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Efficacy and Safety of Daprodustat for Treatment of Anemia of Chronic Kidney Disease in Incident Dialysis Patients
A Randomized Clinical Trial

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IMPORTANCE Daprodustat, a hypoxia-inducible factor prolyl hydroxylase inhibitor, is being evaluated as an oral alternative to conventional erythropoiesis-stimulating agent (ESA) therapy. Few studies of anemia treatment in an incident dialysis (ID) population have been reported.

OBJECTIVE To evaluate the efficacy and safety of daprodustat vs darbepoetin alfa in treating anemia of chronic kidney disease in ID patients.

DESIGN, SETTING, AND PARTICIPANTS This prospective, randomized, open-label clinical trial was conducted from May 11, 2017, through September 24, 2020, in 90 centers across 14 countries. Patients with advanced CKD were eligible if they planned to start dialysis within 6 weeks from screening or had started and received hemodialysis (HD) or peritoneal dialysis (PD) within 90 days before randomization, had a screening hemoglobin (Hb) concentration of 8.0 to 10.5 g/dL (to convert to grams per liter, multiply by 10) and a randomization Hb of 8.0 to 11.0 g/dL, were ESA-naive or had received limited ESA treatment, and were iron-replete.

INTERVENTIONS Randomized 1:1 to daprodustat or darbepoetin alfa.

MAIN OUTCOMES AND MEASURES The primary analysis in the intent-to-treat population evaluated the mean change in Hb concentration from baseline to evaluation period (weeks 28-52) to assess noninferiority of daprodustat vs darbepoetin alfa (noninferiority margin, −0.75 g/dL). The mean monthly intravenous (IV) iron dose from baseline to week 52 was the principal secondary end point. Rates of treatment-emergent and serious adverse events (AEs) were also compared between treatment groups to assess safety and tolerability.

RESULTS A total of 312 patients (median [IQR] age, 55 [45-65] years; 194 [62%] male) were randomized to either daprodustat (157 patients; median [IQR] age, 52.0 [45-63] years; 96 [61%] male) or darbepoetin alfa (155 patients; median [IQR] age, 56.0 [45-67] years; 98 [63%] male); 306 patients (98%) completed the trial. The mean (SD) Hb concentration during the evaluation period was 10.5 (1.0) g/dL for the daprodustat and 10.6 (0.9) g/dL for the darbepoetin alfa group, with an adjusted mean treatment difference of −0.10 g/dL (95% CI, −0.34 to 0.14 g/dL), indicating noninferiority. There was a reduction in mean monthly IV iron use from baseline to week 52 in both treatment groups; however, daprodustat was not superior compared with darbepoetin alfa in reducing monthly IV iron use (adjusted mean treatment difference, 19.4 mg [95% CI, −11.0 to 49.9 mg]). Adverse event rates were 76% for daprodustat vs 72% for darbepoetin alfa.

CONCLUSIONS AND RELEVANCE This randomized clinical trial found that daprodustat was noninferior to darbepoetin alfa in treating anemia of CKD and may represent a potential oral alternative to a conventional ESA in the ID population.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03029208

Visual Abstract

Supplemental content

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The first 90 days of initiating dialysis is a period of high risk for patients, with mortality twice as high as the mortality in the subsequent 9 months.[1-3] Incident dialysis (ID) is arbitrarily defined as dialysis initiated within 90 to 120 days.[1,2,4] Incident dialysis patients undergo abrupt physiological and psychological changes, including metabolic flux from clearances of uremic mediators, correction of anemia, and changes in parameters of metabolic bone disease, blood pressure, and extracellular volume.[2,5] Patients also have evidence of heightened inflammation and protein-calorie malnutrition.[2,5] Few studies have examined the efficacy and safety of erythropoiesis stimulating agents (ESAs) and the novel hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) during this important phase of chronic kidney disease (CKD).

The discovery of the oxygen-sensing pathway and the subsequent identification and testing of compounds that induce the synthesis and secretion of endogenous erythropoietin represent an alternative strategy to correct anemia of CKD. These HIF-PHI compounds stimulate erythropoiesis via the inhibition of HIF-PH domain enzymes.[6] This inhibition stabilizes HIF-α transcription factors and induces HIF-responsive genes involved in adaptation to hypoxia, including endogenous erythropoietin, vascular endothelial growth factor, and certain genes that regulate iron uptake, mobilization, and transport, resulting in decreased hepcidin production.[7,8]

The potential advantages of HIF-PHI agents compared with conventional ESAs include physiologic endogenous erythropoietin levels, oral dosing, greater iron availability for erythropoiesis, and correction of anemia in patients who are hyporesponsive to ESAs.[9-11] Daprodustat is an HIF-PHI agent that increased hemoglobin (Hb) to target goals as effectively as epoetin alfa or darbepoetin alfa in previous clinical trials in patients with CKD and those receiving dialysis.[12-14] However, the efficacy and safety of daprodustat in ID patients has not been examined.

In the recently published open-label randomized Anemia Studies in Chronic Kidney Disease: Erythropoiesis via a Novel Prolyl Hydroxylase Inhibitor Daprodustat–Dialysis (ASCEND-D) and Non-Dialysis (ASCEND-ND) trials,[15,16] some of the authors of this study reported the safety and efficacy of the HIF-PHI daprodustat compared with ESAs in correcting anemia. These studies demonstrated that daprodustat was noninferior to conventional ESAs for hemoglobin efficacy and cardiovascular safety. However, these studies enrolled patients who were comparatively stable physiologically. In this article, we report the primary results from the ASCEND-ID (Anemia Studies in CKD: Erythropoiesis via a Novel PHI Daprodustat in Incident Dialysis) trial to evaluate the efficacy and safety of daprodustat vs darbepoetin alfa for 52 weeks in ID patients.

Key Points

Question Is daprodustat, a hypoxia-inducible factor prolyl hydroxylase inhibitor, an effective oral alternative to darbepoetin alfa in the treatment of anemia of chronic kidney disease (CKD) in incident dialysis (ID) patients?

Findings In this randomized clinical trial of 312 ID patients, daprodustat was noninferior to darbepoetin alfa in treating anemia of CKD; the difference in mean hemoglobin concentration between study arms during the evaluation period was 10.5 g/dL for patients receiving daprodustat and 10.6 g/dL for patients receiving darbepoetin alfa.

Meaning The study results suggest that daprodustat represents an oral alternative treatment to a conventional erythropoiesis-stimulating agent in the ID population.

Methods

Study Design and Oversight

The ASCEND-ID trial was a global, randomized, open-label, active-control-group, phase 3 clinical trial comparing the efficacy and safety of daprodustat and darbepoetin alfa in patients recently initiating hemodialysis (HD) or peritoneal dialysis (PD). The trial was conducted from May 11, 2017, through September 24, 2020 (ClinicalTrials.gov: NCT03029208; EudraCT Number: 2016-000507-86). The study was approved by the ethics committee or institutional review board at each participating institution and was conducted according to the recommendations of Good Clinical Practice and the Declaration of Helsinki.[17] All patients provided written informed consent. The trial protocol, amendments, and reporting and analysis plan are available in Supplement 1. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

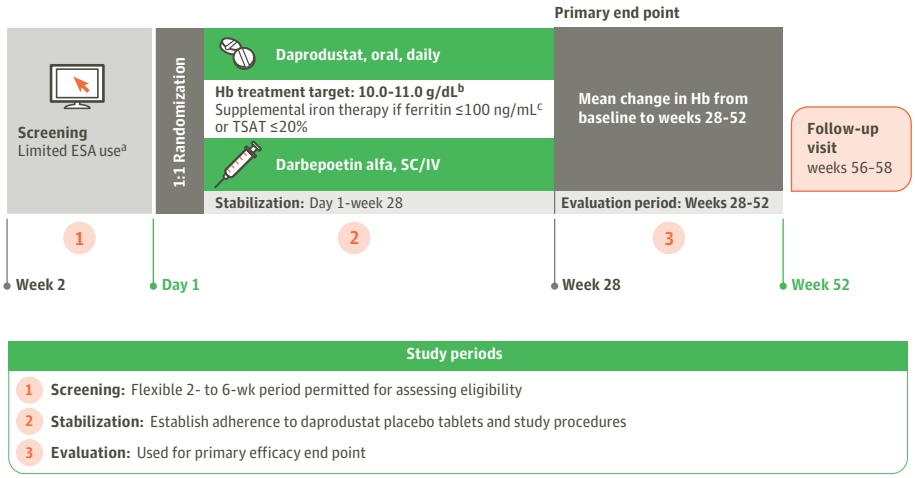
The ASCEND-ID trial consisted of 4 periods: screening, stabilization (day 1 to week 28), evaluation period (weeks 28 to 52), and follow-up (weeks 56 to 58) (**Figure 1**). Randomized patients were evaluated every 2 weeks up to week 8 and then every 4 weeks up to week 52. All patients completed a posttreatment follow-up visit between weeks 56 and 58.

The ASCEND-ID trial was developed in collaboration with the steering committee (eTable 1 in Supplement 2), which provided academic and scientific leadership as well as oversight during the study, as described for the ASCEND-D and ASCEND-ND trials.[15,16,18,19] An external, unblinded, independent data-monitoring committee evaluated safety data.

Eligibility Criteria

Eligibility was determined at the screening visit, with a subset of entry criteria reconfirmed at day 1 (randomization). Patients with advanced CKD were eligible if they planned to start dialysis within 6 weeks from the screening visit or had recently initiated it (started and received HD or PD within 90 days before randomization), had a screening blood Hb concentration of 8.0 to 10.5 g/dL (to convert to grams per liter, multiply by 10.0) and a randomization Hb concentration of 8.0 to 11.0 g/dL, and were iron-replete (serum ferritin level >100 ng/mL [to convert to micrograms per liter, multiply by 1.0] and transferrin saturation >20%). Patients were excluded from the study if they had used any ESA treatment within 8 weeks before screening, except for limited use as a part of dialysis initiation. Complete inclusion and exclusion criteria are provided in eTable 2 in Supplement 2.

Figure 1. ASCEND-ID Study Design



Although investigators and patients were aware of the allocated treatment, the sponsor and steering committee remained blind to aggregate treatment assignment throughout the trial. ESA indicates erythropoiesis-stimulating agent; Hb, hemoglobin; IV, intravenous; rhEPO, recombinant human erythropoietin; SC, subcutaneous; and TSAT, transferrin saturation.

[a] Limited use was defined as no more than 6 weeks of short-acting ESA (rhEPO or biosimilars; maximum of 20 000 U total) or long-acting ESA (darbepoetin alfa [maximum of 100 µg total] or methoxy polyethylene glycol-epoetin beta [maximum of 125 µg total]) received before or after starting dialysis.

[b] SI conversion factor: To convert hemoglobin to grams per liter, multiply by 10.0.

[c] SI conversion factor: To convert ferritin to micrograms per liter, multiply by 1.0.

Randomization

Patients were stratified by dialysis modality (HD vs PD) and by planned vs unplanned or urgent dialysis start. An unplanned or urgent start was defined as no nephrology care or referral within the previous 4 months and/or an HD start with temporary vascular access with no previous planning for chronic dialysis or recent (<2 weeks) PD catheter insertion. Following stratification, patients were randomized 1:1 to daprodustat or darbepoetin alfa. A central randomization approach was used to help protect against allocation bias owing to the open-label design.

Intervention

The starting doses of daprodustat and darbepoetin alfa, based on the HemoCue (point of care) Hb concentration at randomization on day 1, are outlined in eTable 3 in Supplement 2. A protocol-specified dose adjustment algorithm to achieve and maintain Hb concentrations within 10.0 to 11.0 g/dL was applied for both treatments (eTable 4 in Supplement 2).

Iron management criteria (eMethods in Supplement 2) were implemented to ensure patients remained iron replete and not iron overloaded. A rescue algorithm was used to minimize inadequate Hb response to the assigned anemia treatment (eTable 5 in Supplement 2).

Objectives and End Points

The primary objective was to demonstrate the noninferiority of daprodustat compared with darbepoetin alfa in increasing and maintaining the Hb concentration during the evaluation period, assessed as the mean change in Hb concentration from baseline during this period. The key secondary outcome was the mean monthly intravenous (IV) iron dose during the study period (baseline to week 52).

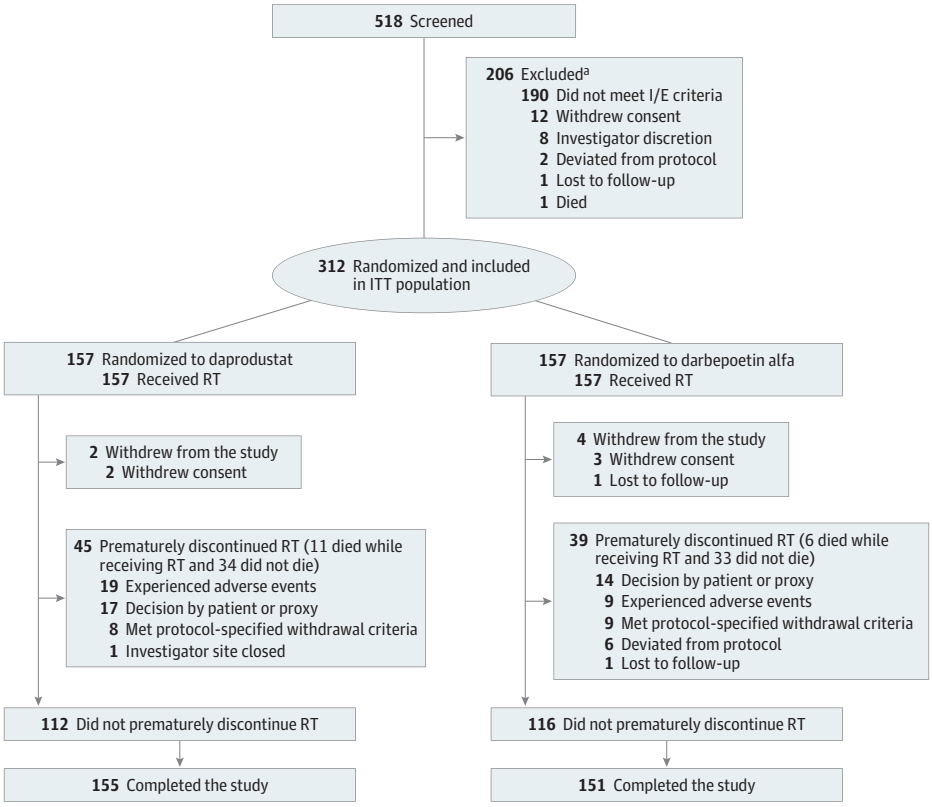
Safety and tolerability were compared between randomized treatment groups, including incidence and severity of treatment-emergent adverse events (AEs) and serious AEs. Although this study was not designed to evaluate major adverse cardiovascular events (MACEs), along with thromboembolic events and hospitalization for heart failure, these were adjudicated by the independent data-monitoring committee, led by the Duke Clinical Research Institute in collaboration with George Clinical.

Statistical Analysis

The study was designed to enroll approximately 300 patients to provide at least 100 patients receiving daprodustat for 1 year to meet International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines for sufficient treatment exposure.[20] With this sample size and the assumption of an SD of 1.5 g/dL between patients for the primary end point, there was more than 90% power to test the primary noninferiority hypothesis.

For the primary end point, the mean change in Hb concentration from baseline to the evaluation period was analyzed using an analysis-of-covariance model adjusting for baseline Hb concentration, dialysis modality type, and dialysis start manner in the intent-to-treat population. Missing Hb values were imputed using multiple imputation assuming missing at random. For each missing value between baseline and week 52 (inclusive), 200 imputed values were generated using a regression model that included treatment, baseline Hb concentration, prior scheduled Hb concentrations, dialysis type, and

Figure 2. CONSORT Diagram



[a] Patients may have had more than 1 reason for exclusion; thus, the numbers sum to more than the total. I/E, inclusion/exclusion; ITT, intent-to-treat; and RT, randomized treatment.

dialysis start manner; Rubin's rules[21] were used to combine the results of the simulated data sets. Noninferiority of daprodustat compared with darbepoetin alfa was declared if the lower bound of the 2-sided 95% CI of the difference in Hb concentration between daprodustat and darbepoetin alfa exceeded −0.75 g/dL. The prespecified noninferiority margin was based on a combination of statistical reasoning, clinical judgment, and regulatory guidance and has been used consistently in other worldwide daprodustat phase 3 studies (detailed rationales are provided in the eMethods in Supplement 2).[15,16] Subgroup analyses were performed to assess consistency with the overall primary Hb results (a complete list of subgroups with rationale is provided in the eMethods in Supplement 2). Although the target range for dose titration was 10.0 to 11.0 g/dL, an Hb analysis range (10.0 to 11.5 g/dL), which factored in Hb variance, was used when assessing efficacy.

The key secondary outcome, IV iron dose, was analyzed in the intent-to-treat population using an analysis-of-covariance model adjusted for baseline monthly IV iron dose, dialysis type, and dialysis start manner. The analysis used on-treatment IV iron data only; data after a red blood cell or whole blood transfusion were excluded. Conditional to the primary outcome of achieving noninferiority at the 1-sided 2.5% significance level, superiority of daprodustat compared with darbepoetin alfa for the IV iron outcome was tested at the 1-sided 2.5% significance level.

The exploratory time to the first on-treatment red blood cell or whole blood transfusion outcome was analyzed using a Cox proportional hazards regression model adjusted for treatment, dialysis type, and dialysis start manner. Statistical analyses were conducted using SAS, version 9.4 (SAS Institute).

Results

Study Population

Overall, 518 patients were screened worldwide, with 206 (40%) not meeting eligibility criteria. Reasons for exclusion after screening are detailed in **Figure 2**. The remaining 312 patients (60%; median [IQR] age, 55 [45-65] years; 194 [62%] male) were randomized at 90 centers in 14 countries to either daprodustat (157 patients; median [IQR] age, 52.0 [45-63] years; 96 [61%] male) or darbepoetin alfa (155 patients; median [IQR] age, 56.0 [45-67] years; 98 [63%] male). Randomized treatment was prematurely discontinued in 45 patients (29%) receiving daprodustat and 39 (25%) receiving darbepoetin alfa; 306 patients (98%) completed the study. Vital status was confirmed in all but 1 of the 312 patients (>99%) at week 52.

Baseline Characteristics and Treatment

Baseline characteristics for the intent-to-treat population are shown in **Table 1** and were generally similar between arms as well as for dialysis type (eTable 6 in Supplement 2). Overall, 252 (81%) of the patients were undergoing HD and 216 (69%) had planned initiation of dialysis.

Table 1. Baseline Characteristics for the ITT Population

Characteristic	Patients[a]	
	Daprodustat (n = 157)	Darbepoetin (n = 155)
Age, median (IQR), y	52.0 (45-63)	56.0 (45-67)
Sex		
Male	96 (61)	98 (63)
Female	61 (39)	57 (37)
Self-identified race and ethnicity		
African American or Black	16 (10)	13 (8)
American Indian or Alaska Native	5 (3)	2 (1)
Asian	26 (17)	31 (20)
Native Hawaiian or other Pacific Islander	0	0
White	110 (70)	107 (69)
Mixed race[b]	0	2 (1)
Dialysis type at randomization		
HD	126 (80)	126 (81)
PD	31 (20)	29 (19)
Dialysis start manner		
Planned	109 (69)	107 (69)
Unplanned	48 (31)	48 (31)
Dialysis status at randomization		
Dialysis not initiated	8 (5)	4 (3)
Receiving dialysis	149 (95)	151 (97)
Baseline BMI, median (IQR)[c]	26.1 (22.4-29.1)	26.3 (22.9-30.5)
Baseline weight, median (IQR), kg[d]	75.0 (63.0-87.4)	74.0 (63.0-87.4)
Cardiovascular disease history	47 (30)	45 (29)
Coronary artery disease	22 (14)	23 (15)
Heart failure	2 (1)	1 (<1)
Valvular heart disease	12 (8)	14 (9)
Angina pectoris	3 (2)	9 (6)
Atrial fibrillation	8 (5)	8 (5)
Myocardial infarction	12 (8)	9 (6)
Stroke	7 (4)	9 (6)
Transient ischemic attack	2 (1)	2 (1)
Cardiac arrest	2 (1)	0
Thromboembolic events	13 (8)	8 (5)
Diabetes	70 (45)	70 (45)
Cancer	3 (2)	4 (3)
Smoking status		
Current	21 (13)	14 (9)
Former	34 (22)	48 (31)
Baseline postdialysis blood pressure, median (IQR), mm Hg[e]		
Systolic	139 (126-150)	140 (120-154)
Diastolic	79 (70-84)	76 (70-85)
Arterial pressure, mean (IQR)	97 (89-106)	97 (86-107)
High-sensitivity CRP, median (IQR), mg/dL[f]	0.3 (0.1-0.7)	0.4 (0.1-0.9)
Albumin, median (IQR), g/dL[g]	3.8 (3.4-4.1)	3.7 (3.5-4.0)
Hemoglobin, g/dL		
Median (IQR)	9.4 (8.7-10.1)	9.5 (8.9-10.0)
Mean (SD)	9.5 (1.0)	9.5 (1.0)
White blood cell count, median (IQR), No./μL[g]	6.6 (5.4-7.8)	6.4 (5.3-8.3)
Platelets, median (IQR), No. $\times 10^3$/μL[g]	219 (171-280)	204 (172-249)
Transferrin saturation, median (IQR), %	28 (23-35)	30 (23-35)

(continued)

Table 1. Baseline Characteristics for the ITT Population (continued)

Characteristic	Patients[a]	
	Daprodustat (n = 157)	Darbepoetin (n = 155)
Ferritin, median (IQR), ng/mL	365 (221-518)	373 (239-649)
Hepcidin, median (IQR), ng/mL	118.4 (76.8-198.6)	124.8 (78.2-205.3)
Cholesterol, median (IQR), mg/dL[h]		
Total	164.1 (139.0-191.1)	164.1 (140.9-187.3)
Low-density lipoprotein	91.9 (71.0-112.0)	90.0 (73.0-110.0)
High-density lipoprotein	46.3 (38.6-60.0)	44.4 (38.6-54.1)
Medication		
Diabetes medications	56 (36)	54 (35)
Insulin	40 (25)	42 (27)
ACE inhibitor or ARB	73 (46)	58 (37)
Beta blocker	80 (51)	77 (50)
Statin	64 (41)	50 (32)
Aspirin	39 (25)	40 (26)
Vitamin K antagonist	3 (2)	3 (2)
Phosphate binder[i]		
Iron-based	2 (1)	3 (2)
Calcium-based	55 (35)	56 (36)
Not calcium- or iron-based	12 (8)	13 (8)
Vitamin D	56 (36)	67 (43)
Calcimimetics	3 (2)	3 (2)
Oral iron	25 (16)	21 (14)
Intravenous iron	105 (67)	109 (70)
Standardized IV iron dose, median (IQR), mg/mo[j]	87.0 (0-229.8)	130.5 (0-279.5)
Standardized IV iron dose, mean (SD), mg/mo	159.3 (207.1)	180.1 (209.9)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; CRP, C-reactive protein; HD, hemodialysis; ITT, intent-to-treat; IV, intravenous; PD, peritoneal dialysis.

SI conversion factors: To convert albumin to grams per liter, multiply by 10.0; cholesterol to millimoles per liter, multiply by 0.0259; CRP to milligrams per liter, multiply by 10.0; ferritin to micrograms per liter, multiply by 1.0; hemoglobin to grams per liter, multiply by 10.0; platelets to number $\times 10^9$ per liter, multiply by 1.0; white blood cell count to number $\times 10^9$ per liter, multiply by 0.001.

[a] All baseline laboratory tests were performed by a central laboratory except for hemoglobin, which uses central laboratory values if available or a point-of-care HemoCue value if the central laboratory value is missing. Data are presented as the number (percentage) of patients unless otherwise indicated.

[b] Patients selected multiple race categories.

[c] For patients with in-clinic dialysis, postdialysis values were used. Data are presented from 154 patients in the daprodustat arm and 153 in the darbepoetin alfa arm.

[d] Data are presented from 155 patients in the daprodustat arm and 153 in the darbepoetin alfa arm.

[e] For patients with in-clinic dialysis, postdialysis values were used. Data are presented from 155 patients in the daprodustat arm and 154 in the darbepoetin alfa arm.

[f] Data are presented from 155 patients in the daprodustat arm and 152 in the darbepoetin alfa arm.

[g] Based on the Safety Population.

[h] Data are presented from 154 patients in the daprodustat arm for cholesterol and high-density lipoprotein and 155 for low-density lipoprotein; data are presented from 150 patients in the darbepoetin alfa arm for cholesterol and high-density lipoprotein and 154 for low-density lipoprotein.

[i] Patients may have used more than 1 type of phosphate binder, so percentages may sum to more than 100.

[j] Includes patients receiving no IV iron.

The mean (SD) baseline Hb concentration was 9.46 (1.00) g/dL in the daprodustat group and 9.49 (0.97) g/dL in the darbepoetin alfa group. Baseline IV iron use was similar between groups (daprodustat, 67%; darbepoetin alfa, 70%), although the median (IQR) standardized IV iron dose at baseline was lower in the daprodustat group (87 mg/mo [0-230 mg/mo]) than in the darbepoetin alfa group (130 mg/mo [0-280 mg/mo]).

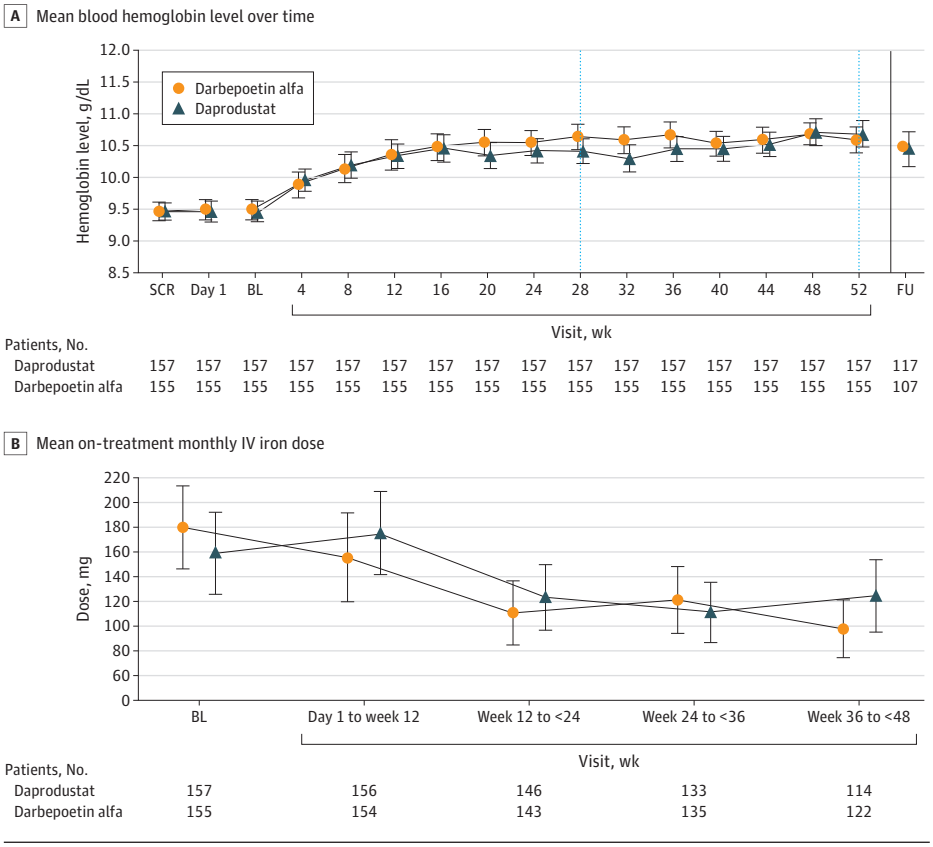
Treatment Exposure and Dosing

Randomized treatment exposure was similar between the 2 arms, with 135 patients (86%) in the daprodustat arm and 139 (90%) in the darbepoetin arm receiving randomized treatment for more than 6 months. The median (IQR) for the daily dose of daprodustat was 2 mg (0-8 mg) and for the 4 weekly doses of darbepoetin alfa was 60 µg (30-160 µg) (eFigure 1 in Supplement 2). The total median (IQR) duration of exposure was 12.0 months (9.6-12.0 months) for the daprodustat arm and 12 months (11.8-12.1 months) for the darbepoetin arm.

Hemoglobin Efficacy

During the evaluation period, the mean (SD) Hb concentration was 10.5 (1.0) g/dL in the daprodustat arm and 10.6 (0.9) g/dL in the darbepoetin alfa arm. The mean Hb concentration for both the daprodustat and the darbepoetin alfa arms remained in the analysis range of 10.0 to 11.5 g/dL (**Figure 3**A). The adjusted mean (SE) change from baseline in the daprodu-

Figure 3. Line Plots for Mean Hemoglobin Levels and Mean On-Treatment Monthly IV Iron Dose



Dashed vertical lines indicate the evaluation period and whiskers, 95% CIs. BL, baseline; FU, follow-up; IV, intravenous; and SCR, screening. To convert hemoglobin to grams per liter, multiply by 10.0.

stat vs darbepoetin alfa groups was 1.02 (0.09) g/dL vs 1.12 (0.09) g/dL, giving a treatment difference of −0.10 g/dL (95% CI, −0.34 to 0.14 g/dL), achieving noninferiority of daprodustat compared with darbepoetin alfa at the prespecified noninferiority margin of −0.75 g/dL.

Subgroup analysis of the primary Hb outcome showed similar results for HD and PD and for a planned and unplanned dialysis start (eFigure 2 in Supplement 2). Supplementary analyses provided findings that were consistent with those of the primary analysis (eFigure 3 in Supplement 2). The Hb response to daprodustat and darbepoetin alfa from baseline to the evaluation period was maintained regardless of the baseline high-sensitivity C-reactive protein level (eTable 7 in Supplement 2).

Markers of Iron Metabolism and Use

Although there was a reduction in mean monthly IV iron use from baseline to week 52 in both treatment groups compared with baseline, daprodustat was not superior to darbepoetin alfa in reducing monthly IV iron use (adjusted mean treatment difference, 19.4 mg/mo [95% CI, -11.0 to 49.9]; Figure 3B). Mean (SD) monthly IV iron use between the 2 treatments groups was generally similar (daprodustat, 142 (161) mg; darbepoetin alfa, 128 (137) mg).

Patients who received daprodustat had an increase in total iron-binding capacity and a reduction in ferritin level, whereas transferrin saturation and the total iron level remained relatively stable (eFigure 4A-D in Supplement 2). Results were similar for patients receiving darbepoetin alfa aside from total iron-binding capacity, which remained similar to baseline, and hepcidin level, which was reduced in both treatment groups. A reduction of 26% (from a mean [IQR] of 112.6 [76.8-198.6] ng/mL to 82.8 [48.0-170.1] ng/mL) in hepcidin level was observed among patients who received daprodustat, and a 10% reduction (from a mean [IQR] of 111.6 [78.2-205.3] to 100.2 [66.5-182.1] ng/mL) was observed among those who received darbepoetin alfa.

Rescue and Transfusions

Three percent of patients in both treatment groups (5 in daprodustat and 5 in darbepoetin alfa) met the rescue criteria, resulting in permanent discontinuation of randomized treatment. The rate of a first occurrence of red blood cell or whole blood transfusion during the on-treatment period was similar between the groups (daprodustat, 18 patients [12%]; darbepoetin alfa, 21 [14%]; hazard ratio, 0.88; 95% CI, 0.47-1.66).

Adverse Events and Other Safety Outcomes

The proportion of patients experiencing treatment-emergent AEs and serious AEs was generally similar between the treatment arms (**Table 2**). Adverse event rates were 76% for daprodustat vs 72% for darbepoetin alfa.

The incidence of potential AEs of special interest was generally similar between treatment groups for each category of

Table 2. Summary of Treatment-Emergent AEs, Serious AEs, and First Occurrence of Adjudicated MACE

Variable	Patients, No. (%)	
	Daprodustat (n = 157)	Darbepoetin (n = 155)
Treatment-emergent AE type[a]		
Any AE	120 (76)	112 (72)
Any serious AE	52 (33)	51 (33)
Most common (≥5%) AEs	120 (76)	112 (72)
Hypertension	29 (18)	25 (16)
Dialysis hypotension	21 (13)	15 (10)
Diarrhea	14 (9)	11 (7)
Fluid overload	14 (9)	9 (6)
Headache	12 (8)	9 (6)
Upper respiratory tract infection	7 (4)	11 (7)
Hypotension	7 (4)	9 (6)
Muscle spasms	7 (4)	9 (6)
Nasopharyngitis	7 (4)	9 (6)
Adjudicated MACE type		
Patients, No.[b]	157	155
First occurrence of MACE	19 (12)	15 (10)
All-cause mortality	14 (9)	9 (6)
Nonfatal myocardial infarction	5 (3)	5 (3)
Nonfatal stroke	0	1 (1)
Incidence rate/100 PYs (2-sided 95% CI)	11.65 (7.02 to 18.20)	9.24 (5.17 to 15.24)
Absolute rate difference/100 PYs (95% CI)[c]	2.41 (−4.61 to 9.43)	

Abbreviations: AE, adverse event; MACE, major adverse cardiovascular event; PY, person-year.

[a] Adverse events were defined as treatment-emergent if they started or became worse on or after treatment start, up to the day after the last nonzero dose date.

[b] All randomized patients.

[c] A rate difference greater than 0 indicated a lower risk with daprodustat compared with darbepoetin alfa.

AEs of special interest (eTable 8 in Supplement 2), aside from a worsening of hypertension, which occurred in 38 patients (24%) in the daprodustat group vs 29 (19%) in the darbepoetin alfa group. However, both randomized treatments showed a similar effect on blood pressure (BP); when focusing on objective measures, the adjusted mean difference in systolic BP was −0.09 mm Hg (95% CI, −4.72 to 4.53) and in diastolic BP was 1.99 mm Hg (95% CI, −0.85 to 4.82). Fewer patients in the daprodustat group (91 [59%]) compared with the darbepoetin alfa group (100 [65%]) experienced on-treatment BP elevations (eTable 9 in Supplement 2). More patients in the daprodustat group required changes in on-treatment BP medication; 87 patients (58%) receiving daprodustat and 73 (50%) receiving darbepoetin alfa required at least 1 change (eTable 9 in Supplement 2).

Exploratory Cardiovascular Outcomes

An assessment of the first occurrence of a MACE showed that 19 patients (12%) randomized to daprodustat vs 15 (10%) randomized to darbepoetin alfa experienced a first MACE (Table 2), whereas the overall rate of all-cause mortality in the daprodustat arm was 11% compared with 8% in the darbepoetin alfa arm.

A first occurrence of a MACE or a thromboembolic event occurred in 26 patients (17%) in the daprodustat group and 27 (17%) in the darbepoetin alfa group, whereas the first occurrence of MACE or a hospitalization for heart failure occurred in 24 patients (15%) in the daprodustat group and 18 (12%) in the darbepoetin alfa group.

Discussion

This randomized clinical trial demonstrated that daprodustat was noninferior to darbepoetin alfa for increasing and maintaining Hb concentration for 52 weeks in patients receiving both incident HD and PD. The difference in Hb change from baseline was 0.10 g/dL between the treatment arms. Furthermore, the response to daprodustat was comparable with the response to darbepoetin alfa across several subgroups and was robust for both treatments, even among patients with higher levels of inflammatory markers such as high-sensitivity C-reactive protein. Iron use, a key secondary outcome, was similar between patients treated with daprodustat and darbepoetin alfa, and there was not a significant reduction in iron use in the daprodustat-treated patients compared with patients treated with darbepoetin alfa. Overall, daprodustat's safety profile appeared to be similar to that of darbepoetin alfa, and no unexpected safety concerns were identified.

Efficacy of daprodustat was observed across key subgroups, ie, in both HD and PD recipients and in those with planned vs unplanned dialysis starts. Effectiveness in ID

patients, especially those who have had an unplanned start, is important, because a high prevalence of ESA hyporesponsiveness and an increased risk of cardiovascular events and death have been found in these patients.[22] Unplanned start of dialysis is frequently associated with the use of a temporary dialysis catheter and metabolic and fluid shifts[23,24] that in turn are associated with a high risk for hospitalization. The daprodustat-induced Hb response was independent of baseline levels of high-sensitivity C-reactive protein, further supporting its efficacy among ID patients who have increased levels of inflammation.

Some indices of iron kinetics differed between treatment groups, especially for hepcidin (an approximate 17% difference between groups) and for total iron-binding capacity, which was increased with daprodustat and unchanged for the comparator; however, there was no between-group difference in IV iron use. The effect of HIF-PHIs on hepcidin levels in ID patients has been previously reported.[14,25] Because iron is mostly delivered intravenously rather than orally in patients receiving dialysis, it is possible that an effect of daprodustat on iron use was not observed because of a greater effect of hepcidin on the egress of iron on the enterocyte. The lack of treatment difference in IV iron use, despite changes in parameters of iron metabolism, is currently unclear, and further study is warranted.

There was no effect on BP values between the daprodustat and darbepoetin alfa arms in this study. Although there was a higher percentage of worsening hypertension in the daprodustat arm than in the darbepoetin alfa arm, the objective BP values were similar.

Other HIF-PHIs have been studied in an ID population, although the definition for "incident" included patients up to 4 months after dialysis initiation, and the size, duration, and follow-up within those studies varied.[26,27] A vadadustat trial of 3923 total patients included a cohort of 369 patients in the pooled dialysis program who initiated dialysis within 16 (incident population) and 12 (prevalent population) weeks of randomization, with a median follow-up of 1.2 years.[26] Roxadustat trials included pooled data from 3 studies for 1530 patents who initiated dialysis within 4 months of randomization and were followed for a mean of approximately 1.5 years, with follow-up varying and minimal follow-up in 2 of the 3 studies for patients who permanently stopped study treatment.[27] Collectively, HIF-PHI studies in the ID population reported to date have demonstrated Hb efficacy and no safety concerns, including cardiovascular safety.

The recently published cardiovascular outcome trials in patients receiving prevalent dialysis (ASCEND-D) and no dialysis (ASCEND-ND) provide further information about the use of daprodustat in patients with CKD.[15,16] These studies, along with the ASCEND-ID study, demonstrated noninferiority for Hb efficacy and for cardiovascular outcomes (eTable 10 in Supplement 2). Although cardiovascular outcomes were adjudicated in the ASCEND-ID study (but not formally tested given the limited duration of the study and the small number of events), cardiovascular safety was generally consistent across treatment groups.

Limitations

The limitations of this study include a relatively short 52-week study treatment length and a small sample size, which limited the evaluation of MACE safety outcomes. The open-label design may have contributed to biased AE reporting. In addition, given that darbepoetin alfa was used in this trial, conclusions about noninferiority to other ESAs may be limited.

Conclusions

In this randomized clinical trial, the ASCEND-ID study showed noninferiority of daprodustat to darbepoetin alfa in the treatment of anemia in ID patients. Monthly IV iron use was similar in both study arms, and although changes in iron kinetics with daprodustat were observed, the significance of these findings is not clear. Daprodustat was effective in maintaining Hb concentrations in a subgroup of patients with an unplanned dialysis start, in patients receiving PD, and in patients with inflammation. The safety profile was similar between treatment groups in this 52-week study; the scientific and medical communities are still waiting for long-term safety data and recommend additional studies.[28] Based on the efficacy and short-term safety data in this study, daprodustat may represent a potential oral alternative to one of the conventional ESAs for patients with CKD who are starting dialysis.

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