Clinical trial results:
A 52-week open-label (sponsor-blind), randomized, active controlled, parallel-group, multi-center study to evaluate the efficacy and safety of daprodustat compared to recombinant human erythropoietin in subjects with anemia associated with chronic kidney disease who are initiating dialysis

Summary

EudraCT number	2016-000507-86
Trial protocol	ES DE PL GB IT
Global end of trial date	24 September 2020

Results information

Result version number	v1 (current)
This version publication date	08 October 2021
First version publication date	08 October 2021

Trial information

Trial identification

Sponsor protocol code	201410

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, TW8 9GS
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	12 March 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare daprodustat to recombinant human erythropoietin (rhEPO) for hemoglobin (Hgb) efficacy (non-inferiority)

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 May 2017
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	United States: 54
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Poland: 22
Country: Number of subjects enrolled	Russian Federation: 72
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	Argentina: 56
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	India: 14
Country: Number of subjects enrolled	Korea, Republic of: 22
Country: Number of subjects enrolled	Malaysia: 14
Country: Number of subjects enrolled	Mexico: 20
Worldwide total number of subjects	312
EEA total number of subjects	37

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)	229
From 65 to 84 years	81
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

This was a multicenter study conducted across 14 countries. Participants were randomized to receive either Daprodustat or Darbepoetin alfa.

Pre-assignment

Screening details:

A total of 312 participants were randomized in the study.

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	Daprodustat

Arm description:

Participants received daprodustat film-coated tablets with titrated dose levels ranging from 1, 2, 4, 6, 8, 10, 12, 16, and 24 milligrams (mg) orally once daily for up to 52 weeks. Study treatment was dose-titrated to achieve and maintain hemoglobin (Hgb) in the target range (10 to 11 grams per deciliter [g/dL]).

Arm type	Experimental
Investigational medicinal product name	Daprodustat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received daprodustat film-coated tablets with dose levels ranging from 1, 2, 4, 6, 8, 10, 12, 16 or 24 mg orally once daily for 52 weeks.

Arm title	Darbepoetin alfa

Arm description:

Participants received darbepoetin alfa as prefilled syringes (PFS) for subcutaneous or intravenous (IV) injection with 4-weekly total dose levels ranging from 20, 30, 40, 60, 80, 120, 160, 200, 300 and 400 microgram (mcg) for 52 weeks. Study treatment was dose-titrated to achieve and maintain Hgb in the target range (10 to 11 g/dL).

Arm type	Active comparator
Investigational medicinal product name	Darbepoetin alfa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use, Intravenous use

Dosage and administration details:

Participants received darbepoetin alfa as PFS for subcutaneous or IV injection with 4-weekly total dose levels ranging from 20, 30, 40, 60, 80, 120, 160, 200, 300 and 400 mcg for 52 weeks.

Number of subjects in period 1	Daprodustat	Darbepoetin alfa
Started	157	155
Completed	155	151
Not completed	2	4
Consent withdrawn by subject	2	3
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Daprodustat
Reporting group description:	
Participants received daprodustat film-coated tablets with titrated dose levels ranging from 1, 2, 4, 6, 8, 10, 12, 16, and 24 milligrams (mg) orally once daily for up to 52 weeks. Study treatment was dose-titrated to achieve and maintain hemoglobin (Hgb) in the target range (10 to 11 grams per deciliter [g/dL]).	
Reporting group title	Darbepoetin alfa
Reporting group description:	
Participants received darbepoetin alfa as prefilled syringes (PFS) for subcutaneous or intravenous (IV) injection with 4-weekly total dose levels ranging from 20, 30, 40, 60, 80, 120, 160, 200, 300 and 400 microgram (mcg) for 52 weeks. Study treatment was dose-titrated to achieve and maintain Hgb in the target range (10 to 11 g/dL).	

Reporting group values	Daprodustat	Darbepoetin alfa	Total
Number of subjects	157	155	312
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	119	110	229
From 65-84 years	38	43	81
85 years and over	0	2	2
Age Continuous Units: Years			
arithmetic mean	53.7	55.8	
standard deviation	± 14.31	± 15.70	-
Sex: Female, Male Units: Participants			
Female	61	57	118
Male	96	98	194
Race/Ethnicity, Customized Units: Subjects			
American Indian (AI) or Alaskan Native (AN)	5	2	7
Asian: Central/South Asian Heritage	7	6	13
Asian: East Asian Heritage	8	16	24
Asian: South East Asian Heritage	11	9	20
Black or African American	16	13	29
White: Arabic/North African Heritage	1	0	1
White: White/Caucasian/European Heritage	109	107	216
Mixed race: AI or AN and White	0	2	2

End points

End points reporting groups

Reporting group title	Daprodustat
Reporting group description:	
Participants received daprodustat film-coated tablets with titrated dose levels ranging from 1, 2, 4, 6, 8, 10, 12, 16, and 24 milligrams (mg) orally once daily for up to 52 weeks. Study treatment was dose-titrated to achieve and maintain hemoglobin (Hgb) in the target range (10 to 11 grams per deciliter [g/dL]).	
Reporting group title	Darbepoetin alfa
Reporting group description:	
Participants received darbepoetin alfa as prefilled syringes (PFS) for subcutaneous or intravenous (IV) injection with 4-weekly total dose levels ranging from 20, 30, 40, 60, 80, 120, 160, 200, 300 and 400 microgram (mcg) for 52 weeks. Study treatment was dose-titrated to achieve and maintain Hgb in the target range (10 to 11 g/dL).	
Subject analysis set title	Daprodustat 1 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received film-coated tablets of daprodustat 1 mg orally once daily for 52 weeks.	
Subject analysis set title	Daprodustat 2 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received film-coated tablets of daprodustat 2 mg orally once daily for 52 weeks.	
Subject analysis set title	Daprodustat 4 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received film-coated tablets of daprodustat 4 mg orally once daily for 52 weeks.	
Subject analysis set title	Daprodustat 6 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received film-coated tablets of daprodustat 6 mg orally once daily for 52 weeks.	
Subject analysis set title	Daprodustat 8 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received film-coated tablets of daprodustat 8 mg orally once daily for 52 weeks.	
Subject analysis set title	Daprodustat 10 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received film-coated tablets of daprodustat 10 mg orally once daily for 52 weeks.	

Primary: Mean Change from Baseline in Hemoglobin (Hgb) During Evaluation Period (Week 28 to Week 52)

End point title	Mean Change from Baseline in Hemoglobin (Hgb) During Evaluation Period (Week 28 to Week 52)
End point description:	
Blood samples were collected from participants for Hgb measurement. Hgb during the evaluation period was defined as the mean of all available post-randomization Hgb values (on and off-treatment) during the evaluation period (Week 28 to Week 52). For the primary analysis missing post-Baseline Hgb values were imputed using pre-specified multiple imputations. Change from Baseline was defined as the average of post-randomization values during the evaluation period minus Baseline value. Baseline was defined as the latest non-missing pre-dose assessment on or before the randomization date. An analysis of covariance (ANCOVA) model including randomization stratification factors Baseline Hgb and treatment was performed to obtain a point estimate and two-sided 95 percent (%) confidence interval (CI) for the treatment difference (daprodustat-darbepoetin alfa). Intent-to-Treat (ITT) Population comprised all randomized participants (who received a treatment randomization number).	

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	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157[1]	155[2]		
Units: Grams per deciliter				
least squares mean (standard error)	1.02 (± 0.086)	1.12 (± 0.085)		

Notes:

[1] - ITT Population.

[2] - ITT Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

An ANCOVA model including randomization stratification factors Baseline Hgb and treatment was performed to obtain a point estimate and two-sided 95% CI for the treatment difference (daprodustat-darbepoetin alfa).

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Least square (LS) mean difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	0.14

Notes:

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

Secondary: Average Monthly Intravenous Iron Dose (milligrams) from Baseline to Week 52

End point title	Average Monthly Intravenous Iron Dose (milligrams) from Baseline to Week 52

End point description:

Total IV iron dose per participant was calculated from Day 1 to the earliest of (Week 52 visit date, first blood [red blood cells or whole blood] transfusion date and treatment stop date plus [+] 1 day) which corresponds to the time while the participant was on randomized treatment and before receiving a blood transfusion. Average monthly IV iron dose was calculated by Total IV iron dose divided by (/) (the number of days from Day 1 to the earliest of [Week 52 visit date, first blood transfusion date and treatment stop date +1] /30.4375 days). Data for participants until they underwent a red blood cells or whole blood transfusion was included in the analysis. Only those participants with data available at the indicated time points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 52

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156[4]	154[5]		
Units: Milligram				
least squares mean (standard error)	144.7 (± 10.90)	125.3 (± 10.97)		

Notes:

[4] - ITT Population.

[5] - ITT Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

An ANCOVA model was used to compare the difference in this average monthly IV iron dose between arms, including factors for Baseline dose, treatment and the randomization stratification factors.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8949
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	19.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11
upper limit	49.9

Secondary: Change from Baseline in Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Blood Pressure (MAP) at Week 52

End point title	Change from Baseline in Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Blood Pressure (MAP) at Week 52

End point description:

SBP, DBP and MAP were measured in a semi-supine or seated position in the dialysis chair after at least a 5-minutes of rest. MAP is an average BP in an individual's arteries during a single cardiac cycle. Change from Baseline was calculated as post-dose visit value minus Baseline value. Baseline was defined as the latest non-missing pre-dose assessment on or before the randomization date. This analysis was carried out by using mixed model repeated measures (MMRM) model. Only those participants with data available at the indicated time points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 52

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153[6]	149[7]		
Units: Millimeter of mercury				
least squares mean (standard error)				
SBP	-3.57 (± 2.063)	-6.80 (± 2.931)		
DBP	0.21 (± 1.216)	-4.01 (± 1.650)		
MAP	-0.95 (± 1.364)	-5.05 (± 1.894)		

Notes:

[6] - ITT Population.

[7] - ITT Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The difference in change from Baseline in SBP at Week 52 was analyzed with a MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8168
Method	Mixed model repeated measures (MMRM)
Parameter estimate	LS mean difference
Point estimate	3.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.82
upper limit	10.27

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

The difference in change from Baseline in DBP at Week 52 was analyzed with a MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9793
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	4.21

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	8.26

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

The difference in change from Baseline in MAP at Week 52 was analyzed with a MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9597
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	8.7

Secondary: Change from Baseline in SBP, DBP, MAP at End of Treatment

End point title	Change from Baseline in SBP, DBP, MAP at End of Treatment

End point description:

SBP, DBP and MAP were measured in a semi-supine or seated position in the dialysis chair after at least a 5-minutes of rest. MAP is an average BP in an individual's arteries during a single cardiac cycle. End of treatment value for the blood pressure parameters were defined as the latest value on or before the last non-zero dose date plus (+) 1 day. Change from Baseline was calculated as post-dose visit value minus Baseline value. Baseline was defined as the latest non-missing pre-dose assessment on or before the randomization date. This analysis was carried out by using ANCOVA model. Only those participants with data available at the indicated time points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and end of treatment (last on-treatment value until Week 52)

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154[8]	153[9]		
Units: Millimeter of mercury				
least squares mean (standard error)				
SBP	-3.23 (± 1.659)	-3.14 (± 1.664)		

DBP	0.60 (± 1.016)	-1.39 (± 1.020)		
MAP	-0.68 (± 1.092)	-1.97 (± 1.096)		

Notes:

[8] - ITT Population.

[9] - ITT Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The difference in change from Baseline in SBP at the derived end of treatment was analyzed with an ANCOVA model including terms for treatment, prognostic randomization stratification factors.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.484
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.72
upper limit	4.53

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

The difference in change from Baseline in DBP at the derived end of treatment was analyzed with an ANCOVA model including terms for treatment, prognostic randomization stratification factors.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9156
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	1.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.85
upper limit	4.82

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

The difference in change from Baseline in MAP at the derived end of treatment was analyzed with an ANCOVA model including terms for treatment, prognostic randomization stratification factors.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7966
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.76
upper limit	4.33

Secondary: Blood Pressure (BP) Exacerbation Events Rate per 100 Participant Years

End point title	Blood Pressure (BP) Exacerbation Events Rate per 100 Participant Years

End point description:

BP exacerbation event is defined (based on post-dialysis BP) as SBP >=25 millimeter of mercury (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.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155[10]	154[11]		
Units: Events per 100 participant year				
number (confidence interval 95%)	352.50 (268.89 to 462.09)	350.00 (267.72 to 457.56)		

Notes:

[10] - ITT Population.

[11] - ITT Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Model estimated exacerbation rates, ratio of model estimated exacerbation rates and CIs were estimated using a negative binomial model for the treatment group comparison.

Comparison groups	Daprodustat v Darbepoetin alfa

Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5174
Method	Negative binomial model
Parameter estimate	Ratio of exacerbation rate
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.39

Secondary: Change From Baseline in Post-randomization Hgb at Week 52

End point title	Change From Baseline in Post-randomization Hgb at Week 52

End point description:

Blood samples were collected from participants for Hgb measurements. Change from Baseline was calculated as post-dose visit value minus Baseline value. Baseline was defined as the latest non-missing pre-dose assessment on or before the randomization date. Only those participants with data available at the indicated time points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 52

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	139[12]	141[13]		
Units: Grams per deciliter				
least squares mean (standard error)	1.17 (± 0.117)	1.13 (± 0.115)		

Notes:

[12] - ITT Population.

[13] - ITT Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

The difference in change from Baseline in post-randomization Hgb at Week 52 was analyzed with a MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms.

Comparison groups	Daprodustat v Darbepoetin alfa

Number of subjects included in analysis	280
Analysis specification	Pre-specified
Analysis type	non-inferiority[14]
Parameter estimate	LS mean difference
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.36

Notes:

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

Secondary: Number of Participants with at Least one Blood Pressure Exacerbation Event During Study

End point title	Number of Participants with at Least one Blood Pressure Exacerbation Event During Study

End point description:

BP exacerbation was defined (based on post-dialysis BP) as: SBP >=25 mmHg increased from Baseline or SBP >=180 mmHg; DBP >=15 mmHg increased from Baseline or DBP >=110 mmHg. Number of participants with at least one blood pressure exacerbation event is presented. Only those participants with data available at the indicated time points were analyzed.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155[15]	154[16]		
Units: Participants	91	100		

Notes:

[15] - ITT Population.

[16] - ITT Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Hgb Responders (Hgb in the Analysis Range of 10 to 11.5 grams/deciliter) During Evaluation Period (Week 28 to Week 52)

End point title	Number of Hgb Responders (Hgb in the Analysis Range of 10 to 11.5 grams/deciliter) During Evaluation Period (Week 28 to Week 52)

End point description:

Mean Hgb during the evaluation period was defined as the mean of all evaluable Hgb values during the evaluation period (Week 28 to Week 52) including any evaluable unscheduled Hgb values that were taken during this time period. Hgb responders were defined as number of participants with a mean Hgb during the evaluation period that falls within the Hgb analysis range of 10-11.5 g/dL. Only those participants with data available at the indicated time points were analyzed.

End point type	Secondary

End point timeframe:

Weeks 28 to 52

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133[17]	133[18]		
Units: Participants	86	87		

Notes:

[17] - ITT Population.

[18] - ITT Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

A Cochran-Mantel-Haenszel (CMH) test adjusted for treatment and randomization stratification factors were used to compare the number of responders between the treatment groups.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5411
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in response rate
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.2
upper limit	10.7

Secondary: Percentage of Time for which Hgb was within the Analysis Range (10 to 11.5 g/dL) During Evaluation Period (Week 28 to Week 52): Non-inferiority analysis

End point title	Percentage of Time for which Hgb was within the Analysis Range (10 to 11.5 g/dL) During Evaluation Period (Week 28 to Week 52): Non-inferiority analysis

End point description:

Percentage of days for which a participant's Hgb was within the analysis range of 10-11.5 g/dL (both inclusive) during the evaluation period (Week 28 to Week 52), including any unscheduled evaluable Hgb values that were taken during this time period was calculated. Percentage of time for which Hgb was within range for a participant was calculated by dividing 'the total number of days that Hgb was within range during Weeks 28 to 52' by 'the total number of days the participant remained on treatment during Weeks 28 to 52'. Only those participants with data available at the indicated time points were analyzed.

End point type	Secondary

End point timeframe:

Weeks 28 to 52

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128[19]	129[20]		
Units: Percentage of days				
median (full range (min-max))	57.0 (0.0 to 100.0)	54.7 (0.0 to 100.0)		

Notes:

[19] - ITT Population.

[20] - ITT Population.

Statistical analyses

Statistical analysis title	Statistical analysis
Statistical analysis description:	
Hodges-Lehmann Estimate of Treatment Difference has been reported.	
Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	non-inferiority[21]
Parameter estimate	Median difference (final values)
Point estimate	2.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.45
upper limit	11.27

Notes:

[21] - Non-inferiority was to be established if the lower limit of the two-sided 95% confidence interval for the treatment difference was greater than non-inferiority margin of -15%.

Secondary: Percentage of Time for which Hgb was within the Analysis Range (10 to 11.5 g/dL) During Evaluation Period (Week 28 to Week 52): Superiority analysis

End point title	Percentage of Time for which Hgb was within the Analysis Range (10 to 11.5 g/dL) During Evaluation Period (Week 28 to Week 52): Superiority analysis

End point description:

Percentage of days for which a participant's Hgb was within the analysis range of 10-11.5 g/dL (both inclusive) during the evaluation period (Week 28 to Week 52), including any unscheduled evaluable Hgb values that were taken during this time period was calculated. Percentage of time for which Hgb was within range for a participant was calculated by dividing 'the total number of days that Hgb was within range during Weeks 28 to 52' by 'the total number of days the participant remained on treatment during Weeks 28 to 52'. Only those participants with data available at the indicated time points were analyzed.

End point type	Secondary

End point timeframe:

Weeks 28 to 52

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128[22]	129[23]		
Units: Percentage of days				
median (full range (min-max))	57.0 (0.0 to 100.0)	54.7 (0.0 to 100.0)		

Notes:

[22] - ITT Population.

[23] - ITT Population.

Statistical analyses

Statistical analysis title	Statistical analysis
Statistical analysis description:	
Mann-Whitney estimate (Probability) of the treatment effect has been presented.	
Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1538
Method	van Elteren test
Parameter estimate	Probability
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.61

Secondary: Number of Participants Permanently Stopping Randomized Treatment Due to Meeting Rescue Criteria

End point title	Number of Participants Permanently Stopping Randomized Treatment Due to Meeting Rescue Criteria
End point description:	
Number of participants permanently stopping randomized treatment due to meeting rescue criteria has been presented.	
End point type	Secondary
End point timeframe:	
Up to Week 52	

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157[24]	155[25]		
Units: Participants	5	5		

Notes:
[24] - ITT Population
[25] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Hazard ratio was estimated using a Cox proportional hazard regression model adjusted for treatment group, dialysis type and dialysis start manner.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5348
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	3.66

Secondary: Change from Baseline in Physical Component Score (PCS) using Short Form (SF)-36 Health-related Quality of Life (HRQoL) Questionnaire at Weeks 8, 12, 28, 52

End point title	Change from Baseline in Physical Component Score (PCS) using Short Form (SF)-36 Health-related Quality of Life (HRQoL) Questionnaire at Weeks 8, 12, 28, 52

End point description:

SF-36 acute version2 is 36-item generic quality of life instrument designed to measure participant's level of performance in following 8 health domains:physical functioning,role-physical(role limitations caused by physical problems),social functioning,bodily pain,mental health,role-emotional(role limitations caused by emotional problems),vitality/general health.Each domain is scored from 0(poorer health) to 100(better health). PCS is average score derived from 4domains(physical functioning,role-physical, bodily pain/general health) representing overall physical health.PCS ranges from 0 to 100;higher scores represent better health.Change from Baseline was calculated as post-dose visit value minus Baseline value.Baseline was defined as latest non-missing pre-dose assessment on or before randomization date. Only those participants with data available at indicated time points were analyzed (represented by n=X in the category titles)

End point type	Secondary

End point timeframe:

Baseline (Day 1), Weeks 8, 12, 28 and 52

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88[26]	88[27]		
Units: Scores on a scale				
least squares mean (standard error)				
Week 8, n=88,86	0.79 (± 0.648)	1.18 (± 0.658)		
Week 12, n=88,88	1.67 (± 0.627)	0.54 (± 0.631)		
Week 28, n=80,74	0.94 (± 0.697)	0.45 (± 0.725)		
Week 52, n=67,65	0.61 (± 0.755)	1.93 (± 0.774)		

Notes:

[26] - ITT Population.

[27] - ITT Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

SF-36 HRQoL PCS domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 8.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6641
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.22
upper limit	1.44

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

SF-36 HRQoL PCS domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 12.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.103
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	1.13

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.63
upper limit	2.89

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

SF-36 HRQoL PCS domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 28.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3157
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.51
upper limit	2.48

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

SF-36 HRQoL PCS domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 52.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8855
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.46
upper limit	0.84

Secondary: Change from Baseline in Mental Component Score (MCS) using SF-36 HRQoL Questionnaire at Weeks 8, 12, 28, 52

End point title	Change from Baseline in Mental Component Score (MCS) using

	SF-36 HRQoL Questionnaire at Weeks 8, 12, 28, 52

End point description:

SF-36 acute version2 is 36-item generic quality of life instrument designed to measure participant's level of performance in following 8 health domains:physical functioning,role-physical(role limitations caused by physical problems),social functioning,bodily pain,mental health,role-emotional(role limitations caused by emotional problems),vitality/general health.Each domain is scored from 0(poorer health) to 100(better health). PCS is average score derived from 4domains(physical functioning,role-physical, bodily pain/general health) representing overall physical health.PCS ranges from 0 to 100;higher scores represent better health.Change from Baseline was calculated as post-dose visit value minus Baseline value.Baseline was defined as latest non-missing pre-dose assessment on or before randomization date. Only those participants with data available at indicated time points were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Baseline (Day 1), Weeks 8, 12, 28 and 52

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88[28]	88[29]		
Units: Scores on a scale				
least squares mean (standard error)				
Week 8, n=88,86	0.10 (± 0.822)	0.76 (± 0.839)		
Week 12, n=88,88	0.08 (± 0.813)	1.60 (± 0.824)		
Week 28, n=80,74	-0.02 (± 0.905)	0.30 (± 0.942)		
Week 52, n=67,65	-0.95 (± 1.029)	-0.72 (± 1.051)		

Notes:

[28] - ITT Population.

[29] - ITT Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

SF-36 HRQoL MCS domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 8.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7146
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.99
upper limit	1.66

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
SF-36 HRQoL MCS domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 12.	
Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.905
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.82
upper limit	0.76

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
SF-36 HRQoL MCS domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 28.	
Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.595
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.91
upper limit	2.28

Statistical analysis title	Statistical analysis 4
Statistical analysis description:	
SF-36 HRQoL MCS domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 52.	
Comparison groups	Daprodustat v Darbepoetin alfa

Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5619
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.17
upper limit	2.7

Secondary: Change from Baseline in SF-36 HRQoL Scores for Bodily Pain, General Health, Mental Health, Role-Emotional, Role-Physical, Social Functioning at Weeks 8, 12, 28, 52

End point title	Change from Baseline in SF-36 HRQoL Scores for Bodily Pain, General Health, Mental Health, Role-Emotional, Role-Physical, Social Functioning at Weeks 8, 12, 28, 52

End point description:

The SF-36 acute version 2 is a 36-item generic quality of life instrument designed to measure a participant's level of performance in the following 8 health domains: bodily pain, general health, mental health, role-emotional (role limitations caused by emotional problems), role-physical (role limitations caused by physical problems), social functioning, physical functioning and vitality. Each domain is scored from 0 (poorer health) to 100 (better health). Each domain score ranges from 0 to 100, higher score indicates a better health state and better functioning. Change from Baseline was calculated as post-dose visit value minus Baseline value. Baseline was defined as the latest non-missing pre-dose assessment on or before the randomization date. Only those participants with data available at the indicated time points were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Baseline (Day 1), Weeks 8, 12, 28 and 52

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88[30]	88[31]		
Units: Scores on a scale				
least squares mean (standard error)				
Bodily pain: Week 8, n=88,86	-0.41 (± 0.833)	-0.55 (± 0.843)		
Bodily pain: Week 12, n=88,88	-0.13 (± 0.892)	-0.06 (± 0.895)		
Bodily pain: Week 28, n=80,74	1.08 (± 0.941)	-1.26 (± 0.976)		
Bodily pain: Week 52, n=67,65	-2.00 (± 1.084)	0.61 (± 1.109)		
General health: Week 8, n=88,86	0.80 (± 0.662)	0.75 (± 0.674)		
General health: Week 12, n=88,88	0.87 (± 0.651)	0.59 (± 0.658)		
General health: Week 28, n=80,74	0.63 (± 0.693)	0.37 (± 0.720)		
General health: Week 52, n=67,65	0.40 (± 0.823)	0.58 (± 0.841)		

Mental health: Week 8, n=88,86	-0.90 (± 0.825)	0.25 (± 0.841)		
Mental health: Week 12, n=88,88	0.01 (± 0.707)	1.42 (± 0.712)		
Mental health: Week 28, n=80,74	-0.69 (± 0.866)	-0.21 (± 0.902)		
Mental health: Week 52, n=67,65	-0.53 (± 0.994)	-0.27 (± 1.013)		
Role-emotional: Week 8, n=88,86	0.83 (± 0.880)	0.50 (± 0.896)		
Role-emotional: Week 12, n=88,88	0.55 (± 0.934)	-0.07 (± 0.946)		
Role-emotional: Week 28, n=80,74	0.91 (± 0.929)	0.39 (± 0.964)		
Role-emotional: Week 52, n=67,65	-1.60 (± 1.193)	-0.11 (± 1.216)		
Role-physical: Week 8, n=88,86	1.34 (± 0.806)	2.64 (± 0.818)		
Role-physical: Week 12, n=88,88	2.39 (± 0.712)	1.69 (± 0.716)		
Role-physical: Week 28, n=80,74	0.62 (± 0.799)	1.49 (± 0.829)		
Role-physical: Week 52, n=67,65	1.49 (± 0.895)	2.22 (± 0.913)		
Social functioning: Week 8, n=88,86	0.52 (± 0.929)	1.55 (± 0.947)		
Social functioning: Week 12, n=88,88	0.98 (± 0.774)	2.15 (± 0.783)		
Social functioning: Week 28, n=80,74	1.03 (± 0.943)	0.95 (± 0.980)		
Social functioning: Week 52, n=67,65	0.39 (± 1.085)	-0.33 (± 1.105)		

Notes:

[30] - ITT Population.

[31] - ITT Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

SF-36 HRQoL bodily pain domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 8.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4523
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.21
upper limit	2.49

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

SF-36 HRQoL bodily pain domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 12.

Comparison groups	Daprodustat v Darbepoetin alfa

Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5222
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.57
upper limit	2.43

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
SF-36 HRQoL bodily pain domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 28.	
Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.044
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	2.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	5.02

Statistical analysis title	Statistical analysis 4
Statistical analysis description:	
SF-36 HRQoL bodily pain domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 52.	
Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9523
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-2.61

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.68
upper limit	0.46

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

SF-36 HRQoL general health domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 8.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4811
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.82
upper limit	1.91

Statistical analysis title	Statistical analysis 6

Statistical analysis description:

SF-36 HRQoL general health domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 12

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3834
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.56
upper limit	2.11

Statistical analysis title	Statistical analysis 7

Statistical analysis description:

SF-36 HRQoL general health domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 28.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3983
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.72
upper limit	2.24

Statistical analysis title	Statistical analysis 8

Statistical analysis description:

SF-36 HRQoL general health domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 52.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5617
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.51
upper limit	2.15

Statistical analysis title	Statistical analysis 9

Statistical analysis description:

SF-36 HRQoL mental health domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 8.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8336
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.48
upper limit	1.18

Statistical analysis title	Statistical analysis 10

Statistical analysis description:

SF-36 HRQoL mental health domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 12.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9188
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	0.57

Statistical analysis title	Statistical analysis 11

Statistical analysis description:

SF-36 HRQoL mental health domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 28.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6495
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.96
upper limit	1.99

Statistical analysis title	Statistical analysis 12

Statistical analysis description:

SF-36 HRQoL mental health domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 52.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5737
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.09
upper limit	2.56

Statistical analysis title	Statistical analysis 13

Statistical analysis description:

SF-36 HRQoL role-emotional domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 8.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3963
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.15
upper limit	2.82

Statistical analysis title	Statistical analysis 14

Statistical analysis description:

SF-36 HRQoL role-emotional domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 12.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.322
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.62

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.01
upper limit	3.25

Statistical analysis title	Statistical analysis 15

Statistical analysis description:

SF-36 HRQoL role-emotional domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 28.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3485
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.13
upper limit	3.18

Statistical analysis title	Statistical analysis 16

Statistical analysis description:

SF-36 HRQoL role-emotional domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 52.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8064
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.87
upper limit	1.9

Statistical analysis title	Statistical analysis 17

Statistical analysis description:

SF-36 HRQoL role-physical domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 8.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8687
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.57
upper limit	0.98

Statistical analysis title	Statistical analysis 18

Statistical analysis description:

SF-36 HRQoL role-physical domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 12.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2435
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.29
upper limit	2.7

Statistical analysis title	Statistical analysis 19

Statistical analysis description:

SF-36 HRQoL role-physical domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 28.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7747
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.87

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.15
upper limit	1.41

Statistical analysis title	Statistical analysis 20
Statistical analysis description:	
SF-36 HRQoL role-physical domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 52.	
Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7141
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.26
upper limit	1.81

Statistical analysis title	Statistical analysis 21
Statistical analysis description:	
SF-36 HRQoL social functioning domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 8.	
Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7803
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.65
upper limit	1.59

Statistical analysis title	Statistical analysis 22

Statistical analysis description:

SF-36 HRQoL social functioning domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 12.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8556
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.35
upper limit	1

Statistical analysis title	Statistical analysis 23

Statistical analysis description:

SF-36 HRQoL social functioning domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 28.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4763
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.61
upper limit	2.77

Statistical analysis title	Statistical analysis 24

Statistical analysis description:

SF-36 HRQoL social functioning domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 52.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3208
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.73

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.35
upper limit	3.8

Secondary: Change from Baseline in Vitality scores using SF-36 HRQoL Questionnaire at Weeks 28, 52

End point title	Change from Baseline in Vitality scores using SF-36 HRQoL Questionnaire at Weeks 28, 52

End point description:

The SF-36 acute version 2 is a 36-item generic quality of life instrument designed to measure a participant's level of performance in the following 8 health domains: physical functioning, role-physical (role limitations caused by physical problems), social functioning, bodily pain, mental health, role-emotional (role limitations caused by emotional problems), vitality and general health. Each domain is scored from 0 (poorer health) to 100 (better health). Vitality ranges from 0 to 100; higher scores represent better health. Change from Baseline was calculated as post-dose visit value minus Baseline value. Baseline was defined as the latest non-missing pre-dose assessment on or before the randomization date. Only those participants with data available at the indicated time points were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Baseline (Day 1), Weeks 28 and 52

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80[32]	74[33]		
Units: Scores on a scale				
least squares mean (standard error)				
Week 28, n=80,74	-0.08 (± 0.866)	0.95 (± 0.902)		
Week 52, n=67,65	0.16 (± 0.907)	1.61 (± 0.925)		

Notes:

[32] - ITT Population.

[33] - ITT Population.

Statistical analyses

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

SF-36 HRQoL vitality domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 52.

Comparison groups	Daprodustat v Darbepoetin alfa

Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8648
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.03
upper limit	1.14

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

SF-36 HRQoL vitality domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 28.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.791
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	1.46

Secondary: Change from Baseline in Physical Functioning domain scores using SF-36 HRQoL Questionnaire at Weeks 28, 52

End point title	Change from Baseline in Physical Functioning domain scores using SF-36 HRQoL Questionnaire at Weeks 28, 52

End point description:

The SF-36 acute version 2 is a 36-item generic quality of life instrument designed to measure a participant's level of performance in the following 8 health domains: physical functioning, role-physical (role limitations caused by physical problems), social functioning, bodily pain, mental health, role-emotional (role limitations caused by emotional problems), vitality and general health. Each domain is scored from 0 (poorer health) to 100 (better health). Physical functioning ranges from 0 to 100; higher scores represent better health. Change from Baseline was calculated as post-dose visit value minus (-) Baseline value. Baseline was defined as the latest non-missing pre-dose assessment on or before the randomization date. Only those participants with data available at the indicated time points were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Baseline (Day 1), Weeks 28 and 52

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80[34]	74[35]		
Units: Scores on a scale				
least squares mean (standard error)				
Week 28, n=80,74	0.55 (± 0.863)	0.83 (± 0.898)		
Week 52, n=67,65	0.14 (± 0.947)	1.58 (± 0.973)		

Notes:

[34] - ITT Population.

[35] - ITT Population.

Statistical analyses

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

SF-36 HRQoL physical functioning domain scor was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 52.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8525
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.12
upper limit	1.26

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

SF-36 HRQoL physical functioning domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 28.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5879
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.28

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.75
upper limit	2.19

Secondary: Change from Baseline in Health Utility EuroQol 5 Dimensions 5 Level (EQ-5D-5L) Questionnaire Score at Week 52

End point title	Change from Baseline in Health Utility EuroQol 5 Dimensions 5 Level (EQ-5D-5L) Questionnaire Score at Week 52

End point description:

EQ-5D-5L consists of 2concepts–EQ-5D-5L descriptive system and EQ Visual Analogue Scale(EQ-VAS).EQ-5D-5L is self-assessment questionnaire,consisting of 5items covering 5dimensions(mobility,self care,usual activities,pain/discomfort and anxiety/depression).Each dimension is measured by 5-point Likert scale(no problems,slight problems,moderate problems,severe problems and extreme problems).Responses for 5 dimensions together formed a 5-figure description of health state(e.g.11111 indicates no problems in all 5dimensions).Each of these 5 figure health states were converted to a single index score by applying country-specific value set formula that attaches weights to dimensions and levels.Range for EQ-5D-5L index score is -0.594(worst health) to 1(full health),higher score better health status.Change from Baseline was calculated as post-dose visit value-Baseline value.Baseline was latest non-missing pre-dose assessment on or before randomization date.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 52

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[36]	25[37]		
Units: Scores on a scale				
least squares mean (standard error)	0.00 (± 0.041)	-0.03 (± 0.040)		

Notes:

[36] - ITT Population.

[37] - ITT Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

MMRM model was fitted from Baseline up to Week 52 with factors for treatment, time, dialysis type, dialysis start manner, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3154
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.03

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.14

Secondary: Change from Baseline in EQ Visual Analogue Scale (EQ-VAS) at Week 52

End point title	Change from Baseline in EQ Visual Analogue Scale (EQ-VAS) at Week 52

End point description:

EQ-5D-5L consists of 2 concepts –EQ-5D-5L descriptive system and EQ-VAS. The EQ-5D-5L is a self-assessment questionnaire, consisting of 5 items covering five dimensions (mobility, self care, usual activities, pain/discomfort and anxiety/depression). Each dimension is measured by 5-point Likert scale (no problems, slight problems, moderate problems, severe problems, and extreme problems). The range for EQ-5D-5L index score is 0 to 1 with '0' is worst health and '1' is full health. EQ VAS records respondent's self-rated health on a vertical VAS, ranging from 0 to 100, where 0 represents worst health one can imagine and 100 represents best health one can imagine. Change from Baseline was calculated as post-dose visit value minus Baseline value. Baseline was defined as the latest non-missing pre-dose assessment on or before the randomization date. Only those participants with data available at indicated time points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 52

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[38]	25[39]		
Units: Scores on a scale				
least squares mean (standard error)	3.4 (± 3.27)	6.8 (± 3.28)		

Notes:

[38] - ITT Population.

[39] - ITT Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

MMRM model was fitted from Baseline up to Week 52 with factors for treatment, time, dialysis type, dialysis start manner, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7651
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-3.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.7
upper limit	5.9

Secondary: Change from Baseline in Chronic Kidney Disease- Anemia Symptoms Questionnaire (CKD-AQ) at Week 52

End point title	Change from Baseline in Chronic Kidney Disease- Anemia Symptoms Questionnaire (CKD-AQ) at Week 52

End point description:

CKD-AQ is 21-item patient reported outcome measure assessing symptoms/symptom impact in participants with anemia associated with CKD. It had 3domains:1.Tired/Low Energy/Weak scale consisting of 10 items;2.Chest Pain/Shortness of Breath scale consisting of 4items; 3.Cognitive scale consisting of 3 items. 4CKD-AQ single items are(shortness of breath, no activity),(severity-short breath, resting),(difficulty standing for long time)/(difficulty sleeping).Single-item were recorded based on 0-100 scoring with 0=worst possible;100=best possible score. 3 domains scores were calculated as average of items in each domain/ranged from 0-100;0=worst possible&100=best possible score.Change from Baseline was calculated as post-dose visit value minus Baseline value.Baseline was defined as latest non-missing pre-dose assessment on or before randomization date. Only those participants with data available at the indicated time points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 52

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76[40]	80[41]		
Units: Scores on a scale				
least squares mean (standard error)				
Tired/Low energy/Weak domain	-2.36 (± 2.007)	4.07 (± 1.990)		
Chest pain/Shortness of breath domain	-1.83 (± 1.593)	2.28 (± 1.557)		
Cognitive domain	-4.17 (± 1.893)	2.43 (± 1.852)		
Shortness of breath, no activity	-1.90 (± 1.861)	1.14 (± 1.826)		
Severity-short breath, Resting	-4.16 (± 1.869)	0.12 (± 1.836)		
Difficulty standing for long time	-2.00 (± 2.812)	3.30 (± 2.754)		
Difficulty sleeping	-5.27 (± 2.667)	1.26 (± 2.611)		

Notes:

[40] - ITT Population.

[41] - ITT Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Tired/Low energy/Weak domain: MMRM model was fitted from Baseline up to Week 52 with factors for treatment, time, dialysis type, dialysis start manner, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9875
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-6.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.05
upper limit	-0.82

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Chest pain/Shortness of breath domain: MMRM model was fitted from Baseline up to Week 52 with factors for treatment, time, dialysis type, dialysis start manner, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9663
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-4.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.52
upper limit	0.3

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Cognitive domain: MMRM model was fitted from Baseline up to Week 52 with factors for treatment, time, dialysis type, dialysis start manner, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa

Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.993
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-6.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.84
upper limit	-1.35

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Shortness of breath, no activity: MMRM model was fitted from Baseline up to Week 52 with factors for treatment, time, dialysis type, dialysis start manner, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8765
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-3.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.19
upper limit	2.12

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

Severity-short breath, Resting: MMRM model was fitted from Baseline up to Week 52 with factors for treatment, time, dialysis type, dialysis start manner, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9464
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-4.27

Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.48
upper limit	0.94

Statistical analysis title	Statistical analysis 6

Statistical analysis description:

Difficulty standing for long time: MMRM model was fitted from Baseline up to Week 52 with factors for treatment, time, dialysis type, dialysis start manner, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9101
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-5.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.09
upper limit	2.47

Statistical analysis title	Statistical analysis 7

Statistical analysis description:

Difficulty sleeping: MMRM model was fitted from Baseline up to Week 52 with factors for treatment, time, dialysis type, dialysis start manner, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9586
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-6.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.9
upper limit	0.86

Secondary: Change from Baseline in Patient Global Impression of Severity (PGI-S)

End point title	Change from Baseline 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 on a 5-point disease severity scale (0=absent, 1=mild, 2=moderate, 3=severe, or 4=very severe). A higher score indicated worse outcome. Change from Baseline was calculated as post-dose visit value minus Baseline value. Baseline was defined as the latest non-missing pre-dose assessment on or before the randomization date. Only those participants with data available at the indicated time points were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Baseline (Day 1), Weeks 8, 12, 28 and 52

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100[42]	103[43]		
Units: Scores on a scale				
least squares mean (standard error)				
Week 8, n=100,100	0.16 (± 0.091)	-0.11 (± 0.092)		
Week 12, n=100,103	0.02 (± 0.077)	-0.03 (± 0.077)		
Week 28, n=92,85	0.09 (± 0.086)	-0.07 (± 0.089)		
Week 52, n=75,77	0.22 (± 0.106)	0.04 (± 0.105)		

Notes:

[42] - ITT Population.

[43] - ITT Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

MMRM model was fitted from Baseline up to Week 8 with factors for treatment, time, dialysis type, dialysis start manner, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.981
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.53

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

MMRM model was fitted from Baseline up to Week 12 with factors for treatment, time, dialysis type, dialysis start manner, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6743
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.26

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

MMRM model was fitted from Baseline up to Week 28 with factors for treatment, time, dialysis type, dialysis start manner, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8997
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.4

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

MMRM model was fitted from Baseline up to Week 52 with factors for treatment, time, dialysis type, dialysis start manner, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa

Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8835
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.47

Secondary: Plasma Concentration of Daprodustat (GSK1278863) and its Metabolites GSK2391220 (M2), GSK2506104 (M3), and GSK2531401 (M13)

End point title	Plasma Concentration of Daprodustat (GSK1278863) and its Metabolites GSK2391220 (M2), GSK2506104 (M3), and GSK2531401 (M13)

End point description:

Pharmacokinetic samples were collected at pre-dose, 0.5, 1, 2 and 3 hours post-dose on Week 4 or 8 or 12 for pharmacokinetic (PK) analysis of daprodustat (GSK1278863) and its metabolites GSK2391220 (M2), GSK2506104 (M3), and GSK2531401 (M13). GSK2391220, GSK2506104 and GSK2531401 are the metabolites of Daprodustat (GSK1278863). Protocol allowed participants to provide pharmacokinetic samples on Week 4 or 8 or 12. Pharmacokinetic Population comprised of participants for whom a pharmacokinetic sample was obtained and analyzed. Only those participants with data available at the indicated time points were analyzed (represented by n=X in the category titles). Blood samples were not collected for PK analysis of daprodustat 12, 16 and 24 mg arms. 99999 indicates, Standard deviation could not be calculated for single participant. 88888 indicates, data is not available.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 1, 2 and 3 hours post-dose; each pharmacokinetic sample was taken at Week 4 or 8 or 12

End point values	Daprodustat 1 mg	Daprodustat 2 mg	Daprodustat 4 mg	Daprodustat 6 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19[44]	26[45]	20[46]	18[47]
Units: Nanogram per milliliter				
arithmetic mean (standard deviation)				
Daprodustat: Pre-Dose, n=19,26,20,18,1,1	2.118 (± 5.0030)	1.015 (± 3.1451)	0.5787 (± 1.5718)	2.867 (± 6.6142)
Daprodustat: 0.5 hour, n=19,26,20,18,0,1	5.675 (± 8.4998)	4.664 (± 8.7508)	10.27 (± 20.425)	12.58 (± 23.742)
Daprodustat: 1 hour, n=19,26,20,18,1,1	12.34 (± 13.435)	21.45 (± 42.160)	36.78 (± 62.497)	45.48 (± 48.765)
Daprodustat: 2 hours, n=19,26,20,18,1,1	12.74 (± 9.9019)	20.36 (± 22.210)	54.68 (± 80.284)	55.62 (± 51.471)
Daprodustat: 3 hours, n=19,26,19,18,1,1	7.719 (± 5.9144)	15.58 (± 13.694)	43.34 (± 66.295)	56.49 (± 74.357)
GSK2391220: Pre-Dose, n=19,26,20,18,1,1	0.7106 (± 0.64028)	2.124 (± 2.8721)	2.087 (± 2.1371)	3.560 (± 4.2255)

GSK2391220: 0.5 hour, n=19,25,20,18,1,1	0.7602 (± 0.67950)	1.807 (± 2.2007)	1.822 (± 2.1355)	2.410 (± 2.8243)
GSK2391220: 1 hour, n=18,26,20,18,1,1	1.123 (± 0.76920)	1.752 (± 1.8589)	1.965 (± 2.2830)	3.140 (± 2.4856)
GSK2391220: 2 hours, n=19,26,20,18,1,1	1.745 (± 1.3160)	2.969 (± 2.4659)	4.008 (± 4.4522)	6.336 (± 4.3723)
GSK2391220: 3 hours, n=19,26,19,18,1,1	1.911 (± 1.2274)	3.535 (± 2.7203)	5.553 (± 6.5157)	9.372 (± 6.6452)
GSK2506104: Pre-Dose, n=19,26,20,18,1,1	1.270 (± 0.96071)	3.508 (± 4.2066)	3.879 (± 3.4207)	5.921 (± 5.8981)
GSK2506104: 0.5 hour, n=19,26,20,18,1,1	1.197 (± 0.85104)	2.788 (± 2.9893)	3.315 (± 3.4249)	4.015 (± 3.7385)
GSK2506104: 1 hour, n=19,26,20,18,1,1	1.364 (± 0.96292)	2.610 (± 2.4761)	3.268 (± 3.4808)	4.333 (± 3.0505)
GSK2506104: 2 hours, n=19,26,20,18,1,1	1.966 (± 1.3440)	3.583 (± 2.8427)	4.989 (± 5.2109)	7.130 (± 4.5105)
GSK2506104: 3 hours, n=19,26,19,18,1,1	2.190 (± 1.3898)	4.145 (± 3.1757)	6.503 (± 7.5130)	9.942 (± 7.0616)
GSK2531401: Pre-Dose, n=19,26,20,18,1,1	1.642 (± 1.4836)	2.729 (± 1.8934)	3.750 (± 3.8006)	5.111 (± 4.0632)
GSK2531401: 0.5 hour, n=19,26,20,18,1,1	1.427 (± 1.2870)	2.170 (± 1.6621)	3.263 (± 3.8737)	3.800 (± 2.8722)
GSK2531401: 1 hour, n=19,26,20,18,1,1	1.399 (± 1.4595)	1.979 (± 1.6316)	3.146 (± 4.0334)	3.776 (± 3.4411)
GSK2531401: 2 hours, n=19,26,20,18,1,1	1.690 (± 1.6309)	2.338 (± 2.1467)	3.711 (± 5.0223)	4.892 (± 4.7877)
GSK2531401: 3 hours, n=19,26,19,18,1,1	1.847 (± 1.7376)	2.734 (± 2.6846)	4.715 (± 7.2788)	6.631 (± 7.1049)

Notes:

[44] - Pharmacokinetic Population.

[45] - Pharmacokinetic Population.

[46] - Pharmacokinetic Population.

[47] - Pharmacokinetic Population.

End point values	Daprodustat 8 mg	Daprodustat 10 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1[48]	1[49]		
Units: Nanogram per milliliter				
arithmetic mean (standard deviation)				
Daprodustat: Pre-Dose, n=19,26,20,18,1,1	0.1030 (± 99999)	0.1090 (± 99999)		
Daprodustat: 0.5 hour, n=19,26,20,18,0,1	88888 (± 88888)	145.0 (± 99999)		
Daprodustat: 1 hour, n=19,26,20,18,1,1	0.9120 (± 99999)	79.60 (± 99999)		
Daprodustat: 2 hours, n=19,26,20,18,1,1	32.00 (± 99999)	27.60 (± 99999)		
Daprodustat: 3 hours, n=19,26,19,18,1,1	25.30 (± 99999)	11.00 (± 99999)		
GSK2391220: Pre-Dose, n=19,26,20,18,1,1	4.450 (± 99999)	6.560 (± 99999)		
GSK2391220: 0.5 hour, n=19,25,20,18,1,1	3.950 (± 99999)	6.740 (± 99999)		
GSK2391220: 1 hour, n=18,26,20,18,1,1	3.900 (± 99999)	10.00 (± 99999)		
GSK2391220: 2 hours, n=19,26,20,18,1,1	4.700 (± 99999)	16.20 (± 99999)		
GSK2391220: 3 hours, n=19,26,19,18,1,1	6.090 (± 99999)	16.60 (± 99999)		

GSK2506104: Pre-Dose, n=19,26,20,18,1,1	8.710 (± 99999)	9.500 (± 99999)		
GSK2506104: 0.5 hour, n=19,26,20,18,1,1	7.740 (± 99999)	8.110 (± 99999)		
GSK2506104: 1 hour, n=19,26,20,18,1,1	7.460 (± 99999)	12.40 (± 99999)		
GSK2506104: 2 hours, n=19,26,20,18,1,1	8.930 (± 99999)	19.60 (± 99999)		
GSK2506104: 3 hours, n=19,26,19,18,1,1	10.10 (± 99999)	22.00 (± 99999)		
GSK2531401: Pre-Dose, n=19,26,20,18,1,1	5.660 (± 99999)	7.760 (± 99999)		
GSK2531401: 0.5 hour, n=19,26,20,18,1,1	4.960 (± 99999)	6.460 (± 99999)		
GSK2531401: 1 hour, n=19,26,20,18,1,1	4.810 (± 99999)	6.630 (± 99999)		
GSK2531401: 2 hours, n=19,26,20,18,1,1	5.190 (± 99999)	8.290 (± 99999)		
GSK2531401: 3 hours, n=19,26,19,18,1,1	5.760 (± 99999)	10.20 (± 99999)		

Notes:

[48] - Pharmacokinetic Population.

[49] - Pharmacokinetic Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Observed concentration at Dosing Interval (Ctau) of Daprodustat (GSK1278863) and its Metabolites GSK2391220 (M2), GSK2506104 (M3), and GSK2531401 (M13)

End point title	Observed concentration at Dosing Interval (Ctau) of Daprodustat (GSK1278863) and its Metabolites GSK2391220 (M2), GSK2506104 (M3), and GSK2531401 (M13)

End point description:

Pharmacokinetic samples were collected at pre-dose, 0.5, 1, 2 and 3 hours post-dose on Week 4 or 8 or 12 for pharmacokinetic analysis of daprodustat (GSK1278863) and its metabolites GSK2391220 (M2), GSK2506104 (M3), and GSK2531401 (M13). GSK2391220, GSK2506104 and GSK2531401 are the metabolites of Daprodustat (GSK1278863). Protocol allowed participants to provide pharmacokinetic samples on Week 4 or 8 or 12. Only those participants with data available at the indicated time points were analyzed. Blood samples were not collected for PK analysis of daprodustat 12, 16 and 24 mg arms. 99999 indicates, Standard deviation could not be calculated for single participant.

End point type	Secondary

End point timeframe:

Pre-Dose, 0.5, 1, 2 and 3 hours post-dose; each pharmacokinetic sample was taken at Week 4 or 8 or 12

End point values	Daprodustat 1 mg	Daprodustat 2 mg	Daprodustat 4 mg	Daprodustat 6 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19[50]	26[51]	20[52]	18[53]
Units: Nanogram per milliliter				
arithmetic mean (standard deviation)				
Daprodustat	2.118 (± 5.0030)	1.015 (± 3.1451)	0.5787 (± 1.5718)	2.867 (± 6.6142)

GSK2391220	0.7106 (± 0.64028)	2.124 (± 2.8721)	2.087 (± 2.1371)	3.560 (± 4.2255)
GSK2506104	1.270 (± 0.96071)	3.508 (± 4.2066)	3.879 (± 3.4207)	5.921 (± 5.8981)
GSK2531401	1.642 (± 1.4836)	2.729 (± 1.8934)	3.750 (± 3.8006)	5.111 (± 4.0632)

Notes:

[50] - Pharmacokinetic Population.

[51] - Pharmacokinetic Population.

[52] - Pharmacokinetic Population.

[53] - Pharmacokinetic Population.

End point values	Daprodustat 8 mg	Daprodustat 10 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1[54]	1[55]		
Units: Nanogram per milliliter				
arithmetic mean (standard deviation)				
Daprodustat	0.1030 (± 99999)	0.1090 (± 99999)		
GSK2391220	4.450 (± 99999)	6.560 (± 99999)		
GSK2506104	8.710 (± 99999)	9.500 (± 99999)		
GSK2531401	5.660 (± 99999)	7.760 (± 99999)		

Notes:

[54] - Pharmacokinetic Population.

[55] - Pharmacokinetic Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Concentration (Cmax) of Daprodustat (GSK1278863) and its Metabolites GSK2391220 (M2), GSK2506104 (M3), and GSK2531401 (M13)

End point title	Maximum Observed Concentration (Cmax) of Daprodustat (GSK1278863) and its Metabolites GSK2391220 (M2), GSK2506104 (M3), and GSK2531401 (M13)

End point description:

Pharmacokinetic samples were collected at pre-dose, 0.5, 1, 2 and 3 hours post-dose on Week 4 or 8 or 12 for pharmacokinetic analysis of daprodustat (GSK1278863) and its metabolites GSK2391220 (M2), GSK2506104 (M3), and GSK2531401 (M13). GSK2391220, GSK2506104 and GSK2531401 are the metabolites of Daprodustat (GSK1278863). Protocol allowed participants to provide pharmacokinetic samples on Week 4 or 8 or 12. Only those participants with data available at the indicated time points were analyzed. Blood samples were not collected for PK analysis of daprodustat 12, 16 and 24 mg arms. 99999 indicates, Standard deviation could not be calculated for single participant.

End point type	Secondary

End point timeframe:

Pre-Dose, 0.5, 1, 2 and 3 hours post-dose; each pharmacokinetic sample was taken at Week 4 or 8 or 12

End point values	Daprodustat 1 mg	Daprodustat 2 mg	Daprodustat 4 mg	Daprodustat 6 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19[56]	26[57]	20[58]	18[59]
Units: Nanogram per milliliter				
arithmetic mean (standard deviation)				
Daprodustat	21.74 (± 10.998)	32.29 (± 40.166)	76.92 (± 81.867)	100.2 (± 74.086)
GSK2391220	2.160 (± 1.2596)	4.139 (± 3.3561)	5.780 (± 6.2840)	10.36 (± 6.3377)
GSK2506104	2.477 (± 1.3625)	5.212 (± 4.5562)	7.075 (± 7.1313)	11.60 (± 6.8731)
GSK2531401	2.283 (± 1.8210)	3.565 (± 2.6091)	5.328 (± 6.9034)	7.836 (± 6.6199)

Notes:

[56] - Pharmacokinetic Population.

[57] - Pharmacokinetic Population.

[58] - Pharmacokinetic Population.

[59] - Pharmacokinetic Population.

End point values	Daprodustat 8 mg	Daprodustat 10 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1[60]	1[61]		
Units: Nanogram per milliliter				
arithmetic mean (standard deviation)				
Daprodustat	32.00 (± 99999)	145.0 (± 99999)		
GSK2391220	6.090 (± 99999)	16.60 (± 99999)		
GSK2506104	10.10 (± 99999)	22.00 (± 99999)		
GSK2531401	5.760 (± 99999)	10.20 (± 99999)		

Notes:

[60] - Pharmacokinetic Population.

[61] - Pharmacokinetic Population.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality, treatment emergent non-serious adverse events and serious adverse events were collected up to follow-up visit (Week 58)

Adverse event reporting additional description:

Safety Population comprised of all randomized participants who received at least one dose of randomized treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Daprodustat

Reporting group description:

Participants received daprodustat film-coated tablets with titrated dose levels ranging from 1, 2, 4, 6, 8, 10, 12, 16, and 24 milligrams (mg) orally once daily for 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]).

Reporting group title	Darbepoetin alfa

Reporting group description:

Participants received darbepoetin alfa as prefilled syringes (PFS) for subcutaneous or intravenous (IV) injection with 4-weekly total dose levels ranging from 20, 30, 40, 60, 80, 120, 160, 200, 300 and 400 microgram (mcg) for 52 weeks. Study treatment was dose-titrated to achieve and maintain hemoglobin in the target range (10 to 11 g/dL).

Serious adverse events	Daprodustat	Darbepoetin alfa	
Total subjects affected by serious adverse events			
subjects affected / exposed	52 / 157 (33.12%)	51 / 155 (32.90%)	
number of deaths (all causes)	17	12	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer metastatic			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid cancer stage I			

subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 157 (1.27%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive urgency			
subjects affected / exposed	1 / 157 (0.64%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocele			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (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	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Steal syndrome			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
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			
Non-cardiac chest pain			
subjects affected / exposed	0 / 157 (0.00%)	2 / 155 (1.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pyrexia			
subjects affected / exposed	1 / 157 (0.64%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	2 / 157 (1.27%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Catheter site haemorrhage			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metrorrhagia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 157 (0.00%)	2 / 155 (1.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 157 (0.64%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 157 (0.00%)	2 / 155 (1.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 157 (0.64%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Asthma			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
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 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device malfunction			
subjects affected / exposed	4 / 157 (2.55%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	1 / 157 (0.64%)	2 / 155 (1.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
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	1 / 157 (0.64%)	4 / 155 (2.58%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site complication			
subjects affected / exposed	0 / 157 (0.00%)	2 / 155 (1.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			

subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia postoperative			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous graft thrombosis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inadequate haemodialysis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Open globe injury			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal dialysate leakage			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal dialysis complication			

subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural haemorrhage			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
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	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Unintentional medical device removal			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (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	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hypertrophic cardiomyopathy			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 157 (0.00%)	3 / 155 (1.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac failure			
subjects affected / exposed	1 / 157 (0.64%)	2 / 155 (1.29%)	
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	1 / 157 (0.64%)	2 / 155 (1.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	2 / 157 (1.27%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve incompetence			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive heart disease			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			

subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (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 / 157 (0.64%)	0 / 155 (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			
Syncope			
subjects affected / exposed	1 / 157 (0.64%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 157 (0.00%)	2 / 155 (1.29%)	
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	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive encephalopathy			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
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 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uraemic encephalopathy			

subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinopathy hypertensive			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 157 (0.00%)	3 / 155 (1.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bloody peritoneal effluent			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic gastropathy			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diarrhoea			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haematoma			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			

subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hydrocholecystis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	1 / 157 (0.64%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (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	4 / 157 (2.55%)	7 / 155 (4.52%)	
occurrences causally related to treatment / all	0 / 7	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peritonitis			

subjects affected / exposed	1 / 157 (0.64%)	3 / 155 (1.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	2 / 157 (1.27%)	2 / 155 (1.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Post procedural infection			
subjects affected / exposed	3 / 157 (1.91%)	0 / 155 (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	0 / 157 (0.00%)	3 / 155 (1.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 157 (0.64%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 157 (0.64%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 157 (0.64%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 157 (0.64%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			

subjects affected / exposed	2 / 157 (1.27%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 157 (0.64%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 157 (0.64%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Clostridial sepsis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related bacteraemia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (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	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (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	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Helicobacter gastritis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leptospirosis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
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 / 157 (0.00%)	1 / 155 (0.65%)	
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	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal infection			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	5 / 157 (3.18%)	3 / 155 (1.94%)	
occurrences causally related to treatment / all	0 / 9	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	2 / 157 (1.27%)	2 / 155 (1.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			

subjects affected / exposed	0 / 157 (0.00%)	3 / 155 (1.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid retention			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
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	Darbepoetin alfa	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	76 / 157 (48.41%)	74 / 155 (47.74%)	
Injury, poisoning and procedural complications			
Arteriovenous fistula site complication			
subjects affected / exposed	4 / 157 (2.55%)	8 / 155 (5.16%)	
occurrences (all)	4	13	
Vascular disorders			
Hypertension			
subjects affected / exposed	27 / 157 (17.20%)	24 / 155 (15.48%)	
occurrences (all)	51	35	
Dialysis hypotension			
subjects affected / exposed	21 / 157 (13.38%)	15 / 155 (9.68%)	
occurrences (all)	34	22	
Hypotension			
subjects affected / exposed	7 / 157 (4.46%)	9 / 155 (5.81%)	
occurrences (all)	8	9	
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 157 (7.64%)	9 / 155 (5.81%)	
occurrences (all)	14	10	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	14 / 157 (8.92%)	10 / 155 (6.45%)	
occurrences (all)	17	10	

Vomiting			
subjects affected / exposed	11 / 157 (7.01%)	5 / 155 (3.23%)	
occurrences (all)	16	5	
Nausea			
subjects affected / exposed	8 / 157 (5.10%)	6 / 155 (3.87%)	
occurrences (all)	13	6	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	7 / 157 (4.46%)	9 / 155 (5.81%)	
occurrences (all)	12	12	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 157 (4.46%)	9 / 155 (5.81%)	
occurrences (all)	12	9	
Catheter site infection			
subjects affected / exposed	5 / 157 (3.18%)	8 / 155 (5.16%)	
occurrences (all)	5	11	
Upper respiratory tract infection			
subjects affected / exposed	7 / 157 (4.46%)	11 / 155 (7.10%)	
occurrences (all)	9	12	
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	9 / 157 (5.73%)	6 / 155 (3.87%)	
occurrences (all)	9	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 October 2017	Amendment 1: Updated time period of planning to start dialysis from the screening to 6 weeks, when appropriate; Removed number of screening participants and stated only an approximate number of randomized participants required; Modified PD inclusion criteria to allow participants on >=4 times/week PD including an incremental schedule; Removed France country specific requirement for Informed Consent process from inclusion criteria; Broadened exclusion to include participation in an interventional study with an investigational agent or device; Removed option to have Early Treatment Discontinuation visit supersede the scheduled visit; Added a provision that in unexpected circumstances where the supply to the site is interrupted, local SOC for anemia management during this time period may be considered; Added direction regarding randomized treatment and study continuation for participants who will be away from the research site for an extended period of time; Added new darbepoetin alfa dose strengths (not available in all countries); Clarified timeframe for iron management criteria; Clarified timing of designated study visits for participants who have not yet initiated dialysis and for participants on dialysis; Shortened visit window for week 2 and 4; Changed time point for blinded data cut need for psychometric validation of the CKD Questionnaire; Revised statistical section to change from 2-sided testing at the 5% level to 1-sided testing at the 2.5% level; for secondary endpoints, to change significance levels to p-values and to correct the time point for various PRO;Provision for possible adjustment to the Dose Adjustment Algorithm triggers for Hgb values 7.5 grams per deciliter (g/dL) to <9.5 g/dL based on review of blinded instream Hgb data; Updated FSH level to confirm menopause in Appendix 5, Female Eligibility Criteria

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported