 to 84 years	349
85 years and over	30

Subject disposition

Recruitment

Recruitment details:

Participants of ≥18 years of age with a diagnosis of chronic kidney disease, with kidney disease outcomes quality initiative stage 3, 4 or 5, anaemic and not receiving dialysis; with an estimated glomerular filtration rate (eGFR) < 60 milliliter per minute per 1.73 meter square (mL/min/1.73 m^2) were enrolled in this study.

Pre-assignment

Screening details:

Participants were randomized in a 1:1 ratio to roxadustat or darbepoetin alfa. Randomization was stratified by 4 factors: region, screening hemoglobin (Hb) values (Hb ≤ 8.0 g/dL versus > 8.0 g/dL), history of cardiovascular, cerebrovascular or thromboembolic diseases and screening eGFR (<30 mL/min/1.73 m^2 versus ≥30 mL/min/1.73 m^2).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Darbepoetin alfa

Arm description:

Participants received initial dose of darbepoetin alfa based upon the weight (either 0.45 microgram per kilogram [µg/kg] of body weight, as a single subcutaneous or intravenous [IV] injection once weekly or 0.75 µg/kg of body weight, as a single subcutaneous injection once every 2 weeks) as per European Summary of Product Characteristics (EU SmPC) along with IV iron supplementation according to the standard of care. Dose-adjustment was performed based upon regular measurement of Hb levels until participants achieved central Hb value of ≥ 11.0 grams per deciliter (g/dL) and Hb increase from baseline 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 darbepoetin alfa dosage was adjusted every 4 weeks to maintain participants Hb level within the target range of 10.0 g/dL and 12.0 g/dL. Participants received darbepoetin alfa for up to a maximum of 104 weeks.

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

Dosage and administration details:

Participants received initial dose of darbepoetin alfa based upon the weight (either 0.45 µg/kg of body weight, as a single subcutaneous or IV injection once weekly or 0.75 µg/kg of body weight, as a single subcutaneous injection once every 2 weeks) as per EU SmPC along with IV iron supplementation according to the standard of care.

Arm title	Roxadustat

Arm description:

Participants received roxadustat orally according to the tiered weight-based approach, with starting dose of 70 milligram (mg) given three times weekly (TIW) to participants weighing between 45 kilogram (kg) up to 70 kg and 100 mg given TIW to participants weighing more than 70 kg up to 160 kg. Dose-titration was performed based upon regular measurement of Hb levels until participants achieved central Hb value of ≥ 11.0 g/dL and Hb increase from baseline of ≥ 1.0 g/dL at two consecutive study visits, separated by at least 5 days. Once target Hb level was reached participants entered maintenance period during which roxadustat dosage was adjusted every 4 weeks to maintain participants Hb level within the target range of 10.0 g/dL and 12.0 g/dL. Participants received roxadustat for up to a maximum of 104 weeks.

Arm type	Experimental

Investigational medicinal product name	Roxadustat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received roxadustat orally according to the tiered weight-based approach, with starting dose of 70 mg given TIW to participants weighing between 45 kg up to 70 kg and 100 mg given TIW to participants weighing more than 70 kg up to 160 kg.

Number of subjects in period 1	Darbepoetin alfa	Roxadustat
Started	293	323
Completed	230	250
Not completed	63	73
Progressive disease	1	-
Death	34	33
Miscellaneous	3	2
Physician decision	3	3
Withdrawal by Subject	18	30
Adverse Event	1	2
Lost to follow-up	3	3

Baseline characteristics

Reporting groups	
Reporting group title	Darbepoetin alfa

Reporting group description:

Participants received initial dose of darbepoetin alfa based upon the weight (either 0.45 microgram per kilogram [µg/kg] of body weight, as a single subcutaneous or intravenous [IV] injection once weekly or 0.75 µg/kg of body weight, as a single subcutaneous injection once every 2 weeks) as per European Summary of Product Characteristics (EU SmPC) along with IV iron supplementation according to the standard of care. Dose-adjustment was performed based upon regular measurement of Hb levels until participants achieved central Hb value of ≥ 11.0 grams per deciliter (g/dL) and Hb increase from baseline 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 darbepoetin alfa dosage was adjusted every 4 weeks to maintain participants Hb level within the target range of 10.0 g/dL and 12.0 g/dL. Participants received darbepoetin alfa for up to a maximum of 104 weeks.

Reporting group title	Roxadustat

Reporting group description:

Participants received roxadustat orally according to the tiered weight-based approach, with starting dose of 70 milligram (mg) given three times weekly (TIW) to participants weighing between 45 kilogram (kg) up to 70 kg and 100 mg given TIW to participants weighing more than 70 kg up to 160 kg. Dose-titration was performed based upon regular measurement of Hb levels until participants achieved central Hb value of ≥ 11.0 g/dL and Hb increase from baseline of ≥ 1.0 g/dL at two consecutive study visits, separated by at least 5 days. Once target Hb level was reached participants entered maintenance period during which roxadustat dosage was adjusted every 4 weeks to maintain participants Hb level within the target range of 10.0 g/dL and 12.0 g/dL. Participants received roxadustat for up to a maximum of 104 weeks.

Reporting group values	Darbepoetin alfa	Roxadustat	Total
Number of subjects	293	323	616
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	65.7	66.8	
standard deviation	± 14.4	± 13.6	-
Gender categorical Units: Subjects			
M	129	145	274
F	164	178	342
Analysis Race Units: Subjects			
White	281	306	587
Black or African American	2	8	10
Asian	10	9	19
Baseline Hb Value Units: Subjects			
<=8.0 g/dL	10	11	21
>8.0 g/dL	283	312	595

End points

End points reporting groups

Reporting group title	Darbepoetin alfa

Reporting group description:

Participants received initial dose of darbepoetin alfa based upon the weight (either 0.45 microgram per kilogram [µg/kg] of body weight, as a single subcutaneous or intravenous [IV] injection once weekly or 0.75 µg/kg of body weight, as a single subcutaneous injection once every 2 weeks) as per European Summary of Product Characteristics (EU SmPC) along with IV iron supplementation according to the standard of care. Dose-adjustment was performed based upon regular measurement of Hb levels until participants achieved central Hb value of ≥ 11.0 grams per deciliter (g/dL) and Hb increase from baseline 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 darbepoetin alfa dosage was adjusted every 4 weeks to maintain participants Hb level within the target range of 10.0 g/dL and 12.0 g/dL. Participants received darbepoetin alfa for up to a maximum of 104 weeks.

Reporting group title	Roxadustat

Reporting group description:

Participants received roxadustat orally according to the tiered weight-based approach, with starting dose of 70 milligram (mg) given three times weekly (TIW) to participants weighing between 45 kilogram (kg) up to 70 kg and 100 mg given TIW to participants weighing more than 70 kg up to 160 kg. Dose-titration was performed based upon regular measurement of Hb levels until participants achieved central Hb value of ≥ 11.0 g/dL and Hb increase from baseline of ≥ 1.0 g/dL at two consecutive study visits, separated by at least 5 days. Once target Hb level was reached participants entered maintenance period during which roxadustat dosage was adjusted every 4 weeks to maintain participants Hb level within the target range of 10.0 g/dL and 12.0 g/dL. Participants received roxadustat for up to a maximum of 104 weeks.

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

End point title	Percentage of Participants With a Hb Response to Treatment at Two Consecutive Visits During the First 24 Weeks of Treatment Without Rescue Therapy

End point description:

Hb response was measured as Yes or No. Response Yes (responders) was defined as: Hb ≥11.0 g/dL and Hb change from baseline by ≥ 1.0 g/dL, for participants with baseline Hb > 8.0 g/dL; or Hb change from baseline by ≥ 2.0 g/dL, for participants with baseline Hb ≤ 8.0 g/dL at two consecutive visits with available data separated by at least 5 days during the first 24 weeks of treatment without having received rescue therapy (red blood cell [RBC] transfusion for all participants or darbepoetin for roxadustat treated participant). The analysis population was the Per Protocol Set (PPS) which consisted of all Full Analysis Set (FAS) participants who did not meet any of exclusion criteria from the PPS. The FAS consisted of all randomized participants who received at least one dose of study drug and had at least one post-dose valid Hb assessment.

End point type	Primary

End point timeframe:

Baseline to week 24

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	273	286		
Units: Percentage of participants				
number (not applicable)	78.0	89.5		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

A generalized linear model as an approximation for the Miettinen and Nurminen method, adjusted for stratification factors (actual) was used to estimate the difference of proportions and 95% confidence interval (CI).

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Difference in percentage
Point estimate	11.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.66
upper limit	17.36

Notes:

[1] - Non-inferiority of roxadustat versus darbepoetin alfa, margin = -15% (non-inferiority is concluded if the lower limit of the 95% confidence interval of the difference was >-15%).

Secondary: Change from Baseline in Hb to the Average Hb of Weeks 28 to 36 Without Rescue Therapy Within 6 Weeks Prior to and During This 8-Week Evaluation Period

End point title	Change from Baseline in Hb to the Average Hb of Weeks 28 to 36 Without Rescue Therapy Within 6 Weeks Prior to and During This 8-Week Evaluation Period

End point description:

Baseline Hb was defined as the mean of all available central laboratory Hb values collected before or including the date of first study drug intake (predose). The analysis population was the PPS, with participants who had available data.

End point type	Secondary

End point timeframe:

Baseline and weeks 28 to 36

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	258		
Units: g/dL				
arithmetic mean (standard deviation)	1.839 (± 0.973)	1.848 (± 1.079)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The model included treatment, visit, visit by treatment interaction, region and history of cardiovascular (CV) disease as fixed class factors and baseline Hb, baseline estimated glomerular filtration rate and baseline Hb by visit as continuous covariates.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	507
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	= 0.839
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.131
upper limit	0.162

Notes:

[2] - Non-Inferiority, margin = -0.75 (non-inferiority is concluded if the lower bound of the 95% confidence interval of the least square mean difference (LSM) is > -0.75 g/dL).

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Baseline and weeks 12 to 28

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	307		
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)	0.049 (± 0.705)	-0.352 (± 0.772)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The model included treatment, visit, visit by treatment interaction, region and history of cardiovascular disease as fixed class factors and baseline LDL, baseline Hb, baseline estimated glomerular filtration rate as continuous covariates.

Comparison groups	Darbepoetin alfa v Roxadustat
Number of subjects included in analysis	584
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-0.403
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	-0.296

Secondary: Time to First Intavenous Iron use

End point title	Time to First Intavenous Iron use

End point description:

Participants were analyzed during the efficacy emergent period. The efficacy emergent period was defined as the evaluation period from the analysis date of first dose intake up to end of treatment (EOT) Visit or last non-missing Hb assessment (for participants who died during the treatment period). For participants who had received more than one intravenous iron, only their first event following study treatment was used. Data reported was analyzed by Kaplan-Meier estimate for cumulative proportion and the 95% confidence interval was calculated with Greenwood's formula. Percentage of participants were reported in this outcome measure. The analysis population was the FAS. Here, N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Weeks 6, 12, 18, 24, 30 and 36

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Percentage of participants				
number (confidence interval 95%)				
Week 6 (N=318, 280)	2.8 (0.9 to 4.6)	0 (0 to 0)		

Week 12 (N=307, 259)	6.7 (3.8 to 9.6)	1.3 (0 to 2.5)		
Week 18 (N=290, 247)	9.2 (5.8 to 12.6)	3.3 (1.3 to 5.2)		
Week 24 (N=281, 243)	10.7 (7.1 to 14.3)	4.3 (2 to 6.5)		
Week 30 (N=272, 231)	12.6 (8.7 to 16.5)	5.3 (2.8 to 7.8)		
Week 36 (N=263, 226)	13.3 (9.3 to 17.3)	6.7 (3.9 to 9.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard Ratio was calculated using stratified Cox Proportional Hazards regression stratifying on cardiovascular history and Region and adjusting on Hb and eGFR at baseline as continuous covariate. Superiority was declared if the upper bound of the 95% CI was below 1.0.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.004
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	0.78

Secondary: Change from Baseline in Short Form-36 (SF-36) Physical Functioning (PF) Sub-Score to the Average PF Sub-Score in Weeks 12 to 28

End point title	Change from Baseline in Short Form-36 (SF-36) Physical Functioning (PF) Sub-Score to the Average PF Sub-Score in Weeks 12 to 28

End point description:

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

End point type	Secondary

End point timeframe:

Baseline and weeks 12 to 28

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	274		
Units: Units on a scale				
arithmetic mean (standard deviation)	2.062 (± 7.838)	0.913 (± 7.182)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The model included treatment, visit (weeks 8, 12 and 28) visit by treatment interaction, region and history of cardiovascular disease as fixed class factors and baseline SF-36 PF, baseline Hb, baseline estimated glomerular filtration rate as continuous covariates.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	= 0.027
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-1.284
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.423
upper limit	-0.145

Notes:

[3] - Non-Inferiority, margin = -3 (non-inferiority is concluded if the lower bound of the 95% confidence interval of the LSM difference is > - 3 points).

Secondary: Change from Baseline in SF-36 Vitality (VT) Sub-Score to the Average VT Sub-Score in Weeks 12 to 28

End point title	Change from Baseline in SF-36 Vitality (VT) Sub-Score to the Average VT Sub-Score in Weeks 12 to 28

End point description:

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

End point type	Secondary

End point timeframe:

Baseline and weeks 12 to 28

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	274		
Units: Units on a scale				
arithmetic mean (standard deviation)	3.881 (± 8.76)	4.077 (± 8.657)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The model included treatment, visit (weeks 8, 12 and 28), visit by treatment interaction, region and history of cardiovascular disease as fixed class factors and baseline SF-36 VT, baseline Hb, baseline eGFR as continuous covariates.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
P-value	= 0.454
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-0.457
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.656
upper limit	0.742

Notes:

[4] - Non-Inferiority, margin = -3 (non-inferiority is concluded if the lower bound of the 95% confidence interval of the LSM difference is > - 3 points).

Secondary: Change from Baseline in Mean Arterial Pressure (MAP) to the Average MAP Value in Weeks 20 to 28: Per Protocol Set

End point title	Change from Baseline in Mean Arterial Pressure (MAP) to the Average MAP Value in Weeks 20 to 28: Per Protocol Set

End point description:

Baseline MAP was defined as the MAP value on day 1. If this value was missing, the latest value prior to first study drug administration was used. MAP was derived as: MAP = (2/3)*diastolic blood pressure (DBP) + (1/3)*systolic blood pressure (SBP). The analysis population was the PPS, with participants who had available data.

End point type	Secondary

End point timeframe:

Baseline and weeks 20 to 28

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	252	265		
Units: Millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)	0.588 (± 8.779)	0.541 (± 8.549)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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 Darbepoetin alfa
Number of subjects included in analysis	517
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
P-value	= 0.547
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-0.372
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.587
upper limit	0.842

Notes:

[5] - Non-Inferiority, margin = 1 mmHg (non-inferiority is concluded if the upper bound of the 95% confidence interval of the LSM difference is < 1).

Secondary: Time to First Occurrence of Hypertension During Weeks 1 to 36: Per Protocol Set

End point title	Time to First Occurrence of Hypertension During Weeks 1 to 36: Per Protocol Set

End point description:

Hypertension was defined as either SBP ≥ 170 mmHg and an increase from baseline ≥ 20 mmHg or as DBP ≥ 110 mmHg and an increase from baseline ≥ 15 mmHg. For participants who had experienced more than one event, only their first event following study treatment was used. Data reported was analyzed by Kaplan-Meier estimate for cumulative proportion. Percentage of participants were reported in this outcome measure. The analysis population was the PPS.

End point type	Secondary

End point timeframe:

Weeks 1 to 36

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	273	286		
Units: Percentage of participants				
number (not applicable)	19.4	17.5		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

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 Darbepoetin alfa
Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
P-value	= 0.336
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.22

Notes:

[6] - Non-Inferiority, hazard ratio margin = 1.3 (non-inferiority is concluded if the upper bound of the 95% confidence interval of the hazard ratio is < 1.3).

Secondary: Change from Baseline in MAP to the Average MAP Value in Weeks 20 to 28: Full Analysis Set

End point title	Change from Baseline in MAP to the Average MAP Value in Weeks 20 to 28: Full Analysis Set

End point description:

Baseline MAP was defined as the MAP value on day 1. If this value was missing, the latest value prior to first study drug administration was used. MAP was derived as: MAP = (2/3)*DBP + (1/3)*SBP. The analysis population was the FAS, with participants who had available data.

End point type	Secondary

End point timeframe:

Baseline and weeks 20 to 28

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	269	294		
Units: mmHg				
arithmetic mean (standard deviation)	0.457 (± 8.741)	0.635 (± 8.529)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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 Darbepoetin alfa
Number of subjects included in analysis	563
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.818
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-0.136
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.299
upper limit	1.026

Secondary: Time to First Occurrence of Hypertension During Weeks 1 to 36: Full Analysis Set

End point title	Time to First Occurrence of Hypertension During Weeks 1 to 36: Full Analysis Set

End point description:

Hypertension was defined as either SBP ≥ 170 mmHg and an increase from baseline ≥ 20 mmHg or as DBP ≥ 110 mmHg and an increase from baseline ≥ 15 mmHg. For participants who had experienced more than one event, only their first event following study treatment was used. Data reported was analyzed by Kaplan-Meier estimate for cumulative proportion. Percentage of participants were reported in this outcome measure. The analysis population was the FAS.

End point type	Secondary

End point timeframe:

Weeks 1 to 36

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Percentage of Participants				
number (not applicable)	18.8	17.4		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

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 was declared if the upper bound of the 95% CI is lower than 1.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.452
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.26

Secondary: Change From Baseline in Hb to the Average Hb Value of Weeks 28 to 52 Regardless Use of Rescue Therapy

End point title	Change From Baseline in Hb to the Average Hb Value of Weeks 28 to 52 Regardless Use of Rescue Therapy

End point description:

Baseline Hb was defined as the mean of all available central laboratory Hb values collected before or including the date of first study drug intake (pre-dose). The analysis population was the FAS, with participants who had available data.

End point type	Secondary

End point timeframe:

Baseline and weeks 28 to 52

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	266	287		
Units: g/dL				
arithmetic mean (standard deviation)	1.673 (± 0.923)	1.718 (± 0.958)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
The model included treatment, visit, visit by treatment interaction, region and history of CV disease as fixed class factors and baseline Hb, baseline eGFR and baseline Hb by visit as continuous covariates.	
Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	553
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.529
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.038
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.081
upper limit	0.157

Secondary: Time to First Hb Response During First 24 Weeks of Treatment Regardless of Administration of Rescue Therapy

End point title	Time to First Hb Response During First 24 Weeks of Treatment Regardless of Administration of Rescue Therapy
End point description:	
Participants were analyzed during the efficacy emergent period. The efficacy emergent period was defined as the evaluation period from the analysis date of first dose intake up to EOT Visit or last non-missing Hb assessment (for participants who died during the treatment period). For participants who had experienced more than one event, only their first event was used. Data reported was analyzed by Kaplan-Meier estimate for cumulative proportion. Percentage of participants were reported in this outcome measure. The analysis population was the FAS.	
End point type	Secondary
End point timeframe:	
Weeks 1 to 24	

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Percentage of participants				
number (not applicable)	77.7	88.8		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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 Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.38
upper limit	1.96

Secondary: Time to First Hb Response During First 24 Weeks of Treatment Without Rescue Therapy

End point title	Time to First Hb Response During First 24 Weeks of Treatment Without Rescue Therapy
End point description:	
Participants were analyzed during the efficacy emergent period. The efficacy emergent period was defined as the evaluation period from the analysis date of first dose intake up to EOT Visit or last non-missing Hb assessment (for participants who died during the treatment period). For participants who had experienced more than one event, only their first event was used. Data reported was analyzed by Kaplan-Meier estimate for cumulative proportion. Percentage of participants were reported in this outcome measure. The analysis population was the FAS.	
End point type	Secondary
End point timeframe:	
Weeks 1 to 24	

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Percentage of participants				
number (not applicable)	77.4	88.2		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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 Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.39
upper limit	1.98

Secondary: Hb Level Averaged Over Weeks 28 to 36, Weeks 44 to 52, Weeks 72 to 80 and Weeks 96 to 104 Without Rescue Therapy

End point title	Hb Level Averaged Over Weeks 28 to 36, Weeks 44 to 52, Weeks 72 to 80 and Weeks 96 to 104 Without Rescue Therapy
End point description:	
Baseline Hb was defined as the mean of all available central laboratory Hb values collected before or including the date of first study drug intake (predose). The analysis population was the FAS. Here, N signifies participants with available data at specified time points.	
End point type	Secondary
End point timeframe:	
Weeks 28 to 36, 44 to 52, 72 to 80 and 96 to 104	

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: g/dL				
least squares mean (confidence interval 95%)				
Weeks 28-36 (N=286, 266)	11.351 (11.247 to 11.455)	11.403 (11.302 to 11.503)		

Weeks 44-52 (N=266, 251)	11.188 (11.082 to 11.294)	11.185 (11.082 to 11.289)		
Weeks 72-80 (N=241, 233)	11.217 (11.110 to 11.324)	11.225 (11.120 to 11.331)		
Weeks 96-104 (N=218, 215)	11.078 (10.960 to 11.196)	11.102 (10.986 to 11.219)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Weeks 28-36 - The model included treatment, visit, visit by treatment interaction, region and history of CV disease as fixed class factors and baseline Hb, baseline estimated glomerular filtration rate and baseline Hb by visit as continuous covariates.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.478
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.051
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.091
upper limit	0.194

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Weeks 44-52 - The model included treatment, visit, visit by treatment interaction, region and history of CV disease as fixed class factors and baseline Hb, baseline estimated glomerular filtration rate and baseline Hb by visit as continuous covariates.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.969
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.149
upper limit	0.143

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Weeks 72-80 - The model included treatment, visit, visit by treatment interaction, region and history of CV disease as fixed class factors and baseline Hb, baseline estimated glomerular filtration rate and baseline Hb by visit as continuous covariates.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.91
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.009
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.157

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Weeks 96-104 - The model included treatment, visit, visit by treatment interaction, region and history of CV disease as fixed class factors and baseline Hb, baseline estimated glomerular filtration rate and baseline Hb by visit as continuous covariates

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.775
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.024
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.188

Secondary: Change From Baseline in Hb to Each Postdosing Time Point Regardless Use of rescue Therapy

End point title	Change From Baseline in Hb to Each Postdosing Time Point Regardless Use of rescue Therapy

End point description:

Baseline Hb was defined as the mean of all available central laboratory Hb values collected before or including the date of first study drug intake (pre-dose). The analysis population was the FAS. Here, N

signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

Baseline 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, and 104

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: g/dL				
least squares mean (confidence interval 95%)				
Hb Change From BL to Week 1(N=308, 273)	0.294 (0.221 to 0.368)	0.381 (0.311 to 0.450)		
Hb Change From BL to Week 2 (N=314, 284)	0.584 (0.500 to 0.667)	0.862 (0.782 to 0.941)		
Hb Change From BL to Week 4 (N=311, 283)	1.073 (0.962 to 1.183)	1.508 (1.403 to 1.613)		
Hb Change From BL to Week 6 (N=306, 278)	1.423 (1.3 to 1.546)	1.845 (1.729 to 1.962)		
Hb Change From BL to Week 8 (N=301, 277)	1.682 (1.554 to 1.810)	2.063 (1.940 to 2.185)		
Hb Change From BL to Week 10 (N=301, 266)	1.611 (1.483 to 1.739)	1.941 (1.819 to 2.062)		
Hb Change From BL to Week 12 (N=288, 263)	2.030 (1.897 to 2.162)	2.330 (2.204 to 2.456)		
Hb Change From BL to Week 14 (N=293, 266)	1.745 (1.616 to 1.875)	1.904 (1.781 to 2.027)		
Hb Change From BL to Week 16 (N= 289, 264)	1.994 (1.864 to 2.124)	2.177 (2.053 to 2.301)		
Hb Change From BL to Week 18 (N=286, 260)	1.609 (1.490 to 1.729)	1.783 (1.699 to 1.896)		
Hb Change From BL to Week 20 (N=282, 262)	1.900 (1.778 to 2.023)	1.986 (1.869 to 2.103)		
Hb Change From BL to Week 22 (N=276, 260)	1.615 (1.499 to 1.731)	1.584 (1.473 to 1.696)		
Hb Change From BL to Week 24 (N=283, 254)	1.554 (1.438 to 1.669)	1.493 (1.383 to 1.603)		
Hb Change From BL to Week 28 (N=276, 252)	1.869 (1.748 to 1.989)	1.803 (1.688 to 1.919)		
Hb Change From BL to Week 32 (N=269, 252)	1.673 (1.549 to 1.797)	1.687 (1.568 to 1.806)		
Hb Change From BL to Week 36 (N=264, 247)	1.781 (1.657 to 1.905)	1.913 (1.793 to 2.032)		
Hb Change From BL to Week 40 (N=266, 254)	1.438 (1.320 to 1.556)	1.625 (1.510 to 1.740)		
Hb Change From BL to Week 44 (N=257, 248)	1.628 (1.502 to 1.754)	1.650 (1.527 to 1.773)		
Hb Change From BL to Week 48 (N=259, 245)	1.447 (1.322 to 1.572)	1.459 (1.338 to 1.581)		
Hb Change From BL to Week 52 (N=254, 242)	1.710 (1.585 to 1.835)	1.682 (1.560 to 1.803)		
Hb Change From BL to Week 56 (N=251, 243)	1.444 (1.321 to 1.567)	1.412 (1.292 to 1.533)		
Hb Change From BL to Week 60 (N=250, 242)	1.670 (1.543 to 1.796)	1.735 (1.611 to 1.859)		

Hb Change From BL to Week 64 (N=247, 236)	1.547 (1.414 to 1.681)	1.546 (1.415 to 1.676)		
Hb Change From BL to Week 68 (N=242, 229)	1.747 (1.620 to 1.875)	1.851 (1.726 to 1.976)		
Hb Change From BL to Week 72 (N=236, 227)	1.548 (1.416 to 1.680)	1.615 (1.486 to 1.745)		
Hb Change From BL to Week 76 (N=231, 225)	1.767 (1.636 to 1.898)	1.745 (1.616 to 1.873)		
Hb Change From BL to Week 80 (N=220, 220)	1.579 (1.451 to 1.707)	1.534 (1.408 to 1.661)		
Hb Change From BL to Week 84 (N=220, 219)	1.679 (1.548 to 1.809)	1.723 (1.594 to 1.853)		
Hb Change From BL to Week 88 (N=219, 220)	1.370 (1.236 to 1.504)	1.424 (1.291 to 1.557)		
Hb Change From BL to Week 92 (N=223, 215)	1.643 (1.505 to 1.780)	1.677 (1.541 to 1.812)		
Hb Change From BL to Week 96 (N=217, 213)	1.404 (1.266 to 1.542)	1.429 (1.293 to 1.566)		
Hb Change From BL to Week 100 (N=215, 204)	1.598 (1.454 to 1.742)	1.488 (1.346 to 1.629)		
Hb Change From BL to Week 104 (N=207, 201)	1.452 (1.299 to 1.606)	1.489 (1.339 to 1.640)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Week 1- The model included treatment, visit, visit by treatment interaction, region and history of CV disease as fixed class factors and baseline Hb, baseline eGFR and baseline Hb by visit as continuous covariates.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.086
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.087
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.012
upper limit	0.185

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Week 2- The model included treatment, visit, visit by treatment interaction, region and history of CV disease as fixed class factors and baseline Hb, baseline eGFR and baseline Hb by visit as continuous covariates.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified

Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.278
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.165
upper limit	0.391

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Week 4- The model included treatment, visit, visit by treatment interaction, region and history of CV disease as fixed class factors and baseline Hb, baseline eGFR and baseline Hb by visit as continuous covariates.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.435
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.284
upper limit	0.586

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

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

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.422
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.254
upper limit	0.59

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
Week 8- The model included treatment, visit, visit by treatment interaction, region and history of CV disease as fixed class factors and baseline Hb, baseline eGFR and baseline Hb by visit as continuous covariates.	
Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.205
upper limit	0.556

Statistical analysis title	Statistical Analysis 6
Statistical analysis description:	
Week 10- The model included treatment, visit, visit by treatment interaction, region and history of CV disease as fixed class factors and baseline Hb, baseline eGFR and baseline Hb by visit as continuous covariates.	
Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.155
upper limit	0.505

Statistical analysis title	Statistical Analysis 7
Statistical analysis description:	
Week 12- The model included treatment, visit, visit by treatment interaction, region and history of CV disease as fixed class factors and baseline Hb, baseline eGFR and baseline Hb by visit as continuous covariates.	
Comparison groups	Roxadustat v Darbepoetin alfa

Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.119
upper limit	0.482

Statistical analysis title	Statistical Analysis 8

Statistical analysis description:

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

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.079
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.159
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.018
upper limit	0.336

Statistical analysis title	Statistical Analysis 9

Statistical analysis description:

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

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.044
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.183
Confidence interval	
level	95 %
sides	2-sided

lower limit	0.005
upper limit	0.361

Statistical analysis title	Statistical Analysis 10

Statistical analysis description:

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

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.037
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.173
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.336

Statistical analysis title	Statistical Analysis 11

Statistical analysis description:

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

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.319
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.085
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.083
upper limit	0.253

Statistical analysis title	Statistical Analysis 12

Statistical analysis description:

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

covariates.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.709
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	0.129

Statistical analysis title	Statistical Analysis 13

Statistical analysis description:

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

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.45
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-0.061
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.219
upper limit	0.097

Statistical analysis title	Statistical Analysis 14

Statistical analysis description:

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

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.44
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-0.065
Confidence interval	

level	95 %
sides	2-sided
lower limit	-0.231
upper limit	0.101

Statistical analysis title	Statistical Analysis 15

Statistical analysis description:

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

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.874
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.157
upper limit	0.184

Statistical analysis title	Statistical Analysis 16

Statistical analysis description:

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

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.132
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.131
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.039
upper limit	0.302

Statistical analysis title	Statistical Analysis 17

Statistical analysis description:

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

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.024
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.187
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.024
upper limit	0.351

Statistical analysis title	Statistical Analysis 18

Statistical analysis description:

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

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.807
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.022
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.153
upper limit	0.197

Statistical analysis title	Statistical Analysis 19

Statistical analysis description:

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

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.89
Method	Mixed models analysis
Parameter estimate	LSM Difference

Point estimate	0.012
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.185

Statistical analysis title	Statistical Analysis 20

Statistical analysis description:

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

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.746
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-0.029
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.201
upper limit	0.144

Statistical analysis title	Statistical Analysis 21

Statistical analysis description:

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

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.715
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-0.032
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.202
upper limit	0.139

Statistical analysis title	Statistical Analysis 22

Statistical analysis description:

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

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.463
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.066
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.242

Statistical analysis title	Statistical Analysis 23

Statistical analysis description:

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

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.987
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-0.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.187
upper limit	0.184

Statistical analysis title	Statistical Analysis 24

Statistical analysis description:

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

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.251

Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.104
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.074
upper limit	0.281

Statistical analysis title	Statistical Analysis 25

Statistical analysis description:

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

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.473
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.067
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.117
upper limit	0.251

Statistical analysis title	Statistical Analysis 26

Statistical analysis description:

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

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.813
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-0.022
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.204
upper limit	0.16

Statistical analysis title	Statistical Analysis 27
Statistical analysis description:	
Week 80- The model included treatment, visit, visit by treatment interaction, region and history of CV disease as fixed class factors and baseline Hb, baseline eGFR and baseline Hb by visit as continuous covariates.	
Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.622
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-0.045
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.223
upper limit	0.134

Statistical analysis title	Statistical Analysis 28
Statistical analysis description:	
Week 84- The model included treatment, visit, visit by treatment interaction, region and history of CV disease as fixed class factors and baseline Hb, baseline eGFR and baseline Hb by visit as continuous covariates.	
Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.632
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.045
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.138
upper limit	0.227

Statistical analysis title	Statistical Analysis 29
Statistical analysis description:	
Week 88- The model included treatment, visit, visit by treatment interaction, region and history of CV disease as fixed class factors and baseline Hb, baseline eGFR and baseline Hb by visit as continuous covariates.	
Comparison groups	Roxadustat v Darbepoetin alfa

Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.568
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.055
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.133
upper limit	0.242

Statistical analysis title	Statistical Analysis 30

Statistical analysis description:

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

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.729
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.034
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.158
upper limit	0.226

Statistical analysis title	Statistical Analysis 31

Statistical analysis description:

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

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.797
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.025
Confidence interval	
level	95 %
sides	2-sided

lower limit	-0.168
upper limit	0.218

Statistical analysis title	Statistical Analysis 32

Statistical analysis description:

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

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.28
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	0.09

Statistical analysis title	Statistical Analysis 33

Statistical analysis description:

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

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.733
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.037
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.177
upper limit	0.251

Secondary: Change From Baseline in Hb to Average Hb Value of Weeks 28 to 36, Weeks 44 to 52, Weeks 72 to 80, Weeks 96 to 104 Regardless of Use of Rescue Therapy

End point title	Change From Baseline in Hb to Average Hb Value of Weeks 28 to 36, Weeks 44 to 52, Weeks 72 to 80, Weeks 96 to 104

	Regardless of Use of Rescue Therapy

End point description:

Baseline Hb was defined as the mean of all available central laboratory Hb values collected before or including the date of first study drug intake (predose). The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

Baseline and weeks 28 to 36, 44 to 52, 72 to 80 and 96 to 104

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: g/dL				
least squares mean (confidence interval 95%)				
Hb Change From BL to Weeks 28-36 (N=287, 266)	1.799 (1.694 to 1.905)	1.825 (1.723 to 1.926)		
Hb Change From BL to Weeks 44-52 (N=267, 252)	1.620 (1.512 to 1.729)	1.619 (1.513 to 1.724)		
Hb Change From BL to Weeks 72-80 (N=243, 233)	1.649 (1.540 to 1.758)	1.652 (1.545 to 1.759)		
Hb Change From BL to Weeks 96-104 (N=223, 217)	1.502 (1.378 to 1.626)	1.486 (1.363 to 1.608)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Weeks 28-36 - The model included treatment, visit, visit by treatment interaction, region and history of CV disease as fixed class factors and baseline Hb, baseline estimated glomerular filtration rate and baseline Hb by visit as continuous covariates.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.727
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.026
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.119
upper limit	0.17

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Weeks 44-52 - The model included treatment, visit, visit by treatment interaction, region and history of CV disease as fixed class factors and baseline Hb, baseline estimated glomerular filtration rate and baseline Hb by visit as continuous covariates.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.985
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-0.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.151
upper limit	0.148

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Weeks 72-80 - The model included treatment, visit, visit by treatment interaction, region and history of CV disease as fixed class factors and baseline Hb, baseline estimated glomerular filtration rate and baseline Hb by visit as continuous covariates.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.965
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.148
upper limit	0.154

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Weeks 96-104 - The model included treatment, visit, visit by treatment interaction, region and history of CV disease as fixed class factors and baseline Hb, baseline estimated glomerular filtration rate and baseline Hb by visit as continuous covariates.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.856
Method	Mixed models analysis

Parameter estimate	LSM Difference
Point estimate	-0.016
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.188
upper limit	0.157

Secondary: Percentage of Hb Values ≥ 10 g/dL and Within 10.0 to 12.0 g/dL in Weeks 28 to 36, Weeks 44 to 52, Weeks 72 to 80 and Weeks 96 to 104 Without Use of Rescue Therapy

End point title	Percentage of Hb Values ≥ 10 g/dL and Within 10.0 to 12.0 g/dL in Weeks 28 to 36, Weeks 44 to 52, Weeks 72 to 80 and Weeks 96 to 104 Without Use of Rescue Therapy

End point description:

Percentage for each participant was calculated from the number of Hb values within 10.0 to 12.0 g/dL / total number of Hb values*100 in weeks 28 to 36, 44 to 52, 72 to 80 and 96 to 104 without use of rescue therapy within 6 weeks prior to and during the 8 week evaluation period. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

Weeks 28 to 36, 44 to 52, 72 to 80 and 96 to 104

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Percentage of Hb values				
arithmetic mean (standard deviation)				
Weeks 28-36, ≥ 10 (N=286, 266)	92.481 (± 19.876)	93.078 (± 20.671)		
Weeks 28-36, Within 10-12 (N=286, 266)	69.217 (± 34.171)	67.896 (± 33.499)		
Weeks 44-52, ≥ 10 (N=266, 251)	89.416 (± 24.833)	90.921 (± 23.123)		
Weeks 44-52, Within 10-12 (N=266, 251)	68.931 (± 35.367)	74.104 (± 32.119)		
Weeks 72-80, ≥ 10 (N=241, 233)	90.343 (± 24.364)	91.494 (± 20.923)		
Weeks 72-80, Within 10-12 (N=241, 233)	67.861 (± 37.024)	69.710 (± 32.444)		
Weeks 96-104, ≥10 (N=218, 215)	87.777 (± 27.03)	90.436 (± 22.725)		
Weeks 96-104, Within 10-12 (N=218, 215)	68.629 (± 35.352)	72.393 (± 33.277)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Hb Rate of Rise > 2 g/dL Within 4 weeks

End point title	Time to First Hb Rate of Rise > 2 g/dL Within 4 weeks

End point description:

Participants were analyzed during the efficacy emergent period. The efficacy emergent period was defined as the evaluation period from the analysis date of first dose intake up to EOT Visit or last non-missing Hb assessment (for participants who died during the treatment period). For participants who had experienced more than one event, only their first event was used. Data reported was analyzed by Kaplan-Meier estimate for cumulative proportion and the 95% confidence interval was calculated with Greenwood's formula. Percentage of participants were reported in this outcome measure. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

Year 0.5, 1, 1.5 and 2

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Percentage of participants				
number (confidence interval 95%)				
Year 0.5 (N=155, 188)	28.9 (23.6 to 34.1)	45.5 (40.0 to 51.0)		
Year 1 (N=131, 171)	30.9 (25.4 to 36.3)	48.8 (43.2 to 54.4)		
Year 1.5 (N=104, 145)	35.0 (29.3 to 40.7)	53.4 (47.7 to 59.1)		
Year 2 (N=10, 22)	37.8 (31.9 to 43.7)	55.3 (49.5 to 61.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

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 Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.36
upper limit	2.22

Secondary: Number of Hospitalizations

End point title	Number of Hospitalizations

End point description:

The number of hospitalizations per participant were calculated during the efficacy emergent period. The efficacy emergent period was defined as the evaluation period from the analysis date of first dose intake up to EOT Visit or last non-missing Hb assessment (for participants who died during the treatment period). The analysis population was the FAS.

End point type	Secondary

End point timeframe:

Baseline to EOT (Up to week 104)

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Hospitalizations				
arithmetic mean (standard deviation)	1.4 (± 2.3)	1.5 (± 2.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Days of Hospitalization per Year

End point title	Number of Days of Hospitalization per Year

End point description:

The number of days of hospitalization per year was calculated as the sum of the durations of all hospitalizations in days (minimum [date of discharge, end of efficacy of emergent period] - date of admission + 1) / (duration of efficacy emergent period in days / 365.25). The efficacy emergent period was defined as the evaluation period from the analysis date of first dose intake up to EOT Visit or last non-missing Hb assessment (for participants who died during the treatment period). The analysis population was the FAS.

End point type	Secondary

End point timeframe:

Baseline to EOT (Up to week 104)

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Days per year				
arithmetic mean (standard deviation)	11.3 (± 27.7)	12.6 (± 22.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Hospitalization

End point title	Time to First Hospitalization

End point description:

Time to first hospitalization in years was defined in years as: (first event date during the efficacy emergent period – analysis date of first dose intake +1)/365.25, and the 'first event date' was defined as 'date of first admission and 'analysis date of first dose intake. Date of end of efficacy emergent period was defined as as the treatment period up to the EOT visit. For participants who have experienced more than one hospitalization, only their first event following study treatment was used. Data reported was analyzed by Kaplan-Meier estimate for cumulative proportion and the 95% confidence interval was calculated with Greenwood's formula. Percentage of participants were reported in this outcome measure. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

Year 0.5, 1, 1.5 and 2

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Percentage of participants				
number (confidence interval 95%)				
Year 0.5 (N=207, 216)	21.8 (17 to 26.7)	31.7 (26.5 to 36.8)		
Year 1 (N=162, 158)	40.4 (34.6 to 46.2)	43.7 (38.2 to 49.3)		
Year 1.5 (N=122, 124)	50.2 (44.2 to 56.1)	55.2 (49.6 to 60.9)		
Year 2 (N=15, 24)	56.7 (50.7 to 62.7)	62.3 (56.7 to 67.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

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 was declared if the upper bound of the 95% CI is below 1.0.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614

Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.079
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.5

Secondary: Time to First Use of RBC Transfusion

End point title	Time to First Use of RBC Transfusion

End point description:

Participants were analyzed during the efficacy emergent period. The efficacy emergent period was defined as the evaluation period from the analysis date of first dose intake up to EOT Visit or last non-missing Hb assessment (for participants who died during the treatment period). For participants who had experienced more than one RBC transfusion, only their first event was used. Data reported was analyzed by Kaplan-Meier estimate for cumulative proportion and the 95% confidence interval was calculated with Greenwood's formula. Percentage of participants were reported in this outcome measure. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

Year 0.5, 1, 1.5 and 2

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Percentage of participants				
number (confidence interval 95%)				
Year 0.5 (N=281, 263)	2.1 (0.4 to 3.8)	3 (1.1 to 4.9)		
Year 1 (N=244, 233)	6.5 (3.5 to 9.5)	7.3 (4.3 to 10.3)		
Year 1.5 (N=214, 207)	9.4 (5.8 to 13)	10.9 (7.2 to 14.6)		
Year 2 (N=31, 34)	11.2 (7.3 to 15.1)	13.9 (9.7 to 18.2)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

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 was declared if the upper bound of the 95% CI is below 1.0.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	2.11

Secondary: Number of RBC Packs

End point title	Number of RBC Packs

End point description:

The number of RBC packs were calculated as the sum of units transfused during the efficacy emergent period. The efficacy emergent period was defined as the evaluation period from the analysis date of first dose intake up to EOT Visit or last non-missing Hb assessment (for participants who died during the treatment period). Participants with no medication records of RBC have their number of RBC packs set to 0. The analysis population was the FAS.

End point type	Secondary

End point timeframe:

Baseline to EOT (Up to week 104)

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: RBC packs				
arithmetic mean (standard deviation)	0.4 (± 1.98)	0.4 (± 1.20)		

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of RBC Transfused

End point title	Volume of RBC Transfused

End point description:

The volume of blood transfused was calculated as the sum of blood volume transfused during the efficacy emergent period. The efficacy emergent period was defined as the evaluation period from the analysis date of first dose intake up to EOT Visit or last non-missing Hb assessment (for participants who died during the treatment period). Participants with no medication records of RBC have their volume set to 0. The analysis population was the FAS.

End point type	Secondary

End point timeframe:

Baseline to EOT (Up to week 104)

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: mL				
arithmetic mean (standard deviation)	334.63 (± 508.40)	97.0 (± 112.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Particpants who Received RBC Transfusions

End point title	Number of Particpants who Received RBC Transfusions

End point description:

Participants who received RBC transfusions during the efficacy emergent period were reported. The efficacy emergent period was defined as the evaluation period from the analysis date of first dose intake up to EOT Visit or last non-missing Hb assessment (for participants who died during the treatment period). The analysis population was the FAS.

End point type	Secondary

End point timeframe:

Baseline to EOT (Up to week 104)

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Participants	28	38		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Use of Rescue Therapy

End point title	Time to First Use of Rescue Therapy

End point description:

Rescue therapy for partcipants in the roxadustat group included RBC transfusion or ESA therapy and for

partcipants in the darbepoetin alfa group included RBC transfusion only. Participants were analyzed during the efficacy emergent period. The efficacy emergent period was defined as the evaluation period from the analysis date of first dose intake up to EOT Visit or last non-missing Hb assessment (for participants who died during the treatment period). For participants who have experienced more than one use of rescue therapy (i.e. RBC and ESA), only their first event was used. Data reported was analyzed by Kaplan-Meier estimate for cumulative proportion and the 95% confidence interval was calculated with Greenwood's formula. Percentage of participants were reported in this outcome measure. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

Year 0.5, 1, 1.5 and 2

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Percentage of participants				
number (confidence interval 95%)				
Year 0.5 (N=278, 263)	2.1 (0.4 to 3.8)	4 (1.8 to 6.2)		
Year 1 (N=241, 233)	6.5 (3.5 to 9.5)	9.3 (6 to 12.7)		
Year 1.5 (N=213, 207)	9.4 (5.8 to 13)	13.3 (9.3 to 17.3)		
Year 2 (N=31, 34)	11.2 (7.3 to 15.1)	16.7 (12.2 to 21.2)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

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 was declared if the upper bound of the 95% CI is below 1.0.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.055
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	2.54

Secondary: Number of Participants who Received Rescue Therapy (Composite of

RBC Transfusions (all Participants) and Darbepoetin alfa use (Roxadustat Treated Participants only)

End point title	Number of Participants who Received Rescue Therapy (Composite of RBC Transfusions (all Participants) and Darbepoetin alfa use (Roxadustat Treated Participants only)

End point description:

Rescue therapy for participants in the roxadustat group included RBC transfusion or ESA therapy and for participants in the darbepoetin alfa group included RBC transfusion only. Participants were analyzed during the efficacy emergent period. The efficacy emergent period was defined as the evaluation period from the analysis date of first dose intake up to EOT Visit or last non-missing Hb assessment (for participants who died during the treatment period). For participants who have experienced more than one use of rescue therapy (i.e. RBC and ESA), only their first event was used. The analysis population was the FAS.

End point type	Secondary

End point timeframe:

Baseline to EOT (Up to week 104)

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Participants	28	46		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Monthly Intravenous Iron per Participant During Weeks 37 to 52 and Weeks 53 to 104

End point title	Mean Monthly Intravenous Iron per Participant During Weeks 37 to 52 and Weeks 53 to 104

End point description:

Participants with no or missing medication records of IV Iron had their monthly IV Iron use set to 0 mg. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

Weeks 37 to 52 and 53 to 104

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: mg per month				
arithmetic mean (standard deviation)				
Weeks 37 to 52 (N=275, 258)	13.208 (± 46.408)	11.208 (± 64.282)		

Weeks 53 to 104 (N=259, 248)	31.315 (± 95.306)	18.702 (± 68.074)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Use of IV Iron Supplementation

End point title	Time to First Use of IV Iron Supplementation

End point description:

Participants were analyzed during the efficacy emergent period. The efficacy emergent period was defined as the evaluation period from the analysis date of first dose intake up to EOT Visit or last non-missing Hb assessment (for participants who died during the treatment period). For participants who had received more than one IV iron, only their first event following study treatment was used. Data reported was analyzed by Kaplan-Meier estimate for cumulative proportion and the 95% confidence interval was calculated with Greenwood's formula. Percentage of participants were reported in this outcome measure. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

Year 0.5, 1, 1.5 and 2

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Percentage of participants				
number (confidence interval 95%)				
Year 0.5 (N=278, 238)	11.8 (8 to 15.6)	4.3 (2 to 6.5)		
Year 1 (N=240, 201)	19.2 (14.5 to 23.9)	10 (6.5 to 13.5)		
Year 1.5 (N=206, 176)	24.2 (19 to 29.4)	15.9 (11.5 to 20.2)		
Year 2 (N=26, 30)	29.1 (23.1 to 35.1)	24.9 (18.8 to 31)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

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 covariate. Superiority was declared if the upper bound of the 95% CI is below 1.0.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified

Analysis type	superiority
P-value	= 0.052
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1

Secondary: Percentage of Participants with Oral Iron Use Only

End point title	Percentage of Participants with Oral Iron Use Only

End point description:

Percentage of participants with oral iron use only were calculated based on total number of participants within the efficacy emergent period. The efficacy emergent period was defined as the evaluation period from the analysis date of first dose intake up to EOT Visit or last non-missing Hb assessment (for participants who died during the treatment period). The analysis population was the FAS.

End point type	Secondary

End point timeframe:

Day 1 to week 36, weeks 37 to 52, weeks 53 to 104, efficacy emergent period (up to week 104)

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Percentage of participants				
number (not applicable)				
During efficacy emergent period	52.7	50.6		
During day 1 to week 36	55.1	55.3		
During week 37 to 52	55.4	55.6		
During week 53 to 104	50.6	53.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Weeks 8, 28, 52 and 104 in Total Cholesterol

End point title	Change From Baseline to Weeks 8, 28, 52 and 104 in Total Cholesterol

End point description:

Baseline was defined as the value on day 1. If baseline value was missing, the latest value prior to first study drug administration was used regardless of fasting. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: mmol/L				
arithmetic mean (standard deviation)				
Change from BL to week 8 (N=311, 282)	-0.046 (± 0.836)	-0.92 (± 0.98)		
Change from BL to week 28 (N=285, 264)	0.016 (± 0.953)	-0.531 (± 1.153)		
Change from BL to week 52 (N=256, 245)	-0.111 (± 1.097)	-0.524 (± 1.232)		
Change from BL to week 104 (N=215, 212)	-0.197 (± 1.171)	-0.695 (± 1.284)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Weeks 8, 28, 52 and 104 in LDL-C/High-Density Lipoprotein cholesterol (HDL-C) Ratio

End point title	Change From Baseline to Weeks 8, 28, 52 and 104 in LDL-C/High-Density Lipoprotein cholesterol (HDL-C) Ratio

End point description:

Baseline was defined as the value on day 1. If baseline value was missing, the latest value prior to first study drug administration was used regardless of fasting. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

Baseline and weeks 8, 28, 52, 104

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Ratio				
arithmetic mean (standard deviation)				
Change from BL to week 8 (N=310, 282)	-0.049 (± 0.629)	-0.209 (± 0.665)		
Change from BL to week 28 (N=284, 262)	0.053 (± 0.747)	0.016 (± 0.893)		
Change from BL to week 52 (N=256, 245)	-0.065 (± 0.871)	0.014 (± 1.095)		
Change from BL to week 104 (N=215, 209)	0.012 (± 1.06)	-0.069 (± 1.579)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Weeks 8, 28, 52 and 104 in Non-HDL Cholesterol

End point title	Change From Baseline to Weeks 8, 28, 52 and 104 in Non-HDL Cholesterol

End point description:

Baseline was defined as the value on day 1. If baseline value was missing, the latest value prior to first study drug administration was used regardless of fasting. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

Baseline and weeks 8, 28, 52, 104

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: mmoL/L				
arithmetic mean (standard deviation)				
Change from BL to week 8 (N=310, 282)	-0.045 (± 0.787)	-0.729 (± 0.9)		
Change from BL to week 28 (N=284, 262)	0.02 (± 0.911)	-0.392 (± 1.098)		
Change from BL to week 52 (N=256, 245)	-0.114 (± 1.062)	-0.383 (± 1.19)		
Change from BL to week 104 (N=215, 211)	-0.15 (± 1.151)	-0.562 (± 1.162)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Weeks 8, 28, 52 and 104 in Apolipoproteins A1 (ApoA1)

End point title	Change From Baseline to Weeks 8, 28, 52 and 104 in Apolipoproteins A1 (ApoA1)

End point description:

Baseline was defined as the value on day 1. If baseline value was missing, the latest value prior to first study drug administration was used regardless of fasting. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

Baseline and weeks 8, 28, 52, 104

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Grams per liter (g/L)				
arithmetic mean (standard deviation)				
Change from BL to week 8 (N=310, 283)	0.026 (± 0.204)	-0.184 (± 0.222)		
Change from BL to week 28 (N=287, 264)	0.055 (± 0.217)	-0.104 (± 0.258)		
Change from BL to week 52 (N=254, 243)	0.027 (± 0.229)	-0.12 (± 0.254)		
Change from BL to week 104 (N=214, 212)	-0.018 (± 0.242)	-0.116 (± 0.311)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Weeks 8, 28, 52 and 104 in Apolipoproteins B (ApoB)

End point title	Change From Baseline to Weeks 8, 28, 52 and 104 in Apolipoproteins B (ApoB)

End point description:

Baseline was defined as the value on day 1. If baseline value was missing, the latest value prior to first study drug administration was used regardless of fasting. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

Baseline and weeks 8, 28, 52, 104

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Milligrams per deciliter (mg/dL)				
arithmetic mean (standard deviation)				
Change from BL to week 8 (N=310, 283)	-0.71 (± 17.791)	-16.5 (± 19.581)		
Change from BL to week 28 (N=287, 264)	0.091 (± 19.672)	-10.659 (± 23.644)		
Change from BL to week 52 (N=254, 243)	-3.539 (± 23.811)	-10.74 (± 25.155)		
Change from BL to week 104 (N=214, 212)	-2.038 (± 25.857)	-13.561 (± 25.461)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Weeks 8, 28, 52 and 104 in ApoB/ApoA1 Ratio

End point title	Change From Baseline to Weeks 8, 28, 52 and 104 in ApoB/ApoA1 Ratio

End point description:

Baseline was defined as the value on day 1. If baseline value was missing, the latest value prior to first study drug administration was used regardless of fasting. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

Baseline and weeks 8, 28, 52, 104

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Ratio				
arithmetic mean (standard deviation)				
Change from BL to week 8 (N=252, 252)	-0.019 (± 0.13)	-0.031 (± 0.185)		
Change from BL to week 28 (N=231, 234)	-0.034 (± 0.159)	-0.026 (± 0.208)		
Change from BL to week 52 (N=204, 217)	-0.038 (± 0.191)	-0.025 (± 0.254)		
Change from BL to week 104 (N=170, 187)	-0.009 (± 0.218)	-0.044 (± 0.238)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Mean LDL Cholesterol < 100 mg/dL

End point title	Number of Participants with Mean LDL Cholesterol < 100 mg/dL

End point description:

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

End point type	Secondary

End point timeframe:

Weeks 12 to 28 and 36 to 52

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Participants				
Weeks 12-28: Yes (Regardless Fasting Status)	111	147		
Weeks 12-28: No (Regardless Fasting Status)	33	20		
Weeks 12-28: Missing (Regardless Fasting Status)	8	10		
Weeks 12-28: Yes (Fasting only)	69	90		
Weeks 12-28: No (Fasting only)	18	11		
Weeks 12-28: Missing (Fasting only)	65	76		
Weeks 36-52: Yes (Regardless Fasting Status)	104	129		
Weeks 36-52: No (Regardless Fasting Status)	31	26		
Weeks 36-52: Missing (Regardless Fasting Status)	17	22		
Weeks 36-52: Yes (Fasting only)	57	78		
Weeks 36-52: No (Fasting only)	22	15		
Weeks 36-52: Missing (Fasting only)	73	84		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Had Achieved Antihypertensive Treatment Goal

End point title	Number of Participants who Had Achieved Antihypertensive Treatment Goal

End point description:

Achieved antihypertensive treatment goal was defined as SBP < 130 mmHg and DBP < 80 mmHg over an evaluation period defined as the average of available values in weeks 12 to 28 and 36 to 52. The analysis population was the FAS.

End point type	Secondary

End point timeframe:

Weeks 12 to 28 and 36 to 52

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Participants				
Weeks 12-28: Yes	64	76		
Weeks 12-28: No	212	228		
Week 12-28: Missing	16	18		
Weeks 36-52: Yes	64	80		
Weeks 36-52: No	193	196		
Weeks 36-52: Missing	35	46		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the Average of Weeks 12 to 28 and Weeks 36 to 52 in SF-36 Physical Component Score (PCS)

End point title	Change from Baseline to the Average of Weeks 12 to 28 and Weeks 36 to 52 in SF-36 Physical Component Score (PCS)

End point description:

Baseline SF-36 PCS was defined as the SF-36 PCS value on day 1.The SF-36 is a QoL instrument designed to assess generic health concepts relevant across age, disease, and treatment groups. The SF-36 contains 36 items that measured eight scales: (1) physical functioning; (2) role limitations due to physical health problems; (3) bodily pain; (4) social functioning; (5) general health perceptions; (6) role limitations due to emotional problems; (7) vitality, energy or fatigue; and (8) mental health. Each scale is transformed into 0-100 score, with higher scores indicating better health status. The PCS was calculated based on all 8 scales and ranged from 5.02-79.78. For each of these above scales, higher scores always indicated better health status. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

Baseline, weeks 12 to 28 and 36 to 52

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Units on a scale				
least squares mean (confidence interval 95%)				
Change from BL to weeks 12-28 (N=303, 272)	2.29 (1.576 to 3.004)	1.222 (0.54 to 1.904)		
Change from BL to weeks 36-52 (N=271, 258)	1.686 (0.939 to 2.433)	1.083 (0.358 to 1.808)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Weeks 12-28 - The model included treatment, visit, visit by treatment interaction, region and history of cardiovascular disease as fixed class factors and baseline SF-36 PCS, baseline Hb, baseline estimated glomerular filtration rate as continuous covariates.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.027
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-1.068
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.012
upper limit	-0.124

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Weeks 36-52 - The model included treatment, visit, visit by treatment interaction, region and history of cardiovascular disease as fixed class factors and baseline SF-36 PCS, baseline Hb, baseline estimated glomerular filtration rate as continuous covariates.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.239
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-0.603
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.606
upper limit	0.401

Secondary: Change From Baseline to the Average of Weeks 12 to 28 and Weeks 36 to 52 in Anemia Subscale (AnS) (Additional Concerns) of Functional Assessment of Cancer Therapy-Anemia (FACT-An) Score

End point title	Change From Baseline to the Average of Weeks 12 to 28 and Weeks 36 to 52 in Anemia Subscale (AnS) (Additional Concerns) of Functional Assessment of Cancer Therapy-Anemia (FACT-An) Score

End point description:

Baseline FACT-An AnS was defined as the FACT-An AnS value on day 1. Together with the Functional Assessment of Cancer Therapy – General (FACT-G), the AnS is referred to as the FACT-An Total. The AnS scale contains 13 fatigue specific items (the fatigue score) plus 7 items related to anemia. The

Anemia AnS score range is 0 to 80. Higher scores indicated better QoL. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

Baseline, weeks 12 to 28 and 36 to 52

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Units on a scale				
least squares mean (confidence interval 95%)				
Change from BL to weeks 12-28 (N=303, 272)	5.238 (4.029 to 6.446)	4.71 (3.558 to 5.861)		
Change from BL to weeks 36-52 (N=272, 257)	4.608 (3.252 to 5.964)	3.661 (2.355 to 4.967)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Weeks 12-28 - The model included treatment, visit, visit by treatment interaction, region and history of cardiovascular disease as fixed class factors and baseline FACT-An AnS, baseline Hb, baseline estimated glomerular filtration rate as continuous covariates.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.517
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-0.528
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.127
upper limit	1.072

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Weeks 36-52 - The model included treatment, visit, visit by treatment interaction, region and history of cardiovascular disease as fixed class factors and baseline FACT-An AnS, baseline Hb, baseline estimated glomerular filtration rate as continuous covariates.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified

Analysis type	superiority
P-value	= 0.308
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-0.947
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.771
upper limit	0.877

Secondary: Change from Baseline to the Average Value of Weeks 12 to 28 and Weeks 36 to 52 in FACT-An Total Score

End point title	Change from Baseline to the Average Value of Weeks 12 to 28 and Weeks 36 to 52 in FACT-An Total Score

End point description:

Baseline FACT-An total Score was defined on day 1. Total Fact-An score is composed of FACT-G and Ans scales. FACT-G contains 27 items that cover four dimensions of well-being: physical well being (PWB) – 7 items, functional well being (FWB) - 7 items, social/family well being (SWB) - 7 items, and emotional well being (EWB) - 6 items. The AnS scale contains 13 fatigue specific items (the Fatigue Score) plus 7 items related to anemia. The total score was obtained by summation of the scores from PWB, SWB, EWB, FWB and AnS. The FACT-An Total Score scale range was 0-188. A higher score indicated better QoL. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

Baseline, weeks 12 to 28 and 36 to 52

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Units on a scale				
least squares mean (confidence interval 95%)				
Change from BL to weeks 12-28 (N=299, 270)	8.665 (6.299 to 11.031)	7.761 (5.501 to 10.02)		
Change from BL to weeks 36-52 (N=268, 255)	7.259 (4.593 to 9.925)	5.492 (2.915 to 8.069)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Week 12-28 - The model included treatment, visit, visit by treatment interaction, region and history of cardiovascular disease as fixed class factors and baseline FACT-An total score, baseline Hb, baseline estimated glomerular filtration rate as continuous covariates.

Comparison groups	Roxadustat v Darbepoetin alfa

Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.57
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-0.904
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.032
upper limit	2.224

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Weeks 36-52 -The model included treatment, visit, visit by treatment interaction, region and history of cardiovascular disease as fixed class factors and baseline FACT-An total score, baseline Hb, baseline estimated glomerular filtration rate as continuous covariates.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.334
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-1.767
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.354
upper limit	1.82

Secondary: Change from Baseline to the Average Value of Weeks 12 to 28 and Weeks 36 to 52 in FACT-An Trial Outcome Index (TOI) Score

End point title	Change from Baseline to the Average Value of Weeks 12 to 28 and Weeks 36 to 52 in FACT-An Trial Outcome Index (TOI) Score

End point description:

Baseline FACT-An total TOI Score was defined on day 1. Total FACT-An TOI score is a sum of PWB subscale score, FWB subscale score and Ans scale score. Fact-An TOI scale contains 14 items that cover four dimensions of well-being: PWB -7 items, FWB -7 items, where score range for each PWB subscale and FWB subscale is 0-28. The AnS scale contains 13 fatigue specific items (the Fatigue Score) plus 7 items related to anemia, where score range for Ans scale is 0-80. The total score was obtained by summation of the scores from PWB, FWB and AnS. The FACT-An Total TOI score range was 0-136. A higher score indicated better QoL. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

Baseline, weeks 12 to 28 and 36 to 52

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Weeks 12-28 (N=300, 270)	6.876 (± 16.960)	6.798 (± 17.830)		
Weeks 36-52 (N=269, 255)	5.595 (± 19.922)	5.602 (± 19.302)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Baseline and weeks 12 to 28

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	300		
Units: Units on a scale				
least squares mean (confidence interval 95%)	4.353 (2.643 to 6.064)	5.137 (3.498 to 6.776)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The model includes treatment, visit, visit by treatment interaction, region and history of CV disease as fixed class factors and baseline EQ-5D 5L VAS, baseline Hb, baseline eGFR as continuous covariates.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	571
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.497
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.784
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.481
upper limit	3.049

Secondary: Change from Baseline to the Average Value of Weeks 12 to 28 and Weeks 36 to 52 in Work Productivity and Activity Impairment-Anemic Symptoms (WPAI:ANS) Score: Percent Work Time Missed

End point title	Change from Baseline to the Average Value of Weeks 12 to 28 and Weeks 36 to 52 in Work Productivity and Activity Impairment-Anemic Symptoms (WPAI:ANS) Score: Percent Work Time Missed

End point description:

WPAI consisted of 6 questions (Q1=Employment status; Q2=Hours absent from work due to anaemic symptoms; Q3=Hours absent from work due to other reasons; Q4=Hours actually worked; Q5=Impact of the anaemic symptoms on productivity while working; Q6=Impact of the anaemic symptoms on productivity while doing regular daily activities other than work) and a 1-week recall period. Higher WPAI scores indicated greater activity impairment. Multiply scores by 100 to express in percentages. Percent work time missed due to problem: Q2/(Q2+Q4). The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

Baseline, weeks 12 to 28 and 36 to 52

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Percent work time				
arithmetic mean (standard deviation)				
Change from BL to weeks 12-28 (N=35,49)	0.842 (± 21)	-3.793 (± 32.987)		
Change from BL to weeks 36-52 (N=23,44)	0.216 (± 23.483)	-0.078 (± 37.047)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the Average Value of Weeks 12 to 28 and Weeks 36 to 52 in WPAI:ANS Score: Percent Impairment While Working

End point title	Change from Baseline to the Average Value of Weeks 12 to 28 and Weeks 36 to 52 in WPAI:ANS Score: Percent Impairment While Working

End point description:

WPAI consisted of 6 questions (Q1=Employment status; Q2=Hours absent from work due to anaemic symptoms; Q3=Hours absent from work due to other reasons; Q4=Hours actually worked; Q5=Impact of the anaemic symptoms on productivity while working; Q6=Impact of the anaemic symptoms on productivity while doing regular daily activities other than work) and a 1-week recall period. Higher WPAI scores indicated greater activity impairment. Percent impairment while working due to problem: Q5/10. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

Baseline, weeks 12 to 28 and 36 to 52

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Percent impairment				
arithmetic mean (standard deviation)				
Change from BL to weeks 12-28 (N=34,50)	-2.433 (± 28.598)	-6.618 (± 22.419)		
Change from BL to weeks 36-52 (N=22,48)	1.083 (± 23.102)	-7.879 (± 25.872)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the Average Value of Weeks 12 to 28 and Weeks 36 to 52 in WPAI:ANS Score: Percent Overall Work Impairment

End point title	Change from Baseline to the Average Value of Weeks 12 to 28 and Weeks 36 to 52 in WPAI:ANS Score: Percent Overall Work Impairment

End point description:

WPAI consisted of 6 questions (Q1=Employment status; Q2=Hours absent from work due to anaemic symptoms; Q3=Hours absent from work due to other reasons; Q4=Hours actually worked; Q5=Impact

of the anaemic symptoms on productivity while working; Q6=Impact of the anaemic symptoms on productivity while doing regular daily activities other than work) and a 1-week recall period. Higher WPAI scores indicated greater activity impairment. Percent overall work impairment due to problem: Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4))x(Q5/10)]. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

Baseline, weeks 12 to 28 and 36 to 52

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Percent impairment				
arithmetic mean (standard deviation)				
Change from BL to weeks 12-28 (N=32,49)	-1.217 (± 20.743)	-6.112 (± 23.21)		
Change From BL to weeks 36-52 (N=21,44)	0.197 (± 23.431)	2.817 (± 30.432)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the Average Value of Weeks 12 to 28 and Weeks 36 to 52 in WPAI:ANS Score: Percent Activity Impairment

End point title	Change from Baseline to the Average Value of Weeks 12 to 28 and Weeks 36 to 52 in WPAI:ANS Score: Percent Activity Impairment

End point description:

WPAI consisted of 6 questions (Q1=Employment status; Q2=Hours absent from work due to anaemic symptoms; Q3=Hours absent from work due to other reasons; Q4=Hours actually worked; Q5=Impact of the anaemic symptoms on productivity while working; Q6=Impact of the anaemic symptoms on productivity while doing regular daily activities other than work) and a 1-week recall period. Higher WPAI scores indicated greater activity impairment. Percent activity impairment due to problem: Q6/10. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

Baseline, weeks 12 to 28 and 36 to 52

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Percent impairment				
arithmetic mean (standard deviation)				
Change from BL to weeks 12-28 (N=300, 269)	-9.34 (± 27.09)	-9.581 (± 27.367)		

Change from BL to weeks 36-52 (N=270, 254)	-8.17 (± 27.486)	-9.365 (± 28.956)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The PGIC is a patient-rated instrument that measured change in participant's overall status on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse), when compared to the start of treatment. The percentage of participants presented included very much improved, much improved and minimally improved. The analysis population was the FAS.

End point type	Secondary

End point timeframe:

Weeks 8, 12, 28, 52, 76, 104, last assessment (week 108)

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Percentage of participants				
number (not applicable)				
Week 8	79.4	76.1		
Week 12	83.6	83.7		
Week 28	81	83		
Week 52	79.8	79.3		
Week 76	74.9	73		
Week 104	76	71.8		
Last Assessment (week 108)	71.4	70.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Each Scheduled Measurement Serum Ferritin

End point title	Change from Baseline to Each Scheduled Measurement Serum Ferritin

End point description:

Baseline assessment was assessment from day 1 visit. If baseline value was missing, the value from screening visit was used. In case of missing data, no imputation rules were applied. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

Baseline and weeks 4, 8, 12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, 100, 104 and end of study (EOS) (up to 108 weeks)

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Picomoles per liter (pmol/L)				
arithmetic mean (standard deviation)				
Week 4 (N=316, 288)	-159.174 (± 218.981)	-190.762 (± 241.695)		
Week 8 (N=307, 280)	-208.356 (± 309.893)	-229.471 (± 255.677)		
Week 12 (N=300, 271)	-201.587 (± 346.59)	-205.722 (± 271.752)		
Week 20 (N=286, 265)	-140.26 (± 338.512)	-99.86 (± 334.486)		
Week 28 (N=286, 262)	-121.574 (± 348.136)	-97.622 (± 366.153)		
Week 36 (N=271, 256)	-120.424 (± 362.08)	-131.801 (± 355.463)		
Week 44 (N=261, 250)	-60.149 (± 425.455)	-120.864 (± 368.902)		
Week 52 (N=254, 241)	-72.383 (± 459.342)	-93.074 (± 521.433)		
Week 60 (N=252, 243)	-47.714 (± 459.319)	-141.264 (± 355.419)		
Week 68 (N=245, 239)	-14.283 (± 464.714)	-110.907 (± 422.28)		
Week 76 (N=235, 230)	3.424 (± 615.735)	-99.697 (± 412.982)		
Week 84 (N=224, 221)	-1.351 (± 576.437)	-126.615 (± 403.693)		
Week 92 (N=222, 219)	-26.73 (± 547.371)	-98.025 (± 460.364)		
Week 100 (N=216, 206)	31.391 (± 750.432)	-95.513 (± 486.758)		
Week 104 (N=212, 208)	26.454 (± 730.126)	-89.276 (± 476.167)		
EOS (N=245, 225)	119.157 (± 697.39)	78.577 (± 680.524)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Each Scheduled Measurement in Transferrin Saturation (TSAT)

End point title	Change from Baseline to Each Scheduled Measurement in Transferrin Saturation (TSAT)

End point description:

Baseline assessment was assessment from day 1 visit. If baseline value was missing, the value from screening visit was used. In case of missing data, no imputation rules were applied. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

Baseline and weeks 4, 8, 12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, 100, 104 and EOS (up to 108 weeks)

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Percentage of saturation				
arithmetic mean (standard deviation)				
Week 4 (N=312, 287)	-2.1 (± 11.5)	-6 (± 10.7)		
Week 8 (N=304, 278)	-2.4 (± 10.6)	-5.9 (± 11.5)		
Week 12 (N=294, 268)	-0.5 (± 12.3)	-2.4 (± 13.2)		
Week 20 (N=286, 263)	2.9 (± 11.6)	1.6 (± 13.9)		
Week 28 (N=284, 263)	4 (± 12.5)	1.1 (± 12.5)		
Week 36 (N=270, 256)	3.9 (± 11.5)	1.6 (± 12)		
Week 44 (N=259, 247)	4.9 (± 12.9)	0.6 (± 12)		
Week 52 (N=252, 242)	5.2 (± 13.2)	1.3 (± 11.8)		
Week 60 (N=250, 238)	4.8 (± 12.7)	0.4 (± 12.4)		
Week 68 (N=245, 237)	6.3 (± 13.1)	1 (± 13.4)		
Week 76 (N=235, 228)	6 (± 13.7)	0.1 (± 12.2)		
Week 84 (N=222, 220)	6.5 (± 13.9)	1.1 (± 12.5)		
Week 92 (N=222, 216)	5.6 (± 13.8)	-0.2 (± 11.7)		
Week 100 (N=214, 201)	5.8 (± 14)	0.6 (± 12.4)		
Week 104 (N=210, 207)	5 (± 13.3)	0.5 (± 11.9)		
EOS (N=242, 222)	4.7 (± 13.9)	5.3 (± 12.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Each Scheduled Measurement in Glycated Hemoglobin (HbA1c)

End point title	Change from Baseline to Each Scheduled Measurement in Glycated Hemoglobin (HbA1c)

End point description:

Percentage of change from baseline to each study visit were calculated for HbA1c. Baseline assessment was assessment from day 1 visit. If baseline value was missing, the value from screening visit was used. In case of missing data, no imputation rules were applied. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

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

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Percentage of HbA1c				
arithmetic mean (standard deviation)				
Week 12 (N=296, 267)	0.001 (± 0.0073)	0.0021 (± 0.0071)		
Week 28 (N=277, 256)	0.0015 (± 0.0067)	0.0009 (± 0.0072)		
Week 36 (N=265, 252)	0.0021 (± 0.0073)	0.0021 (± 0.0075)		
Week 44 (N=254, 249)	0.002 (± 0.0066)	0.0026 (± 0.0077)		
Week 60 (N=250, 242)	0.0019 (± 0.0074)	0.0025 (± 0.0083)		
Week 84 (N=223, 222)	0.0025 (± 0.0077)	0.0024 (± 0.0093)		
Week 104 (N=212, 202)	0.002 (± 0.008)	0.0018 (± 0.0086)		
EOS (N=244, 225)	0.0034 (± 0.0081)	0.0031 (± 0.0087)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Each Scheduled Measurement in Fasting Blood Glucose

End point title	Change from Baseline to Each Scheduled Measurement in Fasting Blood Glucose

End point description:

Baseline assessment was assessment from day 1 visit. If baseline value was missing, the value from screening visit was used. In case of missing data, no imputation rules were applied. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

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, 106 and EOS (up to 108 weeks)

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: mg/dL				
arithmetic mean (standard deviation)				
Week 4 (N=169, 143)	10.3 (± 76.9)	7 (± 62.8)		

Week 8 (N=168, 136)	1.3 (± 40.3)	4.1 (± 60.1)		
Week 12 (N=156, 134)	7.1 (± 58.2)	9.3 (± 64.5)		
Week 20 (N=147, 131)	4.3 (± 57.9)	6.9 (± 69.4)		
Week 28 (N=137, 122)	2.8 (± 37.7)	8.7 (± 66.9)		
Week 36 (N=133, 126)	3.6 (± 45.3)	6.4 (± 52.5)		
Week 44 (N=129, 123)	0.4 (± 45.1)	3.3 (± 44.7)		
Week 52 (N=129, 115)	1.1 (± 41.1)	7.1 (± 69.7)		
Week 60 (N=121, 104)	6.3 (± 43.1)	6.6 (± 65.6)		
Week 68 (N=119, 109)	5.5 (± 48.2)	3.8 (± 66.1)		
Week 76 (N=113, 102)	5.8 (± 55.2)	0.9 (± 41.9)		
Week 84 (N=115, 101)	12 (± 57.4)	1.4 (± 49.1)		
Week 92 (N=107, 95)	2.1 (± 46.5)	6 (± 69.5)		
Week 100 (N=101, 87)	4 (± 48.9)	2.7 (± 45.3)		
Week 104 (N=104, 90)	1 (± 48.6)	-2.6 (± 60.7)		
Week 106 (N=106, 92)	9.2 (± 53.3)	-2.4 (± 31.2)		
EOS (N=116, 100)	9.8 (± 43.6)	2.5 (± 58.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Each Scheduled Measurement in Estimated Glomerular Filtration Rate (eGFR)

End point title	Change from Baseline to Each Scheduled Measurement in Estimated Glomerular Filtration Rate (eGFR)

End point description:

Baseline assessment was assessment from day 1 visit. If baseline value was missing, the value from screening visit was used. In case of missing data, no imputation rules were applied. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

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, 106 and EOS (up to 108 weeks)

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Geometric mean ratio				
geometric mean (confidence interval 95%)				
Week 4 (N=311, 284)	0.97 (0.95 to 0.99)	1.01 (0.99 to 1.03)		
Week 8 (N=300, 272)	0.96 (0.94 to 0.99)	1.01 (0.98 to 1.03)		
Week 12 (N=286, 261)	0.95 (0.93 to 0.98)	1.02 (1.00 to 1.05)		
Week 20 (N=267, 249)	0.93 (0.90 to 0.96)	0.98 (0.95 to 1.01)		

Week 28 (N=252, 244)	0.89 (0.86 to 0.93)	0.93 (0.89 to 0.96)		
Week 36 (N=227, 227)	0.89 (0.85 to 0.93)	0.93 (0.89 to 0.97)		
Week 44 (N=211, 209)	0.89 (0.84 to 0.93)	0.90 (0.86 to 0.93)		
Week 52 (N=200, 191)	0.88 (0.83 to 0.92)	0.90 (0.86 to 0.94)		
Week 60 (N=189, 182)	0.86 (0.82 to 0.91)	0.90 (0.86 to 0.94)		
Week 68 (N=177, 174)	0.84 (0.79 to 0.89)	0.87 (0.83 to 0.91)		
Week 76 (N=167, 166)	0.84 (0.78 to 0.90)	0.83 (0.78 to 0.88)		
Week 84 (N=155, 157)	0.83 (0.77 to 0.89)	0.83 (0.78 to 0.88)		
Week 92 (N=152, 151)	0.85 (0.79 to 0.90)	0.84 (0.79 to 0.90)		
Week 100 (N=145, 141)	0.86 (0.81 to 0.92)	0.84 (0.78 to 0.89)		
Week 104 (N=142, 140)	0.84 (0.79 to 0.91)	0.84 (0.79 to 0.90)		
Week 106 (N=154, 139)	0.86 (0.79 to 0.92)	0.84 (0.78 to 0.90)		
EOS (N=159, 146)	0.85 (0.79 to 0.92)	0.86 (0.81 to 0.91)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Progression of Chronic Kidney Disease Measured by eGFR Slope Over Time

End point title	Rate of Progression of Chronic Kidney Disease Measured by 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 dialysis (acute or chronic) were 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 EOS (Up to week 108)

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: change/ year in ml/min per 1.73 m^2				
least squares mean (confidence interval	-2.89 (-3.51 to	-2.95 (-3.56 to		

95%)	-2.27)	-2.34)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.902
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.93
upper limit	0.82

Secondary: Change from Baseline to Each Scheduled Measurement in Urine Albumin/Creatinine Ratio (UACR)

End point title	Change from Baseline to Each Scheduled Measurement in Urine Albumin/Creatinine Ratio (UACR)

End point description:

Baseline assessment was assessment from day 1 visit. If baseline value was missing, the value from screening visit was used. In case of missing data, no imputation rules were applied. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

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

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Geometric mean ratio				
geometric mean (confidence interval 95%)				
Week 12 (N=230, 214)	1.23 (1.1 to 1.38)	1.19 (1.07 to 1.34)		
Week 24 (N=225, 200)	1.22 (1.08 to 1.39)	1.18 (1.06 to 1.33)		
Week 36 (N=187, 181)	1.18 (1.03 to 1.36)	1.22 (1.07 to 1.4)		

Week 52 (N=164, 147)	1.1 (0.92 to 1.32)	1.28 (1.1 to 1.49)		
Week 64 (N=149, 141)	1.11 (0.9 to 1.38)	1.23 (1.03 to 1.46)		
Week 76 (N=135, 133)	1.18 (0.94 to 1.48)	1.39 (1.14 to 1.7)		
Week 88 (N=122, 119)	1.1 (0.86 to 1.39)	1.21 (0.97 to 1.5)		
Week 104 (N=109, 101)	1.18 (0.92 to 1.51)	1.46 (1.17 to 1.82)		

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:

For participants who had doubled their serum creatinine or had chronic dialysis or renal transplant more than once, only their first occurrence during safety emergent period was used. The safety emergent period was defined as the evaluation period from the analysis date of first drug intake up to 28 days after the end of treatment taking into account the different dosing frequencies of the study treatments. Data reported was analyzed by Kaplan-Meier estimate for cumulative proportion and the 95% confidence interval was calculated with Greenwood's formula. Percentage of participants were reported in this outcome measure. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

Year 0.5, 1, 1.5 and 2

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Percentage of participants				
number (confidence interval 95%)				
Year 0.5 (N=255, 247)	8.6 (5.3 to 11.9)	12.9 (9.1 to 16.6)		
Year 1 (N=196, 186)	27.2 (21.9 to 32.6)	27.4 (22.3 to 32.6)		
Year 1.5 (N=155, 148)	38.8 (32.9 to 44.7)	38.2 (32.5 to 44)		
Year 2 (N=122, 113)	45.4 (39.2 to 51.5)	46.5 (40.5 to 52.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

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 was declared if the upper bound of the 95% CI was below 1.0.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.96
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.29

Secondary: Number of Participants With End Stage Renal Disease (ESRD)

End point title	Number of Participants With End Stage Renal Disease (ESRD)

End point description:

Occurrence of end stage renal disease during the study (i.e from day 1 up to the end of study) was defined as at least one of the following: underwent >30 days dialysis therapy, received kidney transplant, planned kidney transplant, physician recommended renal replacement therapy and participant refused therapy, began dialysis and died < 30 days later. The analysis population was the FAS.

End point type	Secondary

End point timeframe:

Baseline up to EOS (Up to week 108)

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Participants	107	110		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Chronic kidney disease 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. For participants who had chronic dialysis or renal transplant or died, only their first occurrence during the safety emergent period was used. The safety emergent period was defined as the evaluation period from the analysis date of first drug intake up to 28 days after the end of treatment taking into account the different dosing frequencies of the study treatments. Data reported was analyzed by Kaplan-Meier estimate for cumulative proportion and the 95% confidence interval was calculated with Greenwood's formula. Percentage of participants were reported in this outcome measure. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

Year 0.5, 1, 1.5 and 2

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Percentage of participants				
number (confidence interval 95%)				
Year 0.5 (N=255, 247)	10.2 (6.7 to 13.8)	14 (10.1 to 17.9)		
Year 1 (N=196, 186)	29.5 (24.1 to 34.9)	30.9 (25.6 to 36.2)		
Year 1.5 (N=155, 148)	42.6 (36.6 to 48.5)	42.1 (36.4 to 47.8)		
Year 2 (N=122, 113)	51 (44.9 to 57)	49.9 (44 to 55.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

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 was declared if the upper bound of the 95% CI was below 1.0.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.939
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.25

Secondary: Time to Chronic Dialysis or Renal Transplant or Death

End point title	Time to Chronic Dialysis or Renal Transplant or Death

End point description:

For participants who had chronic dialysis or renal transplant or died, only their first occurrence during the safety emergent period was used. The safety emergent period was defined as the evaluation period from the analysis date of first drug intake up to 28 days after the end of treatment taking into account the different dosing frequencies of the study treatments. Data reported was analyzed by Kaplan-Meier estimate for cumulative proportion and the 95% confidence interval was calculated with Greenwood's formula. Percentage of participants were reported in this outcome measure. The analysis population was the FAS. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

Year 0.5, 1, 1.5 and 2

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Percentage of participants				
number (confidence interval 95%)				
Year 0.5 (N=259, 250)	9.2 (5.8 to 12.6)	12.7 (9 to 16.4)		
Year 1 (N=207, 195)	26.2 (21 to 31.4)	27.1 (22 to 32.2)		
Year 1.5 (N=169, 161)	37.7 (31.9 to 43.5)	37.1 (31.6 to 42.7)		
Year 2 (N=139, 126)	45.6 (39.6 to 51.7)	42.9 (37.1 to 48.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

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 was declared if the upper bound of the 95% CI was below 1.0.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.948
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided

lower limit	0.77
upper limit	1.27

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:

For participants who had at least 40% decrease in eGFR from baseline, chronic dialysis or renal transplant during the safety emergent period, only their first occurrence was used. The safety emergent period was defined as the evaluation period from the analysis date of first drug intake up to 28 days after the end of treatment taking into account the different dosing frequencies of the study treatments. Data reported was analyzed by Kaplan-Meier estimate for cumulative proportion and the 95% confidence interval was calculated with Greenwood's formula. The analysis population was the FAS. Percentage of participants were reported in this outcome measure. Here, N signifies participants with available data at specified time points.

End point type	Secondary

End point timeframe:

Year 0.5, 1, 1.5 and 2

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	322		
Units: Percentage of participants				
number (confidence interval 95%)				
Year 0.5 (N=248, 235)	13 (9 to 16.9)	15.4 (11.3 to 19.5)		
Year 1 (N=178, 166)	35.5 (29.8 to 41.3)	34.5 (29 to 40)		
Year 1.5 (N=133, 122)	50.2 (44.1 to 56.3)	47.2 (41.3 to 53.1)		
Year 2 (N=104, 85)	59.3 (53.2 to 65.3)	55.7 (49.7 to 61.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

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 was declared if the upper bound of the 95% CI was below 1.0.

Comparison groups	Roxadustat v Darbepoetin alfa
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.568
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)

Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.17

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

End point title	Number of Participants With Treatment Emergent Adverse Events (TEAEs)

End point description:

An AE was defined as any untoward medical occurrence in a participant who was given the study drug or who had undergone study procedures and did not necessarily have a causal relationship with this treatment. All AEs collected during the safety emergent period were counted as TEAE. The safety emergent period was defined as the evaluation period from the analysis date of first drug intake up to 28 days after the end of treatment taking into account the different dosing frequencies of the study treatments. Based on national cancer institute common terminology criteria (NCI-CTCAE), AEs were graded as grade 1=mild, grade 2=moderate, grade 3 =severe or medically significant, grade 4 =life threatening, grade 5 =death related to AE. All reported deaths after the first study drug administration and up to 28 days after the analysis date of last dose were based on last dosing frequency. The Safety Analysis Set included all randomized participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline up to EOS (Up to week 108)

End point values	Darbepoetin alfa	Roxadustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	293	323		
Units: Participants				
TEAE	271	296		
Drug-Related TEAE	66	78		
Serious TEAE	181	209		
Drug-Related Serious TEAE	9	18		
TEAE Leading to Death	34	34		
Drug-Related TEAE Leading to Death	0	2		
TEAE Leading to Withdrawal of Treatment	11	25		
Drug-Related TEAE Leading to Withdraw of Treatment	1	7		
NCI CTCAE Grades 3 or Higher	164	181		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to end of study (up to week 108)

Adverse event reporting additional description:

Total number of deaths (all causes) includes deaths reported after the time frame above. The safety emergent period was defined as the evaluation period from the analysis date of first drug intake up to 28 days after the end of treatment taking into account the different dosing frequencies of the study treatments.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Darbepoetin alfa

Reporting group description:

Participants received initial dose of darbepoetin alfa based upon the weight (either 0.45 µg/kg of body weight, as a single subcutaneous or IV injection once weekly or 0.75 µg/kg of body weight, as a single subcutaneous injection once every 2 weeks) as per EU SmPC along with IV iron supplementation according to the standard of care. Dose-adjustment was performed based upon regular measurement of Hb levels until participants achieved central Hb value of ≥11.0 g/dL and Hb increase from baseline 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 darbepoetin alfa dosage was adjusted every 4 weeks to maintain participants Hb level within the target range of 10.0 g/dL and 12.0 g/dL. Participants received darbepoetin alfa for up to a maximum of 104 weeks.

Reporting group title	Roxadustat

Reporting group description:

Participants received roxadustat orally according to the tiered weight-based approach, with starting dose of 70 mg given TIW to participants weighing between 45 kg up to 70 kg and 100 mg given TIW to participants weighing more than 70 kg up to 160 kg. Dose-titration was performed based upon regular measurement of Hb levels until participants achieved central Hb value of ≥ 11.0 g/dL and Hb increase from baseline of ≥ 1.0 g/dL at two consecutive study visits, separated by at least 5 days. Once target Hb level was reached participants entered maintenance period during which roxadustat dosage was adjusted every 4 weeks to maintain participants Hb level within the target range of 10.0 g/dL and 12.0 g/dL. Participants received roxadustat for up to a maximum of 104 weeks.

Serious adverse events	Darbepoetin alfa	Roxadustat	
Total subjects affected by serious adverse events			
subjects affected / exposed	181 / 293 (61.77%)	209 / 323 (64.71%)	
number of deaths (all causes)	37	40	
number of deaths resulting from adverse events	34	34	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aortic intramural haematoma			

subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure fluctuation			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
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	1 / 293 (0.34%)	4 / 323 (1.24%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism arterial			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extremity necrosis			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	5 / 293 (1.71%)	8 / 323 (2.48%)	
occurrences causally related to treatment / all	3 / 6	1 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	5 / 293 (1.71%)	5 / 323 (1.55%)	

occurrences causally related to treatment / all	2 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 293 (0.68%)	4 / 323 (1.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypovolaemic shock			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Iliac artery occlusion			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	4 / 293 (1.37%)	3 / 323 (0.93%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
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	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	

deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	2 / 293 (0.68%)	4 / 323 (1.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma gastric			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 293 (0.00%)	4 / 323 (1.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign neoplasm of thyroid gland			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign renal neoplasm			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer stage I			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carcinoma in situ of skin			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic myelomonocytic leukaemia			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatocellular carcinoma			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Meningioma			
subjects affected / exposed	0 / 293 (0.00%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lung			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastasis			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oesophageal adenocarcinoma			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parathyroid tumour benign			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	2 / 293 (0.68%)	2 / 323 (0.62%)	

occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer metastatic			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine neoplasm			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anti-neutrophil cytoplasmic antibody positive vasculitis			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal transplant failure			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sarcoidosis			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
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 / 293 (0.68%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac death			
subjects affected / exposed	0 / 293 (0.00%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Catheter site haemorrhage			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site pain			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 293 (0.34%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	4 / 293 (1.37%)	5 / 323 (1.55%)	

occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 4	0 / 5	
General physical health deterioration			
subjects affected / exposed	4 / 293 (1.37%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	1 / 293 (0.34%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (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	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
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 / 293 (0.00%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Psychiatric disorders			
Alcoholism			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Confusional state			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	2 / 293 (0.68%)	3 / 323 (0.93%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Frustration tolerance decreased			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (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			
Menometrorrhagia			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to	0 / 0	0 / 1	

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial bypass occlusion			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site complication			
subjects affected / exposed	1 / 293 (0.34%)	3 / 323 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site haematoma			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
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	5 / 293 (1.71%)	9 / 323 (2.79%)	
occurrences causally related to treatment / all	2 / 5	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain contusion			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest injury			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complications of transplanted kidney			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fall			
subjects affected / exposed	2 / 293 (0.68%)	3 / 323 (0.93%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Femur fracture			
subjects affected / exposed	0 / 293 (0.00%)	3 / 323 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal dialysis complication			
subjects affected / exposed	2 / 293 (0.68%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound complication			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt malfunction			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt occlusion			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin injury			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic rupture			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Subdural haematoma			
subjects affected / exposed	2 / 293 (0.68%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Synovial rupture			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary anastomotic leak			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access malfunction			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site bruising			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site swelling			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site thrombosis			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood glucose increased			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood potassium increased			
subjects affected / exposed	2 / 293 (0.68%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood sodium increased			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
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	25 / 293 (8.53%)	26 / 323 (8.05%)	
occurrences causally related to	0 / 37	0 / 28	

treatment / all			
deaths causally related to treatment / all	0 / 2	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Occult blood positive			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	2 / 293 (0.68%)	3 / 323 (0.93%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	8 / 293 (2.73%)	5 / 323 (1.55%)	
occurrences causally related to treatment / all	1 / 10	2 / 5	
deaths causally related to treatment / all	0 / 2	1 / 3	
Angina pectoris			
subjects affected / exposed	5 / 293 (1.71%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 293 (0.34%)	3 / 323 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	0 / 293 (0.00%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 293 (0.34%)	4 / 323 (1.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	3 / 293 (1.02%)	3 / 323 (0.93%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 2	
Cardiac failure			
subjects affected / exposed	10 / 293 (3.41%)	12 / 323 (3.72%)	
occurrences causally related to treatment / all	0 / 15	1 / 15	
deaths causally related to treatment / all	0 / 3	0 / 2	
Cardiac failure acute			
subjects affected / exposed	6 / 293 (2.05%)	3 / 323 (0.93%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 3	
Cardiac failure chronic			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	10 / 293 (3.41%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 12	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	

Cardiogenic shock			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery disease			
subjects affected / exposed	3 / 293 (1.02%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Long QT syndrome			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial fibrosis			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 293 (0.00%)	3 / 323 (0.93%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Myocardial ischaemia			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodal arrhythmia			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	1 / 293 (0.34%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trifascicular block			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Congenital cystic kidney disease			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lown-Ganong-Levine syndrome			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinocerebellar ataxia			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary disease			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 293 (0.68%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 293 (0.00%)	6 / 323 (1.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysema			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	4 / 293 (1.37%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 293 (0.68%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	3 / 293 (1.02%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	2 / 293 (0.68%)	4 / 323 (1.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Pulmonary vasculitis			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 293 (0.68%)	3 / 323 (0.93%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 293 (2.05%)	5 / 323 (1.55%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic anaemia			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocoagulable state			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenic purpura			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system lesion			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 293 (0.68%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (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	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	2 / 293 (0.68%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 293 (0.34%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Headache			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic coma			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypoglycaemic unconsciousness			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	3 / 293 (1.02%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Lumbar radiculopathy			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Simple partial seizures			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (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	3 / 293 (1.02%)	6 / 323 (1.86%)	
occurrences causally related to treatment / all	0 / 3	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalamus haemorrhage			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	3 / 293 (1.02%)	4 / 323 (1.24%)	
occurrences causally related to treatment / all	1 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uraemic encephalopathy			
subjects affected / exposed	2 / 293 (0.68%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Glaucoma			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular degeneration			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal artery occlusion			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness neurosensory			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal incarcerated hernia			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal haemorrhage			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 293 (0.00%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bloody peritoneal effluent			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Colitis microscopic			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to	0 / 0	0 / 2	

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 293 (0.68%)	3 / 323 (0.93%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric antral vascular ectasia			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer perforation			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 293 (0.34%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis haemorrhagic			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (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	1 / 293 (0.34%)	3 / 323 (0.93%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedematous pancreatitis			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reactive gastropathy			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
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	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue haemorrhage			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
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	7 / 293 (2.39%)	7 / 323 (2.17%)	
occurrences causally related to treatment / all	0 / 10	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute prerenal failure			
subjects affected / exposed	2 / 293 (0.68%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anuria			
subjects affected / exposed	0 / 293 (0.00%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Azotaemia			
subjects affected / exposed	3 / 293 (1.02%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic kidney disease			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
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	106 / 293 (36.18%)	108 / 323 (33.44%)	
occurrences causally related to treatment / all	0 / 106	3 / 108	
deaths causally related to treatment / all	0 / 2	0 / 1	
Haematuria			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	

deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy toxic			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive uropathy			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal artery stenosis			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	2 / 293 (0.68%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst haemorrhage			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst ruptured			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Urinary bladder rupture			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 293 (0.00%)	3 / 323 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	3 / 293 (1.02%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 293 (0.00%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic congestion			

subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver injury			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decubitus ulcer			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panniculitis			
subjects affected / exposed	0 / 293 (0.00%)	2 / 323 (0.62%)	

occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 293 (0.00%)	3 / 323 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Toxic epidermal necrolysis			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device leakage			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
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			
Back pain			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gouty arthritis			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			

subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 293 (0.34%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Thyroid mass			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Alkalosis			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alkalosis hypochloraemic			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	7 / 293 (2.39%)	3 / 323 (0.93%)	
occurrences causally related to treatment / all	0 / 10	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			

subjects affected / exposed	0 / 293 (0.00%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 293 (0.00%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	1 / 293 (0.34%)	4 / 323 (1.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	6 / 293 (2.05%)	7 / 323 (2.17%)	
occurrences causally related to treatment / all	0 / 6	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypervolaemia			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypochloraemia			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 293 (0.34%)	3 / 323 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 293 (0.68%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	2 / 293 (0.68%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mineral deficiency			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	

deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 293 (0.00%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute hepatitis B			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial pyelonephritis			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchitis			
subjects affected / exposed	2 / 293 (0.68%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis viral			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 293 (0.68%)	3 / 323 (0.93%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	

deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium colitis			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	3 / 293 (1.02%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
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	4 / 293 (1.37%)	3 / 323 (0.93%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 293 (0.00%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis bacterial			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
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 / 293 (0.00%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia pyelonephritis			
subjects affected / exposed	2 / 293 (0.68%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	2 / 293 (0.68%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	0 / 293 (0.00%)	4 / 323 (1.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastritis viral			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	3 / 293 (1.02%)	3 / 323 (0.93%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cyst infection			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
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	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	4 / 293 (1.37%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 293 (0.00%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangitis			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Nosocomial infection			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	3 / 293 (1.02%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	0 / 293 (0.00%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	3 / 293 (1.02%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	14 / 293 (4.78%)	21 / 323 (6.50%)	
occurrences causally related to treatment / all	0 / 17	0 / 23	
deaths causally related to treatment / all	0 / 4	0 / 1	

Pneumonia bacterial			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia viral			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural sepsis			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (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 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyelonephritis acute			
subjects affected / exposed	7 / 293 (2.39%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 10	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis chronic			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst infection			
subjects affected / exposed	0 / 293 (0.00%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salpingo-oophoritis			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	9 / 293 (3.07%)	7 / 323 (2.17%)	
occurrences causally related to treatment / all	0 / 9	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 3	
Skin infection			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 293 (0.00%)	4 / 323 (1.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal skin infection			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal endocarditis			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Tubo-ovarian abscess			
subjects affected / exposed	1 / 293 (0.34%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection bacterial			
subjects affected / exposed	0 / 293 (0.00%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 293 (1.02%)	7 / 323 (2.17%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 293 (0.34%)	5 / 323 (1.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection pseudomonal			
subjects affected / exposed	1 / 293 (0.34%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	3 / 293 (1.02%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Viral infection			
subjects affected / exposed	0 / 293 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Darbepoetin alfa	Roxadustat	
Total subjects affected by non-serious adverse events subjects affected / exposed	203 / 293 (69.28%)	223 / 323 (69.04%)	
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	97 / 293 (33.11%) 149	93 / 323 (28.79%) 129	
Investigations Glomerular filtration rate decreased subjects affected / exposed occurrences (all)	28 / 293 (9.56%) 30	33 / 323 (10.22%) 35	
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	11 / 293 (3.75%) 15	16 / 323 (4.95%) 18	
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	12 / 293 (4.10%) 13	19 / 323 (5.88%) 20	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	13 / 293 (4.44%) 15 12 / 293 (4.10%) 12	16 / 323 (4.95%) 20 20 / 323 (6.19%) 23	
General disorders and administration site conditions Oedema peripheral subjects affected / exposed occurrences (all)	36 / 293 (12.29%) 52	48 / 323 (14.86%) 59	
Psychiatric disorders			

Insomnia			
subjects affected / exposed	8 / 293 (2.73%)	19 / 323 (5.88%)	
occurrences (all)	9	19	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	28 / 293 (9.56%)	27 / 323 (8.36%)	
occurrences (all)	36	38	
Constipation			
subjects affected / exposed	15 / 293 (5.12%)	21 / 323 (6.50%)	
occurrences (all)	18	23	
Nausea			
subjects affected / exposed	24 / 293 (8.19%)	35 / 323 (10.84%)	
occurrences (all)	26	40	
Vomiting			
subjects affected / exposed	19 / 293 (6.48%)	21 / 323 (6.50%)	
occurrences (all)	22	31	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	13 / 293 (4.44%)	20 / 323 (6.19%)	
occurrences (all)	13	27	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	14 / 293 (4.78%)	18 / 323 (5.57%)	
occurrences (all)	19	21	
Back pain			
subjects affected / exposed	16 / 293 (5.46%)	20 / 323 (6.19%)	
occurrences (all)	19	22	
Muscle spasms			
subjects affected / exposed	15 / 293 (5.12%)	25 / 323 (7.74%)	
occurrences (all)	20	33	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	39 / 293 (13.31%)	34 / 323 (10.53%)	
occurrences (all)	44	38	
Hyperphosphataemia			
subjects affected / exposed	15 / 293 (5.12%)	28 / 323 (8.67%)	
occurrences (all)	18	29	

Iron deficiency			
subjects affected / exposed	24 / 293 (8.19%)	20 / 323 (6.19%)	
occurrences (all)	33	24	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	24 / 293 (8.19%)	17 / 323 (5.26%)	
occurrences (all)	29	24	
Bronchitis			
subjects affected / exposed	17 / 293 (5.80%)	21 / 323 (6.50%)	
occurrences (all)	21	27	
Viral upper respiratory tract infection			
subjects affected / exposed	25 / 293 (8.53%)	29 / 323 (8.98%)	
occurrences (all)	30	33	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 May 2015	The changes included: a) Changes in the study dosing regimen as follows: 1. Dosing frequency changed from tiw, biw and qw to tiw only; 2. Initial study drug dose changed from 70, 100 and 150 mg to 70 and 100 mg only; 3. Maximum dose reduced from 3.5 mg/kg to 3.0 mg/kg and maximum absolute dose reduced from 400 mg to 300 mg. b) Reduction in the number of treatment groups changed the randomization ratio of roxadustat:darbepoetin from 2:1 to 1:1. c) Reduction in visit schedule by removal of 12 study visits, resulting in 39 visits.
31 March 2016	The changes included: 1.The number of Hb values assessed during the screening period was reduced from 3 to 2 and the mean Hb entry threshold was increased from ≤ 10.0 g/dL to ≤ 10.5 g/dL. 2.The iron criteria were updated to better reflect clinical practices, therefore inclusion criteria 6 (ferritin ≥ 100 ng/mL) and 7 (transferrin saturation level ≥ 20% at screening) were removed. 3. Exclusion criterion 21 was extended to exclude participants who were close to initiating renal replacement therapy including dialysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported