SUPPLEMENTAL MATERIALS

Item S1: Participant Selection and Study Medication Stopping Criteria

Inclusion Criteria

Patients with anemia associated with chronic kidney disease (CKD) who were not on dialysis were eligible if they met all of the following criteria:

General Criteria

1. **Age:** ≥18 years of age. (Week −4 verification only)
2. **Gender:** Female and male patients. (Week −4 verification only)
    - Females: If of childbearing potential, must agree to use one of the approved contraception methods from Screening until completion of the Follow-up Visit OR of non-childbearing potential, defined as premenopausal females with a documented tubal ligation, hysterectomy, or oophorectomy; or postmenopausal defined as 12 months of spontaneous amenorrhea (in questionable cases, a blood sample with simultaneous follicle stimulating hormone 23.0–116.3 IU/L and estradiol ≤10 pg/mL (or ≤37 pmol/L) is confirmatory). Females on hormone replacement therapy (HRT) whose menopausal status was in doubt were required to use one of the approved contraception methods if they wished to continue their HRT during the study. Otherwise they had to discontinue HRT to allow confirmation of postmenopausal status prior to study enrollment. For most forms of HRT, at least 2 weeks needed to elapse between the cessation of therapy and the blood draw; this interval depended on the type and dosage of HRT. Following confirmation of their postmenopausal status, they could resume use of HRT during the study without use of a contraceptive method.
3. **QTc:** QTcB <470 msec or QTcB <480 msec in patients with bundle branch block. There is no QTc criterion for patients with a predominantly paced rhythm.

CKD-Related Criteria

4. **CKD stage:** Kidney Disease Outcomes Quality Initiative (KDOQI) CKD stages 3/4/5 defined by estimated glomerular filtration rate using the CKD Epidemiology Collaboration (CKD-EPI) formula. *The exception is that the Japanese Society of Nephrology-Chronic Kidney Disease Initiatives (JSN-CKDI) equation was used for Japanese patients from (or recruited at) Japan sites.*
5. **Hemoglobin:**
    a. Group 1 (rhEPO naïve): Baseline hemoglobin of 8.0–11.0 g/dL (inclusive) (**USA sites only:** 8.0–10.0 g/dL, inclusive).
    b. Group 2 (rhEPO users): Baseline hemoglobin of 9.0–11.5 g/dL (inclusive) (**USA sites only:** 9.0–10.5, inclusive).
6. **Recombinant human erythropoietin (rhEPO) use:**
    a. **Group 1:** No current or prior rhEPO use within the past 8 weeks; eg, epoetins (or their biosimilars), darbepoetin, Mircera (methoxy polyethylene glycol-epoetin beta), or their biosimilars.
    b. **Group 2: Stable rhEPO dose for rhEPO users:** Group 2 participants must be using the same rhEPO (epoetins or their biosimilars, or darbepoetin) with total weekly doses that varied by no more than 50% during the four weeks prior to Week −4. At Day 1 (randomization), confirm that total weekly doses varied by no more than 50% during the screening period.
7. **Oral iron therapy:** If on oral iron, then doses must not be changed for the 4 weeks prior to Week −4, during the screening phase, and through the first 4 weeks after randomization.

Exclusion Criteria

Patients were not eligible if they met any of the following criteria:

CKD-Related Criteria

1. **Dialysis:** On dialysis or planning to initiate dialysis during the study.

2. **Renal transplant:** Pre-emptive or scheduled renal transplant.
3. **High rhEPO dose:** An epoetin dose of ≥360 IU/kg/week intravenous (IV) or ≥250 IU/kg/week subcutaneous (SC) or darbepoetin dose of ≥1.8 µg/kg/week IV or SC within the prior 8 weeks through Day 1 (randomization).
4. **Mircera:** Use of Mircera (methoxy polyethylene glycol epoetin beta) within the prior 8 weeks through Day 1 (randomization).
5. **IV iron therapy**: Use of IV iron for 4 weeks prior to screening Week −4, during the screening phase, and through the first 4 weeks after randomization.

Laboratory Test-Based Criteria (Week −4 verification only)

6. **Vitamin B12**: Below the lower limit of the reference range (may rescreen in a minimum of 8 weeks).
7. **Folate**: <2.0 ng/mL (<4.5 nmol/L) (may rescreen in a minimum of 4 weeks).
8. **Ferritin:** <40 ng/mL (<40 µg/L).
9. **Transferrin saturation (TSAT)**: Below the lower limit of the reference range.

Cardiovascular (CV) Disease–Related Criteria

10. **Myocardial infarction (MI) or acute coronary syndrome (ACS):** Within the 8 weeks prior to screening through Day 1 (randomization).
11. **Stroke or transient ischemic attack:** Within the 8 weeks prior to Week −4 screening through Day 1 (randomization).
12. **Heart failure:**
    - Class III/IV heart failure as defined by the New York Heart Association functional classification system diagnosed prior to Week −4 screening through Day 1 (randomization).

- Symptomatic right heart failure diagnosed prior to Week −4 screening through Day 1 (randomization).

13. **Uncontrolled hypertension:** Defined as diastolic blood pressure (DBP) >100 mmHg or systolic blood pressure (SBP) >170 mmHg at Week −4 and reconfirmed at Day 1.
14. **Thrombotic disease:** History of thrombotic disease (eg, venous thrombosis such as deep vein thrombosis or pulmonary embolism, or arterial thrombosis such as new onset or worsening limb ischemia requiring intervention), **except** vascular access thrombosis within the 8 weeks prior to Week −4 screening through Day 1 (randomization).

Other Disease-Related Criteria

15. **Ophthalmology disease**: Meeting any ophthalmologic-related exclusion criteria determined at the screening ophthalmology exam.
16. **Inflammatory disease:** Active chronic inflammatory disease that could impact erythropoiesis (eg, scleroderma, systemic lupus erythematosus, rheumatoid arthritis, celiac disease) diagnosed prior to Week −4 screening through Day 1 (randomization).
17. **Hematological disease:** Any hematological disease including those affecting platelets, white blood cells (WBCs) or red blood cells (RBCs) (eg, sickle cell anemia, myelodysplastic syndromes, hematological malignancy, myeloma, hemolytic anemia and thalassemia), coagulation disorders (eg, antiphospholipid syndrome, Protein C or S deficiency), or any other cause of anemia other than renal disease diagnosed prior to Week −4 screening through Day 1 (randomization).
18. **Liver disease:** Current liver disease, known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones) or evidence at screening of abnormal liver function tests (alanine transaminase [ALT] or aspartate transaminase [AST]) >2.0×upper limit of normal (ULN) or total bilirubin >1.5×ULN]; or other hepatic abnormalities that in the opinion of the investigator would preclude the patient from participation in the study.

NOTE: Those with hepatitis B or hepatitis C were eligible provided these exclusions were not met.

19. **Major surgery:** Major surgery (excluding vascular access surgery) within the prior 8 weeks, during the Week −4 screening phase, or planned during the study.
20. **Transfusion:** Blood transfusion within the prior 8 weeks, during the Week −4 screening phase, or an anticipated need for blood transfusion during the study.
21. **Gastrointestinal (GI) Bleeding:** Evidence of actively bleeding peptic, duodenal, or esophageal ulcer disease OR clinically significant GI bleeding within the 8 weeks prior to Week −4 screening through Day 1 (randomization).
22. **Acute infection:** Clinical evidence of acute infection or history of infection requiring IV antibiotic therapy within the 8 weeks prior to Week −4 screening through Day 1 (randomization).

    NOTE: IV antibiotics as prophylaxis were allowed.
23. **Malignancy:** Patients with a history of malignancy within the prior 5 years, who received treatment for cancer, or who had a strong family history of cancer (eg, familial cancer disorders); with the exception of squamous cell or basal cell carcinoma of the skin that was definitively treated prior to Week −4 screening through Day 1 (randomization).

<u>Concomitant Medication and Other Investigational Product-Related Criteria</u>

24. **Severe allergic reactions:** History of severe allergic or anaphylactic reactions or hypersensitivity to excipients in the investigational product (IP) and rhEPO (refer to local product labelling for details).
25. **Drugs and supplements:** Use of any prescription or nonprescription drugs or dietary supplements that are prohibited from Week −4 screening until the follow-up visit.
26. **Prior IP exposure:** The patient had participated in a clinical trial and had received an experimental IP within the prior 30 days from Week −4 screening through Day 1 (randomization).

General Health-Related Criteria

27. **Other conditions:** Any other condition, clinical or laboratory abnormality, or examination finding that the Investigator considered would put the patient at unacceptable risk.
28. **Pregnancy or lactation:** Pregnant females as determined by positive urine human chorionic gonadotropin test OR women who were lactating at Week −4 screening or during the trial.

Criteria for Permanent Discontinuation From Study Medication and Early Withdrawal

Participants in the daprodustat arms were to permanently discontinue study medication and participants in the control arm were to be withdrawn early for the following reasons:

- Confirmed hemoglobin <7.5 g/dL.
- Receiving blood transfusions.
- Receiving a renal transplant.
- Pregnancy.
- Active GI bleeding or new diagnosis of peptic or duodenal ulcer disease.
- Diagnosis of cancer, with the exception of squamous cell and basal cell carcinoma.
- CV ischemic events or thrombotic events (eg, MI, ACS, stroke, deep venous thrombosis, pulmonary embolism, new onset or worsening limb ischemia) excluding events associated with vascular access.
- An increase in systolic pulmonary artery pressure (sPAP) of ≥20 mmHg from baseline
- Left ventricular dysfunction as defined as a left ventricular ejection fraction (LVEF) drop of ≥10% from baseline **and** LVEF <50%.
- A new diagnosis of symptomatic right heart failure not explainable by fluid overload.

- Progressive neovascularization of the iris, optic disc or retina in either eye not responsive to intravitreal injections of anti-vascular endothelial growth factor (VEGF) or panretinal photocoagulation.
- Continued worsening of macular edema or choroidal neovascularization in either eye despite at least two intravitreal anti-VEGF injections 4–6 weeks apart.
- Development of neovascular glaucoma in either eye.
- New or worsening tractional retinal detachment in either eye.
- New onset or worsening nontraumatic joint inflammation (eg, rheumatic or psoriatic arthritis, or of unknown etiology).
- New onset or clinically significant worsening of HTN inadequately responsive to change in anti-hypertensive therapy, **OR** blood pressure (BP) ≥180/110 mmHg (on a study visit day) which persists for >48 hours despite optimal treatment.
- QTc study medication discontinuation/early withdrawal criteria:
    - QTcB >500 msec, uncorrected QT >600 msec, or increase from baseline of >60 msec based on average of three consecutive ECGs.
    - For participants with underlying bundle branch block:
        - If baseline QTcB <470 msec, then withdraw if on-study QTcB >500 msec based on average QTcB value of three consecutive ECGs.
        - If baseline QTcB 470–480 msec, then withdraw if on-study QTcB >530 msec based on average QTcB value of three consecutive ECGs.
- Meeting liver chemistry abnormalities as outlined in the following bullets:
    - ALT ≥3×ULN **and** bilirubin ≥2×ULN (>35% direct bilirubin) (or ALT ≥3×ULN **and** international normalized ratio (INR) (>1.5, if INR measured).

NOTE: If serum bilirubin fractionation was not immediately available, study medication for that participant would be withdrawn if ALT ≥3×ULN **and** bilirubin ≥2×ULN. Serum bilirubin fractionation would be performed if testing was available.

- ALT ≥5×ULN.
- ALT ≥3×ULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash, or eosinophilia).
- ALT ≥3×ULN persists for ≥4 weeks.

- ALT ≥3×ULN and cannot be monitored weekly for 4 weeks.

Prohibited Medications and Non-Drug Therapies

Any herbal or dietary supplements, unless, in the opinion of an investigator (who could consult the sponsor), the therapy would not interfere with the study were prohibited from screening (Week −4) to the follow-up visit.

New androgen therapy within the 12 weeks prior to screening, at any time during the study, or changes to pre-existing androgen regimen during the study was prohibited.

The Following Exclusions Did Not Apply to the Control Arm (Week 4 Onwards):

- Chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) with the exception of low dose (≤325 mg/day) aspirin/acetylsalicylic acid. Occasional NSAID use was permitted.

The primary route of metabolism of daprodustat involves CYP2C8. Thus, medications were prohibited from 14 days prior to the first dose of IP until 7 days after the last dose of IP, including:

- Inhibitors of CYP2C8: such as fluvoxamine, gemfibrozil, oral ketoconazole, trimethoprim, and herbal supplements containing quercetin.
- Inducers of CYP2C8: such as rifampin/rifampicin.

Daprodustat is an inhibitor of OATP1B1/1B3, and CYP2C8 in vitro. OATP1B1/1B3 and/or CYP2C8 substrates with a **narrow therapeutic index** were prohibited from 7 days prior to the first dose of IP until 7 days after the last dose of IP. These included repaglinide, amodiaquine, and amiodarone (amiodarone was prohibited from 3 months prior to first dose of IP due to its long half-life).

Item S2: Study Design and Study Assessments

Study Design

Figure S1. Study design. rhEPO, recombinant human erythropoietin.

[a]Control participants received standard of care per local guidelines including rhEPO and its analogs.

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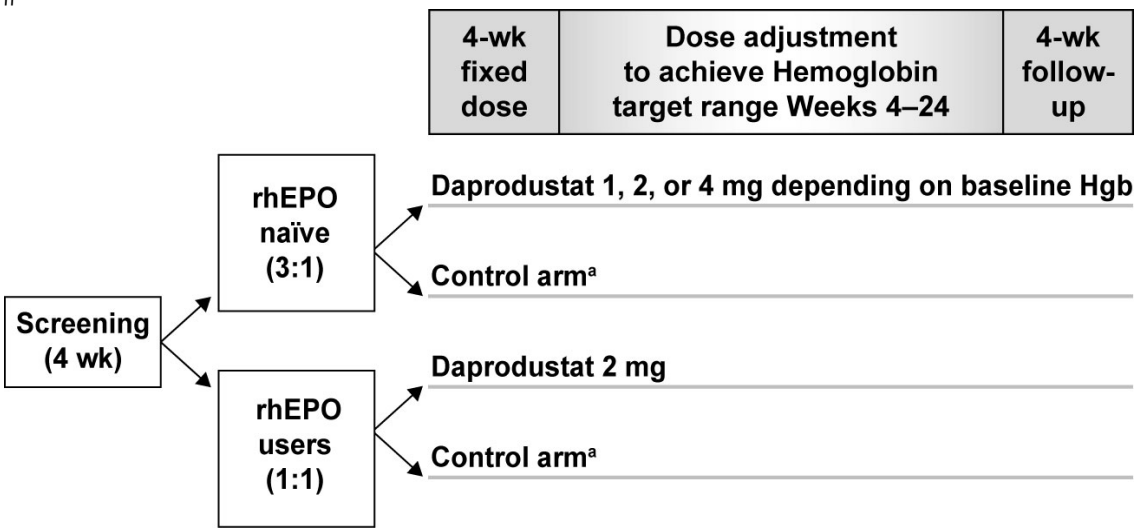

This was a 24-week, phase 2B, randomized, controlled, parallel-group, multicenter study in approximately 228 patients with anemia associated with CKD who were not on dialysis. The study consisted of a screening phase of at least 4 weeks, a 24-week treatment phase, and a follow-up visit that occurred approximately 4 weeks after completing treatment.

Eligible patients were stratified by region (Japan; Not Japan) and baseline hemoglobin. Participants in the rhEPO-naïve group were randomized to receive either daprodustat once daily (QD) or control in a 3:1 ratio; participants in the rhEPO users group were randomized 1:1 to daprodustat QD or control.

Study Assessments

Clinical Laboratory Tests

A point-of-care hemoglobin analyzer (HemoCue®, Brea, CA, USA) was used to measure hemoglobin at the screening and randomization visits to assess for eligibility, and at regular intervals throughout the study to inform changes in study medication.

All other study-required laboratory assessments were performed by a central laboratory, Quest Diagnostics, at regular intervals throughout the study.

- **Hematology:** hemoglobin, hematocrit, platelet count, RBC count, WBC count (absolute) and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), reticulocyte count, RBC indices (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, RBC distribution width).
- **Clinical chemistry:** Total creatine phosphokinase, sodium, potassium, chloride, calcium (albumin-adjusted), albumin, total protein, phosphate, creatinine, glucose, magnesium, ALT*, AST, alkaline phosphatase, total and direct/indirect bilirubin.*

  *Additional follow-up required if liver stopping criteria were met.
- **Iron indices:** Hepcidin, ferritin, transferrin, TSAT, total iron, total iron-binding capacity (TIBC), reticulocyte hemoglobin content (CHr)
- **Biomarkers:** EPO, VEGF
- **Urine protein**
- **Urine pregnancy tests for women of childbearing potential**
- **Additional laboratory measures (Week −4 only)**: folate, vitamin B12, hepatitis B surface antigen

Safety Assessments

SBP, DBP, and heart rate were measured in triplicate at each study-specified visit.

Twelve-lead electrocardiograms (ECGs) were obtained at Week −4 and Day 1 to determine eligibility, and then at Week 4, 12, 24/ending week and follow-up. ECGs were read locally.

Echocardiograms (ECHOs) were recorded in the 2-D, M-Mode, and Doppler formats as recommended by the American Society of Echocardiography. The baseline ECHO was to be recorded during the 4-week screening phase prior to randomization. Subsequent ECHOs were intended to be on-treatment, between Weeks 8–12 and Weeks 20–24; however, an ECHO was obtained at the ending week visit. ECHOs were transmitted to the central reviewer to establish baseline parameters and to determine if a participant met the study medication discontinuation/early withdrawal criteria related to ECHO outputs.

Cardiovascular events, including major adverse cardiovascular events (MACEs), defined as nonfatal myocardial infarction, nonfatal stroke, or death, were collected but were not formally adjudicated.

Ophthalmology exams were performed by the study-designated eye care professional in the same time points as for the ECHOs. Data from these exams were captured on worksheets and transferred to the electronic case report form. Data from the ophthalmology exam during screening determined if a patient was eligible, and data from on-treatment ophthalmology exams were used to determine if a participant met the study medication discontinuation/early withdrawal criteria.

Hemoglobin Entry Criteria

The protocol was amended on May 8, 2014 (Protocol Amendment 4) to allow patients with higher hemoglobin to be enrolled in sites outside of the United States, consistent with guidelines for the participating countries, resulting in the following cohorts:

Dose Assignment

Starting dose was based on data from previous studies with daprodustat and dose-response modeling, as well as baseline hemoglobin level with the intent to achieve and/or maintain hemoglobin within the target range of 9.0 to 10.5 g/dL for participants entering with the low hemoglobin criteria and 10.0 to 11.5 g/dL for participants entering with the high hemoglobin criteria (US sites did not use the high hemoglobin criteria) using a pre-specified dose adjustment algorithm, with dose levels designed to increase or decrease hemoglobin at a controlled rate. Participants were stratified and started daprodustat at doses defined in Table S1.

Table S1. Stratification Variables and Starting Daprodustat Dose

Group	Baseline hemoglobin, g/dL	Starting daprodustat dose if randomized to daprodustat
rhEPO naïve: Japan/not Japan	8.00–8.49	4 mg daprodustat
	8.50–9.49	2 mg daprodustat
	9.50–11.00	1 mg daprodustat
rhEPO users: Japan/not Japan	9.00–9.49	2 mg[a] daprodustat
	9.50–11.50	2 mg[a] daprodustat

Abbreviations: rhEPO, recombinant human erythropoietin.

[a]Participants in Group 2 randomized to daprodustat received an initial 2-mg dose. Group 2 stratification ensured balance between subgroups of baseline hemoglobin level.

Standardization of rhEPO Dose

For this study, rhEPO dose could be administered in three different ways: epoetin IV, epoetin SC, or darbepoetin (IV or SC). The dose of rhEPO was standardized to obtain a continuous single unit prior to rhEPO dose in terms of epoetin IV international unit (IU)/kg/week. The standardization was carried out using the formulas from the Aranesp label and Besarab et al, respectively:

- Weekly darbepoetin IV or SC dose (μg) = weekly epoetin IV dose (IU)/200
- 161 epoetin IV = 113 epoetin SC

1. For participants taking epoetin IV, no adjustment was needed.

Standardized rhEPO IV dose (IU/kg/week) = epoetin IV dose (IU) / (frequency*weight [kg])

2. For participants taking darbepoetin (IV or SC), their dose was converted as follows:

Standardized rhEPO IV dose (IU/kg/week) = (darbepoetin dose [μg] * 200) / (frequency*weight [kg])

3. For participants taking epoetin SC, their dose was converted as follows:

Standardized rhEPO IV dose (IU/kg/week) = 161/113 * (epoetin SC dose [units]) / (frequency* weight [kg])

Where frequency was equal to 4 if the participant took darbepoetin or epoetin SC dose once every 4 weeks, 2 if the participant took darbepoetin or epoetin SC dose every 2 weeks, 0.5 if the participant took the darbepoetin or epoetin SC dose 2 times a week, 0.333 if the participant took the darbepoetin or epoetin SC dose 3 times a week, etc. Weight was recorded at screening Week −4. All rhEPO data were summarized in this standardized manner. When the prior rhEPO dose is referred to in summaries and analyses, it was the above, continuous, standardized rhEPO IV dose variable.

For participants randomized to control, the Principal Investigator decided whether a participant required rhEPO, selected the type of rhEPO (if needed), and chose the rhEPO dose to achieve and maintain hemoglobin levels within the target range, with the historical rhEPO dose and the current hemoglobin value being considered.

Item S3: Iron Protocol

To ensure participants remained iron-replete throughout the study, iron supplementation was monitored and adjusted via a standardized protocol (Table S3).

Protocol waivers or exemptions were not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements were essential and required for study conduct.

Table S2. Iron Protocol (Week 4 Through Week 28)

1) If the ferritin level was ≤100 ng/mL **and/or** the TSAT was ≤30% at any time during the study:
   a. Begin oral iron or increase existing dose of oral iron up to three times a day, as tolerated (eg, ferrous sulfate 325 mg three times a day).
   b. Reevaluate iron indices after 4 weeks of oral therapy.
      1. If the ferritin level was >100 ng/mL **and** the TSAT was >30%, oral iron could be discontinued.
      2. If the ferritin level **and/or** the TSAT remained ≤100 ng/mL and ≤30%, respectively, oral iron could be continued.

2) If the ferritin level was <40 ng/mL **and** the TSAT was <20% at any time during the study:
    a. Consider evaluating the cause(s) of iron deficiency.
    b. Administer a loading course of IV iron per investigator discretion and local clinical guidelines/practice, to be completed before the next scheduled study visit.
    c. Re-evaluate iron indices after the course of IV iron therapy was complete.
        1. If the ferritin level was >100 ng/mL **and** the TSAT was >30%, no further IV iron was required and oral iron, if used, could be discontinued.
        2. If the ferritin level was 40–100 ng/mL **and** the TSAT was 20%–30%, oral iron could be restarted, as per step 1, if it had not been continued.
        3. If the ferritin level remained <40 ng/mL **and** the TSAT remained <20%, the loading course of IV iron could be repeated based on investigator discretion and local clinical guidelines/practice, to be completed before the next scheduled study visit.

Note: Doses greater than 1.0 g of IV iron were not administered during the study.

Item S4: Sample Size Calculation

The planned sample size for this study was driven by exposure requirements to achieve approximately 100 evaluable participants treated with daprodustat, where a participant was considered evaluable if he or she had on-treatment data at Week 24. Within each group, the sample size was planned to enable estimation of mean hemoglobin change from baseline to Week 24 for the daprodustat group with a precision (ie, symmetrical 95% CI half-width) of no more than 0.25 g/dL for rhEPO-naïve group and 0.64 g/dL for the rhEPO user group. The SD for hemoglobin change from baseline at Week 24 was assumed to be 1 g/dL.

In the rhEPO-naïve group, approximately 120 participants were to be randomized to provide a total of 84 evaluable participants (63 to daprodustat and 21 to control). In the rhEPO user group, approximately 35 participants were to be randomized to provide a total of 24 evaluable participants (12 to daprodustat and 12 to control).

Statistical analyses were performed using SAS version 9.1.3 or higher (Cary, NC, USA) on a UNIX platform.

Item S5: Exposure to Study Medication

Table S3. Daprodustat and rhEPO Doses

	Daprodustat (mg)		**Control* (IU/kg/week)**	
	rhEPO naïve (N=136)	**rhEPO user (N=36)**	**rhEPO naïve (N=44)**	**rhEPO user (N=36)**
Median (min, max)				
Baseline	1 (1, 4)	2 (2, 2)	28.3 (0, 390.4)	44.6 (6.9, 233.2)
Week 20	1 (0, 8)	2 (0, 8)	16.5 (0, 96.8)	51.3 (0, 175.3)

*rhEPO dose was standardized in terms of Epoetin IV dose.

Item S6: Sensitivity Summary of Percentage of Time in Hemoglobin Target Range

Table S4: Sensitivity Summary of Percentage of Time in Hemoglobin Target Range Between Weeks 12 and 14 with Retrieved Dropout[a]

	rhEPO Naïve		rhEPO User		Total	
	Daprodustat (N=123)	**Control (N=43)**	**Daprodustat (N=33)**	**Control (N=36)**	**Daprodustat (N=156)**	**Control (N=79)**
N	114	40	31	33	145	73
Within the target range,						
mean (SD)	66.8 (35.50)	50.2 (41.42)	72.6 (34.67)	61.0 (42.70)	68.0 (35.28)	55.1 (42.06)
P25	44.0	8.3	47.6	6.9	44.7	6.9
median[b]	79.2	47.5	92.5	87.7	80.6	61.5
P75	100.0	100.0	100.0	100.0	100.0	100.0
Above the target range						
mean (SD)	22.1 (33.39)	45.1 (43.23)	17.4 (28.51)	31.6 (41.13)	21.1 (32.37)	39.0 (42.54)
P25	0.0	0.0	0.0	0.0	0.0	0.0
median[b]	0.0	33.1	0.0	5.5	0.0	16.8
P75	40.2	91.7	32.5	66.7	37.7	86.7
Below the target range						
mean (SD)	11.1 (24.23)	4.7 (16.87)	10.0 (26.65)	7.4 (24.75)	10.9 (24.67)	5.9 (20.69)
P25	0.0	0.0	0.0	0.0	0.0	0.0
median[b]	0.0	0.0	0.0	0.0	0.0	0.0
P75	3.4	0.0	0.0	0.0	0.0	0.0

Abbreviation: rhEPO, recombinant human erythropoietin; SD, standard deviation.
[a]Target range was 9–10.5 g/dL in the original and 10–11.5 g/dL in the amended criteria.
[b]The minimum and maximum for all values were 0 and 100, respectively.

Item S7: Indices of Hematopoiesis

Table S5. Change From Baseline in Indices of Hematopoiesis (Intent-to-Treat Population)

Analyte	Time Point	Parameter	Combined Daprodustat (N=156)	Combined Control (N=79)
Hematocrit (%)	Baseline	n Mean (SD) Median min, max	156 30.68 (2.79) 30.40 23.9, 38.3	79 31.11 (2.39) 31.20 25.3, 36.5
	Change from baseline at 24 weeks	n Mean (SD) Median min, max	141 1.93 (3.58) 1.50 −8.6, 19.5	66 2.66 (3.26) 2.40 −6.9, 11.5
RBC ($\times 10^{12}$/L)	Baseline	n Mean (SD) Median min, max	156 3.32 (0.41) 3.30 2.5, 5.5	79 3.35 (0.31) 3.30 2.7, 4.0
	Change from baseline at 24 weeks	n Mean (SD) Median min, max	141 0.20 (0.39) 0.10 −0.7, 2.2	66 0.29 (0.35) 0.30 −0.7, 1.3
Reticulocytes (%)	Baseline	n Mean (SD) Median min, max	156 1.66 (0.80) 1.60 0.2, 5.0	79 1.63 (0.84) 1.50 0.2, 3.8
	Change from baseline at 24 weeks	n Mean (SD) Median min, max	141 0.04 (0.65) 0.00 −1.2, 4.1	67 −0.10 (0.69) −0.10 −1.8, 1.4
Reticulocytes (TI/L)	Baseline	n Mean (SD) Median min, max	156 0.05 (0.02) 0.05 <0.01, 0.15	79 0.05 (0.03) 0.05 <0.01, 0.12
	Percent change from baseline at 24 weeks	n Mean (SD) Median min, max	141 33.56 (190.15) 7.13 −63.84, 2109.62	67 18.64 (73.12) −2.27 −71.16, 267.19

Abbreviations: L, liter; RBC, red blood cells; SD, standard deviation; TI, total iron.

Item S8: Measures of Iron Metabolism and Utilization

Following initiation of daprodustat, hepcidin, ferritin and TSAT decreased from baseline, total iron stayed relatively constant, and TIBC increased. The changes were maintained throughout the treatment period. Levels of these parameters in the total control group followed a similar course to the combined daprodustat group, with the exception of TIBC, which remained largely unchanged in the combined control group (Supplemental Figure S2).

Figure S2. Combined daprodustat and combined control mean and 95% confidence interval in ferritin, TSAT, iron, and TIBC **(intent-to-treat population)**

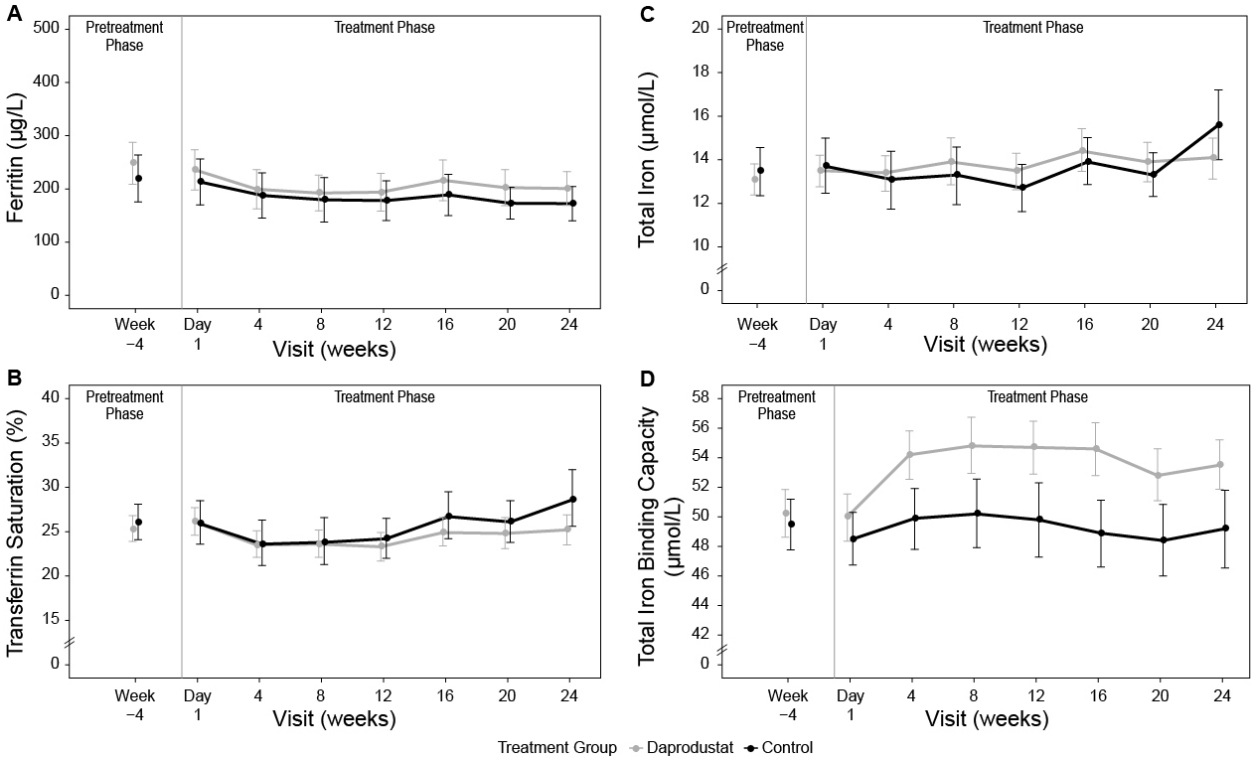

Table S6: Changes From Baseline for Markers of Iron Metabolism (Intent-to-Treat Population)

	Combined Daprodustat (N=156)		Combined Control (N=78)	
	Baseline	**% CFB at Week 24**	**Baseline**	**% CFB at Week 24**
Hepcidin (µg/L)				
n	155	136	77	64
Geometric mean (95% CI)	248.7 (226.0, 273.6)	−17.3 (−25.4, −8.3)	236.8 (201.6, 278.0)	−4.9 (−18.2, 10.6)
CV%	66.1	NA	80.6	NA
TSAT (%)				
n	156	136	78	65
Geometric mean (95% CI)	26.1 (24.6, 27.7)	−4.5 (−10.5, 1.9)	26.0 (23.7, 28.6)	11.9 (−1.7, 27.3)
CV%	38.8	NA	44.4	NA
Ferritin (µg/L)				
n	156	138	79	66
Mean (SD)	236.0 (238.8)	−37.9 (118.3)	213.1 (192.8)	−10.6 (71.2)
TIBC (mmol/L)				
n	156	136	79	65
Mean (SD)	49.4 (8.7)	3.1 (7.2)	49.2 (6.6)	−0.4 (5.9)
Total iron (mmol/L)				
n	156	137	79	66
Mean (SD)	13.5 (4.6)	0.4 (5.2)	13.8 (5.6)	1.7 (7.2)

Abbreviations: CFB, change from baseline; CI, confidence interval; CV, coefficient of variation; NA, not available; SD, standard deviation; TIBC, total iron-binding capacity; TSAT, transferrin saturation.

Item S9: Safety Results: Other Adverse Events of Interest

Other adverse events of interest, based on the mechanism of action or pharmacological activity of hypoxia-inducible factor-prolyl hydroxylase inhibitors, were monitored and evaluated by blinded review based on individual case details during the study. These events included sequelae of excessive erythropoiesis, fatal CV and thromboembolic events, cardiomyopathy, pulmonary artery hypertension, cancer, esophageal and gastric erosions, exacerbation of rheumatoid arthritis, and retinal and choroidal neovascularization. The proportion of these events was the same in both groups (8%).

One participant with advanced CKD (eGFR 6 mL/min/1.73 m^2) and gout who was randomized to daprodustat 1 mg met the protocol-defined liver stopping criteria 2 weeks after treatment initiation, with alanine aminotransferase (ALT) increased to 4.9 times the initial value and normal bilirubin. The participant's ALT normalized approximately 10 weeks from the start of the event.

Table S7: Cardiovascular Assessments

Echocardiography Parameter	Visit		Combined Daprodustat (N=170)	Combined Control (N=80)
LVEF absolute CFB (%)	Baseline	n	161	75
		Mean (SD)	66.270 (6.8200)	65.403 (8.9871)
		Median	66.030	66.730
		min, max	27.12, 82.28	26.01, 78.60
	Weeks 8–12	n	138	67
		Mean (SD)	−0.377 (5.5376)	0.312 (5.5919)
		Median	0.130	−0.050
		min, max	−14.2, 15.82	−12.63, 15.65
	Weeks 20–24	n	121	54
		Mean (SD)	−1.086 (6.1062)	1.013 (8.0862)
		Median	−0.840	−0.100
		min, max	−21.71, 13.69	−17.41, 21.94

Echocardiography Parameter	Visit		Combined Daprodustat (N=170)	Combined Control (N=80)
Estimated right atrial pressure CFB (mmHg)	Baseline	n	148	69
		Mean (SD)	5.5 (3.30)	5.7 (3.35)
		Median	3.0	3.0
		min, max	3, 15	3, 15
	Weeks 8–12	n	120	59
		Mean (SD)	0.0 (3.58)	−0.3 (3.13)
		Median	0.0	0.0
		Min–Max	−12, 12	−7, 7
	Weeks 20–24	n	102	46
		Mean (SD)	−0.4 (3.89)	−0.4 (3.54)
		Median	0.0	0.0
		min, max	−12, 12	−7, 7
Estimated systolic pulmonary artery pressure absolute CFB (mmHg)	Baseline	n	131	61
		Mean (SD)	29.668 (10.5301)	30.920 (11.6975)
		Median	29.500	30.000
		min, max	5.90, 60.10	6.40, 64.30
	Weeks 8–12	n	101	49
		Mean (SD)	−1.229 (7.3576)	−0.159 (8.5048)
		Median	−1.400	0.000
		min, max	−28.90, 15.60	−23.10, 21.20
	Weeks 20–24	n	88	38
		Mean (SD)	−0.538 (9.8572)	−2.600 (8.9342)
		Median	−0.950	−1.900
		min, max	−27.10, 29.70	−27.70, 13.40
Tricuspid regurgitation maximum jet velocity (m/sec)	Baseline	n	140	64
		Mean (SD)	2.398 (0.5204)	2.442 (0.5614)
		Median	2.435	2.475
		min, max	0.85, 3.61	0.92, 3.68
	Weeks 8–12	n	111	53
		Mean (SD)	−0.077 (0.4048)	0.014 (0.3880)
		Median	−0.080	0.000

Echocardiography Parameter	Visit		Combined Daprodustat (N=170)	Combined Control (N=80)
	Weeks 20–24	min, max	−1.33, 1.05	−0.89, 1.11
		n	97	41
		Mean (SD)	−0.011 (0.4782)	−0.080 (0.4384)
		Median	0.030	−0.060
		min, max	−1.87, 0.92	−1.36, 0.80

Abbreviations: CFB, change from baseline; LVEF, left ventricular ejection fraction; SD, standard deviation.

Item S10: Supplemental Materials Reference List

Besarab A, Reyes CM, Hornberger J. Meta-analysis of subcutaneous versus intravenous epoetin in maintenance treatment of anemia in hemodialysis patients. *Am J Kidney Dis* 2002; 40:439-446