Clinical trial results:
A 28-week, randomized, double-blind, placebo-controlled, parallel-group, multi-center, study in recombinant human erythropoietin (rhEPO) naïve non-dialysis participants with anemia associated with chronic kidney disease to evaluate the efficacy, safety and effects on quality of life of daprodustat compared to placebo

Summary

EudraCT number	2017-002270-39
Trial protocol	GB ES PL IT RO
Global end of trial date	07 October 2020

Results information

Result version number	v1 (current)
This version publication date	21 October 2021
First version publication date	21 October 2021

Trial information

Trial identification

Sponsor protocol code	205270

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	22 February 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of daprodustat to placebo on mean change in hemoglobin (Hgb) levels
Secondary objectives of the trial:
To compare the proportion of participants achieving increases in Hgb when treated with daprodustat versus placebo;
To compare daprodustat to placebo for health related quality-of-life;
To compare daprodustat to placebo on additional Hgb endpoints;
To compare daprodustat to placebo on the time to rescue;
To compare daprodustat to placebo for improving symptoms of anemia of chronic kidney disease (CKD);
To compare daprodustat to placebo on the severity and change in symptoms;
To compare daprodustat to placebo for improving health related quality-of-life;
To compare daprodustat to placebo on improving work productivity and regular daily activity impairment;
To compare daprodustat to placebo on improving health status;
To compare daprodustat to placebo on blood pressure (BP)

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 March 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 26
Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	Brazil: 39
Country: Number of subjects enrolled	Canada: 39
Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Mexico: 105
Country: Number of subjects enrolled	Poland: 31
Country: Number of subjects enrolled	Romania: 47
Country: Number of subjects enrolled	Russian Federation: 40
Country: Number of subjects enrolled	Korea, Republic of: 39
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 18

Country: Number of subjects enrolled	United States: 172
Worldwide total number of subjects	614
EEA total number of subjects	115

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)	256
From 65 to 84 years	321
85 years and over	37

Subject disposition

Recruitment

Recruitment details:

This was a multicenter study conducted at 142 centers in 14 countries. Participants were randomized to receive either Daprodustat or Placebo.

Pre-assignment

Screening details:

A total of 1336 participants were screened, of which 722 were screen failures. A total of 614 participants were enrolled in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received matching placebo once daily orally for up to 28 weeks followed by 4 weeks of follow-up.

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

Dosage and administration details:

Participants received matching placebo orally once daily.

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 milligrams (mg) once daily orally for up to 28 weeks, followed by 4 weeks of follow-up. Study treatment was dose-titrated to achieve and maintain hemoglobin in the target range (11 to 12 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 titrated dose levels ranging from 1, 2, 4, 6, 8, 10, 12, 16 milligrams (mg)
once daily orally.

Number of subjects in period 1	Placebo	Daprodustat
Started	307	307
Completed	290	300
Not completed	17	7
Consent withdrawn by subject	4	2
Physician decision	1	-
Adverse event, non-fatal	5	3
Lost to follow-up	7	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo once daily orally for up to 28 weeks followed by 4 weeks of follow-up.	
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 milligrams (mg) once daily orally for up to 28 weeks, followed by 4 weeks of follow-up. Study treatment was dose-titrated to achieve and maintain hemoglobin in the target range (11 to 12 grams per deciliter [g/dL])	

Reporting group values	Placebo	Daprodustat	Total
Number of subjects	307	307	614
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)	121	135	256
From 65-84 years	165	156	321
85 years and over	21	16	37
Age Continuous Units: Years			
arithmetic mean	66.6	65.3	
standard deviation	± 12.93	± 13.43	-
Sex: Female, Male Units: Participants			
Female	178	176	354
Male	129	131	260
Race/Ethnicity, Customized Units: Subjects			
AMERICAN INDIAN OR ALASKA NATIVE	34	34	68
ASIAN: CENTRAL/SOUTH ASIAN HERITAGE	3	6	9
ASIAN:JAPANESE/EAST(E). ASIAN/SOUTH E.ASIA HERITAGE	24	24	48
ASIAN: MIXED ASIAN RACE	1	0	1
BLACK OR AFRICAN AMERICAN	47	44	91
NATIVE HAWAIIAN/OTHER PACIFIC ISLANDER	1	0	1
WHITE	195	197	392
BLACK OR AFRICAN AMERICAN AND WHITE	2	2	4

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received matching placebo once daily orally for up to 28 weeks followed by 4 weeks of follow-up.

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 milligrams (mg) once daily orally for up to 28 weeks, followed by 4 weeks of follow-up. Study treatment was dose-titrated to achieve and maintain hemoglobin in the target range (11 to 12 grams per deciliter [g/dL])

Primary: Mean change in hemoglobin from Baseline and over the evaluation period (mean over Week 24 and 28)

End point title	Mean change in hemoglobin from Baseline and over the evaluation period (mean over Week 24 and 28)

End point description:

Blood samples were collected at given time points from participants for hemoglobin measurements. Evaluation period hemoglobin value was defined as the mean of all available post-randomization hemoglobin values (on and off-treatment) during the evaluation period (Week 24 to Week 28 inclusive). For the primary analysis, the missing post-Baseline hemoglobin 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 value was the latest non-missing pre-dose assessment on or before the randomization date. Analysis was performed using the Analysis of Covariance (ANCOVA) model with terms for treatment, Baseline hemoglobin, and region. Intent-to-Treat (ITT) Population comprised all randomized participants regardless of whether they took study drug.

End point type	Primary

End point timeframe:

Baseline (Day 1) and Week 24 to Week 28

End point values	Placebo	Daprodustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307[1]	307[2]		
Units: Grams per deciliter				
least squares mean (standard error)	0.19 (± 0.062)	1.58 (± 0.061)		

Notes:

[1] - ITT Population

[2] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Treatment group comparisons were based on a ANCOVA model with terms for treatment, Baseline hemoglobin, and region.

Comparison groups	Placebo v Daprodustat

Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.23
upper limit	1.56

Notes:

[3] - One-sided p-value based on test of null hypothesis: (Daprodustat - Placebo) <= 0 versus alternative: difference > 0.

Secondary: Percentage of participants with hemoglobin increase of >=1.0 grams per deciliter from Baseline to evaluation period

End point title	Percentage of participants with hemoglobin increase of >=1.0 grams per deciliter from Baseline to evaluation period

End point description:

Blood samples were collected at given time points for hemoglobin measurements. Evaluation period hemoglobin value was defined as the mean of all available post-randomization hemoglobin values (on and off-treatment) during the evaluation period (Week 24 to Week 28 inclusive). For the primary analysis, the missing post-Baseline hemoglobin values were imputed using pre-specified multiple imputations. Baseline value was the latest non-missing pre-dose assessment on or before the randomization date. Percentage of participants with hemoglobin increase of >=1.0 grams per deciliter from Baseline to evaluation period was analyzed using Cochran-Mantel-Haenszel (CMH) chi-squared test. The percentage values presented has been rounded off.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 24 to Week 28

End point values	Placebo	Daprodustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307[4]	307[5]		
Units: Percentage of participants	18	77		

Notes:

[4] - ITT Population

[5] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Treatment group comparisons were based on a Cochran-Mantel-Haenszel test adjusted for treatment group and region.

Comparison groups	Placebo v Daprodustat

Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response rate
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.63

Notes:

[6] - One-sided p-value was based on test of null hypothesis: (Daprodustat - Placebo) <=0 versus alternative: difference > 0

Secondary: Change from Baseline in short form-36 (SF-36) questionnaire vitality domain score by traditional scoring at Week 28

End point title	Change from Baseline in short form-36 (SF-36) questionnaire vitality domain score by traditional scoring at Week 28

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 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 Perception of Health.Each domain is scored from 0 (poorer health) to 100 (better health). Vitality domain score ranges from 0-100; higher score indicates a better health state & better functioning. Change from Baseline was calculated as Post-Dose Visit Value at Week 28 minus Baseline. For primary analysis, the missing on-treatment Week 28 SF-36 Vitality domain scores were imputed using pre-specified multiple imputations. Baseline value was latest non-missing pre-dose assessment on or before randomization date. Analysis was performed using ANCOVA model with terms for treatment, Baseline score, and region.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 28

End point values	Placebo	Daprodustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307[7]	307[8]		
Units: Scores on a scale				
least squares mean (standard error)	1.93 (± 1.161)	7.29 (± 1.121)		

Notes:

[7] - ITT Population

[8] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis

Statistical analysis description:

Treatment group comparisons were based on ANCOVA model with terms for treatment, Baseline score, and region.

Comparison groups	Placebo v Daprodustat

Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005 [9]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	5.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.17
upper limit	8.56

Notes:

[9] - One-sided p-value based on test of null hypothesis:(Daprodustat-Placebo) <= 0 vs alternative: difference >0.

Secondary: Percentage of participants with Hgb response (Hgb in the 11-12 grams/deciliter range) During Evaluation Period (Week 24 to Week 28 inclusive)

End point title	Percentage of participants with Hgb response (Hgb in the 11-12 grams/deciliter range) During Evaluation Period (Week 24 to Week 28 inclusive)

End point description:

Mean hemoglobin during the evaluation period was defined as the mean of all evaluable hemoglobin values during the evaluation period (Week 24 to Week 28 inclusive) including any evaluable unscheduled hemoglobin values that were taken during this period. Percentage of participants with Hgb response was defined as participants with mean Hgb within range (11-12 grams per deciliter during the evaluation period (Week 24 to Week 28 inclusive) and it was analyzed using Cochran-Mantel-Haenszel (CMH) chi-squared test. The percentage values presented has been rounded off.

End point type	Secondary

End point timeframe:

Week 24 to Week 28

End point values	Placebo	Daprodustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307[10]	307[11]		
Units: Percentage of participants	8	52		

Notes:

[10] - ITT Population

[11] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis

Statistical analysis description:

Treatment group comparisons are based on a Cochran-Mantel-Haenszel test adjusted for treatment group, and region

Comparison groups	Placebo v Daprodustat

Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response rate
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	0.52

Notes:

[12] - One-sided p-value was based on test of null hypothesis: (Daprodustat-Placebo) <=0 versus alternative:
difference >0.

Secondary: Percentage of time with Hgb within the target range (11-12 grams per deciliter) During Evaluation Period (Week 24 to Week 28 inclusive) (Hodges-Lehmann Estimate)

End point title	Percentage of time with Hgb within the target range (11-12 grams per deciliter) During Evaluation Period (Week 24 to Week 28 inclusive) (Hodges-Lehmann Estimate)

End point description:

Percentage of days for which participant's Hgb was within the target range of 11-12 grams per deciliter during the evaluation period (Week 24 to Week 28 inclusive), including any unscheduled evaluable Hgb values that were taken during this time period. Percentage of time for which Hgb was within the target range (11-12 grams per deciliter) for a participant was calculated by dividing 'the total number of days that Hgb was within range during Week 24 to 28' by 'the total number of days the participant remained on treatment during Week 24 to 28'. Only those participants with data available at the indicated time points were analyzed.

End point type	Secondary

End point timeframe:

Week 24 to Week 28

End point values	Placebo	Daprodustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216[13]	252[14]		
Units: Percentage of days				
median (full range (min-max))	0.00 (0.0 to 100.0)	53.59 (0.0 to 100.0)		

Notes:

[13] - ITT Population

[14] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis

Statistical analysis description:

Hodges-Lehmann Estimate of treatment difference has been reported.

Comparison groups	Placebo v Daprodustat

Number of subjects included in analysis	468
Analysis specification	Pre-specified
Analysis type	superiority
Method	Hodges-Lehmann Estimate
Parameter estimate	Difference in treatment effect
Point estimate	38.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	25
upper limit	54.55

Secondary: Percentage of participants with Hgb response (Hgb in the 11-12 grams/deciliter range) During Evaluation Period (Week 24 to Week 28 inclusive) (Mann-Whitney Estimate)

End point title	Percentage of participants with Hgb response (Hgb in the 11-12 grams/deciliter range) During Evaluation Period (Week 24 to Week 28 inclusive) (Mann-Whitney Estimate)

End point description:

Percentage of days for which participant's Hgb was within the target range of 11-12 grams per deciliter during the evaluation period (Week 24 to Week 28 inclusive), including any unscheduled evaluable Hgb values that were taken during this time period. Percentage of time for which Hgb was within the target range (11-12 grams per deciliter) for a participant was calculated by dividing 'the total number of days that Hgb was within range during Week 24 to 28' by 'the total number of days the participant remained on treatment during Week 24 to 28'. Only those participants with data available at the indicated time points were analyzed.

End point type	Secondary

End point timeframe:

Week 24 to Week 28

End point values	Placebo	Daprodustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216[15]	252[16]		
Units: Percentage of days				
median (full range (min-max))	0.00 (0.0 to 100.0)	53.59 (0.0 to 100.0)		

Notes:

[15] - ITT Population

[16] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis

Statistical analysis description:

Mann-Whitney estimate of the treatment difference stratified by region has been presented.

Comparison groups	Placebo v Daprodustat

Number of subjects included in analysis	468
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [17]
Method	van Elteren test
Parameter estimate	Difference in treatment effect
Point estimate	0.768
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.729
upper limit	0.806

Notes:

[17] - One-sided superiority p-value from the van Elteren test

Secondary: Change from Baseline in Post-randomization Hgb at Week 28

End point title	Change from Baseline in Post-randomization Hgb at Week 28

End point description:

Blood samples were collected at given time points for hemoglobin measurements. Change from Baseline in Hgb was analyzed using a mixed model repeated measures (MMRM) approach. Change from Baseline was calculated as Post-dose visit value minus Baseline. Baseline value was 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 28

End point values	Placebo	Daprodustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301[18]	299[19]		
Units: Grams per deciliter				
least squares mean (standard error)	0.20 (± 0.070)	1.56 (± 0.069)		

Notes:

[18] - ITT Population

[19] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis

Statistical analysis description:

Treatment group comparisons were based on MMRM fitted from baseline up to Week 28, with factors for treatment, time, region, Baseline Hb and Baseline Hb by time and treatment by time interactions.

Comparison groups	Placebo v Daprodustat
Number of subjects included in analysis	600
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [20]
Method	MMRM
Parameter estimate	LS Mean difference
Point estimate	1.36

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.16
upper limit	1.55

Notes:

[20] - One-sided superiority p-value from the MMRM model

Secondary: Rate of participants permanently stopping randomized treatment due to meeting rescue criteria

End point title	Rate of participants permanently stopping randomized treatment due to meeting rescue criteria

End point description:

The incidence rate of participants permanently stopping randomized treatment due to meeting rescue criteria is presented.

End point type	Secondary

End point timeframe:

Up to Week 28

End point values	Placebo	Daprodustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307[21]	307[22]		
Units: Events per 100 person year				
number (confidence interval 95%)	18.88 (12.33 to 27.66)	1.33 (0.16 to 4.82)		

Notes:

[21] - ITT Population

[22] - 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 and region.

Comparison groups	Placebo v Daprodustat
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [23]
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.3

Notes:

[23] - One-sided p-value was based on Wald test of null hypothesis: (Daprodustat/Placebo) >=1 versus alternative: ratio<1.

Secondary: Change from Baseline by domain and single item scores on the Chronic Kidney Disease -Anemia Questionnaire (CKD-AQ) symptom questionnaire

End point title	Change from Baseline by domain and single item scores on the Chronic Kidney Disease -Anemia Questionnaire (CKD-AQ) symptom questionnaire

End point description:

CKD-AQ is 21-item patient reported outcomes measure assessing symptoms & symptom impact in participants with anemia associated with CKD.CKD-AQ identified 3 domains:1.Tired/Low Energy/Weak scale consisting of 10items;2.Chest Pain/Shortness of Breath scale consisting of 4items;3.Cognitive scale consisting of 3items;&single items;4.Difficulty Sleeping;5.Difficulty Standing for long periods of time;6.Severity of Shortness of breath while sitting/resting;7.Time with Shortness of breath while not doing activity.Single-item measures were recorded based on 0-100 scoring:0 is worst possible&100 is best possible score.Total domain score is calculated as average of items in each domain &ranged from 0-100:0 is worst possible &100 is best possible score.Change from Baseline was calculated as post-dose visit value minus Baseline.Baseline value was latest non-missing pre-dose assessment on/before 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 28

End point values	Placebo	Daprodustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193[24]	212[25]		
Units: Scores on a scale				
arithmetic mean (standard error)				
Tired/Low Energy/Weak Domain	2.81 (± 1.132)	8.72 (± 1.086)		
Chest Pain/Shortness of Breath Domain	0.62 (± 0.971)	3.55 (± 0.932)		
Cognitive Domain	0.48 (± 1.042)	4.27 (± 0.999)		
Difficulty in Sleeping	2.61 (± 1.643)	5.22 (± 1.577)		
Difficulty Standing for Long Periods of Time	1.55 (± 1.630)	6.19 (± 1.563)		
Severity of Shortness of Breath While Sitting/Rest	0.43 (± 0.995)	3.11 (± 0.954)		
Time with Shortness of BreathnotDoingActivity	0.29 (± 1.083)	2.30 (± 1.037)		

Notes:

[24] - ITT Population

[25] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis was performed by MMRM with factors for treatment, time, region, Baseline value and Baseline value by time and treatment by time interactions for Tired/Low Energy/Weak domain.

Comparison groups	Placebo v Daprodustat

Number of subjects included in analysis	405
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [26]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	5.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.83
upper limit	9

Notes:

[26] - One-sided p-value was based on test of null hypothesis: (Daprodustat-Placebo) <=0 versus alternative: difference >0.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Analysis was performed by MMRM with factors for treatment, time, region, Baseline value and Baseline value by time and treatment by time interactions for Chest Pain/Shortness of Breath Domain.

Comparison groups	Placebo v Daprodustat
Number of subjects included in analysis	405
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0152 [27]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	2.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	5.57

Notes:

[27] - One-sided p-value was based on test of null hypothesis: (Daprodustat-Placebo) <=0 versus alternative: difference >0.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Analysis was performed by MMRM with factors for treatment, time, region, Baseline value and Baseline value by time and treatment by time interactions for Cognitive Domain.

Comparison groups	Placebo v Daprodustat
Number of subjects included in analysis	405
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0045 [28]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	3.79

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	6.63

Notes:

[28] - One-sided p-value was based on test of null hypothesis: (Daprodustat-Placebo) <=0 versus alternative: difference >0.

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Analysis was performed by MMRM with factors for treatment, time, region, Baseline value and Baseline value by time and treatment by time interactions for Difficulty Sleeping

Comparison groups	Placebo v Daprodustat
Number of subjects included in analysis	405
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1267 [29]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	2.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.87
upper limit	7.09

Notes:

[29] - One-sided p-value was based on test of null hypothesis: (Daprodustat-Placebo) <=0 versus alternative: difference >0.

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

Analysis was performed by MMRM with factors for treatment, time, region, Baseline value and Baseline value by time and treatment by time interactions for Difficulty Standing for Long Periods of Time

Comparison groups	Placebo v Daprodustat
Number of subjects included in analysis	405
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0203 [30]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	4.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	9.09

Notes:

[30] - One-sided p-value was based on test of null hypothesis: (Daprodustat-Placebo) <=0 versus alternative: difference >0.

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

Analysis was performed by MMRM with factors for treatment, time, region, Baseline value and Baseline value by time and treatment by time interactions for Severity of Shortness of Breath While Sitting or Resting

Comparison groups	Placebo v Daprodustat
Number of subjects included in analysis	405
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0266 [31]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	2.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	5.39

Notes:

[31] - One-sided p-value was based on test of null hypothesis: (Daprodustat-Placebo) <=0 versus alternative: difference >0.

Statistical analysis title	Statistical Analysis 7

Statistical analysis description:

Analysis was performed by MMRM with factors for treatment, time, region, Baseline value and Baseline value by time and treatment by time interactions for Time with Shortness of Breath While not Doing an Activity

Comparison groups	Placebo v Daprodustat
Number of subjects included in analysis	405
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0907 [32]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	2.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.94
upper limit	4.96

Notes:

[32] - One-sided p-value was based on test of null hypothesis: (Daprodustat-Placebo) <=0 versus alternative: difference >0.

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. Baseline value was the latest non-missing pre-dose assessment on or before the randomization date. Adjusted mean and standard error is presented. 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 28

End point values	Placebo	Daprodustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193[33]	212[34]		
Units: Scores on a scale				
least squares mean (standard error)	-0.04 (± 0.055)	-0.18 (± 0.052)		

Notes:

[33] - ITT Population

[34] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis

Statistical analysis description:

MMRM fitted from Baseline up to Week 28 with factors for treatment, time, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Placebo v Daprodustat
Number of subjects included in analysis	405
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0391 [35]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.02

Notes:

[35] - One-sided p-value was based on test of null hypothesis: (Daprodustat-rhEPO) >=0 versus alternative: difference <0

Secondary: Change from Baseline in the SF-36 physical functioning Domain

End point title	Change from Baseline in the SF-36 physical functioning Domain

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 eight 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 perception of health. Each domain is scored from 0 (poorer health) to 100 (better health). Physical functioning domain score ranges from 0-100; higher score indicates a better health state and better functioning. Change from Baseline was calculated as post-dose visit value minus Baseline. Baseline value was 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 28

End point values	Placebo	Daprodustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190[36]	210[37]		
Units: Scores on a scale				
least squares mean (standard error)	1.23 (± 1.354)	3.80 (± 1.298)		

Notes:

[36] - ITT Population

[37] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis

Statistical analysis description:

MMRM fitted from Baseline up to Week 28 with factors for treatment, time, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Placebo v Daprodustat
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0858 [38]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	2.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.12
upper limit	6.26

Notes:

[38] - One sided p-value was based on test of null hypothesis: (Daprodustat-Placebo) <=0 vs. alternative: difference >0.

Secondary: Change from Baseline of the SF-36 individual items in the vitality Domain

End point title	Change from Baseline of the SF-36 individual items in the vitality Domain

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 eight 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 perception of health. Individual vitality item includes: 1. Did you feel full of life?, 2. Did you have a lot of energy?, 3. Did you feel worn out?, 4. Did you feel tired?. Score of each item in the vitality domain ranges from 0-100; higher score indicates better health state and better functioning. Change from Baseline was calculated as post-dose visit value minus Baseline. Baseline value was 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 28

End point values	Placebo	Daprodustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190[39]	210[40]		
Units: Scores on a scale				
least squares mean (standard error)				
Did you feel full of life?	-0.02 (± 0.070)	0.16 (± 0.067)		
Did you have a lot of energy?	0.09 (± 0.066)	0.26 (± 0.063)		
Did you feel worn out?	0.16 (± 0.067)	0.34 (± 0.064)		
Did you feel tired?	0.08 (± 0.060)	0.34 (± 0.057)		

Notes:

[39] - ITT Population

[40] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

MMRM fitted from Baseline up to Week 28 with factors for treatment, time, region, Baseline value and Baseline value by time and treatment by time interactions for Did you feel full of life?

Comparison groups	Placebo v Daprodustat
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0357 [41]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.36

Notes:

[41] - One sided p-value based on test of null hypothesis: (Daprodustat-Placebo) <=0 versus alternative: difference >0.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

MMRM fitted from Baseline up to Week 28 with factors for treatment, time, region, Baseline value and Baseline value by time and
treatment by time interactions for Did you have a lot of energy?

Comparison groups	Placebo v Daprodustat
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0328 [42]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.17

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.35

Notes:

[42] - One-sided p-value based on test of null hypothesis: (Daprodustat-Placebo) <=0 versus alternative: difference >0.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

MMRM fitted from Baseline up to Week 28 with factors for treatment, time, region, Baseline value and Baseline value by time and
treatment by time interactions for Did you feel worn out?

Comparison groups	Placebo v Daprodustat
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0252 [43]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.37

Notes:

[43] - One-sided p-value based on test of null hypothesis: (Daprodustat-Placebo) <=0 versus alternative: difference >0.

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

MMRM fitted from Baseline up to Week 28 with factors for treatment, time, region, Baseline value and Baseline value by time and treatment by time interactions for Did you feel tired?

Comparison groups	Placebo v Daprodustat
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [44]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.42

Notes:

[44] - One-sided p-value based on test of null hypothesis: (Daprodustat-Placebo) <=0 versus alternative: difference >0.

Secondary: Number of participants currently employed as per work productivity and activity impairment questionnaire: Anemic symptoms clinical practice version

(WPAI-ANS-CPV)

End point title	Number of participants currently employed as per work productivity and activity impairment questionnaire: Anemic symptoms clinical practice version (WPAI-ANS-CPV)

End point description:

WPAI-ANS-CPV is anemia specific questionnaire designed as self-reported quantitative assessment of social functioning related to work and regular daily activities. It contains 2 concepts-work productivity impairment measured via absenteeism (time missed from work), presenteeism (impairment at work) and regular daily activity impairment. WPAI questions (Q) were:1) currently employed, 2) work time missed due to problem, 3) impairment while working due to problem, 4) overall work impairment due to problem, 5) activity impairment due to problem. WPAI generates 4 domain scores:percent (%) of work time missed(absenteeism),% of impairment while working (presenteeism), % of overall work impairment (absenteeism and presenteeism combined), % of activity impairment. Number of participants currently employed as per WPAI-ANS-CPV is presented. Only those participants with data available at the indicated time points were analyzed (represented by n=X in category titles).

End point type	Secondary

End point timeframe:

Week 8, Week 12 and Week 28

End point values	Placebo	Daprodustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249[45]	251[46]		
Units: Participants				
Week 8, No, n=249, 250	195	204		
Week 8, Yes, n=249, 250	54	46		
Week 12, No, n=234, 251	183	212		
Week 12, Yes, n=234, 251	51	39		
Week 28, No, n=193, 213	158	178		
Week 28, Yes, n=193, 213	35	35		

Notes:

[45] - ITT Population

[46] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in WPAI-ANS-CPV: Percent time missed from Work

End point title	Change from Baseline in WPAI-ANS-CPV: Percent time missed from Work

End point description:

WPAI-ANS-CPV is anemia specific questionnaire designed as self-reported quantitative assessment of social functioning related to work&regular daily activities.It contain concepts-work productivity impairment measured via absenteeism(time missed from work),presenteeism(impairment at work)&regular daily activity impairment.WPAI Qs were:1)currently employed,2)work time missed due to problem,3)impairment while working due to problem,4)overall work impairment due to problem,5)activity impairment due to problem.Percent work time missed due to problem was subscale&calculated as: Q2/(Q2+Q4) for those who were currently employed.Subscale score was expressed as impairment percentage (range:0-100%) where higher numbers indicate greater impairment&less productivity.Change from Baseline was calculated as post-dose visit minus Baseline.Baseline was latest non-missing predose assessment on/before randomization date.Only those participants with data available at indicated time points are presented.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 8, Week 12 and Week 28

End point values	Placebo	Daprodustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50[47]	39[48]		
Units: Percentage of time				
arithmetic mean (standard deviation)				
Week 8, n=50, 39	-2.4 (± 28.40)	-6.1 (± 24.92)		
Week 12, n=46, 31	0.9 (± 28.79)	4.2 (± 27.96)		
Week 28, n=28, 25	0.0 (± 33.59)	0.3 (± 31.01)		

Notes:

[47] - ITT Population

[48] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in WPAI-ANS-CPV: mean hours missed from work in the past 7 days

End point title	Change from Baseline in WPAI-ANS-CPV: mean hours missed from work in the past 7 days

End point description:

WPAI-ANS-CPV is anemia specific questionnaire designed as self-reported quantitative assessment of social functioning related to work and regular daily activities. It contains 2 concepts-work productivity impairment measured via absenteeism (time missed from work), presenteeism (impairment at work) and regular daily activity impairment. WPAI questions (Q) were: 1) currently employed, 2) work time missed due to problem, 3) impairment while working due to problem, 4) overall work impairment due to problem, 5) activity impairment due to problem. Change from Baseline was calculated as post-dose visit value minus Baseline. Baseline value was the latest non-missing pre-dose assessment on or before the randomization date. Only those participants with data available at indicated time points are presented (presented by n=X in category titles).

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 8, Week 12 and Week 28

End point values	Placebo	Daprodustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50[49]	39[50]		
Units: Percentage of hours				
arithmetic mean (standard deviation)				
Week 8, n=50, 39	0.1 (± 18.46)	-1.8 (± 11.88)		
Week 12, n=46, 31	1.4 (± 14.07)	2.4 (± 16.83)		
Week 28, n=28, 25	0.3 (± 19.90)	1.0 (± 14.24)		

Notes:

[49] - ITT Population

[50] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in WPAI: Percent Impairment at Work

End point title	Change from Baseline in WPAI: Percent Impairment at Work

End point description:

WPAI-ANS-CPV is anemia specific questionnaire designed as self-reported quantitative assessment of social functioning related to work&regular daily activities.It contains2concepts-work productivity impairment measured via absenteeism(time missed from work),presenteeism(impairment at work)&regular daily activity impairment.WPAI Qs:1)currently employed,2)work time missed due to problem,3)impairment while working due to problem,4)overall work impairment due to problem,5)activity impairment due to problem.% Impairment while Working due to Problem was subscale&calculated asQ5/10 for those who were currently employed,actually worked in past7day.Subscale score was expressed as impairment percentage(range:0-100%),higher number indicate greater impairment,less productivity.Change fromBaseline=post-dose visit value-Baseline.Baseline was latest non-missing pre-dose assessment on/before randomization date.Only participants with data available at indicated time point are presented(n=X)

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 8, Week 12 and Week 28

End point values	Placebo	Daprodustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45[51]	32[52]		
Units: Percentage of impairment				
arithmetic mean (standard deviation)				
Week 8, n=45, 32	-5.1 (± 18.42)	-11.3 (± 24.06)		
Week 12, n=41, 26	-4.6 (± 18.99)	-8.8 (± 23.38)		
Week 28, n=24, 20	-9.6 (± 25.62)	-9.0 (± 22.92)		

Notes:

[51] - ITT Population

[52] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in WPAI: Percent overall work impairment

End point title	Change from Baseline in WPAI: Percent overall work impairment

End point description:

WPAI-ANS-CPV is anemia specific questionnaire designed as self-reported quantitative assessment of social functioning related to work & regular daily activities. WPAI Questions(Q)were:1)currently employed,2)work time missed due to problem,3)impairment while working due to problem,4)overall

work impairment due to problem,5)activity impairment due to problem.Percent overall work impairment due to problem was subscale & calculated as: Q2/(Q2+Q4)+[(1-Q2/(Q2+Q4))×(Q5/10)] for those who were currently employed.Subscale score was expressed as impairment percentage (range:0-100%) where higher numbers indicate greater impairment. Change from Baseline was calculated as post-dose visit value minus Baseline. Baseline was latest non-missing pre-dose assessment on/before randomization date. Only those participants with data available at indicated time points were analyzed (n=X).

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 8, Week 12 and Week 28

End point values	Placebo	Daprodustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45[53]	32[54]		
Units: Percentage of impairment				
arithmetic mean (standard deviation)				
Week 8, n=45, 32	-4.3 (± 24.04)	-12.0 (± 25.90)		
Week 12, n=41, 26	0.5 (± 25.81)	-3.2 (± 33.35)		
Week 28, n=24, 20	-9.3 (± 37.45)	-8.4 (± 19.12)		

Notes:

[53] - ITT Population

[54] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in WPAI: Percent regular daily activity impairment

End point title	Change from Baseline in WPAI: Percent regular daily activity impairment

End point description:

WPAI-ANS-CPV is anemia specific questionnaire designed as self-reported quantitative assessment of social functioning related to work and regular daily activities.WPAI Questions (Q) were: 1) currently employed, 2) work time missed due to problem, 3) impairment while working due to problem, 4) overall work impairment due to problem, 5) activity impairment due to problem. Percent activity impairment due to problem was a subscale and calculated as: Q5/10 for all respondents. Subscale score was expressed as an impairment percentage (range: 0-100%) where higher numbers indicate greater impairment. Change from Baseline was calculated as post-dose visit value minus Baseline. Baseline value was the latest non-missing pre-dose assessment on or before randomization date.Only those participants with data available at the indicated time points were analyzed (represented by n=X in category titles).

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 8, Week 12 and Week 28

End point values	Placebo	Daprodustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246[55]	248[56]		
Units: Percentage of impairment				
arithmetic mean (standard deviation)				
Week 8, n=243, 248	-4.6 (± 23.67)	-7.7 (± 24.53)		
Week 12, n=228, 246	-5.2 (± 25.40)	-8.6 (± 24.58)		
Week 28, n=187, 210	-6.7 (± 28.93)	-12.2 (± 27.50)		

Notes:

[55] - ITT Population

[56] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EuroQol 5 Dimension 5 Level Health Utility Index (EQ-5D-5L) utility score

End point title	Change from Baseline in EuroQol 5 Dimension 5 Level Health Utility Index (EQ-5D-5L) utility score

End point description:

The EQ-5D-5L is a self-assessment questionnaire, consisting of 5 items covering 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is measured by a 5-point Likert scale (1: no problems, 2: slight problems, 3: moderate problems, 4: severe problems, and 5: extreme problems). The responses for the five dimension together form a five-figure description of health state. Each of these five-figure health states has attached valuation (utility score), expressed as single index on a scale from 0-1, where 1 is full health and 0 is worst health. The higher the score the better the health status. Change from Baseline was calculated as post-dose visit value minus Baseline. Baseline value was the latest non-missing pre-dose assessment on or before the randomization date. Only those participants with data available at indicated time points are presented.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 28

End point values	Placebo	Daprodustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106[57]	116[58]		
Units: Scores on a scale				
least squares mean (standard error)	0.01 (± 0.015)	0.03 (± 0.014)		

Notes:

[57] - ITT Population

[58] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis

Statistical analysis description:

Based on MMRM model fitted from Baseline up to Week 28 with factors for treatment, time, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Placebo v Daprodustat

Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1098 [59]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.07

Notes:

[59] - One-sided p-value was based on test of null hypothesis: (Daprodustat-Placebo) <=0 versus. alternative: difference >0.

Secondary: Change from Baseline in EuroQol visual analogue scale (EQ-VAS) score

End point title	Change from Baseline in EuroQol visual analogue scale (EQ-VAS) score

End point description:

The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled 'the best health you can imagine' and 'the worst health you can imagine' at the time of completion. It is a self-assessment visual analogue scale, ranging from 0=worst imaginable to 100=best. Change from Baseline was calculated as post-dose visit value minus Baseline. Baseline value was the latest non-missing pre-dose assessment on or before the randomization date. Adjusted mean and standard error is presented. Only those participants with data available at indicated time points are presented.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 28

End point values	Placebo	Daprodustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106[60]	116[61]		
Units: Scores on a scale				
least squares mean (standard error)	0.80 (± 1.427)	5.30 (± 1.373)		

Notes:

[60] - ITT Population

[61] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis

Statistical analysis description:

Mixed model repeated measures model fitted from Baseline up to Week 28 with factors for treatment, time, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Placebo v Daprodustat

Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012 [62]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	8.4

Notes:

[62] - One-sided p-value was based on test of null hypothesis: (Daprodustat-Placebo) <=0 vs. alternative: difference >0.

Secondary: Change from Baseline in systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) at Week 28

End point title	Change from Baseline in systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) at Week 28

End point description:

SBP, DBP and MAP were measured with participants in a seated position after at least a 5-minute of rest. MAP is the average BP in an individual's arteries during a single cardiac cycle. Change from Baseline was calculated as post-dose visit value minus Baseline. Baseline value was 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 28

End point values	Placebo	Daprodustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202[63]	230[64]		
Units: Millimeters of mercury (mmHg)				
least squares mean (standard error)				
SBP	-0.63 (± 1.045)	-0.23 (± 0.981)		
DBP	-0.96 (± 0.625)	0.84 (± 0.587)		
MAP	-0.82 (± 0.674)	0.49 (± 0.632)		

Notes:

[63] - ITT Population

[64] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

MMRM model fitted from Baseline up to Week 28, with factors for treatment, time, region, Baseline SBP and Baseline SBP by time and treatment by time interactions.

Comparison groups	Placebo v Daprodustat
Number of subjects included in analysis	432
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6106 [65]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.42
upper limit	3.22

Notes:

[65] - One-sided p-value was based on test of null hypothesis: (Daprodustat - Placebo) >= 0 versus alternative:
difference <0

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

MMRM model fitted from Baseline up to Week 28, with factors for treatment, time, region, Baseline DBP and Baseline DBP by time and treatment by time interactions.

Comparison groups	Placebo v Daprodustat
Number of subjects included in analysis	432
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9819 [66]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	3.49

Notes:

[66] - One-sided p-value was based on test of null hypothesis: (Daprodustat - Placebo) >= 0 versus alternative:
difference < 0

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

MMRM model fitted from Baseline up to Week 28, with factors for treatment, time, region, Baseline MAP and Baseline MAP by time and treatment by time interactions.

Comparison groups	Placebo v Daprodustat
Number of subjects included in analysis	432
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9215 [67]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	1.31

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	3.13

Notes:

[67] - One-sided p-value was based on test of null hypothesis: (Daprodustat - Placebo) >= 0 versus alternative:
difference <0

Secondary: Percentage of participants with at least one BP) exacerbation event

End point title	Percentage of participants with at least one BP) exacerbation event

End point description:

Percentage of participants with at least one BP exacerbation event is presented. BP exacerbation is defined as: SBP exacerbation: SBP >= 25 mmHg increase from Baseline or SBP >= 180 mmHg; DBP exacerbation: DBP >= 15 mmHg increase from Baseline or DBP >= 110 mmHg. Percentage of participants with at least one BP exacerbation event is presented. The percentage values presented has been rounded off.

End point type	Secondary

End point timeframe:

Up to Week 28

End point values	Placebo	Daprodustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	307		
Units: Percentage of participants	26	32		

Statistical analyses

Statistical analysis title	Statistical Analysis

Statistical analysis description:

Cochran-Mantel-Haenszel test was performed for treatment group comparison.

Comparison groups	Placebo v Daprodustat
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.068 [68]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response rate
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.13

Notes:

[68] - One-sided p-value based on test of null hypothesis: (Daprodustat - Placebo) <= 0 versus alternative: difference > 0.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All cause mortality, serious adverse events (SAEs) and non-serious AEs were collected up to follow-up (Week 32).

Adverse event reporting additional description:

Safety Population comprised of all randomized participants who received at least 1 dose of study treatment.Treatment emergent non-serious adverse events & serious adverse events are reported.One participant who was randomized to placebo accidently received daprodustat during study & was evaluated in daprodustat treatment group for safety outcome.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received matching placebo once daily orally for up to 28 weeks followed by 4 weeks of follow-up.

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 milligrams (mg) once daily orally for up to 28 weeks, followed by 4 weeks of follow-up. Study treatment was dose-titrated to achieve and maintain hemoglobin in the target range (11 to 12 grams per deciliter [g/dL])

Serious adverse events	Placebo	Daprodustat	
Total subjects affected by serious adverse events			
subjects affected / exposed	68 / 306 (22.22%)	62 / 308 (20.13%)	
number of deaths (all causes)	16	10	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary tumour benign			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			

subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 306 (0.65%)	2 / 308 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	3 / 306 (0.98%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
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			

Death			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 306 (0.33%)	3 / 308 (0.97%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 306 (0.33%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute interstitial pneumonitis			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial hyperreactivity			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pleural effusion			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 306 (0.00%)	2 / 308 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			

subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney rupture			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant dysfunction			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			

subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	2 / 306 (0.65%)	3 / 308 (0.97%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	4 / 306 (1.31%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	2 / 306 (0.65%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 306 (0.00%)	3 / 308 (0.97%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bradycardia			
subjects affected / exposed	2 / 306 (0.65%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	0 / 306 (0.00%)	2 / 308 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (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	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial flutter			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 306 (0.33%)	4 / 308 (1.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tricuspid valve incompetence			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 306 (0.00%)	3 / 308 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autonomic nervous system imbalance			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			

subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (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			
Anaemia			
subjects affected / exposed	8 / 306 (2.61%)	2 / 308 (0.65%)	
occurrences causally related to treatment / all	1 / 9	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tympanic membrane perforation			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Ulcerative keratitis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 306 (0.65%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vomiting			
subjects affected / exposed	1 / 306 (0.33%)	2 / 308 (0.65%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 306 (0.65%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 306 (0.33%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (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 / 306 (0.33%)	0 / 308 (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 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
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			
Skin ulcer			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	5 / 306 (1.63%)	5 / 308 (1.62%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal failure			
subjects affected / exposed	6 / 306 (1.96%)	2 / 308 (0.65%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
End stage renal disease			
subjects affected / exposed	2 / 306 (0.65%)	2 / 308 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal impairment			
subjects affected / exposed	2 / 306 (0.65%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Azotaemia			
subjects affected / exposed	1 / 306 (0.33%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary retention			
subjects affected / exposed	2 / 306 (0.65%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
IgA nephropathy			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy toxic			

subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal haematoma			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atlantoaxial instability			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (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			
Sepsis			
subjects affected / exposed	2 / 306 (0.65%)	2 / 308 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 306 (0.65%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary tract infection			
subjects affected / exposed	4 / 306 (1.31%)	2 / 308 (0.65%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	2 / 306 (0.65%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 306 (0.33%)	2 / 308 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 306 (0.00%)	2 / 308 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
COVID-19			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endophthalmitis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (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 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (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 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoglycaemia			

subjects affected / exposed	1 / 306 (0.33%)	2 / 308 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	1 / 306 (0.33%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 306 (0.00%)	1 / 308 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 306 (0.33%)	0 / 308 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Daprodustat	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 306 (14.38%)	49 / 308 (15.91%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	14 / 306 (4.58%)	21 / 308 (6.82%)	
occurrences (all)	14	27	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	21 / 306 (6.86%)	12 / 308 (3.90%)	
occurrences (all)	23	14	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	17 / 306 (5.56%)	24 / 308 (7.79%)	
occurrences (all)	22	26	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 April 2018	Country Specific Protocol ITA-1: Edited footnote 11 to include evaluation of all iron parameters at Week 4 in Section 2: Schedule of Activities; Exclude participants with a lower electrocardiogram (ECG) criteria based on Frederica's QT Interval Corrected for Heart Rate (QTcF) and not Bazett's QT Interval Corrected for Heart Rate (QTcB); exclude participants with second or third degree atrioventricular (AV) block in Exclusion Criteria (Crit) Exclusion 18; replaced QTcB with QTcF in Electrocardiograms section.
23 August 2019	Amendment 1:Added footnote17 to state when study treatment should be dispensed;Revised footnote9 to permit HemoCue Hgb retest with new blood sample; Revised footnote12 to clarify the purpose of participant reminder card;Edited footnote15 to add ultrasound assessments for ADPKD participants at end of treatment.Added row to conduct assessment regarding HCRU by participants at each visit starting with Day1 & after study treatment discontinuation;Added renal ultrasound for ADPKD participants upon discontinuation of study treatment ;Updated risk assessment table with language related to IB update;Added secondary & exploratory endpoints objectives related to BP exacerbations & concomitant medications;Revised secondary endpoints for work productivity& regular daily activity impairment captured on WPAI-ANS-CPV;Amended exploratory objectives for Hgb change to evaluate participants achieving Hgb increase of >=1.0 g/dL instead of >=1.2g/dL;Updated exploratory objective to capture time to first rhEPO Transfusion use;Edited inclusion Crit5 to provide clarity for requirements of compliance with oral iron dosing prior to Day1 & removed need for stable iron dose prior to screening;Edited ex crit 13 edited to include use of investigational device;Added ex crit22 for uncontrolled hypertension;Instructions to repeat & average HemoCue Hgb assessment for Hgb <8.5 g/dL;Added information regarding discontinuation of study treatment in participants with ADPKD;Added language related to alternative methods of follow-up;Added language regarding alternative methods of follow-up for participants potentially lost to follow-up;Added language regarding retests with new blood sample entering HemoCue Hgb values into IRT system;Added worsening of hypertension as additional AESI; Added guidance on conducting ultrasound for participants with ADPKD based on different clinical scenarios in study;Changes made to provide guidance regarding the conduct of study at French site only.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported