Clinical trial results:
A Phase 3 randomized, double-blind, active-controlled, parallel-group, multi-center study in hemodialysis participants with anemia of chronic kidney disease to evaluate the efficacy, safety and pharmacokinetics of three-times weekly dosing of daprodustat compared to recombinant human erythropoietin, following a switch from recombinant human erythropoietin or its analogs

Summary

EudraCT number	2017-004372-56
Trial protocol	ES FR GB PL IT RO
Global end of trial date	19 June 2020

Results information

Result version number	v1 (current)
This version publication date	04 July 2021
First version publication date	04 July 2021

Trial information

Trial identification

Sponsor protocol code	204837

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.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	17 November 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of daprodustat to epoetin alfa on hemoglobin (Hgb) efficacy when administered three-times weekly to hemodialysis-dependent participants (noninferiority).

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 September 2018
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	Korea, Republic of: 23
Country: Number of subjects enrolled	Romania: 9
Country: Number of subjects enrolled	Poland: 24
Country: Number of subjects enrolled	Russian Federation: 98
Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Spain: 32
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Argentina: 42
Country: Number of subjects enrolled	Brazil: 31
Country: Number of subjects enrolled	United States: 107
Worldwide total number of subjects	407
EEA total number of subjects	87

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	263
From 65 to 84 years	133
85 years and over	11

Subject disposition

Recruitment

Recruitment details:

This was a multicenter study conducted at 90 centers in 13 countries. Participants were randomized to receive either Daprodustat or Epoetin alfa.

Pre-assignment

Screening details:

A total of 595 participants were screened, of which 188 were screen failures. A total of 407 participants were enrolled in the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Daprodustat

Arm description:

Participants received daprodustat tablets with titrated dose levels ranging from 2, 4, 8, 12, 16, 20, 24, 32 and 48 milligrams (mg) orally three-times weekly up to 52 weeks. Study treatment was dose-titrated to achieve and maintain hemoglobin in the target range (10 to 11 grams per deciliter [g/dL]). In order to maintain the study blind, participants also received saline intravenous (IV) injection once weekly or three-times weekly depending on dose level, up to 52 weeks as an inactive treatment for the IV formulation. All participants were followed up at 4 to 6 weeks after last dose.

Arm type	Experimental
Investigational medicinal product name	Daprodustat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Daprodustat tablets were given with titrated dose levels ranging from 2, 4, 8, 12, 16, 20, 24, 32 and 48 milligrams (mg) orally three-times weekly for 52 weeks.

Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Saline was administered as an IV injection once weekly or three-times weekly, depending on dose level for 52 weeks.

Arm title	Epoetin alfa

Arm description:

Participants received epoetin alfa with titrated dose levels ranging from 1500 Units to 60,000 Units total weekly dose and administered as IV injection once weekly or three-times weekly depending on dose level up to 52 weeks. Study treatment was dose-titrated to achieve and maintain hemoglobin in the target range (10 to 11 g/dL). In order to maintain the study blind, participants also received placebo tablets matching to daprodustat orally three-times weekly up to 52 weeks as an inactive treatment for the tablet formulation. All participants were followed up at 4 to 6 weeks after last dose.

Arm type	Active comparator

Investigational medicinal product name	Epoetin alfa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Epoetin alfa doses ranging from 1500 units to 60,000 units were administered as intravenous (IV) injections once weekly or three-times weekly, depending on dose level for 52 weeks.

Investigational medicinal product name	Placebo matching daprodustat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablets matching daprodustat were given orally three-times weekly for 52 weeks.

Number of subjects in period 1	Daprodustat	Epoetin alfa
Started	270	137
Completed	269	135
Not completed	1	2
Consent withdrawn by subject	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Daprodustat

Reporting group description:

Participants received daprodustat tablets with titrated dose levels ranging from 2, 4, 8, 12, 16, 20, 24, 32 and 48 milligrams (mg) orally three-times weekly up to 52 weeks. Study treatment was dose-titrated to achieve and maintain hemoglobin in the target range (10 to 11 grams per deciliter [g/dL]). In order to maintain the study blind, participants also received saline intravenous (IV) injection once weekly or three-times weekly depending on dose level, up to 52 weeks as an inactive treatment for the IV formulation. All participants were followed up at 4 to 6 weeks after last dose.

Reporting group title	Epoetin alfa

Reporting group description:

Participants received epoetin alfa with titrated dose levels ranging from 1500 Units to 60,000 Units total weekly dose and administered as IV injection once weekly or three-times weekly depending on dose level up to 52 weeks. Study treatment was dose-titrated to achieve and maintain hemoglobin in the target range (10 to 11 g/dL). In order to maintain the study blind, participants also received placebo tablets matching to daprodustat orally three-times weekly up to 52 weeks as an inactive treatment for the tablet formulation. All participants were followed up at 4 to 6 weeks after last dose.

Reporting group values	Daprodustat	Epoetin alfa	Total
Number of subjects	270	137	407
Age Categorical Units: Participants			
19-64 Years	167	96	263
>= 65 Years	103	41	144
Sex: Female, Male Units: Participants			
Female	121	56	177
Male	149	81	230
Race/Ethnicity, Customized Units: Subjects			
BLACK OR AFRICAN AMERICAN	49	32	81
AMERICAN INDIAN OR ALASKAN NATIVE	1	1	2
ASIAN - CENTRAL/SOUTH ASIAN HERITAGE	1	0	1
ASIAN - EAST ASIAN HERITAGE	16	9	25
ASIAN - SOUTH EAST ASIAN HERITAGE	3	0	3
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1	0	1
WHITE - ARABIC/NORTH AFRICAN HERITAGE	1	4	5
WHITE - WHITE/CAUCASIAN/EUROPEAN HERITAGE	193	90	283
MIXED WHITE RACE	1	0	1
MIXED RACE	1	1	2
UNKNOWN	3	0	3

End points

End points reporting groups

Reporting group title	Daprodustat
Reporting group description:	
Participants received daprodustat tablets with titrated dose levels ranging from 2, 4, 8, 12, 16, 20, 24, 32 and 48 milligrams (mg) orally three-times weekly up to 52 weeks. Study treatment was dose-titrated to achieve and maintain hemoglobin in the target range (10 to 11 grams per deciliter [g/dL]). In order to maintain the study blind, participants also received saline intravenous (IV) injection once weekly or three-times weekly depending on dose level, up to 52 weeks as an inactive treatment for the IV formulation. All participants were followed up at 4 to 6 weeks after last dose.	
Reporting group title	Epoetin alfa
Reporting group description:	
Participants received epoetin alfa with titrated dose levels ranging from 1500 Units to 60,000 Units total weekly dose and administered as IV injection once weekly or three-times weekly depending on dose level up to 52 weeks. Study treatment was dose-titrated to achieve and maintain hemoglobin in the target range (10 to 11 g/dL). In order to maintain the study blind, participants also received placebo tablets matching to daprodustat orally three-times weekly up to 52 weeks as an inactive treatment for the tablet formulation. All participants were followed up at 4 to 6 weeks after last dose.	
Subject analysis set title	Daprodustat 2 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received daprodustat tablets 2 mg orally three-times weekly at the time of the pharmacokinetic visit.	
Subject analysis set title	Daprodustat 4 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received daprodustat tablets 4 mg orally three-times weekly at the time of the pharmacokinetic visit.	
Subject analysis set title	Daprodustat 8 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received daprodustat tablets 8 mg orally three-times weekly at the time of the pharmacokinetic visit.	
Subject analysis set title	Daprodustat 12 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received daprodustat tablets 12 mg orally three-times weekly at the time of the pharmacokinetic visit.	
Subject analysis set title	Daprodustat 16 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received daprodustat tablets 16 mg orally three-times weekly at the time of the pharmacokinetic visit.	
Subject analysis set title	Daprodustat 20 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received daprodustat tablets 20 mg orally three-times weekly at the time of the pharmacokinetic visit.	
Subject analysis set title	Daprodustat 24 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received daprodustat tablets 24 mg orally three-times weekly at the time of the pharmacokinetic visit.	
Subject analysis set title	Daprodustat 32 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received daprodustat tablets 32 mg orally three-times weekly at the time of the pharmacokinetic visit.

Subject analysis set title	Daprodustat 48 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received daprodustat tablets 48 mg orally three-times weekly at the time of the pharmacokinetic visit.

Primary: Mean change from Baseline in hemoglobin levels over the evaluation period (Week 28 to Week 52)

End point title	Mean change from Baseline in hemoglobin levels over the evaluation period (Week 28 to Week 52)

End point description:

Blood samples were collected from participants for hemoglobin measurements. Hemoglobin during the evaluation period was defined as the mean of all available post-randomization hemoglobin values (on and off-treatment) during the evaluation period (Week 28 to Week 52). For the primary analysis, the missing post-Baseline hemoglobin values were imputed using pre-specified multiple imputations. Baseline value was the latest non-missing pre-dose assessment on or before the randomization date, including those from unscheduled visits. Change from Baseline was defined as the average of post-randomization values during the evaluation period minus Baseline value. Analysis was performed using the Analysis of Covariance (ANCOVA) model with terms for treatment, Baseline hemoglobin, and region. All Randomized (Intent-to-treat [ITT]) Population comprised of all randomized participants. Any participant who received a treatment randomization number was considered to have been randomized.

End point type	Primary

End point timeframe:

Baseline (Pre-dose on Day 1) and evaluation period (Week 28 to Week 52)

End point values	Daprodustat	Epoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270[1]	137[2]		
Units: Grams per deciliter (g/dL)				
least squares mean (standard error)	-0.04 (± 0.045)	0.02 (± 0.066)		

Notes:

[1] - All Randomized (ITT) Population

[2] - All Randomized (ITT) Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Epoetin alfa v Daprodustat
Number of subjects included in analysis	407
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Least square (LS) mean difference
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	0.1

Notes:

[3] - Non-inferiority was to be established if the lower limit of the two-sided 95 percent (%) confidence interval (CI) for the treatment difference is greater than the pre-specified non-inferiority margin of -0.75 g/dL.

Secondary: Mean average monthly on-treatment intravenous (IV) iron dose per participant

End point title	Mean average monthly on-treatment intravenous (IV) iron dose per participant

End point description:

Average monthly IV iron dose (mg) per participant during Day 1 to Week 52 was determined by calculating the total IV iron dose per participant from Day 1 to Week 52 while the participant was on study treatment and dividing by (the number of days the participant was on study treatment divided by 30.4375 days). Analysis was performed using the ANCOVA model with terms for treatment, Baseline monthly IV iron dose, and region. Only those participants with data available at specified time points were analyzed.

End point type	Secondary

End point timeframe:

Day 1 to Week 52

End point values	Daprodustat	Epoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270[4]	136[5]		
Units: Milligrams				
least squares mean (standard error)	98.11 (± 11.049)	106.23 (± 15.569)		

Notes:

[4] - All Randomized (ITT) Population

[5] - All Randomized (ITT) Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Daprodustat v Epoetin alfa
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3354
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-8.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-45.66
upper limit	29.41

Secondary: Change from Baseline in hemoglobin levels at Week 52

End point title	Change from Baseline in hemoglobin levels at Week 52

End point description:

Blood samples were collected from participants for hemoglobin measurements. Baseline value was the latest non-missing pre-dose assessment on or before the randomization date, including those from unscheduled visits. Change from Baseline was defined as the post-randomization visit value minus Baseline value. Analysis was performed using a mixed model repeated measures (MMRM) model fitted to hemoglobin data collected after Baseline up to Week 52, excluding values collected during the stabilization period (Day 1 to Week 28). The model included factors for treatment, time, region, Baseline hemoglobin and Baseline hemoglobin by time and treatment by time interaction terms. Only those participants with data available at specified time points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Pre-dose on Day 1) and Week 52

End point values	Daprodustat	Epoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	252[6]	128[7]		
Units: Grams per deciliter				
least squares mean (standard error)	-0.03 (± 0.069)	0.11 (± 0.098)		

Notes:

[6] - All Randomized (ITT) Population

[7] - All Randomized (ITT) Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Daprodustat v Epoetin alfa
Number of subjects included in analysis	380
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
Parameter estimate	LS mean difference
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	0.1

Notes:

[8] - Non-inferiority was to be established if the lower limit of the two-sided 95 % CI for the treatment difference is greater than the pre-specified non-inferiority margin of -0.75 g/dL.

Secondary: Percentage of time with hemoglobin in the analysis range (10 to 11.5 grams/deciliter) over evaluation period (Week 28 to Week 52)

End point title	Percentage of time with hemoglobin in the analysis range (10 to 11.5 grams/deciliter) over evaluation period (Week 28 to Week 52)

End point description:

Participants received treatment during the study to achieve or maintain hemoglobin level in the target range. Percentage of time for which hemoglobin level was maintained within the analysis range (10 to 11.5 grams/deciliter) has been presented. Only those participants with at least one evaluable hemoglobin value during the evaluation period were analyzed.

End point type	Secondary

End point timeframe:

Week 28 to Week 52

End point values	Daprodustat	Epoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	215[9]	107[10]		
Units: Percentage of days				
median (inter-quartile range (Q1-Q3))	70.83 (50.98 to 91.07)	61.76 (29.69 to 85.19)		

Notes:

[9] - All Randomized (ITT) Population

[10] - All Randomized (ITT) Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hodges-Lehmann Estimate of Treatment Difference has been reported.

Comparison groups	Daprodustat v Epoetin alfa
Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
P-value	= 0.0034
Method	Van Elteren's test
Parameter estimate	Median difference (final values)
Point estimate	11.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.83
upper limit	19.56

Notes:

[11] - Non-inferiority was to be established if the lower limit of the two-sided 95% CI for the treatment difference was above the non-inferiority margin of - 15%.

Secondary: Number of hemoglobin responders in the hemoglobin analysis range (10 to 11.5 grams/deciliter) over evaluation period (Week 28 to Week 52)

End point title	Number of hemoglobin responders in the hemoglobin analysis range (10 to 11.5 grams/deciliter) over evaluation period (Week 28 to Week 52)

End point description:

Mean hemoglobin during the evaluation period was defined as the mean of all evaluable hemoglobin values during the evaluation period (Week 28 to Week 52) including any evaluable unscheduled hemoglobin values that were taken during this time period. Hemoglobin responders were defined as the number of participants with a mean hemoglobin during the evaluation period that falls within the hemoglobin analysis range of 10-11.5 grams/deciliter. Only those participants with at least one evaluable hemoglobin value during the evaluation period were analyzed.

End point type	Secondary

End point timeframe:

Week 28 to Week 52

End point values	Daprodustat	Epoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	215[12]	107[13]		
Units: Participants	172	68		

Notes:

[12] - All Randomized (ITT) Population

[13] - All Randomized (ITT) Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Daprodustat v Epoetin alfa
Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0007
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in response rate
Point estimate	0.1645
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	0.27

Secondary: Percentage of participants permanently stopping study treatment due to meeting rescue criteria

End point title	Percentage of participants permanently stopping study treatment due to meeting rescue criteria

End point description:

Percentage of participants permanently stopping study treatment due to meeting rescue criteria has been presented.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Daprodustat	Epoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270[14]	137[15]		
Units: Percentage of participants				
number (not applicable)	2.2	2.2		

Notes:

[14] - All Randomized (ITT) Population

[15] - All Randomized (ITT) Population

Statistical analyses

Statistical analysis title	Statistical Analysis

Statistical analysis description:

Hazard ratio is estimated using a Cox proportional hazard regression model adjusted for treatment group and region.

Comparison groups	Daprodustat v Epoetin alfa
Number of subjects included in analysis	407
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5308
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	4.22

Secondary: Change from Baseline in systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) at Week 52

End point title	Change from Baseline in systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) at Week 52

End point description:

Measurements for SBP, DBP and MAP were taken with the participant in a semi-supine or seated position in the dialysis chair after at least a 5-minute rest period. MAP is the average BP in an individual's arteries during a single cardiac cycle. Baseline value was the latest non-missing pre-dose assessment on or before the randomization date, including those from unscheduled visits. Change from Baseline was defined as the on-treatment visit value minus Baseline value. Analysis was performed using MMRM model with treatment group, time, region, Baseline value, Baseline value*time, treatment group*time as variables. Only those participants with data available at specified time points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Week -4) and Week 52

End point values	Daprodustat	Epoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	266[16]	133[17]		
Units: Millimeter of mercury (mmHg)				
least squares mean (standard error)				
SBP	-3.18 (± 1.470)	0.55 (± 2.252)		
DBP	-2.52 (± 0.764)	-0.29 (± 1.176)		
MAP	-2.72 (± 0.907)	-0.12 (± 1.389)		

Notes:

[16] - All Randomized (ITT) Population

[17] - All Randomized (ITT) Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: SBP	
Comparison groups	Daprodustat v Epoetin alfa
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.083
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-3.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.03
upper limit	1.56

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: DBP	
Comparison groups	Daprodustat v Epoetin alfa
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.057
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-2.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.99
upper limit	0.54

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
MAP	
Comparison groups	Daprodustat v Epoetin alfa
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.059
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.86
upper limit	0.67

Secondary: Change from Baseline in SBP, DBP and MAP at end of treatment

End point title	Change from Baseline in SBP, DBP and MAP at end of treatment

End point description:

Measurements for SBP, DBP and MAP were taken with the participant in a semi-supine or seated position in the dialysis chair after at least a 5-minute rest period. MAP is the average BP in an individual's arteries during a single cardiac cycle. Baseline value was the latest non-missing pre-dose assessment on or before the randomization date, including those from unscheduled visits. Change from Baseline was defined as the last on-treatment visit value minus Baseline value. Analysis was performed using ANCOVA model with terms for treatment group, region and Baseline value. Adjusted mean and standard error have been presented. Only those participants with data available at specified time points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Week -4) and end of treatment (last on-treatment value until Week 52)

End point values	Daprodustat	Epoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270[18]	136[19]		
Units: Millimeter of mercury (mmHg)				
arithmetic mean (standard error)				
SBP	-1.4 (± 1.24)	-0.9 (± 1.75)		
DBP	-1.8 (± 0.66)	-0.8 (± 0.93)		
MAP	-1.7 (± 0.78)	-0.8 (± 1.09)		

Notes:

[18] - All Randomized (ITT) Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: SBP	
Comparison groups	Daprodustat v Epoetin alfa
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.407
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.73
upper limit	3.72

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: DBP	
Comparison groups	Daprodustat v Epoetin alfa
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.179
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.29
upper limit	1.19

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: MAP	
Comparison groups	Daprodustat v Epoetin alfa

Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.261
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	1.78

Secondary: Blood pressure (BP) exacerbation event rate per 100 participant years

End point title	Blood pressure (BP) exacerbation event rate per 100 participant years

End point description:

BP exacerbation event is defined (based on post-dialysis BP) as SBP >=25 mmHg increased from Baseline or SBP >=180 mmHg; or DBP >=15 mmHg increased from Baseline or DBP >=110 mmHg. The BP exacerbation events per 100 participant years was estimated using the Negative Binomial Model. Only those participants with data available at specified time points were analyzed.

End point type	Secondary

End point timeframe:

Up to 52 weeks

End point values	Daprodustat	Epoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270[20]	136[21]		
Units: Events per 100 participant years				
number (confidence interval 95%)	250.45 (210.69 to 297.72)	356.91 (280.95 to 453.41)		

Notes:

[20] - All Randomized (ITT) Population

[21] - All Randomized (ITT) Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Daprodustat v Epoetin alfa
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0093
Method	Negative binomial model
Parameter estimate	Ratio of exacerbation rate
Point estimate	0.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.94

Secondary: Number of participants with at least one BP exacerbation event during the study

End point title	Number of participants with at least one BP exacerbation event during the study

End point description:

BP exacerbation (based on post-dialysis BP) is defined as: SBP >=25 mmHg increased from Baseline or SBP >=180mmHg; or DBP >=15 mmHg increase from Baseline or DBP >=110 mmHg. Number of participants with at least 1 BP exacerbation event have been reported. Only those participants with data available at specified time points were analyzed.

End point type	Secondary

End point timeframe:

Up to 52 weeks

End point values	Daprodustat	Epoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270[22]	136[23]		
Units: Participants	151	91		

Notes:

[22] - All Randomized (ITT) Population

[23] - All Randomized (ITT) Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline at Weeks 8, 12, 28 and 52 in Patient Global Impression of Severity (PGI-S)

End point title	Change from Baseline at Weeks 8, 12, 28 and 52 in Patient Global Impression of Severity (PGI-S)

End point description:

The PGI-S is a 1-item questionnaire designed to assess participant’s impression of disease severity of their anemia of Chronic kidney disease (CKD). It is measured on a 5-point disease severity scale ranging from 0 (absent) to 4 (very severe), higher score indicates more disease severity. Baseline value was the latest non-missing pre-dose assessment on or before the randomization date, including those from unscheduled visits. Change from Baseline in on-treatment PGI-S scores was defined as the on-treatment visit value minus Baseline value. Analysis was performed using MMRM model fitted from Baseline up to Week 52 with factors for treatment, time, region, Baseline value and Baseline value by time and treatment by time interactions. Only those participants with data available at specified time points were analyzed (represented as n=X in the category titles).

End point type	Secondary

End point timeframe:

Baseline (Pre-dose on Day 1) and Weeks 8, 12, 28, 52

End point values	Daprodustat	Epoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270[24]	137[25]		
Units: Scores on a scale				
least squares mean (standard error)				
Week 8; n=248, 126	-0.10 (± 0.048)	0.05 (± 0.068)		
Week 12; n=243, 120	-0.13 (± 0.050)	-0.01 (± 0.071)		
Week 28; n=211, 106	-0.07 (± 0.054)	0.03 (± 0.077)		
Week 52; n=170, 85	-0.11 (± 0.063)	0.04 (± 0.088)		

Notes:

[24] - All Randomized (ITT) Population

[25] - All Randomized (ITT) Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Week 8	
Comparison groups	Daprodustat v Epoetin alfa
Number of subjects included in analysis	407
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0323
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.01

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Week 12	
Comparison groups	Daprodustat v Epoetin alfa
Number of subjects included in analysis	407
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0921
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.12

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.06

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: Week 28	
Comparison groups	Daprodustat v Epoetin alfa
Number of subjects included in analysis	407
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1291
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.08

Statistical analysis title	Statistical Analysis 4
Statistical analysis description: Week 52	
Comparison groups	Daprodustat v Epoetin alfa
Number of subjects included in analysis	407
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0859
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	0.06

Secondary: Pre-dose trough concentration (Ctau) of daprodustat (GSK1278863) and its metabolites GSK2391220 (M2), GSK2487818 (M4), GSK2506102 (M5), GSK2506104 (M3), GSK2531398 (M6) and GSK2531401 (M13)

End point title	Pre-dose trough concentration (Ctau) of daprodustat

	(GSK1278863) and its metabolites GSK2391220 (M2), GSK2487818 (M4), GSK2506102 (M5), GSK2506104 (M3), GSK2531398 (M6) and GSK2531401 (M13)

End point description:

Blood samples were collected at indicated time points for pharmacokinetic analysis of daprodustat (GSK1278863) and its metabolites: GSK2391220 (M2), GSK2487818 (M4), GSK2506102 (M5), GSK2506104 (M3), GSK2531398 (M6) and GSK2531401 (M13). Pharmacokinetic Population comprised of all randomized participants for whom a post-Baseline pharmacokinetic sample was obtained and analyzed. Only those participants with data available at specified time points were analyzed (represented as n=X in the category titles). 99999 indicates that data was not available as geometric coefficient of variation could not be calculated for single participant.

End point type	Secondary

End point timeframe:

Pre-dose on Day 1; Pre-dose and at 0.5, 1, 2, 3 hours post-dose on any one post-Baseline visit day between Week 8 and Week 52

End point values	Daprodustat 2 mg	Daprodustat 4 mg	Daprodustat 8 mg	Daprodustat 12 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8[26]	20[27]	51[28]	59[29]
Units: Nanograms per milliliter				
geometric mean (geometric coefficient of variation)				
Daprodustat; n=1, 2, 10, 18, 14, 9, 6, 3, 2	6.2400 (± 99999)	1.1207 (± 494.71)	0.1786 (± 77.35)	0.3727 (± 277.88)
GSK2391220; n=4, 17,42, 57, 40, 25, 16, 3, 3	0.8623 (± 241.17)	0.5893 (± 255.59)	0.6341 (± 123.92)	1.1572 (± 184.51)
GSK2487818; n=1, 4, 5, 20, 14, 7, 4, 3, 2	0.3620 (± 99999)	0.2867 (± 111.67)	0.1594 (± 16.91)	0.2996 (± 105.55)
GSK2506102; n=4, 17, 45, 59, 43, 27, 16, 3, 3	0.9951 (± 122.94)	0.8372 (± 121.27)	0.9634 (± 95.99)	1.5100 (± 105.50)
GSK2506104; n=6, 17, 45, 59, 43, 27, 16, 3, 3	0.9750 (± 408.49)	1.9588 (± 163.27)	2.0381 (± 124.74)	3.5141 (± 136.72)
GSK2531398; n=2, 7, 22, 41, 33, 20, 15, 3, 3	1.1778 (± 20.55)	0.6069 (± 271.48)	0.2362 (± 76.76)	0.4444 (± 144.99)
GSK2531401; n=6, 17, 45, 59, 44, 27, 16, 3, 3	1.4466 (± 190.80)	3.5579 (± 102.68)	4.0910 (± 148.03)	6.8137 (± 102.34)

Notes:

[26] - Pharmacokinetic Population

[27] - Pharmacokinetic Population

[28] - Pharmacokinetic Population

[29] - Pharmacokinetic Population

End point values	Daprodustat 16 mg	Daprodustat 20 mg	Daprodustat 24 mg	Daprodustat 32 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	45[30]	28[31]	16[32]	3[33]
Units: Nanograms per milliliter				
geometric mean (geometric coefficient of variation)				
Daprodustat; n=1, 2, 10, 18, 14, 9, 6, 3, 2	0.3443 (± 100.78)	0.3871 (± 161.05)	0.1621 (± 42.17)	0.2768 (± 140.82)
GSK2391220; n=4, 17,42, 57, 40, 25, 16, 3, 3	1.1654 (± 191.57)	1.1792 (± 168.59)	1.4987 (± 136.35)	1.6974 (± 6.82)
GSK2487818; n=1, 4, 5, 20, 14, 7, 4, 3, 2	0.3027 (± 69.12)	0.2868 (± 109.23)	0.2585 (± 30.72)	0.2414 (± 29.66)

GSK2506102; n=4, 17, 45, 59, 43, 27, 16, 3, 3	1.5480 (± 122.95)	1.6555 (± 133.94)	3.2099 (± 67.36)	1.6892 (± 30.44)
GSK2506104; n=6, 17, 45, 59, 43, 27, 16, 3, 3	3.3872 (± 182.27)	3.6000 (± 173.62)	6.5730 (± 99.82)	4.2068 (± 15.44)
GSK2531398; n=2, 7, 22, 41, 33, 20, 15, 3, 3	0.3917 (± 169.77)	0.3728 (± 197.51)	0.3992 (± 153.15)	0.3963 (± 16.52)
GSK2531401; n=6, 17, 45, 59, 44, 27, 16, 3, 3	5.6037 (± 130.97)	8.4611 (± 128.74)	11.7372 (± 65.37)	6.0453 (± 140.63)

Notes:

[30] - Pharmacokinetic Population

[31] - Pharmacokinetic Population

[32] - Pharmacokinetic Population

[33] - Pharmacokinetic Population

End point values	Daprodustat 48 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	3[34]			
Units: Nanograms per milliliter				
geometric mean (geometric coefficient of variation)				
Daprodustat; n=1, 2, 10, 18, 14, 9, 6, 3, 2	0.3486 (± 68.34)			
GSK2391220; n=4, 17,42, 57, 40, 25, 16, 3, 3	1.3531 (± 19.28)			
GSK2487818; n=1, 4, 5, 20, 14, 7, 4, 3, 2	0.2111 (± 80.56)			
GSK2506102; n=4, 17, 45, 59, 43, 27, 16, 3, 3	1.8595 (± 48.36)			
GSK2506104; n=6, 17, 45, 59, 43, 27, 16, 3, 3	4.1894 (± 23.78)			
GSK2531398; n=2, 7, 22, 41, 33, 20, 15, 3, 3	0.2280 (± 56.68)			
GSK2531401; n=6, 17, 45, 59, 44, 27, 16, 3, 3	16.2584 (± 41.06)			

Notes:

[34] - Pharmacokinetic Population

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum observed concentration (Cmax) of daprodustat (GSK1278863) and its metabolites GSK2391220 (M2), GSK2487818 (M4), GSK2506102 (M5), GSK2506104 (M3), GSK2531398 (M6) and GSK2531401 (M13)

End point title	Maximum observed concentration (Cmax) of daprodustat (GSK1278863) and its metabolites GSK2391220 (M2), GSK2487818 (M4), GSK2506102 (M5), GSK2506104 (M3), GSK2531398 (M6) and GSK2531401 (M13)

End point description:

Blood samples were collected at indicated time points for pharmacokinetic analysis of daprodustat (GSK1278863) and its metabolites: GSK2391220 (M2), GSK2487818 (M4), GSK2506102 (M5), GSK2506104 (M3), GSK2531398 (M6) and GSK2531401 (M13). Only those participants with data available at specified time points were analyzed (represented as n=X in the category titles).

End point type	Secondary

End point timeframe:

Pre-dose on Day 1; Pre-dose and at 0.5, 1, 2, 3 hours post-dose on any one post-Baseline visit day between Week 8 and Week 52

End point values	Daprodustat 2 mg	Daprodustat 4 mg	Daprodustat 8 mg	Daprodustat 12 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8[35]	20[36]	51[37]	59[38]
Units: Nanograms per milliliter				
geometric mean (geometric coefficient of variation)				
Daprodustat; n=8, 20, 49, 57, 45, 28, 16, 3, 3	44.5832 (± 227.65)	51.9261 (± 227.59)	113.4049 (± 179.69)	143.8790 (± 233.09)
GSK2391220; n=8, 19, 50, 59, 45, 28, 16, 3, 3	2.6298 (± 60.93)	4.0224 (± 134.91)	6.3826 (± 198.78)	8.9535 (± 126.76)
GSK2487818; n=7, 18, 47, 56, 45, 28, 16, 3, 3	2.0320 (± 73.45)	3.2703 (± 143.75)	6.3474 (± 175.79)	8.0134 (± 146.43)
GSK2506102; n=8, 19, 51, 59, 45, 28, 16, 3, 3	0.8328 (± 101.92)	1.4018 (± 84.93)	2.0385 (± 85.59)	2.8357 (± 68.15)
GSK2506104; n=8, 19, 51, 59, 45, 28, 16, 3, 3	3.2020 (± 81.23)	5.2039 (± 98.70)	7.5220 (± 131.81)	10.8186 (± 84.31)
GSK2531398; n=8, 17, 46, 59, 45, 27, 16, 3, 3	1.2731 (± 57.92)	2.3676 (± 84.23)	3.7348 (± 131.10)	3.8017 (± 177.36)
GSK2531401; n=7, 19, 51, 59, 45, 28, 16, 3, 3	2.0473 (± 100.05)	4.0012 (± 88.64)	5.4631 (± 120.63)	8.8488 (± 80.17)

Notes:

[35] - Pharmacokinetic Population

[36] - Pharmacokinetic Population

[37] - Pharmacokinetic Population

[38] - Pharmacokinetic Population

End point values	Daprodustat 16 mg	Daprodustat 20 mg	Daprodustat 24 mg	Daprodustat 32 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	45[39]	28[40]	16[41]	3[42]
Units: Nanograms per milliliter				
geometric mean (geometric coefficient of variation)				
Daprodustat; n=8, 20, 49, 57, 45, 28, 16, 3, 3	126.6824 (± 288.50)	212.5087 (± 152.47)	290.3163 (± 87.39)	197.7071 (± 36.53)
GSK2391220; n=8, 19, 50, 59, 45, 28, 16, 3, 3	9.5131 (± 167.92)	11.8995 (± 172.35)	22.3378 (± 95.60)	9.3582 (± 71.78)
GSK2487818; n=7, 18, 47, 56, 45, 28, 16, 3, 3	6.4276 (± 278.04)	9.6617 (± 207.18)	19.9693 (± 94.09)	8.4327 (± 64.98)
GSK2506102; n=8, 19, 51, 59, 45, 28, 16, 3, 3	3.2007 (± 89.86)	3.5712 (± 96.48)	6.4555 (± 59.57)	2.4981 (± 71.38)
GSK2506104; n=8, 19, 51, 59, 45, 28, 16, 3, 3	11.5783 (± 130.74)	13.8509 (± 125.27)	24.4926 (± 84.96)	9.5457 (± 73.58)
GSK2531398; n=8, 17, 46, 59, 45, 27, 16, 3, 3	4.0850 (± 209.29)	6.1029 (± 137.40)	10.7532 (± 98.46)	4.6296 (± 72.00)
GSK2531401; n=7, 19, 51, 59, 45, 28, 16, 3, 3	8.4814 (± 93.83)	10.7368 (± 90.83)	14.7926 (± 59.24)	7.1458 (± 174.98)

Notes:

[39] - Pharmacokinetic Population

[40] - Pharmacokinetic Population

[41] - Pharmacokinetic Population

[42] - Pharmacokinetic Population

End point values	Daprodustat 48 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	3[43]			
Units: Nanograms per milliliter				
geometric mean (geometric coefficient of variation)				
Daprodustat; n=8, 20, 49, 57, 45, 28, 16, 3, 3	310.1938 (± 190.69)			
GSK2391220; n=8, 19, 50, 59, 45, 28, 16, 3, 3	31.6698 (± 84.08)			
GSK2487818; n=7, 18, 47, 56, 45, 28, 16, 3, 3	29.3042 (± 72.06)			
GSK2506102; n=8, 19, 51, 59, 45, 28, 16, 3, 3	7.1245 (± 87.62)			
GSK2506104; n=8, 19, 51, 59, 45, 28, 16, 3, 3	30.4034 (± 79.13)			
GSK2531398; n=8, 17, 46, 59, 45, 27, 16, 3, 3	14.7844 (± 81.18)			
GSK2531401; n=7, 19, 51, 59, 45, 28, 16, 3, 3	20.1044 (± 67.56)			

Notes:

[43] - Pharmacokinetic Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent serious adverse events (SAEs) and non-serious adverse events (non-serious AEs) were collected up to 52 weeks.

Adverse event reporting additional description:

Safety Population was used to assess SAEs and non-serious AEs, which comprised of all randomized participants who have taken at least 1 dose of study treatment. One participant from Randomized (ITT) Population (N=407) did not receive study treatment, hence was not included in Safety Population (N=406).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Daprodustat

Reporting group description:

Participants received daprodustat tablets with titrated dose levels ranging from 2, 4, 8, 12, 16, 20, 24, 32 and 48 milligrams (mg) orally three-times weekly up to 52 weeks. Study treatment was dose-titrated to achieve and maintain hemoglobin in the target range (10 to 11 grams per deciliter [g/dL]). In order to maintain the study blind, participants also received saline intravenous (IV) injection once weekly or three-times weekly depending on dose level, up to 52 weeks as an inactive treatment for the IV formulation. All participants were followed up at 4 to 6 weeks after last dose.

Reporting group title	Epoetin alfa

Reporting group description:

Participants received epoetin alfa with titrated dose levels ranging from 1500 Units to 60,000 Units total weekly dose and administered as IV injection once weekly or three-times weekly depending on dose level up to 52 weeks. Study treatment was dose-titrated to achieve and maintain hemoglobin in the target range (10 to 11 g/dL). In order to maintain the study blind, participants also received placebo tablets matching to daprodustat orally three-times weekly up to 52 weeks as an inactive treatment for the tablet formulation. All participants were followed up at 4 to 6 weeks after last dose.

Serious adverse events	Daprodustat	Epoetin alfa	
Total subjects affected by serious adverse events			
subjects affected / exposed	80 / 270 (29.63%)	47 / 136 (34.56%)	
number of deaths (all causes)	18	10	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lip and/or oral cavity cancer			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal cancer			

subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Smooth muscle cell neoplasm			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 270 (0.74%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	2 / 270 (0.74%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 270 (0.37%)	2 / 136 (1.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	2 / 270 (0.74%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 270 (0.37%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extremity necrosis			

subjects affected / exposed	2 / 270 (0.74%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 270 (0.37%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	1 / 270 (0.37%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial occlusive disease			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brachiocephalic vein stenosis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dialysis induced hypertension			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant hypertension			

subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 270 (0.74%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Asthenia			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Catheter site inflammation			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related thrombosis			

subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thirst			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fatigue			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	3 / 270 (1.11%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 270 (0.37%)	3 / 136 (2.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 270 (0.74%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 270 (0.37%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 270 (0.00%)	2 / 136 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 270 (0.37%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Asthma			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
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 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			

subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
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 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Thrombosis in device			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
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			
Arteriovenous fistula thrombosis			
subjects affected / exposed	7 / 270 (2.59%)	3 / 136 (2.21%)	
occurrences causally related to treatment / all	0 / 9	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	2 / 270 (0.74%)	2 / 136 (1.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site complication			
subjects affected / exposed	2 / 270 (0.74%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 270 (0.37%)	2 / 136 (1.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft occlusion			

subjects affected / exposed	1 / 270 (0.37%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula occlusion			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site haematoma			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (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 haemorrhage			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous graft site stenosis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropod bite			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			

subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
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 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sternal fracture			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
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 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access complication			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access malfunction			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site thrombosis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site pseudoaneurysm			

subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Congenital cystic kidney disease			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 270 (0.00%)	3 / 136 (2.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 270 (0.37%)	2 / 136 (1.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	3 / 270 (1.11%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	2 / 270 (0.74%)	0 / 136 (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	1 / 270 (0.37%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 270 (0.37%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac failure			
subjects affected / exposed	2 / 270 (0.74%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
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	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	4 / 270 (1.48%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	2 / 270 (0.74%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic hyperglycaemic coma			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
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	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Headache			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive encephalopathy			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (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 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			

subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myoclonus			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 270 (0.74%)	3 / 136 (2.21%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normocytic anaemia			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 270 (0.37%)	2 / 136 (1.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 270 (0.74%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diarrhoea			
subjects affected / exposed	1 / 270 (0.37%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nausea			
subjects affected / exposed	1 / 270 (0.37%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 270 (0.37%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic gastritis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic gastroparesis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric antral vascular ectasia			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric dilatation			

subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis relapsing			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (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 stone			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			

subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (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			
Diabetic foot			
subjects affected / exposed	0 / 270 (0.00%)	2 / 136 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 270 (0.00%)	2 / 136 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urethral			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			

subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical spinal stenosis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathic arthropathy			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (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			
Pneumonia			
subjects affected / exposed	9 / 270 (3.33%)	5 / 136 (3.68%)	
occurrences causally related to treatment / all	0 / 9	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 1	
Clostridium difficile colitis			
subjects affected / exposed	2 / 270 (0.74%)	1 / 136 (0.74%)	
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	2 / 270 (0.74%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	1 / 270 (0.37%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 270 (0.74%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 270 (0.37%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	2 / 270 (0.74%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acinetobacter infection			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter colitis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter bacteraemia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis infectious			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Enterococcal bacteraemia			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (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 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (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	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site cellulitis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Localised infection			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			

subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis Escherichia coli			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteus infection			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomembranous colitis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (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 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin bacterial infection			

subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubo-ovarian abscess			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (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 / 270 (0.37%)	0 / 136 (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	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 270 (0.37%)	0 / 136 (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			
Fluid overload			
subjects affected / exposed	2 / 270 (0.74%)	2 / 136 (1.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	3 / 270 (1.11%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	2 / 270 (0.74%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			

subjects affected / exposed	1 / 270 (0.37%)	1 / 136 (0.74%)	
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	0 / 270 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Daprodustat	Epoetin alfa	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	74 / 270 (27.41%)	42 / 136 (30.88%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	22 / 270 (8.15%)	14 / 136 (10.29%)	
occurrences (all)	35	19	
Hypotension			
subjects affected / exposed	12 / 270 (4.44%)	9 / 136 (6.62%)	
occurrences (all)	16	13	
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 270 (4.07%)	13 / 136 (9.56%)	
occurrences (all)	13	26	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 270 (2.59%)	8 / 136 (5.88%)	
occurrences (all)	9	9	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	23 / 270 (8.52%)	14 / 136 (10.29%)	
occurrences (all)	36	19	
Vomiting			
subjects affected / exposed	15 / 270 (5.56%)	13 / 136 (9.56%)	
occurrences (all)	16	15	
Nausea			

subjects affected / exposed	6 / 270 (2.22%)	11 / 136 (8.09%)	
occurrences (all)	8	21	
Abdominal pain			
subjects affected / exposed	7 / 270 (2.59%)	9 / 136 (6.62%)	
occurrences (all)	8	9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported