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SUPPLEMENTAL METHODS

Study Procedures and Assessments

Blood Sampling

Blood samples for hemoglobin analysis via HemoCue (HemoCue AB. Angelholm, Sweden) and the central laboratory were collected at screening, Day 1 (randomization), every 2 weeks until Week 8, and every 4 weeks until Week 52. An additional sample was collected at follow-up for analysis by the central laboratory. Samples taken at screening, randomization, every 12 weeks until Week 52, and at follow-up were also used for additional hematology assessments, clinical chemistry, and iron data.

BP and Heart Rate Monitoring

BP and heart rate were recorded at screening, Day 1, every 2 weeks until Week 8, and then every 4 weeks until Week 52. Triplicate measurements were taken on Day 1 and Week 52 (early treatment discontinuation visit for participants who permanently discontinued study treatment). BP elevation was defined as an increase in systolic BP of ≥25 mmHg from baseline or systolic BP ≥180 mmHg or an increase in diastolic BP of ≥15 mmHg from baseline or diastolic BP ≥110 mmHg.

Safety

Safety assessments were conducted at screening, Day 1, every 2 weeks until Week 8, every 4 weeks until Week 52, and at follow-up.

AESIs were defined for daprodustat based on data from non-clinical and clinical studies, current information about HIF-associated pathophysiology, and identified risks for ESAs. A programmatic approach for identifying potential AESIs was implemented using a broad set of predefined terms of interest.

Statistical Analysis

Other secondary endpoints were also analyzed using the ITT population. Regions were defined as follows: 1: Republic of Korea, 2: Poland, Romania, Russian Federation, 3: Australia, Canada, France, Italy, Spain, United Kingdom 4: Argentina, Brazil, and 5: United States. For the hemoglobin responder analysis, a Cochran-Mantel-Haenszel Chi-squared test, adjusting for treatment and region, was used to compare the proportion of responders between the treatment groups. Baseline ESA hyporesponders were defined as participants with Erythropoietin Resistance Index (ERI) ≥2.0 U/kg/wk/g/L (prior epoetin) or ≥0.008 µg/kg/wk/g/L (prior darbepoetin alfa) or ≥0.01 µg/kg/wk/g/L (prior methoxy polyethylene glycol [PEG]-epoetin beta), or if treated with the equivalent of ≥450 U/kg/week IV epoetin.

Subgroup analyses were conducted using analogous statistical models to the primary analysis, with the addition of subgroup and treatment-by-subgroup interaction terms. Although subgroup analyses were pre-planned, these analyses are noted as post-hoc because the methods used to generate the interaction p-value were modified post-hoc to use Rubin's rules.

The secondary safety endpoint of change from baseline in BP at Week 52 analyses were conducted via a mixed model for repeated measures approach with an unstructured covariance matrix to compare the difference between treatment arms in the ITT population. The model included factors for treatment, time, region, baseline BP parameter, and the baseline BP parameter by time and treatment by time interaction terms. Additional safety endpoints were assessed descriptively using the safety population, except for MACE, which was investigated in the ITT population. Analyses for the ratio of model estimated BP elevation rate was based on a negative binomial model with treatment and region as covariates and the logarithm of time on-treatment as an offset variable.

Calculation of cardiovascular risk score

A risk score for two-year cardiovascular mortality and morbidity in a hemodialysis population has been

developed and was calculated at baseline for each participant[1].

The following table describes how the published risk score was calculated:

Parameter (unit) and values	Risk score points
Age, years	
≤39	-5
40 to 49	-2
50 to 59	0
60 to 69	2
70 to 79	4
≥80	6
Smoking status	
Current	1
Former	2
Non-smoker	0
Cardiovascular disease history	
Yes	7
No	0
Pre-dialysis systolic BP, mmHg	
<120	3
120 to <130	0
130 to <140	1
140 to <160	1
≥160	2
CKD etiology	
Hypertension/vascular	1
Glomerulonephritis	0
Diabetes	4
Tubulo-interstitial	-1
Polycystic kidney disease	0
Unknown renal diagnosis	0
Intradialytic weight change, kg	
< -2.2	3
-2.2 to < -1.7	2
-1.7 to < -1.2	1
> -1.2	0
Hemoglobin, g/dL	
<10.0	1
10.0 to <12.0	0
≥12.0	-3
Reactive protein, mg/L	

<2.4	0
2.4 to <6.8	1
6.8 to <18.0	1
≥18.0	3
Serum albumin, g/L	
<35	2
≥35	0
Creatinine, mg/dL	
<4.93	3
4.93 to <6.13	0
6.13 to <7.67	1
≥7.67	0
Calcium, mg/dL	
<8.4	0
8.4 to <10.4	0
≥10.4	5
Total cumulated risk points	
BP, blood pressure; CKD, chronic kidney disease.	

Since creatinine was not routinely collected in this study, it was assumed to be the same in all hemodialysis participants (i.e. <4.93, resulting in 3 risk score points). Cardiovascular disease (CVD) history was defined as having a yes response to any of the following medical history conditions: angina pectoris, myocardial infarction, stroke, coronary artery disease, transient ischaemic attack, heart failure, atrial fibrillation, cardiac arrest, and/or valvular heart disease. Intradialytic weight change was calculated using the Week -4 post-dialysis weight in kg minus the Week -4 pre-dialysis weight in kg.

Baseline hemoglobin categories were defined based on g/dL units (i.e. <10, 10-<12 and >12) and used central laboratory hemoglobin values if available. If a baseline central laboratory hemoglobin value were not available, a baseline HemoCue hemoglobin value was used.

Risk score points for CKD etiology was determined based on the following approach:

i. Participants with diabetic renal disease were assigned 4 points

ii. All other participants who had hypertensive renal disease were assigned 1 point

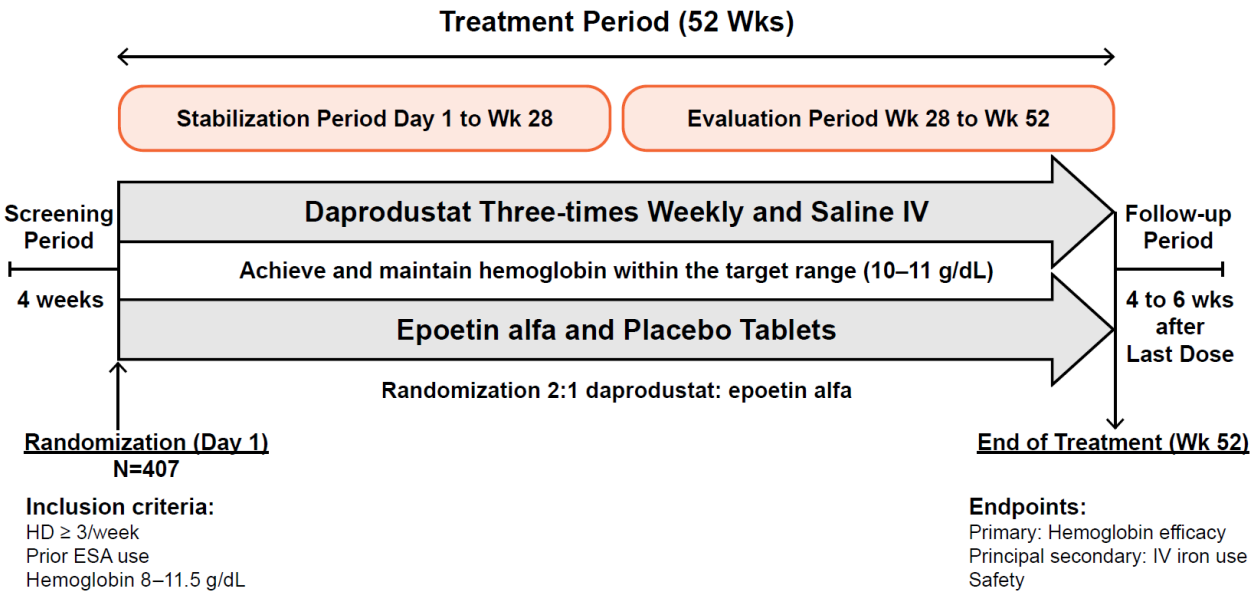
iii. All other participants who had interstitial nephritis were assigned -1 point

iv. All other participants who had a medical history of polycystic kidney, autosomal dominant or did not have any of these medical history terms selected were assigned 0 points

The overall cardiovascular risk score was determined by summing up the individual risk scores for the 11 risk factors.

SUPPLEMENTAL FIGURES

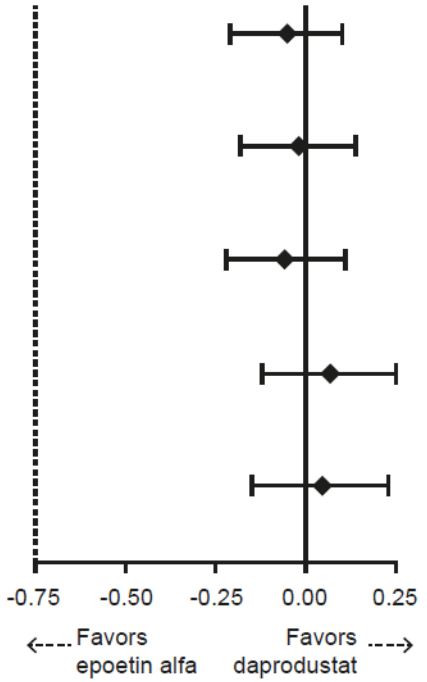
Supplemental Figure 1. Study design



ESA, erythropoiesis-stimulating agent; HD, hemodialysis; IV, intravenous; Wk(s), week(s)

Supplemental Figure 2. Supportive analyses of primary efficacy endpoint

Analysis	Treatment	n/N (%)	Adjusted Mean Hemoglobin (g/dL) Difference (95% CI)
Primary: Post-randomization hemoglobin, Wk 28–52 (Intent-to-treat)	Daprodustat	270/270 (100%)	-0.05 (-0.21, 0.10)
	Epoetin alfa	137/137 (100%)	
Evaluable hemoglobin, Wk 28–52 (Intent-to-treat)	Daprodustat	215/270 (80%)	-0.02 (-0.18, 0.14)
	Epoetin alfa	107/137 (78%)	
Evaluable hemoglobin, Wk 28–52 (Intent-to-treat)	Daprodustat	143/143 (100%)	-0.06 (-0.22, 0.11)
	Epoetin alfa	82/82 (100%)	
Post-randomization hemoglobin, Wk 28–36 (Intent-to-treat)	Daprodustat	270/270 (100%)	0.07 (-0.12, 0.25)
	Epoetin alfa	137/137 (100%)	
Evaluable hemoglobin, Wk 28–36 (Intent-to-treat)	Daprodustat	213/270 (79%)	0.04 (-0.15, 0.23)
	Epoetin alfa	105/137 (77%)	

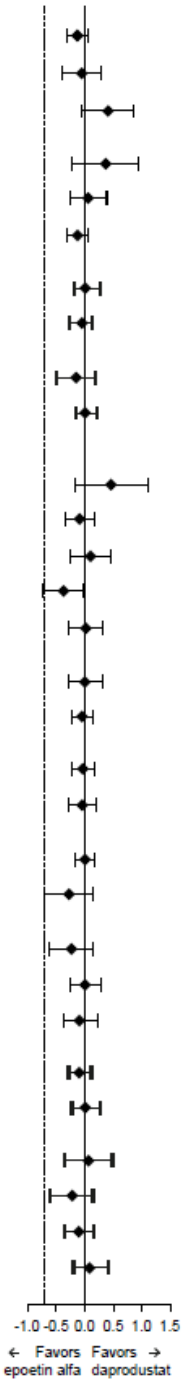


Note: A supportive analysis was performed for the primary ITT analysis, repeating the analysis using an alternative evaluation period (Week 28 to 36). Per-protocol (PP) population: All ITT participants who did not have PP population exclusions. This population was the basis for the supportive analysis of the primary efficacy parameter. Participants were analyzed according to the treatment to which they were randomized. The PP population was not planned to be analyzed if this population comprised more than 80% of the ITT population.

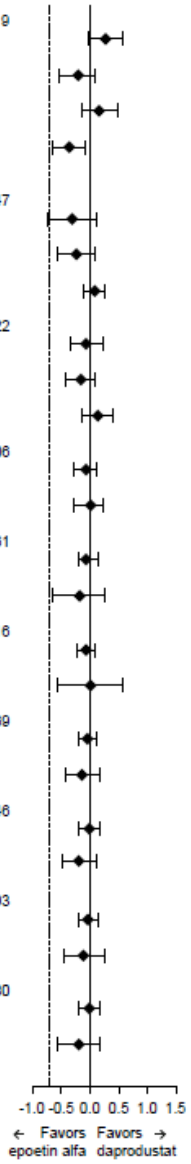
CI, confidence interval; ITT, intent-to-treat; Wk, week.

Supplemental Figure 3. Adjusted means for the analysis of post-randomization hemoglobin change from baseline to the evaluation period by subgroup (Intent-to-treat population; Post hoc analysis)

Subgroup	Treatment	n	Adjusted mean difference (95% CI)	P-Value (two sided) for interaction
Age (grouping 1)				0.0839
<65 years	Daprodustat	167	-0.14 (-0.33, 0.05)	
	Epoetin alfa	96		
65 to <75 years	Daprodustat	66	-0.06 (-0.41, 0.29)	
	Epoetin alfa	24		
≥75 years	Daprodustat	37	0.41 (-0.05, 0.88)	
	Epoetin alfa	16		
Race				0.2322
Asian	Daprodustat	20	0.37 (-0.24, 0.98)	
	Epoetin alfa	9		
Black or African American	Daprodustat	49	0.07 (-0.27, 0.41)	
	Epoetin alfa	32		
White	Daprodustat	195	-0.13 (-0.32, 0.06)	
	Epoetin alfa	94		
Sex				0.5053
Female	Daprodustat	121	0.01 (-0.23, 0.25)	
	Epoetin alfa	56		
Male	Daprodustat	149	-0.10 (-0.31, 0.11)	
	Epoetin alfa	81		
Ethnicity				0.3613
Hispanic or Latino	Daprodustat	69	-0.18 (-0.52, 0.15)	
	Epoetin alfa	33		
Not Hispanic or Latino	Daprodustat	198	0.00 (-0.18, 0.18)	
	Epoetin alfa	104		
Region				0.1840
1: Asia Pacific	Daprodustat	15	0.48 (-0.18, 1.14)	
	Epoetin alfa	8		
2: Eastern Europe	Daprodustat	87	-0.08 (-0.35, 0.19)	
	Epoetin alfa	44		
3: Western Europe/Canada/Australia	Daprodustat	49	0.09 (-0.27, 0.46)	
	Epoetin alfa	24		
4: Latin America	Daprodustat	48	-0.38 (-0.76, 0.00)	
	Epoetin alfa	25		
5: USA	Daprodustat	71	0.00 (-0.31, 0.30)	
	Epoetin alfa	36		
Region combined				0.7269
USA	Daprodustat	71	0.00 (-0.31, 0.31)	
	Epoetin alfa	36		
Non-USA	Daprodustat	199	-0.07 (-0.25, 0.12)	
	Epoetin alfa	101		
Standardized prior ESA dose group				0.8858
<7,000 U/week	Daprodustat	145	-0.03 (-0.24, 0.17)	
	Epoetin alfa	84		
≥7,000 U/week	Daprodustat	125	-0.06 (-0.31, 0.20)	
	Epoetin alfa	53		
rhEPO Hypo-responder				0.2337
No	Daprodustat	233	-0.01(-0.18, 0.16)	
	Epoetin alfa	116		
Yes	Daprodustat	37	-0.29 (-0.72, 0.14)	
	Epoetin alfa	21		
Hemoglobin Category at Baseline				0.5347
<10g/dL	Daprodustat	66	-0.27 (-0.65, 0.11)	
	Epoetin alfa	26		
≥10 and ≤11g/dL	Daprodustat	141	-0.01 (-0.27, 0.26)	
	Epoetin alfa	60		
>11g/dL	Daprodustat	63	-0.09 (-0.40, 0.22)	
	Epoetin alfa	51		
Post-Dialysis BMI Category at Baseline				0.4211
<30 kg/m²	Daprodustat	191	-0.09 (-0.28, 0.9)	
	Epoetin alfa	98		
≥30 kg/m²	Daprodustat	78	0.05 (-0.24, 0.34)	
	Epoetin alfa	39		
Post-Dialysis Weight Cat.1 at Baseline				0.4673
Quartile 1: <63.30kg	Daprodustat	69	0.05 (-0.28, 0.37)	
	Epoetin alfa	31		
Quartile 2: 63.30 to <74.20kg	Daprodustat	67	-0.23 (-0.53, 0.07)	
	Epoetin alfa	36		
Quartile 3: 74.20 to <87.00kg	Daprodustat	68	-0.11 (-0.43, 0.21)	
	Epoetin alfa	33		
Quartile 4: ≥87.00kg	Daprodustat	66	0.09 (-0.22, 0.40)	
	Epoetin alfa	37		



Subgroup	Treatment	n	Adjusted mean difference (95% CI)	P-Value (two sided) for interaction
hsCRP Quartiles at Baseline				0.0119
Quartile 1: < 1.70 mg/L	Daprodustat	67	0.27 (-0.05, 0.59)	
	Epoetin alfa	33		
Quartile 2: 1.70 to < 4.30 mg/L	Daprodustat	65	-0.24 (-0.56, 0.08)	
	Epoetin alfa	31		
Quartile 3: 4.30 to < 11.10 mg/L	Daprodustat	74	0.16 (-0.16, 0.47)	
	Epoetin alfa	31		
Quartile 4: ≥ 11.10 mg/L	Daprodustat	60	-0.37 (-0.67, -0.07)	
	Epoetin alfa	41		
Smoking History				0.1247
Current smoker	Daprodustat	25	-0.32 (-0.75, 0.12)	
	Epoetin alfa	23		
Former smoker	Daprodustat	62	-0.24 (-0.57, 0.08)	
	Epoetin alfa	34		
Never smoked	Daprodustat	183	0.07 (-0.13, 0.27)	
	Epoetin alfa	80		
Dialysis Vintage at Randomization				0.3122
<2 years	Daprodustat	82	-0.08 (-0.36, 0.21)	
	Epoetin alfa	42		
≥2 to <5 Years	Daprodustat	95	-0.17 (-0.43, 0.08)	
	Epoetin alfa	52		
≥5 Years	Daprodustat	93	0.12 (-0.16, 0.40)	
	Epoetin alfa	43		
History of Diabetes				0.6806
No	Daprodustat	165	-0.08 (-0.28, 0.12)	
	Epoetin alfa	84		
Yes	Daprodustat	105	-0.01 (-0.26, 0.24)	
	Epoetin alfa	53		
History of Stroke				0.5561
No	Daprodustat	244	-0.03 (-0.20, 0.14)	
	Epoetin alfa	118		
Yes	Daprodustat	26	-0.18 (-0.64, 0.28)	
	Epoetin alfa	19		
History of Myocardial Infarction				0.8316
No	Daprodustat	239	-0.06 (-0.22, 0.11)	
	Epoetin alfa	128		
Yes	Daprodustat	31	0.01 (-0.57, 0.59)	
	Epoetin alfa	9		
History of HF				0.6369
No	Daprodustat	204	-0.03 (-0.21, 0.15)	
	Epoetin alfa	104		
Yes	Daprodustat	66	-0.12 (-0.44, 0.20)	
	Epoetin alfa	33		
History of Thromboembolic Events				0.3946
No	Daprodustat	218	-0.03 (-0.21, 0.16)	
	Epoetin alfa	101		
Yes	Daprodustat	52	-0.19 (-0.50, 0.13)	
	Epoetin alfa	36		
Hospitalization within 6 months of Screening				0.7593
No	Daprodustat	216	-0.04 (-0.21, 0.14)	
	Epoetin alfa	108		
Yes	Daprodustat	54	-0.10 (-0.45, 0.25)	
	Epoetin alfa	29		
ACEI/ARB Use at Baseline				0.4280
No	Daprodustat	220	-0.03 (-0.20, 0.15)	
	Epoetin alfa	116		
Yes	Daprodustat	50	-0.19 (-0.57, 0.18)	
	Epoetin alfa	21		

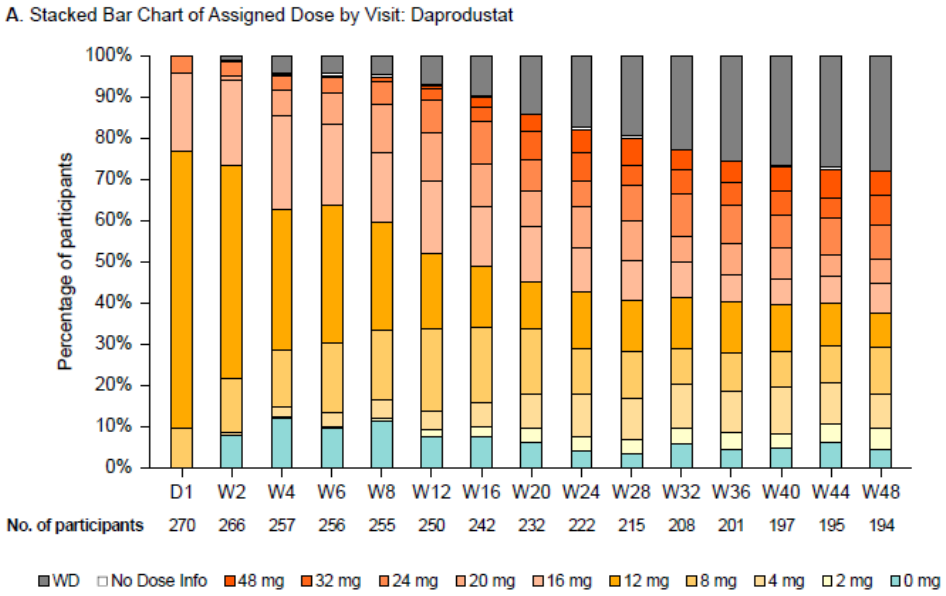


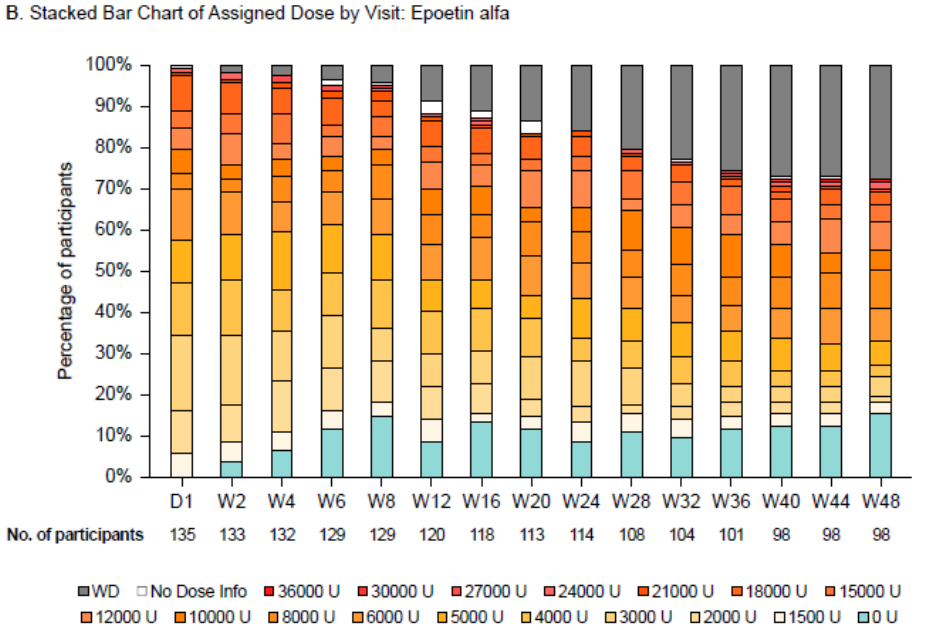
Note: Post-randomization values include on- and off-treatment values. For Region Subgroups : Based on an ANCOVA model with terms for treatment, baseline hemoglobin, subgroup and treatment by subgroup interaction. For Hemoglobin Category at Baseline subgroup: Based on an ANCOVA model with terms for treatment, region, subgroup and treatment by subgroup interaction. For Other Subgroups: Based on an ANCOVA model with terms for treatment, baseline hemoglobin, region subgroup and

treatment by subgroup interaction. Hemoglobin values during the evaluation period include both observed and imputed values.

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; CI, confidence interval; ESA, erythropoiesis-stimulating agent; HF, heart failure; hsCRP, high-sensitivity C-reactive protein; mycocardial infarction; rhEPO, recombinant human erythropoetin.

Supplemental Figure 4. Stacked bar chart of assigned dose by visit for (A) daprodustat and (B) epoetin alfa (Intent-to-treat population)





Note: "WD" includes subjects who were permanently IP discontinued, and subjects who withdrew from the study. "No dose info" includes subjects with missing data due to skipped visits, unavailable randomized treatment, or other reasons. 1 subject in the epoetin group who was randomized but never dosed, is not included in the stacked bar chart.

SUPPLEMENTAL TABLES

Supplemental Table 1. Inclusion, exclusion, and stopping criteria

Inclusion criteria

- Male or female, between 18 and 99 years of age
- A female is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
    - Not a woman of childbearing potential (WOCBP), or a WOCBP who agrees to follow the contraceptive guidance from at least 28 days prior to first dose of study treatment and for at least 28 days after the last dose of study treatment.
- Use of any approved recombinant human erythropoietin (rhEPO) or analogue for at least 8 weeks prior to the screening visit and continuing during the screening period until randomization
- Anemia of CKD being treated with erythropoiesis-stimulating agents (ESA)
- Receiving in-center hemodialysis (HD; including hemofiltration or hemodiafiltration) for greater than 90 days and at least 3 times per week
- Hemoglobin at screening within the range of 8 to 11.5 g/dL. If hemoglobin is 11.6 to 11.9 g/dL, up to two retests are allowed; the retest value must be between 8 g/dL and 11.5 g/dL
- Hemoglobin at randomization within the range of 8 g/dL to 11 g/dL when receiving at least the minimum dose of ESA. Hemoglobin >11 g/dL to 11.5 g/dL at randomization permitted if receiving greater than the minimum dose of ESA
- Minimum ESA at randomization were: epoetins, 1500 U/week (IV) or 1000 U/week subcutaneous (SC); darbepoetin alfa, 20 μg/4 weeks (IV and SC), and methoxy polyethylene glycol [PEG]-epoetin beta 30 μg/month (IV and SC)
- Capable of giving signed informed consent

Exclusion criteria

- Planned kidney transplantation within 52 weeks after randomization
- Ferritin ≤100 ng/mL or transferrin saturation (TSAT) ≤20% at screening
- Anemia other than anemia of CKD
- History of bone marrow aplasia or pure red cell aplasia
- Gastrointestinal bleeding
- Myocardial infarction, acute coronary syndrome, stroke, or transient ischemic attack within 8 weeks prior to screening through to randomization
- Bazett's correction of Q-wave to T-wave interval (QTcB) >500 msec (or >530 msec in participants with bundle branch block) at randomization
- Chronic class IV heart failure, and uncontrolled hypertension
- Liver disease or known hepatic or biliary abnormalities
- History of malignancy within 2 years of screening through to Day 1
- Use of a strong inhibitor of cytochrome P2C8 (CYP2C8; eg, gemfibrozil) or a strong inducer of CYP2C8 (eg, rifampin/rifampicin)
- Severe allergic reactions: History of severe allergic or anaphylactic reactions or hypersensitivity to excipients in the investigational product (refer to daprodustat Investigator's Brochure), or epoetin (refer to product labeling)
- Other interventional study participation: Use of another investigational agent within 30 days or within five half-lives of the investigational agent (whichever is longer) or currently participating in a study of an investigational device prior to screening through to randomization (Day 1)
- Prior treatment with daprodustat: Any prior treatment with daprodustat for treatment duration of >30 days
- Other conditions: Any other condition, clinical or laboratory abnormality, or examination finding that the investigator considers would put the participant at unacceptable risk, which may affect study compliance (eg, intolerance to rhEPO) or prevent understanding of the aims or investigational procedures or possible consequences of the study

Stopping criteria included:

- Need for rescue treatment.
- Pregnancy.

- Switch to peritoneal dialysis or home HD or to a standing dialysis schedule that was less often than three-times-weekly
- Kidney transplant
- Diagnosis of cancer
- Liver chemistry abnormalities
- Need for prohibited medication

Participants who permanently discontinued study treatment remained in the study and were expected to attend study visits unless they were actively withdrawn from the study

Supplemental Table 2. Study objectives and endpoints

Objectives	Endpoints
Primary	
• To compare the effect of daprodustat with epoetin on hemoglobin efficacy when administered three-times-weekly to hemodialysis (HD)-dependent patients (non-inferiority)	• Mean change in hemoglobin from baseline to the average during the evaluation period (mean over Weeks 28 to 52)
Principal Secondary (tested for superiority, adjusted for multiplicity)	
• To compare daprodustat administered three-times-weekly to epoetin on the use of IV iron	• Average monthly IV iron dose (mg)/participant to Week 52
Safety	
• To compare the safety and tolerability of daprodustat administered three-times-weekly to epoetin	• Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) including AEs of special interest (AESI) and major adverse cardiovascular events (MACE) • Reasons for discontinuation of study treatment • Absolute values and changes from baseline in laboratory parameters, blood pressure (BP) and heart rate
Secondary (endpoints tested for superiority*, with no multiplicity adjustment)	
• To compare the effect of daprodustat administered three-times-weekly to epoetin on hemoglobin variability	• Hemoglobin change from baseline to Week 52[a] • % time hemoglobin in analysis range (10 g/dL to 11.5 g/dL) during the evaluation period[a] • N (%) hemoglobin responders, defined as participants with mean hemoglobin within the hemoglobin analysis range 10 g/dL to 11.5 g/dL during the evaluation period

Objectives	Endpoints
• To compare daprodustat administered three-times-weekly to epoetin on the time to rescue	• Time to permanently stopping study treatment due to meeting rescue criteria
• To compare the effect of daprodustat administered three-times-weekly to epoetin on blood pressure (BP)	• Change from baseline in systolic BP, diastolic BP and mean arterial pressure (MAP) at Week 52 and at the end of study treatment • Number of BP elevation events per 100 person-years • N (%) with at least one BP elevation event during study
• To generate pharmacokinetic parameters of daprodustat and predominant metabolites following three-times-weekly dosing	• Plasma daprodustat, M2, M3, M4, M5, M6 and M13 PK parameters pre-dose trough (Ctau) and maximum concentration (C_{max})
• To compare daprodustat administered three-times-weekly to epoetin on global symptom severity	• Change from baseline at Weeks 8,12, 28, and 52 in Patient Global Impression of Change (PGI-C)
Exploratory (no statistical testing planned)	
• To evaluate graphical relationships between exposure parameters and selected efficacy endpoints of daprodustat administered three-times-weekly	• Extrapolated C_{max} of daprodustat vs the percent time within the hemoglobin target range during the evaluation period • Extrapolated C_{max} of daprodustat vs mean hemoglobin over the 52-week treatment period • Mean weekly daprodustat dose over 52 weeks vs the percent time within the hemoglobin target range during the evaluation period • Mean weekly daprodustat dose over 52 weeks vs mean hemoglobin over the 52-week treatment period
• To evaluate graphical relationships between daprodustat administered three-times-weekly against MACE and the combined safety endpoint of MACE + thromboembolic event + hospitalization for congestive heart failure (CHF)	• Extrapolated C_{max} of daprodustat in participants without MACE compared with those with MACE (as well as for the combined safety endpoint of MACE + thromboembolic event + hospitalization for CHF)

Objectives	Endpoints
	• Mean weekly daprodustat dose in participants without MACE compared with those with MACE (as well as for the combined safety endpoint of MACE + thromboembolic event + hospitalization for CHF)
• To compare the effect of daprodustat administered three-times-weekly to epoetin on BP and BP medication changes	• Observed and change from baseline in systolic BP, diastolic BP, and MAP by visit • Number of BP medications per participant by visit • Change from baseline in the number or dose of BP medications per participant by visit • N (%) of participants who had no change in the number or dose of BP medications from baseline by visit • N (%) of participants who had an increase in the number or dose of BP medications from baseline by visit • N (%) of participants who had a decrease in the number or dose of BP medications from baseline by visit
• To further compare the effect of daprodustat administered three-times-weekly to epoetin on hemoglobin variability	• Hemoglobin observed and change from baseline across all visits • % of time hemoglobin is above, within and below the analysis range of 10 g/dL to 11.5 g/dL during the evaluation period • Number (%) of participants with mean hemoglobin above, within and below the hemoglobin analysis range during the evaluation period • Number (%) of participants with a hemoglobin <7.5 g/dL during the evaluation period • Number of times hemoglobin <7.5 g/dL during the evaluation period • Number (%) of participants with a >1 g/dL increase in hemoglobin within any 2-week period (assessed at Week 2 through Week

Objectives	Endpoints
	8), or with a >2 g/dL increase in hemoglobin within any 4-week period up to Week 52 • Number (%) of participants with a >1 g/dL decrease in hemoglobin within any 2-week period (assessed at Week 2 through Week 8), or with a >2 g/dL decrease in hemoglobin within any 4-week period up to Week 52 • N (%) of participants with a hemoglobin value ≥12 g/dL during the evaluation period • Number of times hemoglobin ≥12 g/dL during the evaluation period • % of time hemoglobin ≥12 g/dL during the evaluation period
• To compare the effect of daprodustat administered three-times-weekly to epoetin on measures of iron parameters	• Observed and change from baseline in hepcidin, ferritin, transferrin saturation (TSAT), total iron, and total iron binding capacity (TIBC) across all visits • Average quarterly ferritin • Average quarterly TSAT • Average quarterly IV iron dose/participant • N (%) of participants who met iron management criteria • N (%) of participants who reduced IV iron supplementation relative to baseline (defined as total iron [mg] over 4 weeks prior to randomization) during evaluation period (defined as average monthly IV iron dose [mg] over Weeks 28 to 52)
• To compare the effect of daprodustat administered three-times-weekly to epoetin on the need for red blood cell (RBC) and whole blood transfusions	• Number (%) of participants who receive at least one RBC or whole blood transfusion by Week 52 • Number of RBC and whole blood transfusions per 100 person-years • Number of RBC and whole blood units per 100 person-years

Objectives	Endpoints
• Characterize the pharmacodynamic effect of daprodustat administered three-times-weekly on erythropoietin, vascular endothelial growth factor (VEGF) and RBC	• Maximum observed change from baseline in erythropoietin • Maximum observed % change from baseline in VEGF • Change from baseline in hematocrit, RBC count, and reticulocyte count
• To compare the effect of daprodustat administered three-times-weekly to epoetin on lipid parameters.	• Observed and % change from baseline in lipid parameters by visit [total cholesterol, direct low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C)]
• To evaluate the daprodustat dose adjustment scheme	• Assigned dose by visit and at Day 1, Week 28, and Week 52 • Most recent dose prior to Week 28, Week 52 and end of study treatment • Number (%) of participants with 0, 1, 2, or >2 dose adjustments during the following periods: o Day 1 to < Week 28 o Week 28 to < Week 52 o Day 1 to < Week 52 • Number of dose adjustments during the following periods: o Day 1 to < Week 28 o Week 28 to < Week 52 o Day 1 to < Week 52 • Number of dose adjustments per year during Day 1 to < Week 52 • Time dose held for hemoglobin ≥12 g/dL
• To further compare daprodustat administered three-times-weekly to epoetin on global symptom severity and change	• Shift tables (baseline to Weeks 8, 12, 28, and 52) in Patient Global Impression of Severity • N (%) of participants within each PGI-C symptom change level at Weeks 8, 12, 28, and 52
Conversion from g/dL to g/L is 1:10 and from g/dL to mmol/L is 0.6206. [a]Hemoglobin change from baseline to Week 52 was tested for non-inferiority, using the -0.75 g/dL margin used in the primary analysis. % time hemoglobin in analysis range was tested first for non-inferiority, then for superiority. The non-inferiority analysis used a margin of 15% less time in range and if non-inferiority was established, nominal superiority was achieved if the one-sided p-value is <0.025.	

Supplemental Table 3. Daprodustat starting dose

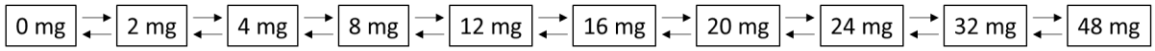
Prior ESA Dose			Daprodustat Dose
Epoetins (including biosimilars) (U/week IV)[a]	Darbepoetin (μg/4week SC/IV)[b]	Methoxy polyethylene glycol [PEG]-epoetin beta (μg/month SC/IV)[c, d]	(mg, three-times-weekly)
1500 to 2000	20 to 30	30 to 40	8
> 2000 to < 10000	>30 to 150	>40 to 180	12
≥ 10,000 to < 20000	>150 to 300	>180 to 360	16
≥ 20,000	>300	>360	24

a. Standardized rhEPO IV dose (U/week) = 161/113 * (epoetin SC dose (units) / (frequency) [2].
b. Conversion of 250 U:1 μg (epoetin IV:darbepoetin alfa) utilized and rounded to the nearest available dose strength [3].
c. Conversion of 1:1.2 μg (darbepoetin alfa:methoxy PEG-epoetin beta) utilized and rounded to the nearest available dose strength [4].
d. Conversion of 208 U:1 μg (epoetin IV: methoxy PEG-epoetin beta).

ESA, erythropoiesis stimulating agent; IV, intravenous; SC, subcutaneous; rhEPO, recombinant human erythropoietin; U, units.

Supplemental Table 4. Dose information for daprodustat and epoetin alfa

A. Daprodustat dose steps



B. Epoetin alfa dose steps

Total weekly dose (units)	Dose and frequency
0	0 U once a week
1500	1500 U once a week
2000	2000 U once a week
3000	3000 U once a week
4000	4000 U once a week
5000	5000 U once a week
6000	6000 U once a week
8000	8000 U once a week
10,000	10,000 U once a week
12,000	4000 U three times a week
15,000	5000 U three times a week
18,000	6000 U three times a week
21,000	7000 U three times a week
24,000	8000 U three times a week
27,000	9000 U three times a week
30,000	10,000 U three times a week
36,000	12,000 U three times a week
42,000	14,000 U three times a week
48,000	16,000 U three times a week
60,000	20,000 U three times a week

Supplemental Table 5. Study treatment dose adjustment schemes

HemoCue hemoglobin (g/dL) at current study visit[a]	HemoCue hemoglobin change since last study visit[a]	Study treatment dose adjustment[e]
<7.5[b]	Any change	Hemoglobin repeated and values averaged[f]; if confirmed, dose was increased to the next higher dose step
7.5 to <9.5	Decreasing or No change (as of January 28, 2019, redefined as decrease, no change or an increase of <0.5 g/dL)[g]	Dose increased to the next higher dose step
7.5 to <9.5	Increasing (as of January 28, 2019, redefined as increase of ≥0.5 g/dL)[h]	Dose maintained
≥9.5 to <10 at two consecutive visits	Decreasing or No change	Dose increased to the next higher dose step
≥9.5 to ≤11.5	Any change	Dose maintained
>11 to ≤11.5 at two consecutive visits	Increasing or No change	Dose decreased to the next lower dose step
>11.5 to <12	Decreasing	Dose maintained
>11.5 to <12	Increasing or No change	Dose decreased to the next lower dose step
≥12[c]	Any change	Hemoglobin repeated and values averaged[f;] if confirmed, dose was temporarily interrupted and hemoglobin re-checked at next study visit 1; dose restarted at one dose step lower when hemoglobin <11.5 g/dL and provided it has been at least 2 weeks from the prior study visit
Any	>2 g/dL increase over 4 weeks (>1 g/dL increase over 2 weeks[d])	Hemoglobin repeated and values averaged[f]; if confirmed, dose decreased to the next lower dose step
Any	>2 g/dL decrease over 4 weeks (>1 g/dL decrease over 2 weeks[d])	Hemoglobin repeated and values averaged[f]; if confirmed, dose increased to the next higher dose step

a. Study visit refers to scheduled visits, ie, every 2 weeks until Week 8, and then every 4 weeks through Week 52.
b. This rule applied to any scheduled visit or unscheduled visit, provided it had been at least 2 weeks from the prior study visit.
c. This rule applied to any scheduled or unscheduled visit.
d. This rule applied to Week 2 through Week 8 visits only.

e. Those receiving the highest dose of study treatment who required a dose increase maintained the same dose, while those receiving the lowest dose of study treatment that required a dose decrease received inactive study treatment (placebo/saline).
f. HemoCue hemoglobin was repeated at the same study visit to confirm hemoglobin (using the same sample) and take an average.
g. No change was redefined as an increase of <0.5 g/dL following review of blinded instream hemoglobin data from Study 200807/ASCEND-D.
h. Increasing was redefined as an increase of ≥0.5 g/dL based on review of blinded instream hemoglobin data from Study 200807/ASCEND-D.

ASCEND-D, Anemia Studies in Chronic Kidney Disease: Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor Daprodustat-Dialysis.

Supplemental Table 6. Rescue algorithm for anemia management

<table>
<tr><td colspan="2">Evaluate Participant for Rescue if:
HemoCue hemoglobin remains <9 g/dL (at a scheduled study visit, Week 4 onwards) despite three[a] consecutive dose increases above the starting or post-rescue[b] dose (where HemoCue hemoglobin is <9 g/dL prior to each dose increase) or
HemoCue hemoglobin is <7.5 g/dL[c] despite a dose increase at the prior study visit[d]</td></tr>
<tr><td>Step 1:
Initial
Intervention</td><td>The following actions will be taken for the initial intervention:
Continue with study treatment (increase dose if HemoCue hemoglobin <7.5 g/dL; otherwise maintain current dose)
A single course of IV iron up to 1000 mg, in addition to following the iron management criteria, if clinically indicated
Transfusion of up to two units of packed red blood cells, if clinically indicated
At the next study visit, in 4 ± 1 weeks after the initial intervention, recheck HemoCue hemoglobin as described below in Step 2 (Rescue). Earlier checks of HemoCue hemoglobin may be obtained to advise further intervention as clinically indicated.</td></tr>
<tr><td>Step 2:
Rescue</td><td>Check HemoCue hemoglobin 4 ± 1 weeks after the initial intervention
Study treatment should be permanently discontinued, and the participant should be rescued according to local clinical practice:</td></tr>
</table>

	• If HemoCue hemoglobin remains <9 g/dL, despite initial intervention, based on the average of two HemoCue hemoglobin values[c] or • If more than two units of packed red blood cells were needed for transfusion (and was not related to acute bleeding) The participant will remain in the study and follow the planned visit schedule.

Note: The rescue algorithm did not apply to participants with a low hemoglobin due to an acute or subacute event with an identifiable cause, such as gastrointestinal bleed or blood loss due to surgery. In these cases, treatment was directed to the specific cause and study treatment could continue at the current dose, unless hemoglobin increased to ≥12 g/dL as a result of the participant being transfused, in which case the study treatment was interrupted. Transfusion administered in such cases was not considered to be rescue therapy.

a. Two consecutive dose increases if starting/post-rescue dose is daprodustat/placebo 24 mg or epoetin/saline 42000 U per week; one dose increase if starting/post-rescue dose is daprodustat/placebo 32 mg or epoetin/saline 48000 U per week; and no prior dose increase if starting/post-rescue dose is daprodustat/placebo 48 mg or epoetin/saline 60000 U per week (top dose). This criterion applied to both study treatments for each participant and was met when either study treatment reaches one of the specified doses; if both, then follow criteria based on highest dose level.
b. For participants who were previously evaluated for rescue and who were able to continue in the trial, "post-rescue" dose was the dose of study treatment that a participant was receiving at the study visit after the initial intervention.
c. HemoCue hemoglobin was repeated at the same study visit to confirm hemoglobin (using the same sample); average of 2 values was taken.
d. A dose increase at the prior study visit was not required if the dose was already at the top dose (daprodustat/placebo 48 mg or epoetin/saline 60000 U per week).

IV, intravenous.

Supplemental Table 7. On-treatment average monthly intravenous iron use (Intent-to-treat population)

		Daprodustat (n=270)	Epoetin (n=137)
Participants with intravenous iron use, n (%):			
At baseline	n	270	137
	No	100 (37)	38 (28)
	Yes	170 (63)	99 (72)
During the EP (Week 28–52)	n	217	109
	No	135 (62)	65 (60)
	Yes	82 (38)	44 (40)
From Day 1 to Week 52	n	270	136
	No	131 (49)	67 (49)
	Yes	139 (51)	69 (51)
Average monthly intravenous iron dose (mg)			
At baseline	n	270	137
	Mean (SD)	185.7 (281.677)	176.8 (177.802)
	Median	108.7	144.9
	Min, Max	0.0, 2650.2	0.0, 828.2
During the evaluation period (Week 28–52)	n	217	109
	Mean (SD)	104.9 (222.5)	103.1 (244.7)
	Median	0.0	0.0
	Min, Max	0.0, 1304.5	0.0, 1852.5
From Day 1 to Week 52	n	270	136
	Mean (SD)	99.0 (187.1)	104.4 (210.8)
	Median	8.3	12.7
	Min, Max	0.0, 1304.5	0.0, 1304.5

Supplemental Table 8. On-treatment average monthly intravenous iron dose during Day 1 to Week 52 (Intent-to-treat population)

	Daprodustat (n=270)	Epoetin (n=137)
Number of participants during day 1 to Week 52 (%)	270 (100)	136 (99)[b]
Baseline monthly IV iron dose (mg) mean (SD)	185.7 (281.677)	175.4 (177.7)
Average monthly IV iron dose (mg) during Day 1 to Week 52 mean (SD)	99.0 (187.1)	104.4 (210.8)
Adjusted mean average monthly IV iron dose during Day 1 to Week 52 (SE)[a]	98.1 (11.0)	106.2 (15.6)
Adjusted mean treatment difference (daprodustat-epoetin)[a]	-8.1	
Two-sided 95% CI for adjusted mean difference[a]	(-45.7, 29.4)	
One-sided p-value[a]	0.34	

a. Based on an ANCOVA model with terms for treatment, baseline monthly IV iron dose, and region. One-sided p-value based on test of null hypothesis: (daprodustat–epoetin) ≥ 0 vs alternative: difference <0.
b. One participant in the epoetin group was randomized but did not receive any study treatment and is therefore excluded from the analysis of on-treatment IV iron use.

ANCOVA, analysis of covariance; CI, confidence interval; ITT, intent-to-treat; IV, intravenous; SD, standard deviation; SE, standard error.

Supplemental Table 9. Adverse events (Safety population)

AE overview	Daprodustat (n=270)	Epoetin (n=136)
Treatment-emergent adverse events[a], n (%)		
Any AE	203 (75)	107 (79)
Severe AEs	49 (18)	29 (21)
Drug-related AEs	39 (14)	20 (15)
Treatment-emergent serious adverse events, n (%)		
Any SAE (fatal and non-fatal)	80 (30)	47 (35)
Drug-related SAEs	3 (1)	4 (3)
Fatal SAEs	6 (2)	3 (2)
Drug-related fatal SAEs	0	0
Treatment-emergent adverse events leading to permanent discontinuation of study treatment, n (%)	20 (7)	8 (6)
Follow-up adverse events[b], n (%)		
Any follow-up AEs	74 (27)	46 (34)
Treatment-emergent adverse events (≥5%)	**Daprodustat (n=270)**	**Epoetin (n=136)**
Any event, n (%)	203 (75)	107 (79)
Hypertension	24 (9)	15 (11)
Diarrhea	24 (9)	14 (10)
Vomiting	15 (6)	14 (10)
Headache	12 (4)	13 (10)
Hypotension	13 (5)	10 (7)
Pneumonia	15 (6)	8 (6)
Dyspnea	10 (4)	9 (7)
Nausea	7 (3)	12 (9)
Pyrexia	9 (3)	9 (7)
Abdominal pain	8 (3)	9 (7)
Treatment-emergent drug-related adverse events (≥1%)	**Daprodustat (n=270)**	**Epoetin (n=136)**
Any event	39 (14)	20 (15)
Hypertension	5 (2)	3 (2)
Diarrhea	4 (1)	2 (1)
Nausea	4 (1)	1 (<1)
Vomiting	3 (1)	1 (<1)
Treatment-emergent serious adverse events (≥1%)	**Daprodustat (n=270)**	**Epoetin (n=136)**
Any event, n (%)	80 (30)	47 (35)
Pneumonia	9 (3)	5 (4)
Arteriovenous fistula thrombosis	7 (3)	3 (2)
Anemia	2 (<1)	3 (2)
Acute respiratory failure	3 (1)	1 (<1)
Cerebrovascular accident	4 (1)	0

AE overview	Daprodustat (n=270)	Epoetin (n=136)
Dyspnea	1 (<1)	3 (2)
Fluid overload	2 (<1)	2 (1)
Head injury	2 (<1)	2 (1)
Hyperkalemia	3 (1)	1 (<1)
Angina unstable	0	3 (2)
Atrial fibrillation	1 (<1)	2 (1)
Fall	1 (<1)	2 (1)
Gastritis	1 (<1)	2 (1)
Hypotension	1 (<1)	2 (1)
Myocardial infarction	3 (1)	0
Diabetic foot	0	2 (1)
Hematuria	0	2 (1)
Pulmonary embolism	0	2 (1)
Treatment-emergent fatal serious adverse events	**Daprodustat (n=270)**	**Epoetin (n=136)**
Any event, n (%)	6 (2)	3 (2)
Pneumonia	1 (<1)	1 (<1)
Acute myocardial infarction	1 (<1)	0
Asthenia	1 (<1)	0
Cardiac arrest	0	1 (<1)
Cardiac failure	1 (<1)	0
Diarrhea	1 (<1)	0
Enteritis infectious	1 (<1)	0
Hemorrhagic stroke	1 (<1)	0
Laryngitis	1 (<1)	0
Myocardial infarction	1 (<1)	0
Pyrexia	1 (<1)	0
Respiratory failure	1 (<1)	0
Squamous cell carcinoma of lung	0	1 (<1)
Thirst	1 (<1)	0

[a]Treatment-emergent AEs are defined as AEs with onset date or AE worsening date on or after treatment start date and on or before the last non-zero dose date plus 1 day.
[b]Follow-up AEs are defined as AEs with onset date or AE worsening date after the last non-zero dose date plus 1 day.
AE, adverse event; SAE, serious adverse event.

Supplemental Table 10. Overview of treatment-emergent potential adverse events of special interest[a]

(Safety population)

Preferred Term	Daprodustat (n=270)		Epoetin (n=136)		Daprodustat vs. Epoetin Relative Risk ([Two-sided 95% CI] Post-hoc])
	n (%)	Rate/100 person-years	n (%)	Rate/100 person-years	
Death, myocardial infarction, stroke, heart failure, thromboembolic events, thrombosis of vascular access	52 (19)	26.2	27 (20)	29.6	0.97 (0.64, 1.47)
Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis	1 (<1)	0.46	0	0	
Cardiomyopathy	1 (<1)	0.46	1 (<1)	0.97	0.50 (0.03, 7.99)
Pulmonary artery hypertension	1 (<1)	0.46	1 (<1)	0.97	0.50 (0.03, 7.99)
Cancer-related mortality or tumor progression and recurrence	3 (1)	1.37	2 (1)	1.94	0.76 (0.13, 4.47)
Esophageal and gastric erosions	7 (3)	3.22	2 (1)	1.95	1.76 (0.37, 8.37)
Proliferative retinopathy, macular edema, choroidal neovascularization	5 (2)	2.30	1 (<1)	0.97	2.52 (0.30, 21.34)
Exacerbation of rheumatoid arthritis	0	0	0	0	
Worsening hypertension	33 (12)	16.2	20 (15)	21.4	0.83 (0.50, 1.39)

[a]AESIs were defined for daprodustat based on data from nonclinical and clinical studies, current information about HIF-associated pathophysiology, and identified risks for ESAs. A programmatic approach for identifying potential AESIs was implemented using a broad set of predefined terms of interest

AESI, adverse event of special interest; CI, confidence interval.

Supplemental Table 11. Summary of first occurrence of adjudicated MACE during the time period for follow-up of cardiovascular events (Intent-to-treat population)

	Daprodustat (n=270)	Epoetin (n=137)
Adjudicated Event Type, n (%)		
Number of participants[a]	270	137
First occurrence of MACE	33 (12.2)	14 (10.2)
All-cause mortality	16 (5.9)	9 (6.6)
Non-fatal myocardial infarction	10 (3.7)	5 (3.6)
Non-fatal stroke	7 (2.6)	0
Analysis		
Number of participants[a]	270	137
First occurrence of adjudicated MACE, n (%)	33 (12.2)	14 (10.2)
Censored, n (%)	237 (87.8)	123 (89.8)
Incidence rate per 100 person-years (two-sided 95% CI)	12.3 (8.5, 17.3)	10.02 (5.5, 16.8)
Absolute rate difference per 100 person-years (95% CI)[b]	2.3 (-4.4, 9.0)	

[a]All randomized participants.
[b]A rate difference <0 indicates a lower risk with daprodustat compared with epoetin.
Time period for follow-up of cardiovascular events: AE onset date or AE worsening date is after the last non-zero dose date plus 1 day.
AE, adverse event; CI, confidence interval; MACE, major adverse cardiovascular event.

Supplemental Table 12. Summary of participants with an adjudicated fatal and non-fatal stroke (Intent-to-treat population; Post hoc analysis)

Participants with adjudicated stroke event	Daprodustat (n=8)
Age in years, median (min, max)	72 (44, 88)
Sex, female n	6
Race n *White* *Black* *Other*	 7 1 0
Cardiovascular risk score, median (min, max)[a]	19.5 (14, 24)
Study days to onset of first stroke, median (min, max)	142 (44, 344)
Study treatment dose (mg)	
Starting dose, median (min, max)	12 (8, 16)
Dose prior to or on day of event, median (min, max)	4 (0, 16)
Maximum dose prior to event, median (min, max)	12 (8, 20)
Participants with an increase in hemoglobin of >1 g/dL in any 2-week period or >2 g/dL in any 4-week period prior to adjudicated stroke, n	7
Days from hemoglobin increase to stroke event, median (min, max)[b]	84 (8, 329)

[a]A risk score for 2-year cardiovascular mortality and morbidity in a HD population has been developed [1] and was calculated at baseline for each HD participant.
[b]For participants with more than one increase in hemoglobin prior to adjudicated stroke, the days to the increase closest to the adjudicated stroke event are summarized.
Max, maximum; min, minimum.

Supplemental Table 13. Summary of analysis of change from baseline to Week 52 in on-treatment post-dialysis blood pressure parameters (Intent-to-treat population)

						Comparison to epoetin[a]	
Parameter	**Treatment Group**	**N**	**n**	**Adjusted Mean**	**SE of Adjusted Mean**	**Adjusted Mean Difference (Two-sided 95% CI)**	**1-sided p-value**
Systolic BP (mmHg)	Daprodustat	270	266	-3.2	1.47	-3.7 (-9.0, 1.6)	0.08
	Epoetin	137	133	0.6	2.25		
Diastolic BP (mmHg)	Daprodustat	270	266	-2.5	0.76	-2.2 (-5.0, 0.5)	0.06
	Epoetin	137	133	-0.3	1.18		
MAP (mmHg)	Daprodustat	270	266	-2.7	0.91	-2.6 (-5.9, 0.7)	0.06
	Epoetin	137	133	-0.1	1.39		

[a]Treatment group comparisons are based on the MMRM model: mean change = treatment group + time + region + baseline value + baseline value*time + treatment group*time, using an unstructured covariance matrix. One-sided p-value based on test of null hypothesis: (daprodustat-epoetin) ≥0 vs alternative: difference <0.

Only participants with a non-missing baseline and at least one post-baseline value were included in this analysis.

CI, confidence interval; MAP, mean arterial pressure; MMRM, mixed model repeated measures; SE, standard error.

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