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

Summary

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

Results information

Result version number	v2 (current)
This version publication date	13 June 2021
First version publication date	18 July 2019
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	1517-CL-0613

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final

Date of interim/final analysis	06 July 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	06 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy:

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

Evidence for comparator: -

Actual start date of recruitment	21 November 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 31
Country: Number of subjects enrolled	Bulgaria: 156
Country: Number of subjects enrolled	Croatia: 59
Country: Number of subjects enrolled	Czechia: 16
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Georgia: 6
Country: Number of subjects enrolled	Germany: 35
Country: Number of subjects enrolled	Hungary: 136
Country: Number of subjects enrolled	Italy: 40
Country: Number of subjects enrolled	Poland: 29
Country: Number of subjects enrolled	Portugal: 17
Country: Number of subjects enrolled	Romania: 40
Country: Number of subjects enrolled	Russian Federation: 98
Country: Number of subjects enrolled	Serbia: 86

Country: Number of subjects enrolled	Slovakia: 32
Country: Number of subjects enrolled	Spain: 29
Country: Number of subjects enrolled	United Kingdom: 14
Worldwide total number of subjects	836
EEA total number of subjects	632

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	452
From 65 to 84 years	361
85 years and over	23

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Roxadustat

Arm description:

Participants received roxadustat three times a week (TIW) for at least 52 weeks up to a maximum of 104 weeks. Treatment dosage was adjusted according to the pre-specified rule of keeping the participant’s Hb levels between 10.0 to 12.0 g/dL. Dose adjustment steps were as follows: 20, 40, 50, 70, 100, 150, 200, 250, 300, and 400 mg. Oral iron treatment of 200 mg was allowed for supplementation to support erythropoiesis. Treatment with intravenous iron was allowed only if certain protocol criteria were met.

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

Dosage and administration details:

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

Arm title	ESA (Erythropoiesis-Stimulating Agent)

Arm description:

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

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

Dosage and administration details:	
Participants received epoetin alfa once a week, twice a week, or three times a week (TIW). Epoetin alfa dosage was adjusted to maintain Hb level within the target range. Dosing of epoetin alfa was per UK SmPC of Eprex®. Participants received IV iron supplementation according to the standard of care.	
Investigational medicinal product name	Darbepoetin alfa
Investigational medicinal product code	
Other name	Aranesp®
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intravenous use, Subcutaneous use
Dosage and administration details:	
Participants received darbepoetin alfa once a week or once every other week. Darbepoetin alfa dosage was adjusted to maintain Hb level within the target range. Dosing of darbepoetin alfa was per EU SmPC of Aranesp®. Participants received IV iron supplementation according to the standard of care.	

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

Baseline characteristics

Reporting groups	
Reporting group title	Roxadustat
Reporting group description:	
Participants received roxadustat three times a week (TIW) for at least 52 weeks up to a maximum of 104 weeks. Treatment dosage was adjusted according to the pre-specified rule of keeping the participant's Hb levels between 10.0 to 12.0 g/dL. Dose adjustment steps were as follows: 20, 40, 50, 70, 100, 150, 200, 250, 300, and 400 mg. Oral iron treatment of 200 mg was allowed for supplementation to support erythropoiesis. Treatment with intravenous iron was allowed only if certain protocol criteria were met.	
Reporting group title	ESA (Erythropoiesis-Stimulating Agent)
Reporting group description:	
Participants received epoetin alfa once weekly, twice weekly or TIW and darbepoetin alfa once a week or once every other week. Participants were treated for at least 52 weeks up to a maximum of 104 weeks. Treatment dosage was adjusted according to the pre-specified rule of keeping the participant's Hb levels between 10.0 to 12.0 g/dL. Participants were not allowed to switch from epoetin alfa to darbepoetin alfa or vice versa.	

Reporting group values	Roxadustat	ESA (Erythropoiesis-Stimulating Agent)	Total
Number of subjects	415	421	836
Age categorical			
Units: Subjects			
Age continuous			
The analysis population was the All randomized population, which consisted of participants who were randomized into the study.			
Units: years			
arithmetic mean	61	61.8	
standard deviation	± 13.8	± 13.4	-
Gender categorical			
The analysis population was the All randomized population, which consisted of participants who were randomized into the study.			
Units: Subjects			
Male	246	236	482
Female	169	185	354
Race			
The analysis population was the All randomized, which consisted of participants who were randomized into the study.			
Units: Subjects			
WHITE	405	408	813
BLACK OR AFRICAN AMERICAN	6	6	12
ASIAN	2	3	5
OTHER	2	4	6
Baseline Hemoglobin (Hb) Value			
The analysis population was the All randomized, which consisted of participants who were randomized into the study.			
Units: Subjects			
<=11.0 g/dL	267	266	533
>11.0 g/dL	148	155	303

Baseline Mean Hb			
Baseline Hb was defined as the mean of four latest central laboratory Hb values prior or on the same date as first study drug intake (pre-dose). The analysis population was the All randomized, which consisted of participants who were randomized into the study.			
Units: g/dL			
arithmetic mean	10.75	10.77	
standard deviation	± 0.62	± 0.62	-

End points

End points reporting groups

Reporting group title	Roxadustat

Reporting group description:

Participants received roxadustat three times a week (TIW) for at least 52 weeks up to a maximum of 104 weeks. Treatment dosage was adjusted according to the pre-specified rule of keeping the participant's Hb levels between 10.0 to 12.0 g/dL. Dose adjustment steps were as follows: 20, 40, 50, 70, 100, 150, 200, 250, 300, and 400 mg. Oral iron treatment of 200 mg was allowed for supplementation to support erythropoiesis. Treatment with intravenous iron was allowed only if certain protocol criteria were met.

Reporting group title	ESA (Erythropoiesis-Stimulating Agent)

Reporting group description:

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

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

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

End point description:

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

End point type	Primary

End point timeframe:

Baseline and weeks 28 to 36

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

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

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

Notes:

[1] - Non Inferiority, Margin = -0.75

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

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

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

End point description:

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

End point type	Primary

End point timeframe:

Baseline and weeks 28 to 52

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

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

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

Notes:

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

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

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Weeks 28 to 36

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

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

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

Notes:

[5] - Non-inferiority of roxadustat versus ESA (the non-inferiority margin for the difference between groups is -15%).
[6] - p-value for non-inferiority test based on 1-sided significance level

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Baseline and weeks 12 to 28

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The model includes treatment arm, region, CV History, previous ESA treatment, visits and visit by

treatment as categorical variables and baseline LDL, baseline Hb as continuous variables.

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

Notes:

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

Secondary: Mean Monthly Intravenous (IV) Iron Use

End point title	Mean Monthly Intravenous (IV) Iron Use

End point description:

Participants with no or missing medication records of IV Iron have their monthly IV Iron use set to 0 mg. For participants who took IV Iron, but without a dosing frequency, the average values were set to missing. The analysis population was the FAS, with participants who had available data.

End point type	Secondary

End point timeframe:

Day 1 to week 36

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

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

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	832
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [8]

Method	ANCOVA
Parameter estimate	LSM Difference
Point estimate	-31.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.4
upper limit	-22.4

Notes:

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

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Baseline and weeks 12 to 28

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

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

Comparison groups	ESA (Erythropoiesis-Stimulating Agent) v Roxadustat
Number of subjects included in analysis	767
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]

P-value	< 0.05 [10]
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.205
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.649
upper limit	1.059

Notes:

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

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

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Baseline and weeks 12 to 28

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

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

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	768
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	LSM Difference

Point estimate	0.856
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.115
upper limit	1.828

Notes:

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

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Baseline and weeks 20 to 28

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

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

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	761
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05 [12]
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-0.849
Confidence interval	
level	95 %
sides	2-sided

lower limit	-1.971
upper limit	0.273

Notes:

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

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

End point title	Time to First Occurrence of an Increase in Blood Pressure in PPS

End point description:

Increase in Blood Pressure was defined as either: Systolic Blood Pressure (SBP) ≥ 170 mmHg and an increase from BL ≥ 20 mmHg, or as: Diastolic Blood Pressure (DBP) ≥ 100 mmHg and an increase from BL ≥ 15 mmHg. For participants who have experienced more than one event, only their first event following study treatment was used. Data reported was analyzed by Kaplan-Meier estimate for cumulative proportion and the 95% confidence interval was calculated with Greenwood's formula. The analysis population was the PPS, with participants who had available data.

End point type	Secondary

End point timeframe:

Weeks 1 to 36

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

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

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	783
Analysis specification	Pre-specified
Analysis type	non-inferiority[13]
P-value	< 0.05 [14]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.924
Confidence interval	

level	95 %
sides	2-sided
lower limit	0.669
upper limit	1.276

Notes:

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

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

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Baseline and weeks 20 to 28

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

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

Comparison groups	ESA (Erythropoiesis-Stimulating Agent) v Roxadustat
Number of subjects included in analysis	782
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.308 [15]
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	-0.579
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.694
upper limit	0.536

Notes:

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

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

End point title	Time to First Occurrence of an Increase in Blood Pressure in FAS

End point description:

Increase in Blood Pressure was defined as either: SBP ≥ 170 mmHg and an increase from BL ≥ 20 mmHg, or as: DBP ≥ 100 mmHg and an increase from BL ≥ 15 mmHg. Data reported was analyzed by Kaplan-Meier estimate for cumulative proportion and the 95% confidence interval was calculated with Greenwood's formula. The analysis population was the FAS, with participants who had available data.

End point type	Secondary

End point timeframe:

Weeks 1 to 36

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Hazard Ratio was calculated using stratified Cox Proportional Hazards regression stratifying on region, CV history, previous ESA treatment, and adjusting on Hb at baseline as continuous covariate. Superiority was declared if the upper bound of the 95% CI is lower than 1.

Comparison groups	ESA (Erythropoiesis-Stimulating Agent) v Roxadustat
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.582 [16]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.915
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.668

upper limit	1.254

Notes:

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

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Weeks 28 to 36

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

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

Comparison groups	ESA (Erythropoiesis-Stimulating Agent) v Roxadustat
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.609 [17]
Method	Miettinen and Nurminen method
Parameter estimate	Difference of Percentages
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	6.5

Notes:

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

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

End point title	Change From BL in Hb to Each Postdosing Time Point

End point description:

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

End point type	Secondary

End point timeframe:

Baseline and weeks 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18,20, 22, 24, 26, 28, 30, 32, 34, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72,76, 80, 84, 88, 92, 96, 100, and 104

End point values	Roxadustat	ESA (Erythropoiesis-Stimulating Agent)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	420		
Units: g/dL				
least squares mean (confidence interval 95%)				
Hb Change From BL to Week 1 [N=407,411]	0.232 (0.164 to 0.300)	0.068 (0.000 to 0.135)		
Hb Change From BL to Week 2 [N=401,411]	0.496 (0.420 to 0.572)	0.054 (-0.022 to 0.129)		
Hb Change From BL to Week 3 [N=394,408]	0.633 (0.552 to 0.714)	0.071 (-0.008 to 0.151)		
Hb Change From BL to Week 4 [N=399,413]	0.803 (0.715 to 0.891)	0.095 (0.009 to 0.181)		
Hb Change From BL to Week 5 [N=399,407]	0.723 (0.633 to 0.812)	-0.045 (-0.133 to 0.043)		
Hb Change From BL to Week 6 [N=391,405]	0.868 (0.776 to 0.959)	0.138 (0.048 to 0.228)		
Hb Change From BL to Week 7 [N=389,404]	0.698 (0.606 to 0.791)	-0.031 (-0.122 to 0.060)		
Hb Change From BL to Week 8 [N=393,402]	0.816 (0.724 to 0.907)	0.116 (0.026 to 0.206)		
Hb Change From BL to Week 10 [N=396,409]	0.640 (0.546 to 0.734)	-0.019 (-0.111 to 0.073)		
Hb Change From BL to Week 12 [N=384,399]	0.732 (0.634 to 0.830)	0.139 (0.043 to 0.235)		
Hb Change From BL to Week 14 [N=383,400]	0.508 (0.409 to 0.608)	0.005 (-0.093 to 0.103)		
Hb Change From BL to Week 16 [N=381,401]	0.613 (0.511 to 0.716)	0.244 (0.144 to 0.344)		
Hb Change From BL to Week 18 [N=378,395]	0.380 (0.283 to 0.477)	0.017 (-0.078 to 0.112)		
Hb Change From BL to Week 20 [N=376,394]	0.501 (0.405 to 0.596)	0.217 (0.124 to 0.309)		
Hb Change From BL to Week 22 [N=370,395]	0.266 (0.170 to 0.363)	0.069 (-0.025 to 0.163)		
Hb Change From BL to Week 24 [N=362,387]	0.262 (0.168 to 0.356)	0.075 (-0.017 to 0.166)		
Hb Change From BL to Week 26 [N=359,387]	0.316 (0.220 to 0.412)	0.073 (-0.020 to 0.165)		

Hb Change From BL to Week 28 [N=360,388]	0.549 (0.452 to 0.647)	0.342 (0.248 to 0.437)		
Hb Change From BL to Week 30 [N=351,380]	0.333 (0.236 to 0.429)	0.106 (0.013 to 0.198)		
Hb Change From BL to Week 32 [N=345,376]	0.310 (0.211 to 0.409)	0.111 (0.016 to 0.207)		
Hb Change From BL to Week 34 [N=342,374]	0.364 (0.268 to 0.460)	0.084 (-0.007 to 0.176)		
Hb Change From BL to Week 36 [N=339,373]	0.482 (0.382 to 0.581)	0.225 (0.130 to 0.321)		
Hb Change From BL to Week 40 [N=336,373]	0.199 (0.095 to 0.304)	0.064 (-0.036 to 0.163)		
Hb Change From BL to Week 44 [N=328,367]	0.335 (0.221 to 0.448)	0.252 (0.145 to 0.360)		
Hb Change From BL to Week 48 [N=323,365]	0.158 (0.047 to 0.270)	0.131 (0.027 to 0.236)		
Hb Change From BL to Week 52 [N=308,363]	0.385 (0.273 to 0.496)	0.186 (0.082 to 0.290)		
Hb Change From BL to Week 56 [N=311,360]	0.217 (0.104 to 0.329)	0.069 (-0.035 to 0.174)		
Hb Change From BL to Week 60 [N=299,353]	0.368 (0.256 to 0.479)	0.171 (0.067 to 0.275)		
Hb Change From BL to Week 64 [N=289,344]	0.181 (0.067 to 0.295)	-0.093 (-0.198 to 0.012)		
Hb Change From BL to Week 68 [N=290,349]	0.306 (0.195 to 0.416)	0.100 (-0.002 to 0.202)		
Hb Change From BL to Week 72 [N=284,339]	0.109 (-0.005 to 0.222)	-0.009 (-0.113 to 0.095)		
Hb Change From BL to Week 76 [N=278,338]	0.401 (0.280 to 0.521)	0.189 (0.079 to 0.299)		
Hb Change From BL to Week 80 [N=274,327]	0.087 (-0.028 to 0.203)	-0.015 (-0.120 to 0.091)		
Hb Change From BL to Week 84 [N=270,328]	0.318 (0.199 to 0.438)	0.126 (0.017 to 0.235)		
Hb Change From BL to Week 88 [N=258,326]	0.026 (-0.091 to 0.144)	-0.018 (-0.124 to 0.088)		
Hb Change From BL to Week 92 [N=255,313]	0.357 (0.232 to 0.483)	0.154 (0.041 to 0.267)		
Hb Change From BL to Week 96 [N=253,312]	0.126 (0.010 to 0.242)	-0.058 (-0.163 to 0.046)		
Hb Change From BL to Week 100 [N=248,311]	0.302 (0.175 to 0.430)	0.138 (0.024 to 0.253)		
Hb Change From BL to Week 104 [N=240,299]	0.232 (0.100 to 0.363)	0.133 (0.014 to 0.251)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

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

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [18]
Method	Mixed models analysis

Parameter estimate	LSM Difference
Point estimate	0.164
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.072
upper limit	0.256

Notes:

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

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

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

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [19]
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.443
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.339
upper limit	0.546

Notes:

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

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Week 3 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.

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

Notes:

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

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

Notes:

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

Statistical analysis title	Statistical analysis 5
Statistical analysis description:	
Week 5 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.	
Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [22]
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.768
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.645
upper limit	0.89

Notes:

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

Statistical analysis title	Statistical analysis 6
Statistical analysis description:	
Week 6 - The model included treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline Hb as continuous covariates.	
Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [23]
Method	Mixed models analysis
Parameter estimate	LSM Difference

Point estimate	0.729
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.604
upper limit	0.855

Notes:

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

Statistical analysis title	Statistical analysis 7

Statistical analysis description:

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

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [24]
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.729
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.603
upper limit	0.856

Notes:

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

Statistical analysis title	Statistical analysis 8

Statistical analysis description:

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

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

Notes:

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

Statistical analysis title	Statistical analysis 9

Statistical analysis description:

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

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

Notes:

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

Statistical analysis title	Statistical analysis 10

Statistical analysis description:

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

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [27]
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.593
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.459
upper limit	0.727

Notes:

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

Statistical analysis title	Statistical analysis 11

Statistical analysis description:

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

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

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

Notes:

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

Statistical analysis title	Statistical analysis 12

Statistical analysis description:

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

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [29]
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.369
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.229
upper limit	0.51

Notes:

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

Statistical analysis title	Statistical analysis 13

Statistical analysis description:

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

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

Notes:

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

Statistical analysis title	Statistical analysis 14

Statistical analysis description:

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

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

Notes:

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

Statistical analysis title	Statistical analysis 15

Statistical analysis description:

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

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [32]
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.197
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.065
upper limit	0.329

Notes:

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

Statistical analysis title	Statistical analysis 16

Statistical analysis description:

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

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

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

Notes:

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

Statistical analysis title	Statistical analysis 17

Statistical analysis description:

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

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [34]
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.243
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.113
upper limit	0.373

Notes:

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

Statistical analysis title	Statistical analysis 18

Statistical analysis description:

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

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

Notes:

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

Statistical analysis title	Statistical analysis 19

Statistical analysis description:

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

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

Notes:

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

Statistical analysis title	Statistical analysis 20

Statistical analysis description:

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

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [37]
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.199
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.064
upper limit	0.334

Notes:

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

Statistical analysis title	Statistical analysis 21

Statistical analysis description:

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

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [38]
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.279
Confidence interval	
level	95 %
sides	2-sided

lower limit	0.15
upper limit	0.409

Notes:

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

Statistical analysis title	Statistical analysis 22

Statistical analysis description:

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

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [39]
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.256
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.121
upper limit	0.391

Notes:

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

Statistical analysis title	Statistical analysis 23

Statistical analysis description:

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

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

Notes:

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

Statistical analysis title	Statistical analysis 24

Statistical analysis description:

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

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	833

Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.293 [41]
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.082
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.071
upper limit	0.236

Notes:

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

Statistical analysis title	Statistical analysis 25

Statistical analysis description:

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

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.723 [42]
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.027
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.123
upper limit	0.177

Notes:

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

Statistical analysis title	Statistical analysis 26

Statistical analysis description:

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

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009 [43]
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.199
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.049
upper limit	0.348

Notes:

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

Statistical analysis title	Statistical analysis 27

Statistical analysis description:

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

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.056 [44]
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.147
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.004
upper limit	0.298

Notes:

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

Statistical analysis title	Statistical analysis 28

Statistical analysis description:

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

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

Notes:

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

Statistical analysis title	Statistical analysis 29

Statistical analysis description:

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

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority

P-value	< 0.001 [46]
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.275
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.122
upper limit	0.427

Notes:

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

Statistical analysis title	Statistical analysis 30

Statistical analysis description:

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

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006 [47]
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.206
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.059
upper limit	0.353

Notes:

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

Statistical analysis title	Statistical analysis 31

Statistical analysis description:

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

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.127 [48]
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.118
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.033
upper limit	0.269

Notes:

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

Statistical analysis title	Statistical analysis 32

Statistical analysis description:

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

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01 [49]
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.211
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.051
upper limit	0.371

Notes:

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

Statistical analysis title	Statistical analysis 33

Statistical analysis description:

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

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

Notes:

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

Statistical analysis title	Statistical analysis 34

Statistical analysis description:

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

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority

P-value	= 0.018 [51]
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.192
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.033
upper limit	0.351

Notes:

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

Statistical analysis title	Statistical analysis 35

Statistical analysis description:

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

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.576 [52]
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.044
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.111
upper limit	0.2

Notes:

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

Statistical analysis title	Statistical analysis 36

Statistical analysis description:

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

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017 [53]
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.203
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.037
upper limit	0.369

Notes:

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

Statistical analysis title	Statistical analysis 37

Statistical analysis description:

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

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019 [54]
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.184
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.031
upper limit	0.338

Notes:

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

Statistical analysis title	Statistical analysis 38

Statistical analysis description:

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

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

Notes:

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

Statistical analysis title	Statistical analysis 39

Statistical analysis description:

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

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority

P-value	= 0.267 [56]
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.099
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.076
upper limit	0.273

Notes:

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

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Weeks 28-36 - The model includes treatment arm, region, CV History, previous ESA treatment, visits and visit by treatment as categorical variables and baseline Hb as continuous variable.

Comparison groups	ESA (Erythropoiesis-Stimulating Agent) v Roxadustat

Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [57]
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.237
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.127
upper limit	0.347

Notes:

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

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Weeks 44-52 - The model includes treatment arm, region, CV History, previous ESA treatment, visits and visit by treatment as categorical variables and baseline Hb as continuous variable.

Comparison groups	ESA (Erythropoiesis-Stimulating Agent) v Roxadustat
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.086 [58]
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.105
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.015
upper limit	0.225

Notes:

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

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

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

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

upper limit	0.284

Notes:

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

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Weeks 28-36 - The model includes treatment arm, region, CV History, previous ESA treatment, visits and visit by treatment as categorical variables and baseline Hb as continuous variable.

Comparison groups	ESA (Erythropoiesis-Stimulating Agent) v Roxadustat
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.235
Confidence interval	
level	95 %
sides	2-sided

lower limit	0.125
upper limit	0.346

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
Weeks 44-52 - The model includes treatment arm, region, CV History, previous ESA treatment, visits and visit by treatment as categorical variables and baseline Hb as continuous variable.	
Comparison groups	ESA (Erythropoiesis-Stimulating Agent) v Roxadustat
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.104
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.024
upper limit	0.232

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
Weeks 96-104 - The model includes treatment arm, region, CV History, previous ESA treatment, visits and visit by treatment as categorical variables and baseline Hb as continuous variable.	
Comparison groups	ESA (Erythropoiesis-Stimulating Agent) v Roxadustat
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.036
Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.149
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.288

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

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

End point description:

Percentage for each participant was calculated as Number of Hb values >= 10.0 g/dL / Total number of

Hb values*100 in weeks 28 to 36, 44 to 52 and 96 to 104 without use of rescue therapy within 6 weeks prior to and during the 8 week evaluation period. The analysis population was the FAS, with participants who had available data. N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

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

End point values	Roxadustat	ESA (Erythropoiesis-Stimulating Agent)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	420		
Units: percentage of Hb values				
arithmetic mean (standard deviation)				
Weeks 28-36 [N=364,393]	93.002 (± 18.320)	87.286 (± 25.114)		
Weeks 44-52[N=331,371]	89.421 (± 24.267)	86.914 (± 25.366)		
Weeks 96-104[N=254,318]	88.858 (± 24.708)	83.543 (± 30.296)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

Weeks 28-36 [N=364, 393]	76.326 (± 28.175)	76.098 (± 28.991)		
Weeks 44-52 [N=331, 371]	75.891 (± 31.047)	74.634 (± 30.589)		
Weeks 96-104 [N=254, 318]	76.522 (± 30.378)	73.690 (± 33.040)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Hospitalizations

End point title	Number of Hospitalizations

End point description:

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

End point type	Secondary

End point timeframe:

Baseline to End of Treatment (EOT) (Up to week 104)

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

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Days of Hospitalization per Year

End point title	Number of Days of Hospitalization per Year

End point description:

The number of days of hospitalizations per year was calculated as the sum of the durations of all non-HD hospitalizations in days (Date of discharge – Date of admission + 1)] / (duration of efficacy emergent period in days / 365.25). In case of missing dates, the hospitalization duration was imputed by the average duration per stay derived from the participants with non-missing duration within the same treatment group. The analysis population was the FAS, with participants who had available data.

End point type	Secondary

End point timeframe:

Baseline to EOT (Up to week 104)

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

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Hospitalization

End point title	Time to First Hospitalization

End point description:

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

End point type	Secondary

End point timeframe:

Baseline to EOT (Up to week 104)

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Hazard Ratio was calculated using stratified Cox Proportional Hazards regression stratifying on region, CV history, previous ESA treatment and adjusting on Hb at baseline as continuous covariate. Superiority was declared if the upper bound of the 95% CI was below 1.0.

Comparison groups	ESA (Erythropoiesis-Stimulating Agent) v Roxadustat
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.164 [60]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.154
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.943
upper limit	1.411

Notes:

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

Secondary: Time to First Use of Rescue Therapy

End point title	Time to First Use of Rescue Therapy

End point description:

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

End point type	Secondary

End point timeframe:

Baseline to EOT (Up to week 104)

End point values	Roxadustat	ESA (Erythropoiesis-Stimulating Agent)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	420		
Units: Percentage of participants				
number (confidence interval 95%)				

Year 0.5	3.9 (2.0 to 5.8)	3.2 (1.5 to 4.8)		
Year 1	8.2 (5.4 to 11.1)	8.4 (5.6 to 11.1)		
Year 1.5	11.4 (8.1 to 14.8)	10.9 (7.8 to 14.0)		
Year 2	12.8 (9.3 to 16.4)	14.4 (10.8 to 18.0)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Hazard Ratio was calculated using stratified Cox Proportional Hazards regression stratifying on region, CV history, previous ESA treatment and adjusting on Hb at baseline as continuous covariate. Superiority was declared if the upper bound of the 95% CI was below 1.0.

Comparison groups	ESA (Erythropoiesis-Stimulating Agent) v Roxadustat
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.917
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.979
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.656
upper limit	1.462

Secondary: Time to First RBC Transfusion

End point title	Time to First RBC Transfusion

End point description:

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

End point type	Secondary

End point timeframe:

Baseline to EOT (Up to week 104)

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Hazard Ratio was calculated using stratified Cox Proportional Hazards regression stratifying on region, CV history, previous ESA treatment, and adjusting on Hb at baseline as continuous covariate. Superiority was declared if the upper bound of the 95% CI was below 1.0.

Comparison groups	ESA (Erythropoiesis-Stimulating Agent) v Roxadustat
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.501 [61]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.867
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.573
upper limit	1.313

Notes:

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

Secondary: Mean Monthly Number of RBC Packs Per Participant

End point title	Mean Monthly Number of RBC Packs Per Participant

End point description:

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

End point type	Secondary

End point timeframe:

Baseline to EOT (Up to week 104)

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The model included treatment arm, region, CV History, previous ESA treatment as categorical variables and baseline Hb as continuous variable.

Comparison groups	ESA (Erythropoiesis-Stimulating Agent) v Roxadustat
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.507 [62]
Method	ANCOVA
Parameter estimate	LSM Difference
Point estimate	-0.006
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.01

Notes:

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

Secondary: Mean Monthly Volume of RBC Transfusion Per Participant

End point title	Mean Monthly Volume of RBC Transfusion Per Participant

End point description:

During Efficacy Emergent Period, the mean monthly volume of blood transfused are calculated as the sum of blood volume and units transfused between the first dose and up to the last dose in the period divided by duration of efficacy emergent period (in days) divided by 28 days. The Efficacy Emergent Period was defined as the evaluation period from the Analysis date of first dose intake up to EOT Visit or last non-missing Hb assessment (for participants who died during the treatment period). The analysis population was the FAS.

End point type	Secondary

End point timeframe:

Baseline to EOT (Up to week 104)

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

Statistical analyses

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

Secondary: Time to First Use of IV Iron Supplementation

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

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Hazard Ratio was calculated using stratified Cox Proportional Hazards regression stratifying on region, CV history, previous ESA treatment and adjusting on Hb at baseline as continuous covariate. Superiority was declared if the upper bound of the 95% CI was below 1.0.

Comparison groups	ESA (Erythropoiesis-Stimulating Agent) v Roxadustat
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.368
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.291
upper limit	0.465

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

End point title	Mean Monthly Intravenous (IV) Iron per Participant During Weeks 37-52 and Weeks 53-104

End point description:

Participants with no or missing medication records of IV Iron had their monthly IV Iron use set to 0 mg. The analysis population was the FAS.

End point type	Secondary

End point timeframe:

Weeks 37-52 and weeks 53-104

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Weeks 37-52 - Participants with no or missing medication records of IV Iron had their monthly IV Iron use set to 0 mg. The model includes treatment arm, region, CV History, previous ESA treatment as categorical variables and baseline Hb as continuous variable.

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LSM Difference
Point estimate	-35.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.8
upper limit	-18.4

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Weeks 53-104 - Participants with no or missing medication records of IV Iron had their monthly IV Iron use set to 0 mg. The model includes treatment arm, region, CV History, previous ESA treatment as categorical variables and baseline Hb as continuous variable.

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LSM Difference
Point estimate	-48.7
Confidence interval	
level	95 %

sides	2-sided
lower limit	-70.3
upper limit	-27

Secondary: Percentage of Participants with Oral Iron Use Only

End point title	Percentage of Participants with Oral Iron Use Only

End point description:

Percentage of participants with/without IV iron was calculated based on total number of participants within the efficacy emergent period. The Efficacy Emergent Period is defined as the evaluation period from the Analysis date of first dose intake up to EOT Visit or last non-missing Hb assessment (for participants who died during the treatment period).The analysis population was the FAS.

End point type	Secondary

End point timeframe:

Baseline to EOT (Up to week 104)

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

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From BL to Each Post-dosing Study Visit in Total Cholesterol

End point description:

Baseline assessment was the assessment from Day 1 visit. If baseline value was missing, then the latest screening period value was used as the baseline regardless of fasting status. The analysis population was the FAS, with participants who had available data at all time points. N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and week 8, 28, 52, 104

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Baseline and week 8, 28, 52, 104

End point values	Roxadustat	ESA (Erythropoiesis-Stimulating Agent)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	420		
Units: Ratio				
arithmetic mean (standard deviation)				
Change from BL to Week 8 [N=390,411]	-0.245 (± 0.818)	-0.060 (± 0.726)		
Change from BL to Week 28 [N=362,393]	-0.155 (± 1.046)	-0.057 (± 0.922)		
Change from BL to Week 52 [N=317,361]	-0.345 (± 0.904)	-0.078 (± 0.886)		
Change from BL to Week 104 [N=246,307]	-0.261 (± 1.167)	-0.013 (± 1.048)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Baseline and week 8, 28, 52, 104

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point type	Secondary

End point timeframe:

Baseline and week 8, 28, 52, 104

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Baseline and week 8, 28, 52, 104

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Baseline and week 8, 28, 52, 104

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Weeks 12 to 28

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Weeks 12 to 28

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

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

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From BL to the Average of Weeks 12 to 28 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. SF-36 contains 36-item that measures 8 scales with scores ranging from 0-100: physical functioning (PF); role limitations due to physical health problems (RP); bodily pain (BP); social functioning (SF); general health perceptions (GH); role limitations due to emotional problems (RE); vitality, energy or fatigue (VT); and mental health (MH). These scores are normed to the US population (norm-based scoring had very little impact on results when data was collected in Western European countries) to have a mean of 50 and standard deviation of 10. The PCS was calculated based on all 8 scales and ranges from 5.02-79.78. For each of these above scales, higher scores always indicating better health status. The analysis population was the FAS, with participants who had available data at all time point.

End point type	Secondary

End point timeframe:

Baseline and weeks 12 to 28

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

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

Comparison groups	ESA (Erythropoiesis-Stimulating Agent) v Roxadustat
Number of subjects included in analysis	788
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.161 [63]

Method	Mixed models analysis
Parameter estimate	LSM Difference
Point estimate	0.521
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.208
upper limit	1.25

Notes:

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

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Baseline and weeks 12 to 28

End point values	Roxadustat	ESA (Erythropoiesis-Stimulating Agent)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	384	403		
Units: Units on a scale				
least squares mean (confidence interval 95%)	0.400 (-0.624 to 1.424)	0.274 (-0.709 to 1.257)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The model includes treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline FACT-An Ans, baseline Hb, as continuous covariates.

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	787
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.845
Method	Mixed models analysis

Parameter estimate	LSM Difference
Point estimate	0.126
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.135
upper limit	1.387

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

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

End point description:

Baseline 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 (PWB) - 7 items, functional (FWB) - 7 items, social/family (SWB) - 7 items, and emotional (EWB) - 6 items. The AnS scale contains 13 fatigue specific items (the Fatigue Score) plus 7 items related to anemia. The total score is obtained by summation of the scores from PWB, SWB, EWB, FWB and AnS. The FACT-An Total Score scale range is 0-188. A higher score indicates better QoL. The analysis population was the FAS, with participants who had available data at all time points.

End point type	Secondary

End point timeframe:

Baseline and weeks 12 to 28

End point values	Roxadustat	ESA (Erythropoiesis-Stimulating Agent)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	383	403		
Units: Units on a scale				
least squares mean (confidence interval 95%)	-0.501 (-2.581 to 1.580)	-0.373 (-2.367 to 1.622)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The model includes treatment, visit, visit by treatment interaction, Previous ESA Treatment, region and history of CV disease as fixed class factors and baseline FACT-An Ans, baseline Hb, as continuous covariates.

Comparison groups	Roxadustat v ESA (Erythropoiesis-Stimulating Agent)
Number of subjects included in analysis	786
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.922
Method	Mixed models analysis
Parameter estimate	LSM Difference

Point estimate	-0.128
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.703
upper limit	2.447

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Baseline and weeks 12 to 28

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

time points.

End point type	Secondary

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Change From BL in Serum Hepcidin

End point title	Change From BL in Serum Hepcidin

End point description:

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

End point type	Secondary

End point timeframe:

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

End point values	Roxadustat	ESA (Erythropoiesis-Stimulating Agent)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	420		
Units: µg/L				
arithmetic mean (standard deviation)				
Week 4 [N=387,400]	-14.265 (± 42.393)	-4.265 (± 33.518)		

Week 12 [N=375,391]	-12.298 (± 41.335)	-6.741 (± 38.507)		
Week 20 [N=361,382]	-15.149 (± 43.152)	-11.818 (± 41.596)		
Week 36 [N=332,366]	-23.405 (± 43.033)	-14.530 (± 43.449)		
Week 52 [N=310,357]	-32.709 (± 42.342)	-17.522 (± 47.307)		
Week 104 [N=242,298]	-40.101 (± 48.611)	-18.735 (± 51.632)		
EOS (up to 108 weeks) [N=280,320]	-27.192 (± 52.169)	-17.664 (± 51.688)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From BL in Serum Ferritin

End point title	Change From BL in Serum Ferritin

End point description:

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

End point type	Secondary

End point timeframe:

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

End point values	Roxadustat	ESA (Erythropoiesis-Stimulating Agent)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	420		
Units: pmol/L				
arithmetic mean (standard deviation)				
Week 4 [N=400,408]	-214.64 (± 824.96)	-141.78 (± 456.15)		
Week 8 [N=394,405]	-245.37 (± 668.51)	-160.75 (± 607.39)		
Week 12 [N=389,404]	-269.76 (± 761.24)	-179.47 (± 586.95)		
Week 20 [N=379,396]	-337.94 (± 645.73)	-246.89 (± 727.64)		
Week 28 [N=363,392]	-427.46 (± 699.95)	-265.21 (± 816.64)		
Week 36 [N=343,379]	-507.34 (± 726.61)	-269.26 (± 855.01)		
Week 44 [N=328,371]	-545.14 (± 668.02)	-323.30 (± 986.38)		
Week 52 [N=318,365]	-615.19 (± 677.97)	-347.58 (± 1058.87)		

Week 60 [N=304,359]	-622.55 (± 675.22)	-394.40 (± 837.81)		
Week 68 [N=293,349]	-604.47 (± 773.19)	-456.16 (± 1039.18)		
Week 76 [N=283,339]	-646.76 (± 838.76)	-447.70 (± 967.63)		
Week 84 [N=274,333]	-629.31 (± 1060.24)	-454.44 (± 1193.43)		
Week 92 [N=258,326]	-749.58 (± 828.32)	-371.64 (± 1157.18)		
Week 100 [N=250,313]	-746.86 (± 796.74)	-364.78 (± 1802.37)		
Week 104 [N=248,308]	-753.82 (± 791.12)	-348.70 (± 1292.49)		
EOS (up to 108 weeks) [N=290,323]	-554.53 (± 910.01)	-166.94 (± 2035.26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From BL in Transferrin Saturation (TSAT)

End point title	Change From BL in Transferrin Saturation (TSAT)

End point description:

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

End point type	Secondary

End point timeframe:

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

End point values	Roxadustat	ESA (Erythropoiesis-Stimulating Agent)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	412	420		
Units: Percentage of saturation				
arithmetic mean (standard deviation)				
Week 4 [N=392,402]	-4.151 (± 16.147)	-2.331 (± 13.178)		
Week 8 [N=383,399]	-3.681 (± 17.062)	-3.128 (± 14.461)		
Week 12 [N=381,397]	-2.643 (± 17.551)	-3.189 (± 13.912)		
Week 20 [N=363,387]	-3.782 (± 16.634)	-4.398 (± 14.444)		
Week 28 [N=356,385]	-5.463 (± 17.798)	-3.829 (± 15.216)		
Week 36 [N=336,372]	-5.351 (± 17.803)	-4.022 (± 15.471)		

Week 44 [N=320,358]	-6.069 (± 16.349)	-5.254 (± 15.144)		
Week 52 [N=313,353]	-7.278 (± 17.244)	-5.788 (± 14.666)		
Week 60 [N=295,348]	-6.997 (± 16.774)	-5.187 (± 16.097)		
Week 68 [N=287,338]	-7.279 (± 17.809)	-6.237 (± 15.934)		
Week 76 [N=275,332]	-7.156 (± 17.682)	-6.623 (± 16.395)		
Week 84 [N=270,331]	-7.867 (± 17.654)	-5.378 (± 17.771)		
Week 92 [N=251,320]	-6.996 (± 19.850)	-6.259 (± 16.605)		
Week 100 [N=248,308]	-8.379 (± 17.809)	-6.354 (± 17.147)		
Week 104 [N=243,299]	-7.650 (± 17.842)	-5.054 (± 17.195)		
EOS (up to 108 weeks) [N=283,321]	-5.466 (± 16.626)	-3.763 (± 17.813)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From BL in Glycated Hemoglobin (HbA1c) Level to Weeks 12, 28, 36, 44, 52, 60, 84, 104 and EOS (up to Week 108)

End point title	Change From BL in Glycated Hemoglobin (HbA1c) Level to Weeks 12, 28, 36, 44, 52, 60, 84, 104 and EOS (up to Week 108)

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

End point type	Secondary

End point timeframe:

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

End point values	Roxadustat	ESA (Erythropoiesis -Stimulating Agent)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	419		
Units: percentage of Glycated Hemoglobin				
arithmetic mean (standard deviation)				
Week 12 [N=385,401]	0.0009 (± 0.0071)	-0.0005 (± 0.0057)		
Week 28 [N=360,389]	-0.0004 (± 0.0067)	-0.0006 (± 0.0064)		

Week 36 [N=342,378]	-0.0001 (± 0.0065)	-0.0004 (± 0.0067)		
Week 44 [N=327,370]	-0.0001 (± 0.0069)	-0.0006 (± 0.0067)		
Week 52 [N=317,363]	-0.0001 (± 0.0070)	-0.0007 (± 0.0068)		
Week 60 [N=303,355]	0.0000 (± 0.0080)	-0.0004 (± 0.0070)		
Week 84 [N=269,331]	0.0003 (± 0.0072)	0.0001 (± 0.0078)		
Week 104 [N=242,305]	0.0000 (± 0.0075)	-0.0003 (± 0.0082)		
EOS (up to 108 weeks) [N=286,319]	0.0011 (± 0.0076)	0.0001 (± 0.0080)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Baseline up to EOS (Up to week 108)

End point values	Roxadustat	ESA (Erythropoiesis-Stimulating Agent)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	414	420		
Units: Participants				
TEAE	359	361		
Drug-Related TEAE	77	35		
Serious TEAE	210	189		
Drug-Related Serious TEAE	33	10		
TEAE Leading to Death	67	55		
Drug-Related TEAE Leading to Death	5	2		
TEAE Leading to Withdrawal of Treatment	35	16		

Drug-Related TEAE Leading to Withdraw of Treatment	9	1		
TEAE NCI CTC Grades 3 or Higher	181	149		
Death During the Safety Emergent Period	64	51		
Death	78	59		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Roxadustat

Reporting group description:

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

Reporting group title	ESA (Erythropoiesis-Stimulating Agent)

Reporting group description:

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

Serious adverse events	Roxadustat	ESA (Erythropoiesis-Stimulating Agent)	
Total subjects affected by serious adverse events			
subjects affected / exposed	210 / 414 (50.72%)	189 / 420 (45.00%)	
number of deaths (all causes)	78	59	
number of deaths resulting from adverse events	67	55	
Vascular disorders			
Aortic dissection			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial disorder			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	4 / 414 (0.97%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic vascular disorder			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dry gangrene			
subjects affected / exposed	1 / 414 (0.24%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 414 (0.00%)	3 / 420 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	10 / 414 (2.42%)	5 / 420 (1.19%)	
occurrences causally related to treatment / all	3 / 10	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	3 / 414 (0.72%)	3 / 420 (0.71%)	
occurrences causally related to treatment / all	0 / 4	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypotension			
subjects affected / exposed	4 / 414 (0.97%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Intermittent claudication			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant hypertension			
subjects affected / exposed	1 / 414 (0.24%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 414 (0.24%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	2 / 414 (0.48%)	4 / 420 (0.95%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peripheral artery occlusion			
subjects affected / exposed	0 / 414 (0.00%)	3 / 420 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	2 / 414 (0.48%)	0 / 420 (0.00%)	

occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	2 / 414 (0.48%)	4 / 420 (0.95%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Steal syndrome			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian artery thrombosis			
subjects affected / exposed	1 / 414 (0.24%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 414 (0.24%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis necrotising			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Venous stenosis			
subjects affected / exposed	1 / 414 (0.24%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	

deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Catheter placement			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Therapy cessation			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma gastric			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	2 / 414 (0.48%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign lung neoplasm			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign renal neoplasm			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to	0 / 0	0 / 1	

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carcinoid tumour pulmonary			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon adenoma			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 414 (0.24%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal adenocarcinoma			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer metastatic			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Haemangioma of bone			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypopharyngeal neoplasm			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney angiomyolipoma			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	3 / 414 (0.72%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Malignant neoplasm of choroid			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metastases to liver			
subjects affected / exposed	2 / 414 (0.48%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic neoplasm			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian neoplasm			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parathyroid tumour benign			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Penile cancer			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	2 / 414 (0.48%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Refractory anaemia with an excess of blasts			

subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin cancer			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anti-neutrophil cytoplasmic antibody positive vasculitis			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal transplant failure			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

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

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 414 (0.24%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device site phlebitis			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 414 (0.00%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 414 (0.97%)	4 / 420 (0.95%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	

deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	1 / 414 (0.24%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Sudden death			
subjects affected / exposed	7 / 414 (1.69%)	3 / 420 (0.71%)	
occurrences causally related to treatment / all	1 / 7	0 / 3	
deaths causally related to treatment / all	1 / 7	0 / 3	
Vascular stent stenosis			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 414 (0.00%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fear of falling			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder due to a general medical condition			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organic brain syndrome			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian disorder			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine polyp			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula aneurysm			
subjects affected / exposed	0 / 414 (0.00%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula occlusion			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site complication			
subjects affected / exposed	6 / 414 (1.45%)	5 / 420 (1.19%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	2 / 414 (0.48%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula thrombosis			
subjects affected / exposed	29 / 414 (7.00%)	15 / 420 (3.57%)	
occurrences causally related to treatment / all	6 / 37	4 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous graft site haemorrhage			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous graft site stenosis			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous graft thrombosis			
subjects affected / exposed	1 / 414 (0.24%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	1 / 1	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back injury			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Comminuted fracture			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	

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

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

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

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

deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 414 (0.24%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access malfunction			
subjects affected / exposed	2 / 414 (0.48%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site haemorrhage			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood potassium increased			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram abnormal			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	3 / 414 (0.72%)	3 / 420 (0.71%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 3	0 / 1	
Acute left ventricular failure			
subjects affected / exposed	2 / 414 (0.48%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	9 / 414 (2.17%)	11 / 420 (2.62%)	
occurrences causally related to treatment / all	0 / 9	1 / 13	
deaths causally related to treatment / all	0 / 4	1 / 6	
Angina pectoris			
subjects affected / exposed	5 / 414 (1.21%)	6 / 420 (1.43%)	
occurrences causally related to treatment / all	1 / 5	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 414 (0.00%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	2 / 414 (0.48%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 1	
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 414 (0.24%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	12 / 414 (2.90%)	8 / 420 (1.90%)	
occurrences causally related to treatment / all	1 / 14	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 414 (0.24%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	0 / 414 (0.00%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac arrest			
subjects affected / exposed	4 / 414 (0.97%)	8 / 420 (1.90%)	
occurrences causally related to treatment / all	0 / 4	0 / 9	
deaths causally related to treatment / all	0 / 2	0 / 6	
Cardiac failure			
subjects affected / exposed	8 / 414 (1.93%)	9 / 420 (2.14%)	
occurrences causally related to treatment / all	0 / 8	0 / 9	
deaths causally related to treatment / all	0 / 5	0 / 3	
Cardiac failure acute			
subjects affected / exposed	3 / 414 (0.72%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 414 (0.24%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	5 / 414 (1.21%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac fibrillation			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 414 (0.24%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	1 / 1	0 / 1	
Cardiogenic shock			
subjects affected / exposed	2 / 414 (0.48%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiopulmonary failure			
subjects affected / exposed	3 / 414 (0.72%)	1 / 420 (0.24%)	

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

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

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

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

occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary alveolar haemorrhage			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	4 / 414 (0.97%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	1 / 3	0 / 1	
Pulmonary hypertension			
subjects affected / exposed	2 / 414 (0.48%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary infarction			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary oedema			
subjects affected / exposed	6 / 414 (1.45%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	1 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory arrest			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	2 / 414 (0.48%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 414 (1.21%)	7 / 420 (1.67%)	
occurrences causally related to	1 / 5	0 / 8	

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

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

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

occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	2 / 414 (0.48%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 414 (0.00%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 414 (0.00%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular dementia			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo CNS origin			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Angle closure glaucoma			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to	0 / 0	0 / 1	

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye haemorrhage			
subjects affected / exposed	1 / 414 (0.24%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall haematoma			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute abdomen			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal incontinence			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic gastritis			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Constipation			
subjects affected / exposed	1 / 414 (0.24%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 414 (0.48%)	3 / 420 (0.71%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	

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

Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 414 (0.00%)	6 / 420 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal ischaemia			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal necrosis			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 414 (0.24%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Intestinal obstruction			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ulcer perforation			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haematoma			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal haemorrhage			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 414 (0.24%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 414 (0.48%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 414 (0.00%)	3 / 420 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	

deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcerative gastritis			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 414 (0.48%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 414 (0.24%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
End stage renal disease			
subjects affected / exposed	0 / 414 (0.00%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haematuria			
subjects affected / exposed	1 / 414 (0.24%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 414 (0.00%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	

deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst ruptured			
subjects affected / exposed	1 / 414 (0.24%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral perforation			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinoma			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 414 (0.24%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 414 (0.24%)	3 / 420 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Cutaneous vasculitis			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot			
subjects affected / exposed	0 / 414 (0.00%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ingrowing nail			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Neurodermatitis			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash vesicular			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin lesion			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin necrosis			
subjects affected / exposed	1 / 414 (0.24%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic epidermal necrolysis			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urticaria			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Device failure			
subjects affected / exposed	2 / 414 (0.48%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	4 / 414 (0.97%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula discharge			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint contracture			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mobility decreased			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteitis			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	

deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	2 / 414 (0.48%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 414 (0.24%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sarcopenia			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperparathyroidism secondary			
subjects affected / exposed	3 / 414 (0.72%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic goitre			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 414 (0.24%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	

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

Hypervolaemia			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abdominal infection			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess neck			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute hepatitis B			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	2 / 414 (0.48%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site infection			

subjects affected / exposed	3 / 414 (0.72%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	2 / 414 (0.48%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary sepsis			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	5 / 414 (1.21%)	3 / 420 (0.71%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 414 (0.48%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis infective			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	2 / 414 (0.48%)	3 / 420 (0.71%)	

occurrences causally related to treatment / all	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Device related sepsis		
subjects affected / exposed	3 / 414 (0.72%)	3 / 420 (0.71%)
occurrences causally related to treatment / all	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0
Diabetic gangrene		
subjects affected / exposed	2 / 414 (0.48%)	0 / 420 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Diverticulitis		
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Encephalomyelitis		
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Endocarditis		
subjects affected / exposed	2 / 414 (0.48%)	0 / 420 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Enterobacter bacteraemia		
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Enterococcal sepsis		
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Erysipelas		
subjects affected / exposed	1 / 414 (0.24%)	3 / 420 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 3

deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 414 (0.24%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal oesophagitis			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	5 / 414 (1.21%)	4 / 420 (0.95%)	
occurrences causally related to treatment / all	0 / 6	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer helicobacter			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 414 (0.00%)	6 / 420 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal candidiasis			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			
subjects affected / exposed	0 / 414 (0.00%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Incision site infection			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious colitis			
subjects affected / exposed	0 / 414 (0.00%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	2 / 414 (0.48%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 414 (0.00%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 414 (0.48%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device site joint infection			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis bacterial			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis bacterial			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Penile abscess			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periodontitis			
subjects affected / exposed	0 / 414 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	10 / 414 (2.42%)	3 / 420 (0.71%)	
occurrences causally related to treatment / all	0 / 15	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peritonitis bacterial			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	15 / 414 (3.62%)	21 / 420 (5.00%)	
occurrences causally related to treatment / all	0 / 15	0 / 22	
deaths causally related to treatment / all	0 / 2	0 / 6	
Pneumonia pneumococcal			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 414 (0.24%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyelonephritis chronic			
subjects affected / exposed	2 / 414 (0.48%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyonephrosis			
subjects affected / exposed	1 / 414 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

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

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

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

Non-serious adverse events	Roxadustat	ESA (Erythropoiesis-Stimulating Agent)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	210 / 414 (50.72%)	209 / 420 (49.76%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	66 / 414 (15.94%)	75 / 420 (17.86%)	
occurrences (all)	101	116	
Hypotension			
subjects affected / exposed	30 / 414 (7.25%)	26 / 420 (6.19%)	
occurrences (all)	40	40	
Injury, poisoning and procedural complications			
Arteriovenous fistula thrombosis			
subjects affected / exposed	27 / 414 (6.52%)	18 / 420 (4.29%)	
occurrences (all)	34	21	
Nervous system disorders			
Headache			
subjects affected / exposed	36 / 414 (8.70%)	29 / 420 (6.90%)	
occurrences (all)	41	39	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	33 / 414 (7.97%)	32 / 420 (7.62%)	
occurrences (all)	51	60	
Nausea			
subjects affected / exposed	27 / 414 (6.52%)	8 / 420 (1.90%)	
occurrences (all)	29	10	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	15 / 414 (3.62%)	33 / 420 (7.86%)	
occurrences (all)	21	48	
Endocrine disorders			
Hyperparathyroidism secondary			
subjects affected / exposed	21 / 414 (5.07%)	16 / 420 (3.81%)	
occurrences (all)	21	17	
Metabolism and nutrition disorders			
Iron deficiency			
subjects affected / exposed	30 / 414 (7.25%)	51 / 420 (12.14%)	
occurrences (all)	39	64	

Infections and infestations			
Bronchitis			
subjects affected / exposed	29 / 414 (7.00%)	27 / 420 (6.43%)	
occurrences (all)	38	34	
Viral upper respiratory tract infection			
subjects affected / exposed	28 / 414 (6.76%)	39 / 420 (9.29%)	
occurrences (all)	61	68	
Upper respiratory tract infection			
subjects affected / exposed	14 / 414 (3.38%)	21 / 420 (5.00%)	
occurrences (all)	19	29	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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

Notes: