ORIGINAL ARTICLE

Daprodustat for the Treatment of Anemia in Patients Not Undergoing Dialysis

Ajay K. Singh, M.B., B.S., M.B.A., Kevin Carroll, Ph.D., John J.V. McMurray, M.D., Scott Solomon, M.D., Vivekanand Jha, M.D., Kirsten L. Johansen, M.D., Renato D. Lopes, M.D., Ph.D., Iain C. Macdougall, M.D., Gregorio T. Obrador, M.D., Sushrut S. Waikar, M.D., Christoph Wanner, M.D., David C. Wheeler, M.B., Ch.B., M.D., Andrzej Więcek, M.D., Ph.D., Allison Blackorby, M.Sc., Borut Cizman, M.D., Alexander R. Cobitz, M.D., Ph.D., Rich Davies, M.Sc., Tara L. DiMino, M.D., Lata Kler, Ph.D., Amy M. Meadowcroft, Pharm.D., Lin Taft, Ph.D., and Vlado Perkovic, M.B., B.S., Ph.D., for the ASCEND-ND Study Group*

ABSTRACT

BACKGROUND

Daprodustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor. In patients with chronic kidney disease (CKD) who are not undergoing dialysis, the efficacy and safety of daprodustat, as compared with the conventional erythropoiesis-stimulating agent darbepoetin alfa, are unknown.

METHODS

In this randomized, open-label, phase 3 trial with blinded adjudication of cardiovascular outcomes, we compared daprodustat with darbepoetin alfa for the treatment of anemia in patients with CKD who were not undergoing dialysis. The primary outcomes were the mean change in the hemoglobin level from baseline to weeks 28 through 52 and the first occurrence of a major adverse cardiovascular event (MACE; a composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke).

RESULTS

Overall, 3872 patients were randomly assigned to receive daprodustat or darbepoetin alfa. The mean (±SD) baseline hemoglobin levels were similar in the two groups. The mean (±SE) change in the hemoglobin level from baseline to weeks 28 through 52 was 0.74±0.02 g per deciliter in the daprodustat group and 0.66±0.02 g per deciliter in the darbepoetin alfa group (difference, 0.08 g per deciliter; 95% confidence interval [CI], 0.03 to 0.13), which met the prespecified noninferiority margin of −0.75 g per deciliter. During a median follow-up of 1.9 years, a first MACE occurred in 378 of 1937 patients (19.5%) in the daprodustat group and in 371 of 1935 patients (19.2%) in the darbepoetin alfa group (hazard ratio, 1.03; 95% CI, 0.89 to 1.19), which met the prespecified noninferiority margin of 1.25. The percentages of patients with adverse events were similar in the two groups.

CONCLUSIONS

Among patients with CKD and anemia who were not undergoing dialysis, daprodustat was noninferior to darbepoetin alfa with respect to the change in the hemoglobin level from baseline and with respect to cardiovascular outcomes. (Funded by GlaxoSmithKline; ASCEND-ND ClinicalTrials.gov number, NCT02876835.)

From Brigham and Women's Hospital (A.K.S., S.S.), Harvard Medical School (A.K.S., S.S.), and Boston University School of Medicine and Boston Medical Center (S.S.W.) — all in Boston; KJC Statistics, Cheadle (K.C.), the British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow (J.J.V.M.), the School of Public Health, Imperial College London (V.J.), King's College Hospital (I.C.M.), and the Department of Renal Medicine, University College London (D.C.W.), London, and GlaxoSmithKline, Brentford (L.K.) — all in the United Kingdom; George Institute for Global Health, New Delhi, and Prasanna School of Public Health, Manipal Academy of Higher Education, Manipal — both in India (V.J.); Hennepin Healthcare, University of Minnesota, Minneapolis (K.L.J.); Duke University Medical Center, Duke Clinical Research Institute, Durham, NC (R.D.L.); Universidad Panamericana School of Medicine, Mexico City (G.T.O.); the University of Würzburg, Würzburg, Germany (C.W.); the Medical University of Silesia, Katowice, Poland (A.W.); GlaxoSmithKline, Collegeville, PA (A.B., B.C., A.R.C., R.D., T.L.D., A.M.M., L.T.); and the University of New South Wales, Sydney (V.P.). Dr. Singh can be contacted at ajay_singh@hms.harvard.edu or at Brigham and Women's Hospital, 75 Francis St., Medical Research Building, 4th Fl., Boston, MA 02115.

*A complete list of the ASCEND-ND Study Group investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on November 5, 2021, at NEJM.org.

DOI: 10.1056/NEJMoa2113380

Anemia is a common complication of chronic kidney disease (CKD).[1-3] Trials in which erythropoiesis-stimulating agents (ESAs), a common therapy for anemia in patients with CKD,[1,3,4] have been used to normalize the hemoglobin level to 13.0 to 14.0 g per deciliter have shown increased risks of cardiovascular events, venous thromboembolism, and death.[1,5]

The parenteral administration of ESAs may be inconvenient for patients.[6-8] Consequently, the oral hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitors are a potential alternative approach to treatment of anemia in patients with CKD. These agents stimulate endogenous erythropoietin production by stabilizing the HIF-α subunit, allowing it to dimerize with the HIF-β subunit and to stimulate genes involved in protection against hypoxia, including the erythropoietin gene.[9,10] HIF prolyl hydroxylase inhibitors also influence iron homeostasis through effects on transferrin, transferrin receptor expression, hepcidin, and other iron-related proteins.[9,10]

Phase 2 trials involving patients with CKD who were receiving dialysis[11] and those who were not receiving dialysis[12] showed that daprodustat, an orally active HIF prolyl hydroxylase inhibitor, had a good safety profile and had efficacy over 24 weeks. In the current trial, ASCEND-ND (Anemia Studies in Chronic Kidney Disease: Erythropoiesis via a Novel Prolyl Hydroxylase Inhibitor Daprodustat–Non-Dialysis), we evaluated the efficacy and safety of the HIF prolyl hydroxylase inhibitor daprodustat, as compared with the conventional ESA darbepoetin alfa, in patients with CKD who were not undergoing dialysis.

Methods

Trial Design and Oversight

The sponsor, GlaxoSmithKline, and an academic steering committee designed and oversaw the trial conduct and analysis. The members of the academic steering committee are listed in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. The trial was conducted and reported in accordance with the protocol (which includes the statistical analysis plan), available at NEJM.org. The trial was approved by the ethics committee at each center. An independent data monitoring committee oversaw the safety of the patients. Analyses that were conducted by the sponsor were independently replicated by an academic group at the Robertson Centre for Biostatistics at the University of Glasgow.

The first draft of the manuscript was prepared by the first author, who had unrestricted access to the data, and was reviewed and edited by all the authors. All the authors made the decision to submit the manuscript for publication and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. Earlier versions of the manuscript and figures were drafted with editorial assistance funded by the sponsor.

Patients

Adults were eligible for screening if they had stage 3 to 5 CKD and were not currently receiving dialysis or scheduled to start dialysis within 90 days, met the hemoglobin and ESA criteria, and had a serum ferritin level of more than 100 ng per milliliter and a transferrin saturation above 20%. Patients who had anemia that was unrelated to CKD, a recent cardiovascular event, or current or recent cancer were excluded. A complete list of inclusion and exclusion criteria is provided in Table S2.

Trial Procedures

The trial consisted of four periods: screening, placebo run-in, treatment, and follow-up (Fig. S1). The patients were evaluated at least every 4 weeks during the first year of the trial and at least every 12 weeks thereafter.

Patients who provided written informed consent and who met all inclusion and exclusion criteria received placebo tablets during a 4-week run-in period, and those who had received ESA therapy previously continued to receive an ESA during the screening and run-in periods. Patients were eligible to undergo randomization if they met the criteria for adherence to the placebo run-in period and had a hemoglobin level of 8.0 to 10.0 g per deciliter (in patients who were not receiving an ESA) or 8.0 to 11.0 g per deciliter (in patients who were receiving an ESA).

Eligible patients underwent randomization in a 1:1 ratio (with the use of balanced blocks) to receive either oral daprodustat or subcutaneous darbepoetin alfa. The investigators used an interactive voice-response or Web-response system to determine the treatment assignments. Randomization was stratified according to use or nonuse

of an ESA, geographic region, and participation or nonparticipation in an ambulatory blood-pressure monitoring substudy. Although the investigators and patients were aware of the treatment assignments, the sponsor and steering committee remained unaware of the aggregate treatment assignments throughout the trial.

TREATMENT ADJUSTMENT

We used a trial-specific algorithm for both treatment groups to achieve and maintain the hemoglobin level in the target range of 10.0 to 11.0 g per deciliter (Table S3). The starting dose of daprodustat was between 1 and 4 mg daily, according to the baseline hemoglobin level if the patient was not receiving an ESA and according to the ESA dose if the patient was receiving an ESA; stepped changes ranging from 1 to 24 mg were available for dose adjustments (Table S4).

The starting dose of darbepoetin alfa was based on the patient's weight and hemoglobin level at the time of randomization if the patient was not receiving an ESA or on the previous ESA dose if the patient was receiving an ESA. Stepped changes in the dose were predefined, and most steps increased the dose by 25 to 33%. A rescue algorithm, which included a provision for the use of intravenous iron, a red-cell transfusion, or both (Table S5), and a protocol for iron management (Table S6) were also provided.

OUTCOMES

The trial had two primary noninferiority outcomes: the mean change in the hemoglobin level from baseline to the primary evaluation period (weeks 28 through 52) and the first occurrence of an adjudicated major adverse cardiovascular event (MACE; a composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke). These and other cardiovascular events were adjudicated by an independent committee led by the Duke Clinical Research Institute in collaboration with a contract research organization, George Clinical, whose members were unaware of the treatment assignments. Details regarding the adjudication charter are provided in Section S1 in the Supplementary Appendix.

The principal secondary outcomes, each tested for superiority, were the time to the first occurrence of a MACE (as described above but tested for superiority rather than noninferiority), the first occurrence of a MACE or a thromboembolic event, the first occurrence of a MACE or hospitalization for heart failure, and the first occurrence of CKD progression.

STATISTICAL ANALYSIS

The trial was originally designed to enroll approximately 4500 patients, with follow-up until 945 adjudicated first MACEs had occurred in order to exclude a noninferiority margin of 1.20. To accelerate trial closeout because of the coronavirus disease 2019 pandemic, the noninferiority margin was changed to 1.25 in a protocol amendment issued on July 30, 2020, before the unblinding of the trial data.[13] This noninferiority margin aligned with that used in other clinical trials of HIF prolyl hydroxylase inhibitors,[14] and although the target number of events was reduced to 664, a power of approximately 90% was maintained. The revised trial size provided greater than 99% power for comparison of the effect of daprodustat and darbepoetin alfa on the change in the hemoglobin level from baseline, with a noninferiority margin of −0.75 g per deciliter.

In the intention-to-treat population (all the patients who had undergone randomization), the two primary outcomes were tested in parallel for noninferiority at a one-sided alpha level of 0.025. The MACE composite outcome was analyzed with the use of a Cox proportional-hazards model with adjustment for treatment group, use or nonuse of an ESA, and geographic region. Additional prespecified supplementary MACE analyses were conducted and included an on-treatment analysis that was restricted to events that had occurred between the initiation of a trial drug and 28 days after the last dose, the date of trial completion, or withdrawal, whichever occurred first.

For the primary hemoglobin outcome, the mean change from baseline to the evaluation period was assessed with the use of an analysis-of-covariance model after adjustment for the baseline hemoglobin level and the variables used in the MACE model. Missing hemoglobin values were imputed with the use of multiple imputation under the "missing at random" assumption.

The principal secondary superiority analyses would proceed only if noninferiority was established for both primary outcomes. We analyzed the secondary cardiovascular outcomes using an approach that was similar to that used for the primary outcomes, and we evaluated the outcome

of CKD progression using the Fine and Gray subdistribution hazard model, with adjustment for the same factors as the MACE analysis and with death from any cause treated as a competing risk. The Holm–Bonferroni method was used to adjust for multiplicity. We conducted subgroup analyses using statistical models that were similar to those used in the primary and principal secondary analyses, with the addition of the subgroup term and treatment-by-subgroup interaction terms. All analyses were performed with the use of SAS software, version 9.4, or R software, version 3.6.2 or later.

RESULTS

PATIENTS

From December 5, 2016, through December 7, 2020, a total of 3872 patients were randomly assigned to receive daprodustat or darbepoetin alfa at 506 centers in 39 countries (Fig. S2). The characteristics of the patients — including the estimated glomerular filtration rate, coexisting conditions, history of cardiovascular disease, and previous ESA dose in patients who had received an ESA — were well balanced between the trial groups at baseline (Table 1). The mean (±SD) baseline hemoglobin level was 9.9±0.9 g per deciliter across the two groups. Baseline characteristics according to the use or nonuse of an ESA have been published previously.[13] The trial sample was representative of the population with CKD not undergoing dialysis (Table S7). Specifically, a post hoc analysis showed that 32.7% of the trial patients in the United States were Black.

Daprodustat was discontinued prematurely for reasons other than death in 571 of 1937 patients (29.5%), and darbepoetin alfa was discontinued prematurely for reasons other than death in 560 of 1935 patients (28.9%) (Fig. S3). Nineteen patients (<1.0%) in the daprodustat group and 12 patients (<1.0%) in the darbepoetin alfa group had unknown vital status at the end of the trial. The median duration of follow-up for evaluation of cardiovascular events was 1.9 years (interquartile range, 1.0 to 2.7); this duration provided 7210 total person-years of follow-up.

PRIMARY EFFICACY OUTCOMES AND MEDIAN DOSES

The mean (±SE) change in the hemoglobin level from baseline to weeks 28 through 52 was 0.74±0.02 g per deciliter in the daprodustat group and 0.66±0.02 g per deciliter in the darbepoetin alfa group (difference, 0.08 g per deciliter; 95% confidence interval [CI], 0.03 to 0.13), which met the prespecified noninferiority margin (Table 2 and Fig. 1). Supplementary analyses provided findings that were consistent with those of the primary analysis (Fig. S4). The effect of daprodustat as compared with darbepoetin alfa was generally consistent across the prespecified subgroups (Fig. S5).

A rapid increase in the hemoglobin level, defined as an increase of more than 2 g per deciliter during any 4-week period from randomization through the first year, was observed in 2% or less of the patients in both trial groups. The median doses are presented in Figure S6; 97% of the patients who received daprodustat and 98% of those who received darbepoetin alfa adhered to the trial regimen.

PRIMARY SAFETY OUTCOME

A first MACE occurred in 378 of 1937 patients (19.5%) in the daprodustat group and in 371 of 1935 patients (19.2%) in the darbepoetin alfa group (hazard ratio, 1.03; 95% CI, 0.89 to 1.19); thus, the prespecified noninferiority margin of 1.25 was met (Table 2 and Fig. 2A). The results were generally consistent across prespecified subgroups (Fig. S7). These results were also broadly consistent with those in other supplementary intention-to-treat analyses (Fig. S8). However, the on-treatment MACE analysis, which censored data on patients at 28 days after the date of the last dose, showed a higher incidence of a first MACE during the treatment period in the daprodustat group (14.1%) than in the darbepoetin alfa group (10.5%) (hazard ratio, 1.40; 95% CI, 1.17 to 1.68).

The analysis of values over the treatment period as defined did not take into account the different dosing intervals in the daprodustat and darbepoetin alfa groups, which resulted in different observation periods. Post hoc analyses were conducted to explore the effect of the different dosing frequencies in this definition. These post hoc analyses were more consistent with the results of the primary analysis. Additional results of time-to-event analyses, including the components of the MACE composite outcome, are shown in Table S8.

KEY SECONDARY OUTCOMES

The results of superiority testing were not significant for the four principal secondary outcomes: the first occurrence of MACE in the daprodustat group as compared with the darbepoetin alfa group (hazard ratio, 1.03; 95% CI, 0.89 to 1.19), MACE or thromboembolic events (hazard ratio, 1.06; 95% CI, 0.93 to 1.22), MACE or hospitalization for heart failure (hazard ratio, 1.09; 95% CI, 0.95 to 1.24), and CKD progression (subdistribution hazard ratio, 0.98; 95% CI, 0.84 to 1.13) (Table 2 and Fig. 2). The incidence of death from any cause was similar in the two groups (hazard ratio, 1.03; 95% CI, 0.87 to 1.20).

The decreases in the hepcidin level and transferrin saturation and the increases in total iron-binding capacity from baseline were greater in the daprodustat group than in the darbepoetin alfa group (Table 1, Table 3, and Fig. S9). The decreases in ferritin levels were similar and the total iron levels were stable and similar in the two groups.

A total of 39 of 1937 patients (2.0%) in the daprodustat group and 64 of 1935 patients (3.3%) in the darbepoetin alfa group met the criteria for rescue therapy (i.e., a hemoglobin level <9.0 g per deciliter or transfusion of more than 2 units of packed red cells) and permanently discontinued the assigned treatment (hazard ratio, 0.63; 95% CI, 0.42 to 0.94) (Fig. S10). The percentages of patients who received at least one red-cell or whole-blood transfusion during the treatment period were similar in the daprodustat group (12.8%) and the darbepoetin alfa group (13.5%) (hazard ratio, 0.96; 95% CI, 0.81 to 1.14) (Fig. S11).

ADVERSE EVENTS

Two patients (both in the darbepoetin alfa group) were excluded from the safety analyses because they did not receive the assigned treatment (Fig. 2). Serious adverse events that started or worsened after the initiation of trial treatment were reported in 850 of 1937 patients in the daprodustat group (43.9%) and 703 of 1933 patients in the darbepoetin alfa group (36.4%). Table 3 and Table S9 include the most common adverse events, and Table S10 includes the most common serious adverse events; there was no notable excess of any event in the daprodustat group relative to the darbepoetin alfa group.

The incidences of the prespecified adverse events of special interest during trial treatment were generally consistent across the treatment groups except for cancer and esophageal or gastric erosions, which occurred significantly more often in the daprodustat group (Table 3). Post hoc analyses of the differential dosing frequencies (Table S11) showed attenuation of the imbalance for cancer events, but not for erosions. Daprodustat was similar to darbepoetin alfa with respect to the effect on blood pressure and the use of antihypertensive medications (Table S12).

DISCUSSION

Daprodustat was as effective as darbepoetin alfa in increasing and maintaining hemoglobin levels in patients with CKD and anemia who were not receiving dialysis. The effect of daprodustat on hemoglobin levels was consistent across prespecified subgroups. Daprodustat was also noninferior to darbepoetin alfa with respect to cardiovascular safety in the primary analysis. In addition, daprodustat and darbepoetin alfa had a similar effect with respect to the definitions of MACE expanded to include thromboembolic events and hospitalization for heart failure.

The results of our trial contrast with the pooled results of the PRO$_2$TECT trials.[14] In those trials, vadadustat, as compared with darbepoetin alfa, did not meet the prespecified noninferiority criterion for cardiovascular safety.[14] The reason for this difference is uncertain, since the PRO$_2$TECT trials and our trial had an identical primary MACE composite outcome and showed similar numbers of patients who had MACE outcome events.[14] Data are lacking from adequately powered trials comparing roxadustat with a conventional ESA in this population with respect to cardiovascular outcomes.

In contrast to our primary analysis in the intention-to-treat population, in which the incidences of MACE were similar in the two groups, the analysis of on-treatment MACE results favored darbepoetin alfa over daprodustat. Given the markedly different half-lives of daprodustat and darbepoetin alfa, different dosing frequencies were associated with different actual treatment periods for these two agents (daily for daprodustat and every 1 week, 2 weeks, or 4 weeks, according to the dose, for darbepoetin alfa). Post hoc analyses to account for the different dosing frequencies and to align the definitions of the

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Daprodustat (N=1937)	Darbepoetin Alfa (N=1935)
Demographic		
Median age (IQR) — yr	67 (57–75)	67 (57–74)
Female sex — no. (%)	1102 (56.9)	1071 (55.3)
Race or ethnic group — no. (%)†		
White	1098 (56.7)	1055 (54.5)
Asian	525 (27.1)	537 (27.8)
Black	183 (9.4)	185 (9.6)
American Indian or Alaska Native	88 (4.5)	100 (5.2)
Mixed	36 (1.9)	51 (2.6)
Native Hawaiian or other Pacific Islander	7 (<1.0)	7 (<1.0)
Clinical		
Median body-mass index (IQR)‡	26.9 (23.3–31.2)	26.6 (23.3–31.0)
Nonuse of an ESA — no. (%)	1030 (53.2)	1032 (53.3)
CKD stage — no. (%)		
Stage 2	9 (<1.0)	8 (<1.0)
Stage 3	336 (17.3)	363 (18.8)
Stage 4	875 (45.2)	894 (46.2)
Stage 5	716 (37.0)	670 (34.6)
Missing data	1 (<1.0)	0
Coexisting condition — no. (%)		
Hypertension	1828 (94.4)	1829 (94.5)
Diabetes	1076 (55.5)	1118 (57.8)
Glomerulonephritis	208 (10.7)	189 (9.8)
Autosomal dominant polycystic kidney disease	65 (3.4)	57 (2.9)
Cardiovascular disease§	716 (37.0)	716 (37.0)
Coronary artery disease	369 (19.1)	400 (20.7)
Heart failure	265 (13.7)	254 (13.1)
Valvular heart disease	147 (7.6)	151 (7.8)
Angina pectoris	150 (7.7)	145 (7.5)
Stroke	128 (6.6)	128 (6.6)
Myocardial infarction	128 (6.6)	127 (6.6)
Atrial fibrillation	115 (5.9)	90 (4.7)
Transient ischemic attack	63 (3.3)	73 (3.8)
Cardiac arrest	23 (1.2)	19 (1.0)
Thromboembolic event — no. (%)¶	80 (4.1)	70 (3.6)
Cancer — no. (%)	101 (5.2)	86 (4.4)
Laboratory values‖		
Hemoglobin — g/dl		
Median (IQR)	9.8 (9.2–10.5)	9.9 (9.2–10.5)
Mean	9.9±0.9	9.8±0.9

Table 1. (Continued)

Characteristic	Daprodustat (N=1937)	Darbepoetin Alfa (N=1935)
Median estimated GFR (IQR) — ml/min/1.73 m^2	17.0 (12.0–26.0)	18.0 (12.0–27.0)
Median high-sensitivity C-reactive protein (IQR) — mg/liter	2.0 (0.8–5.3)	2.0 (0.8–5.5)
Median albumin (IQR) — g/dl**	4.0 (3.7–4.2)	4.0 (3.7–4.2)
Median hepcidin (IQR) — ng/ml	105.6 (61.7–165.9)	105.3 (61.2–169.8)
Median transferrin saturation (IQR) — %	30.0 (24.0–37.0)	29.0 (23.0–36.0)
Median ferritin (IQR) — ng/ml	267.0 (164.0–456.0)	275.0 (171.0–449.0)
Median total iron-binding capacity (IQR) — μmol/liter	45.0 (40.0–50.0)	44.0 (40.0–49.0)
Median total iron (IQR) — μmol/liter	13.0 (10.0–16.0)	13.0 (10.0–16.0)
Median intact parathyroid hormone level (IQR) — pg/ml**	129.2 (69.3–242.2)	123.5 (63.6–242.2)
Median total cholesterol (IQR) — mg/dl	158.3 (131.3–193.1)	158.3 (131.3–191.1)
Low-density lipoprotein	84.2 (64.1–110.8)	84.2 (64.9–110.0)
High-density lipoprotein	46.3 (36.7–56.0)	46.3 (36.7–56.0)
Iron — no. (%)		
Oral	967 (49.9)	949 (49.0)
Intravenous††	226 (11.7)	228 (11.8)
Median previous ESA dose, standardized to intravenous epoetin (IQR) — U/wk	3944 (2500–6279)	3920 (2455–6351)

* Plus–minus values are means ±SD. Data are for the intention-to-treat population unless otherwise noted. All baseline laboratory tests were performed at a central laboratory except for hemoglobin, for which central-laboratory values are reported if available, or a point-of-care HemoCue value was used if the central-laboratory value was missing. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for iron-binding capacity and iron to micrograms per deciliter, divide by 0.1791. CKD denotes chronic kidney disease, ESA erythropoiesis-stimulating agent, GFR glomerular filtration rate, and IQR interquartile range.
† Race or ethnic group was reported by the patient.
‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Patients may be counted in multiple rows.
¶ Thromboembolic events include pulmonary embolism, deep-vein thrombosis, retinal-vein occlusion, arteriovenous graft thrombosis, arteriovenous fistula thrombosis, and central venous catheter thrombosis.
‖ All baseline laboratory tests were performed at a central laboratory except for hemoglobin, for which central-laboratory values are reported if available, and a point-of-care HemoCue value was used if the central-laboratory value was missing.
** Data were evaluated in the safety population (1937 patients in the daprodustat group and 1933 patients in the darbepoetin alfa group).
†† A summary of intravenous iron use during the treatment period, according to quarter, is provided in Table S13.

treatment period showed results that were more consistent with those of the intention-to-treat analysis than with those of the analysis of MACE results during the treatment period. As has been described elsewhere,[15] concerns have been raised regarding potential confounding associated with the use of on-treatment analyses.

The prespecified analysis involving the composite outcome indicated that daprodustat, as compared with darbepoetin alfa, did not delay progression of CKD, and there was no imbalance between the treatment groups with respect to any of the components of the composite outcome that included both surrogate and hard outcomes. These observations were consistent with the results of the PRO_2TECT trials.[14] Together, these data suggest that it is unlikely that HIF prolyl hydroxylase inhibitors slow CKD progression in a clinically significant manner.

Two other findings are of clinical interest. In our trial, we evaluated a rapid increase in the hemoglobin level, as measured by an increase of more than 2.0 g per deciliter over 4 weeks. This increase occurred infrequently and did not differ

Table 2. Primary and Principal Secondary Outcomes.*

Outcome	Daprodustat (N=1937)		Darbepoetin Alfa (N=1935)		Treatment Effect (95% CI)	P Value†
	Value	No. of Events	Value	No. of Events		
Primary efficacy outcome — g/dl						
Change in hemoglobin level from baseline to wk 28–52‡	0.74±0.02	—	0.66±0.02	—	Mean adjusted difference, 0.08 (0.03–0.13)	<0.001
Primary cardiovascular outcome — no. (%)						
MACE	378 (19.5)	464	371 (19.2)	441	Hazard ratio, 1.03 (0.89–1.19)	0.005
Death from any cause	252 (13.0)	301	259 (13.4)	298	—	—
Nonfatal myocardial infarction	96 (5.0)	125	91 (4.7)	116	—	—
Nonfatal stroke	30 (1.5)	38	21 (1.1)	27	—	—
Principal secondary cardiovascular outcomes — no. (%)						
MACE	378 (19.5)	464	371 (19.2)	441	Hazard ratio, 1.03 (0.89–1.19)	—
MACE or thromboembolic event	422 (21.8)	561	405 (20.9)	506	Hazard ratio, 1.06 (0.93–1.22)	—
Death from any cause	244 (12.6)	301	249 (12.9)	298	—	—
Nonfatal myocardial infarction	91 (4.7)	125	88 (4.5)	116	—	—
Nonfatal stroke	28 (1.4)	38	21 (1.1)	27	—	—
Nonfatal thromboembolic event	59 (3.0)	97	47 (2.4)	65	—	—
Deep-vein thrombosis	13 (0.7)	17	18 (0.9)	22	—	—
Pulmonary embolism	5 (0.3)	11	0	1	—	—
Vascular access thrombosis	41 (2.1)	69	29 (1.5)	42	—	—
MACE or hospitalization for heart failure	444 (22.9)	663	417 (21.6)	577	Hazard ratio, 1.09 (0.95– 1.24)	—
Death from any cause	225 (11.6)	301	237 (12.2)	298	—	—
Nonfatal myocardial infarction	86 (4.4)	125	81 (4.2)	116	—	—
Nonfatal stroke	26 (1.3)	38	17 (0.9)	27	—	—
Nonfatal hospitalization for heart failure	107 (5.5)	199	82 (4.2)	136	—	—
Principal secondary renal outcome — no./total no. (%)						
Progression of CKD	343/1220 (28.1)	464	359/1265 (28.4)	501	Subdistribution hazard ratio, 0.98 (0.84–1.13)	—
Confirmed 40% decrease in estimated GFR	173/1220 (14.2)	175	191/1265 (15.1)	195	—	—
Dialysis§	162/1220 (13.3)	266	158/1265 (12.5)	279	—	—
Kidney transplantation	8/1220 (0.7)	23	10/1265 (0.8)	27	—	—

* Plus–minus values are means ±SE. Primary outcomes were assessed for noninferiority, and secondary outcomes were assessed for superiority. MACE denotes major adverse cardiovascular event.
† The listed P values are one-sided and are compared against a threshold of 0.025 for noninferiority.
‡ Data include both observed and imputed values.
§ This category includes dialysis for at least 90 days or dialysis that was indicated but not initiated.

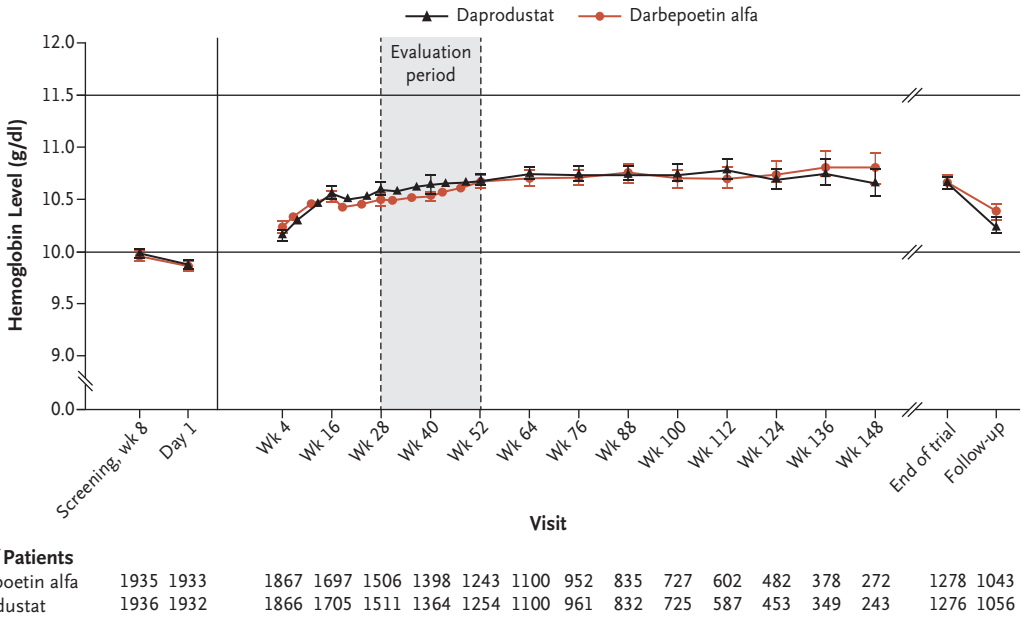


Figure 1. Hemoglobin Level, According to Visit (Intention-to-Treat Population).

Shown are the mean hemoglobin levels over the trial duration among patients with chronic kidney disease (CKD) who were not undergoing dialysis and who were assigned to receive daprodustat or darbepoetin alfa. Visits on or before day 1 include only pretreatment values. Visits after day 1 include all available values after randomization, regardless of whether the patient received trial treatment. The hemoglobin target range for dose changes was 10.0 to 11.0 g per deciliter. The horizontal lines represent the hemoglobin analysis range (10.0 to 11.5 g per deciliter), which is an extension of the hemoglobin target range to allow for variability. The I bars indicate 95% confidence intervals.

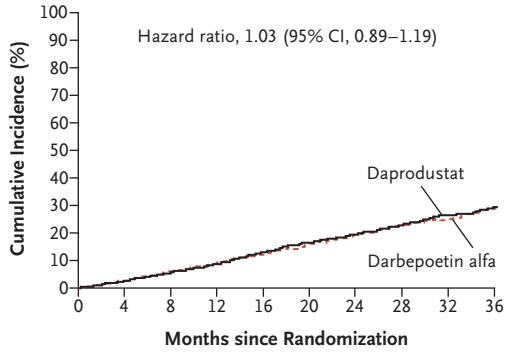
in the two treatment groups. The observed changes in iron metabolism in patients assigned to daprodustat may indicate more efficient iron incorporation into red cells; these beneficial differences persisted over time and are consistent with effects noted previously.[12] Studies to further explore the effect of daprodustat on iron kinetics are lacking.

Although the safety profile of daprodustat was generally similar to that of darbepoetin alfa, two adverse events of special interest were more frequent among patients who received daprodustat — cancer-related death and tumor progression and recurrence, as well as esophageal and gastric erosions. Post hoc analyses conducted in the intention-to-treat population or that accounted for dosing frequency showed attenuation of the imbalance for cancer events, but not for erosions. These observations warrant further study.

This trial has several limitations. First, the open-label design and patient awareness of treatment assignment may have biased reporting of adverse events. Second, since HIF activates transcription of many cytokines, which may have oncogenic or other potential long-term adverse effects, the observation time for this trial (although extended) may still be insufficient to characterize the full risks. Third, we used darbepoetin alfa as the ESA comparator, which might limit conclusions about noninferiority to other ESAs. Finally, the prespecified definitions for MACE during the treatment period and treatment-related adverse events did not take into account the different dosing frequencies.

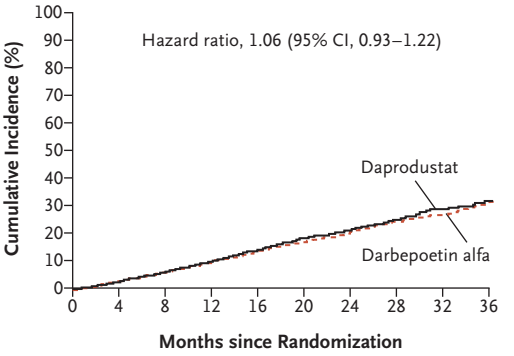
In this trial, we found that daprodustat was noninferior to darbepoetin alfa, both in the treatment of anemia in patients with CKD who were not undergoing dialysis and with respect to cardiovascular outcomes. This trial showed that daprodustat and darbepoetin alfa had similar efficacy.

A MACE



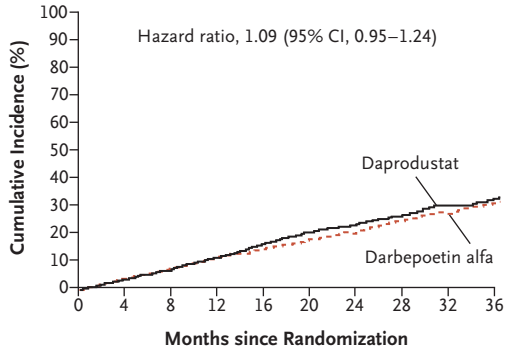
No. at Risk										
Darbepoetin alfa	1935	1825	1582	1412	1221	1038	843	660	474	291
Daprodustat	1937	1834	1601	1414	1207	1024	840	647	468	288

B MACE or Thromboembolic Events



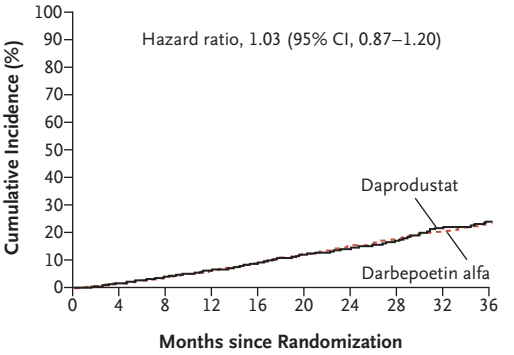
No. at Risk										
Darbepoetin alfa	1935	1820	1573	1400	1203	1019	823	639	456	275
Daprodustat	1937	1830	1589	1394	1186	999	815	624	448	273

C MACE or Hospitalization for Heart Failure



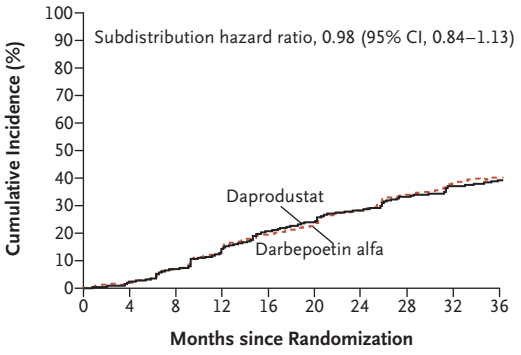
No. at Risk										
Darbepoetin alfa	1935	1802	1548	1377	1189	1012	820	636	455	279
Daprodustat	1937	1812	1571	1372	1156	976	800	611	445	275

D Death from Any Cause



No. at Risk										
Darbepoetin alfa	1935	1847	1613	1459	1269	1085	890	698	503	313
Daprodustat	1937	1853	1629	1455	1262	1086	897	693	497	308

E CKD Progression



No. at Risk										
Darbepoetin alfa	1265	1188	994	828	684	570	434	316	224	128
Daprodustat	1220	1148	966	804	642	535	427	313	211	136

Figure 2. Kaplan–Meier Plots of Time to First Occurrence of Adjudicated Cardiovascular Events and Death from Any Cause, and Cumulative Incidence Plot of Time to CKD Progression (Intention-to-Treat Population).

Patients at risk were all the patients who underwent randomization (Panels A through D) or all those who underwent randomization and had a baseline estimated glomerular filtration rate of at least 15 ml per minute per 1.73 m^2 (Panel E). MACE denotes major adverse cardiovascular event.

Table 3. Adverse Events and Laboratory Values (Safety Population).

Variable	Daprodustat (N=1937)		Darbepoetin Alfa (N=1933)		Relative Risk (95% CI)	P Value*
	Value	No. of Events	Value	No. of Events		
Adverse events — no. (%)†						
Any adverse event	1545 (79.8)	10,265	1487 (76.9)	9514	—	—
Any serious adverse event	850 (43.9)	1,960	703 (36.4)	1693	—	—
Adverse events of special interest‡						
Thrombosis or tissue ischemia due to excessive erythropoiesis	5 (0.3)	6	3 (0.2)	3	1.66 (0.40–6.95)	0.48
Cardiomyopathy	6 (0.3)	6	7 (0.4)	7	0.86 (0.29–2.54)	0.78
Pulmonary-artery hypertension	15 (0.8)	16	9 (0.5)	11	1.66 (0.73–3.79)	0.22
Cancer-related death or tumor progression or recurrence	72 (3.7)	82	49 (2.5)	67	1.47 (1.03–2.10)	0.04
Esophageal or gastric erosions	70 (3.6)	86	41 (2.1)	45	1.70 (1.16–2.49)	0.005
Proliferative retinopathy, macular edema, or choroidal neovascularization	54 (2.8)	70	44 (2.3)	55	1.22 (0.83–1.81)	0.31
Exacerbation of rheumatoid arthritis	2 (0.1)	2	4 (0.2)	4	0.50 (0.09–2.72)	0.41
Worsening of hypertension	344 (17.8)	489	363 (18.8)	519	0.95 (0.83–1.08)	0.41
Median laboratory measures at wk 52 (IQR)§						
Estimated GFR — ml/min/1.73 m^2	17.0 (11.0–25.0)	—	18.0 (12.0–27.0)	—	—	—
High-sensitivity C-reactive protein — mg/liter	2.3 (0.8–5.7)	—	2.2 (0.8–6.2)	—	—	—
Albumin — g/dl	3.9 (3.6–4.1)	—	3.9 (3.6–4.2)	—	—	—
Hepcidin — ng/ml¶	82.7 (43.0–142.4)	—	120.1 (66.5–201.1)	—	—	—
Transferrin saturation — %¶	29.0 (22.0–35.0)	—	32.0 (24.0–41.0)	—	—	—
Ferritin — ng/ml¶	240.0 (135.0–425.0)	—	262.0 (150.5–447.5)	—	—	—
Total iron-binding capacity — μmol/liter¶	50.0 (45.0–55.0)	—	44.0 (39.0–49.0)	—	—	—
Total iron — μmol/liter¶	14.0 (11.0–17.0)	—	14.0 (11.0–18.0)	—	—	—
Intact parathyroid hormone — pg/ml	157.6 (77.9–315.3)	—	148.6 (73.1–291.5)	—	—	—
Total cholesterol — mg/dl¶	148.6 (121.6–179.5)	—	154.4 (129.3–187.3)	—	—	—
Low-density lipoprotein	76.8 (57.1–101.2)	—	84.2 (64.1–108.1)	—	—	—
High-density lipoprotein	42.5 (34.7–54.1)	—	46.3 (37.6–56.0)	—	—	—

* The listed unadjusted P values are two-sided and were calculated with the use of the Cochran–Mantel–Haenszel chi-square test. A P value of less than 0.05 is considered to indicate statistical significance.

† Listed are adverse events that started or worsened on or after the initiation of the trial treatment and on or before the day after the patient's last dose of trial treatment.

‡ Adverse events of special interest were defined on the basis of data from clinical and nonclinical studies of daprodustat, current information about pathophysiological effects associated with hypoxia-inducible factor, and previously identified risks related to ESAs. A programmatic approach for these potential events was implemented with the use of a broad set of terms of interest, which are listed in the statistical analysis plan. Adverse events that may have indicated thrombosis, tissue ischemia, or both are listed in the statistical analysis plan.

§ All laboratory tests were performed in a central laboratory. Laboratory data are listed for all the patients who remained in the study at week 52 and continued to receive their assigned treatment.

¶ Data were evaluated in the intention-to-treat population.

Supported by GlaxoSmithKline.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank Delyth Jones of GlaxoSmithKline for providing strategic statistical support; and Fishawack Indicia, part of Fishawack Health, for providing editorial support.

REFERENCES

1. Babitt JL, Lin HY. Mechanisms of anemia in CKD. J Am Soc Nephrol 2012;23:1631-4.
2. Weiss G, Ganz T, Goodnough LT. Anemia of inflammation. Blood 2019;133:40-50.
3. Batchelor EK, Kapitsinou P, Pergola PE, Kovesdy CP, Jalal DI. Iron deficiency in chronic kidney disease: updates on pathophysiology, diagnosis, and treatment. J Am Soc Nephrol 2020;31:456-68.
4. Wilhelm-Leen ER, Winkelmayer WC. Mortality risk of darbepoetin alfa versus epoetin alfa in patients with CKD: systematic review and meta-analysis. Am J Kidney Dis 2015;66:69-74.
5. Food and Drug Administration. Information for healthcare professionals: erythropoiesis stimulating agents (ESA) [Aranesp (darbepoetin), Epogen (epoetin alfa), and Procrit (epoetin alfa)]. 2007 (https://wayback.archive-it.org/7993/20170723113601/https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126481.htm).
6. Aranesp prescribing information. Thousand Oaks, CA: Amgen, 2019 (https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/aranesp/ckd/aranesp_pi_hcp_english.pdf).
7. Epogen prescribing information. Thousand Oaks, CA: Amgen, 2018 (https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/epogen/epogen_pi_hcp_english.pdf).
8. Clement FM, Klarenbach S, Tonelli M, Wiebe N, Hemmelgarn B, Manns BJ. An economic evaluation of erythropoiesis-stimulating agents in CKD. Am J Kidney Dis 2010;56:1050-61.
9. Kaplan JM, Sharma N, Dikdan S. Hypoxia-inducible factor and its role in the management of anemia in chronic kidney disease. Int J Mol Sci 2018;19:19.
10. Sugahara M, Tanaka T, Nangaku M. Prolyl hydroxylase domain inhibitors as a novel therapeutic approach against anemia in chronic kidney disease. Kidney Int 2017;92:306-12.
11. Meadowcroft AM, Cizman B, Holdstock L, et al. Daprodustat for anemia: a 24-week, open-label, randomized controlled trial in participants on hemodialysis. Clin Kidney J 2019;12:139-48.
12. Holdstock L, Cizman B, Meadowcroft AM, et al. Daprodustat for anemia: a 24-week, open-label, randomized controlled trial in participants with chronic kidney disease. Clin Kidney J 2019;12:129-38.
13. Perkovic V, Blackorby A, Cizman B, et al. ASCEND-ND: study design and baseline characteristics. Nephrol Dial Transplant 2021;36:Suppl 1 (https://academic.oup.com/ndt/article/36/Supplement_1/gfab085.0022/6288634).
14. Chertow GM, Pergola PE, Farag YMK, et al. Vadadustat in patients with anemia and non–dialysis-dependent CKD. N Engl J Med 2021;384:1589-600.
15. DeMets DL, Cook T. Challenges of non-intention-to-treat analyses. JAMA 2019;321:145-6.