ORIGINAL ARTICLE

Daprodustat for the Treatment of Anemia in Patients Undergoing Dialysis

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ABSTRACT

BACKGROUND

Among patients with chronic kidney disease (CKD), the use of recombinant human erythropoietin and its derivatives for the treatment of anemia has been linked to a possibly increased risk of stroke, myocardial infarction, and other adverse events. Several trials have suggested that hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitors (PHIs) are as effective as erythropoiesis-stimulating agents (ESAs) in increasing hemoglobin levels.

METHODS

In this randomized, open-label, phase 3 trial, we assigned patients with CKD who were undergoing dialysis and who had a hemoglobin level of 8.0 to 11.5 g per deciliter to receive an oral HIF-PHI (daprodustat) or an injectable ESA (epoetin alfa if they were receiving hemodialysis or darbepoetin alfa if they were receiving peritoneal dialysis). The two primary outcomes were the mean change in the hemoglobin level from baseline to weeks 28 through 52 (noninferiority margin, −0.75 g per deciliter) and the first occurrence of a major adverse cardiovascular event (a composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke), with a noninferiority margin of 1.25.

RESULTS

A total of 2964 patients underwent randomization. The mean (±SD) baseline hemoglobin level was 10.4±1.0 g per deciliter overall. The mean (±SE) change in the hemoglobin level from baseline to weeks 28 through 52 was 0.28±0.02 g per deciliter in the daprodustat group and 0.10±0.02 g per deciliter in the ESA group (difference, 0.18 g per deciliter; 95% confidence interval [CI], 0.12 to 0.24), which met the prespecified noninferiority margin of −0.75 g per deciliter. During a median follow-up of 2.5 years, a major adverse cardiovascular event occurred in 374 of 1487 patients (25.2%) in the daprodustat group and in 394 of 1477 (26.7%) in the ESA group (hazard ratio, 0.93; 95% CI, 0.81 to 1.07), which also met the prespecified noninferiority margin for daprodustat. The percentages of patients with other adverse events were similar in the two groups.

CONCLUSIONS

Among patients with CKD undergoing dialysis, daprodustat was noninferior to ESAs regarding the change in the hemoglobin level from baseline and cardiovascular outcomes. (Funded by GlaxoSmithKline; ASCEND-D ClinicalTrials.gov number, NCT02879305.)

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Most patients with chronic kidney disease (CKD) who are receiving dialysis treatment have anemia, which is associated with a reduced quality of life, more frequent blood transfusions, and an elevated risk of cardiovascular events.[1,2] Previous clinical trials have raised safety concerns about the use of conventional erythropoiesis-stimulating agents (ESAs) to treat anemia.[3-6] Recombinant human erythropoietin and its derivatives have been linked to a possibly increased risk of stroke, myocardial infarction, vascular access thrombosis, tumor progression, or death when treatment is targeting a normal hemoglobin level (i.e., 13.0 to 14.0 g per deciliter).[3,4,6] As a result, cautious use of ESAs and partial correction of anemia are recommended.[7,8]

Hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitors (PHIs) are investigational agents that may offer an alternative oral treatment option for anemia associated with CKD.[7] By stabilizing HIF, these compounds increase the secretion of endogenous erythropoietin and the production of red cells.[9,10] Several trials have suggested that HIF-PHIs are as effective as ESAs in increasing hemoglobin levels, and safety data on these new agents are emerging.[11,12] Here, we report the results of a phase 3 randomized trial, ASCEND-D (Anemia Studies in Chronic Kidney Disease: Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor Daprodustat–Dialysis), involving patients who were undergoing maintenance dialysis, including those with ESA hyporesponsiveness. In this trial, we examined the hematologic efficacy, cardiovascular safety, and iron kinetics of the oral HIF-PHI daprodustat as compared with conventional therapy with ESAs.

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. The safety of trial patients was overseen by an independent data monitoring committee. 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 and last authors, 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.

Patients

Adults with CKD who had been undergoing dialysis for at least 90 days, had received an ESA for at least 6 weeks, and who had a hemoglobin level between 8.0 and 12.0 g per deciliter were eligible for screening. Patients were required to have 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.[13] All the patients provided written informed consent.

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.

Consenting patients who met all the inclusion and exclusion criteria during the screening period entered a 4-week placebo run-in period. Previous ESA therapy was continued during the screening and run-in periods. Patients were eligible for randomization if they met the criteria for adherence to the placebo run-in period and had a hemoglobin level of 8.0 to 11.5 g per deciliter. Patients underwent randomization with the use of balanced blocks in a 1:1 ratio to receive either oral daprodustat or an injectable ESA (intravenous epoetin alfa among those receiving hemodialysis and subcutaneous darbepoetin alfa among those receiving peritoneal dialysis). Investigators used an interactive voice- or Web-response system to determine treatment assignments. Randomization was stratified according to the type of dialysis, geographic region, and participation in an ambulatory substudy monitoring blood pressure. Investigators

and patients were aware of the assigned treatments, but the sponsor and members of the 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 a hemoglobin level in the target range of 10.0 to 11.0 g per deciliter (Table S3). The starting dose of daprodustat was between 4 and 12 mg daily, according to the patient's previous ESA dose, and stepped changes in the dose from 1 to 24 mg were available for dose adjustments (Table S4). The starting dose of the ESA was also based on the previous ESA dose and hemoglobin level at the time of randomization. Dose steps were predefined, and most steps represented a change in dose of 25 to 33%. A rescue algorithm, which included a provision for intravenous iron or red-cell transfusion (Table S5) and a protocol for iron management (Table S6), was also provided.

OUTCOMES

The trial had two primary noninferiority outcomes: the mean change in the hemoglobin level from baseline to the average during 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 contract research organization George Clinical, whose members were unaware of treatment assignments. (Details regarding the adjudication charter are provided in Section S1 of the Supplementary Appendix.)

The principal secondary outcomes, each tested for superiority, were the average monthly dose of intravenous iron administered from baseline through week 52, 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, and the first occurrence of a MACE or hospitalization for heart failure.

STATISTICAL ANALYSIS

The trial was originally designed to enroll approximately 3000 patients, with follow-up until 945 adjudicated first MACEs had occurred with a noninferiority margin of 1.20. To accelerate trial closeout because of the coronavirus disease 2019 (Covid-19) 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 was aligned with the margin used in other HIF-PHI clinical trials,[11] and although the target number of events was reduced to 664, approximately 90% power was maintained. The revised trial size provided more than 99% power for the comparison of the effect of daprodustat and an ESA on the change in the hemoglobin level from baseline, with a noninferiority margin of −0.75 g per deciliter.

The two primary outcomes were tested in parallel in the intention-to-treat population (including all the patients who had undergone randomization) for noninferiority at a one-sided alpha level of 0.025. We used a Cox proportional-hazards model to analyze the MACE composite after adjustment for treatment group, dialysis type, 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 or 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 on the assumption that data were missing at random.

Principal secondary superiority analyses would proceed only if noninferiority was established for the two primary outcomes. We used an approach that was similar to that for the primary analysis to evaluate the secondary cardiovascular outcomes and the outcome for intravenous-iron therapy (until the first transfusion or week 52). The Holm–Bonferroni method was used to adjust for multiplicity. Subgroup analyses were performed with the use of analogous statistical models, 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.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Daprodustat (N=1487)	ESA (N=1477)
Demographic		
Median age (IQR) — yr	58 (48–67)	59 (47–68)
Male sex — no. (%)	851 (57.2)	847 (57.3)
Race or ethnic group — no. (%)†		
White	995 (66.9)	982 (66.5)
Black	228 (15.3)	233 (15.8)
Asian	176 (11.8)	181 (12.3)
Mixed	43 (2.9)	24 (1.6)
Native Hawaiian or other Pacific Islander	26 (1.7)	25 (1.7)
American Indian or Alaska Native	19 (1.3)	32 (2.2)
Clinical		
Median body-mass index (IQR)‡	26.8 (23.0–31.2)	26.8 (23.2–31.3)
Dialysis type at randomization — no. (%)		
Hemodialysis	1316 (88.5)	1308 (88.6)
Peritoneal dialysis	171 (11.5)	169 (11.4)
Time since initiation of dialysis at screening — no. (%)		
0 to <2 yr	453 (30.5)	451 (30.5)
2 to <5 yr	535 (36.0)	529 (35.8)
≥5 yr	499 (33.6)	497 (33.6)
ESA hyporesponsiveness — no. (%)§	183 (12.3)	180 (12.2)
Coexisting condition — no. (%)		
Cardiovascular disease¶	666 (44.8)	665 (45.0)
Coronary artery disease	347 (23.3)	334 (22.6)
Heart failure	267 (18.0)	254 (17.2)
Valvular heart disease	166 (11.2)	178 (12.1)
Angina pectoris	156 (10.5)	141 (9.5)
Atrial fibrillation	132 (8.9)	136 (9.2)
Myocardial infarction	122 (8.2)	135 (9.1)
Stroke	96 (6.5)	110 (7.4)
Transient ischemic attack	71 (4.8)	57 (3.9)
Cardiac arrest	23 (1.5)	21 (1.4)
Hypertension	1366 (91.9)	1373 (93.0)
Thromboembolic event‖	273 (18.4)	242 (16.4)
Diabetes	615 (41.4)	617 (41.8)
Cancer	74 (5.0)	72 (4.9)
Laboratory values**		
Hemoglobin — g/dl		
Mean	10.35±0.97	10.39±0.98
Median (IQR)	10.4 (9.7–11.1)	10.5 (9.8–11.1)
Median hepcidin (IQR) — ng/ml	172.7 (109.3–256.0)	179.6 (108.4–251.9)
Median transferrin saturation (IQR) — %	33 (26–41)	32 (26–42)
Median ferritin (IQR) — ng/ml	589 (344–976)	604 (341–948)

Table 1. (Continued.)

Characteristic	Daprodustat (N=1487)	ESA (N=1477)
Median total iron-binding capacity (IQR) — μmol/liter	39 (34–43)	39 (34– 43)
Median total iron (IQR) — μmol/liter	13 (10–16)	13 (10–16)
Median high-sensitivity C-reactive protein (IQR) — mg/liter	4.0 (1.6–10.9)	4.0 (1.5–9.8)
Median potassium (IQR) — mmol/liter††	4.9 (4.4–5.4)	4.9 (4.4–5.4)
Median albumin-corrected calcium (IQR) — mg/dl††	9.0 (8.5–9.4)	9.0 (8.5–9.4)
Median phosphate (IQR) — mg/dl††	5.0 (4.0–6.2)	5.1 (4.2–6.2)
Median intact parathyroid hormone (IQR) — pg/ml††	312.4 (143.4–564.1)	330.0 (168.1–568.9)
Median total cholesterol (IQR) — mg/dl	152.5 (125.5–183.4)	152.5 (125.5–183.4)
Low-density lipoprotein	81.9 (61.0–103.1)	81.1 (61.0–103.9)
High-density lipoprotein	40.5 (32.8–50.2)	40.5 (32.8–52.1)
Intravenous iron		
Patients receiving therapy — no./total no. (%)	956/1487 (64.3)	943/1477 (63.8)
Dose — mg/mo‡‡		
Mean	139.2±171.1	137.4±174.7
Median (IQR)	100.0 (0–217.4)	97.1 (0–217.4)
Median previous ESA dose, standardized to intravenous epoetin (IQR) — U/wk§§	5850 (3206–10075)	5699 (3242–9534)

* Plus–minus values are means ±SD. Data are for the intention-to-treat population unless otherwise noted. To convert the values for iron and iron-binding capacity to micrograms per deciliter, divide by 0.1791. To convert the values for potassium to milligrams per deciliter, divide by 0.2558. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. ESA denotes erythropoiesis-stimulating agent, and IQR interquartile range.
† Race or ethnic group was reported by the patients.
‡ The body-mass index is the weight in kilograms (after dialysis) divided by the square of the height in meters.
§ ESA hyporesponsiveness was defined as an ESA Resistance Index (ERI) of at least 2.0 in patients who had previously received epoetin or the previous receipt of the equivalent of at least 450 U per kilogram of intravenous epoetin alfa per week. The ERI is calculated as the standardized dose of ESA (in units per week) during the 8-week screening period divided by the patient's baseline estimated dry weight (in kilograms) and by the hemoglobin level (in grams per liter) on day 1.
¶ Patients could have more than one type of cardiovascular disease.
‖ 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 by a central laboratory except for hemoglobin, for which central laboratory values are reported if available or a point-of-care HemoCue value if the central laboratory value was missing.
†† Data were evaluated in the safety population (1482 patients in the daprodustat group and 1474 patients in the ESA group).
‡‡ Data are included for patients who received no intravenous iron.
§§ Not listed are data for 3 patients who had received an ESA but either did not receive the ESA within the prespecified time period or did not have a record of their ESA intake.

RESULTS

PATIENTS

From November 23, 2016, through August 10, 2018, a total of 2964 patients underwent randomization at 431 centers in 35 countries (Fig. S2). The characteristics of the patients — including history of cardiovascular disease, previous ESA dose, and use of intravenous iron — were well balanced between the trial groups at baseline (Table 1). Overall, 88.5% of the patients were undergoing hemodialysis, and 12.2% were considered to have ESA hyporesponsiveness on the basis of the ESA-resistance index or receipt of an epoetin dose of at least 450 U per kilogram of body weight per week. The mean (±SD) baseline hemoglobin level was 10.4±1.0 g per deciliter across the two groups. In general, the patients were representative of the population with CKD undergoing dialysis (Table S7). Specifically, in the United States, a post hoc analysis showed that 39.0% of the trial patients were Black.

The trial drug was stopped prematurely for reasons other than death in 671 of 1487 patients (45.1%) in the daprodustat group and in 662 of 1477 patients (44.8%) in the ESA group (Figs. S2 and S3). At the end of the trial, vital status was unknown for 35 patients in the daprodustat group

Table 2. Primary and Principal Secondary Outcomes (Intention-to-Treat Population).*

Outcome	Daprodustat (N=1487)		ESA (N=1477)		Treatment Effect (95% CI)	P Value†
	Value	No. of Events	Value	No. of Events		
Primary efficacy outcome						
Change in hemoglobin level from baseline to wk 28–52 — g/dl‡	0.28±0.02	—	0.10±0.02	—	Mean adjusted difference, 0.18 (0.12 to 0.24)	<0.001
Primary cardiovascular outcome — no. (%)						
MACE§	374 (25.2)	455	394 (26.7)	514	Hazard ratio, 0.93 (0.81 to 1.07)	<0.001
Death from any cause	244 (16.4)	294	233 (15.8)	300	—	—
Nonfatal myocardial infarction	101 (6.8)	126	126 (8.5)	170	—	—
Nonfatal stroke	29 (2.0)	35	35 (2.4)	44	—	—
Principal secondary cardiovascular outcomes — no. (%)¶						
MACE	374 (25.2)	455	394 (26.7)	514	Hazard ratio, 0.93 (0.81 to 1.07)	—
MACE or thromboembolic event	497 (33.4)	747	543 (36.8)	877	Hazard ratio, 0.88 (0.78 to 1.00)	—
Death from any cause	209 (14.1)	294	204 (13.8)	300	—	—
Nonfatal myocardial infarction	90 (6.1)	126	107 (7.2)	170	—	—
Nonfatal stroke	27 (1.8)	35	29 (2.0)	44	—	—
Nonfatal thromboembolic event	171 (11.5)	292	203 (13.7)	363	—	—
Deep-vein thrombosis	15 (1.0)	24	14 (0.9)	20	—	—
Pulmonary embolism	2 (0.1)	7	5 (0.3)	13	—	—
Vascular access thrombosis	154 (10.4)	261	184 (12.5)	330	—	—
MACE or hospitalization for heart failure	425 (28.6)	609	433 (29.3)	665	Hazard ratio, 0.97 (0.85 to 1.11)	—
Death from any cause	220 (14.8)	294	215 (14.6)	300	—	—
Nonfatal myocardial infarction	92 (6.2)	126	112 (7.6)	170	—	—
Nonfatal stroke	28 (1.9)	35	33 (2.2)	44	—	—
Nonfatal hospitalization for heart failure	85 (5.7)	154	73 (4.9)	151	—	—
Principal secondary efficacy outcome¶						
Adjusted mean monthly intravenous iron dose from baseline to wk 52 — mg	90.8±3.3	—	99.9±3.3	—	Mean difference, –9.1 (–18.4 to 0.2)	—

* Plus–minus values are means ±SE. 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.
§ Data regarding the primary safety analysis for first adjudication of major adverse cardiovascular events that excludes patients who had a major Good Clinical Practice violation are provided in Table S12 in the Supplementary Appendix.
¶ The principal secondary cardiovascular outcomes were assessed for superiority in the intention-to-treat population. The principal secondary efficacy outcome was assessed for superiority among the patients who were receiving the assigned treatment from day 1 through week 52 (1482 in the daprodustat group and 1472 in the ESA group).

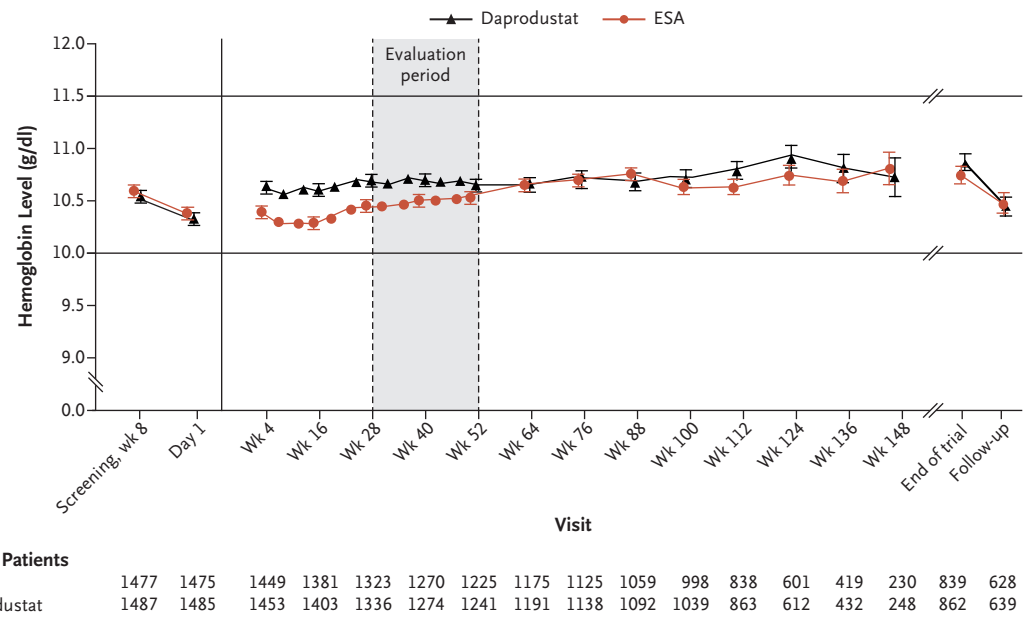

Figure 1. Hemoglobin Level According to Visit (Intention-to-Treat Population).

Shown are the mean hemoglobin levels among patients with chronic kidney disease who were undergoing dialysis and who were assigned to receive daprodustat or an erythropoiesis-stimulating agent (ESA) during the trial. 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 the 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 target range to allow for variability. The I bars indicate 95% confidence intervals.

and 26 in the ESA group. The median duration of follow-up for evaluation of cardiovascular events was 2.5 years (interquartile range, 2.2 to 2.9), which provided 7028 total person-years of follow-up.

PRIMARY EFFICACY OUTCOME

The mean (±SE) change in the hemoglobin level from baseline to weeks 28 through 52 was 0.28± 0.02 g per deciliter with daprodustat and 0.10± 0.02 g per deciliter with ESA therapy, for a difference of 0.18 g per deciliter (95% confidence interval [CI], 0.12 to 0.24), which met the prespecified noninferiority margin for daprodustat (Table 2 and Fig. 1). Supplementary analyses provided findings that were consistent with the primary analysis (Fig. S4). The effect of daprodustat as compared with ESA therapy was generally consistent across the prespecified subgroups (Fig. S5).

A rapid increase in the hemoglobin level, which was defined as an increase of more than 2 g per deciliter during a 4-week period, was observed in 50 of 1218 patients (4.1%) in the daprodustat group and in 20 of 1247 patients (1.6%) in the ESA group during the first 4 weeks. Thereafter, for any 4-week period during the first year, the percentage of patients with a rapid increase in the hemoglobin level was 2% or less in the two treatment groups. Median doses are presented in Figure S6; 95% of the patients were adherent to the trial regimen.

PRIMARY SAFETY OUTCOME

A first MACE occurred in 374 of 1487 patients (25.2%) in the daprodustat group and in 394 of 1477 patients (26.7%) in the ESA group (hazard ratio, 0.93; 95% CI, 0.81 to 1.07), results that met the prespecified noninferiority margin of 1.25 (Table 2 and Fig. 2). The effect of treatment was generally consistent across prespecified subgroups (Fig. S7). These results were consistent with other supplementary intention-to-treat and on-treatment analyses (Fig. S8). Additional time-to-event analyses, including the components of the MACE composite, are shown in Table S8.

KEY SECONDARY OUTCOMES

The results of superiority testing for daprodustat as compared with ESA were not significant regard-

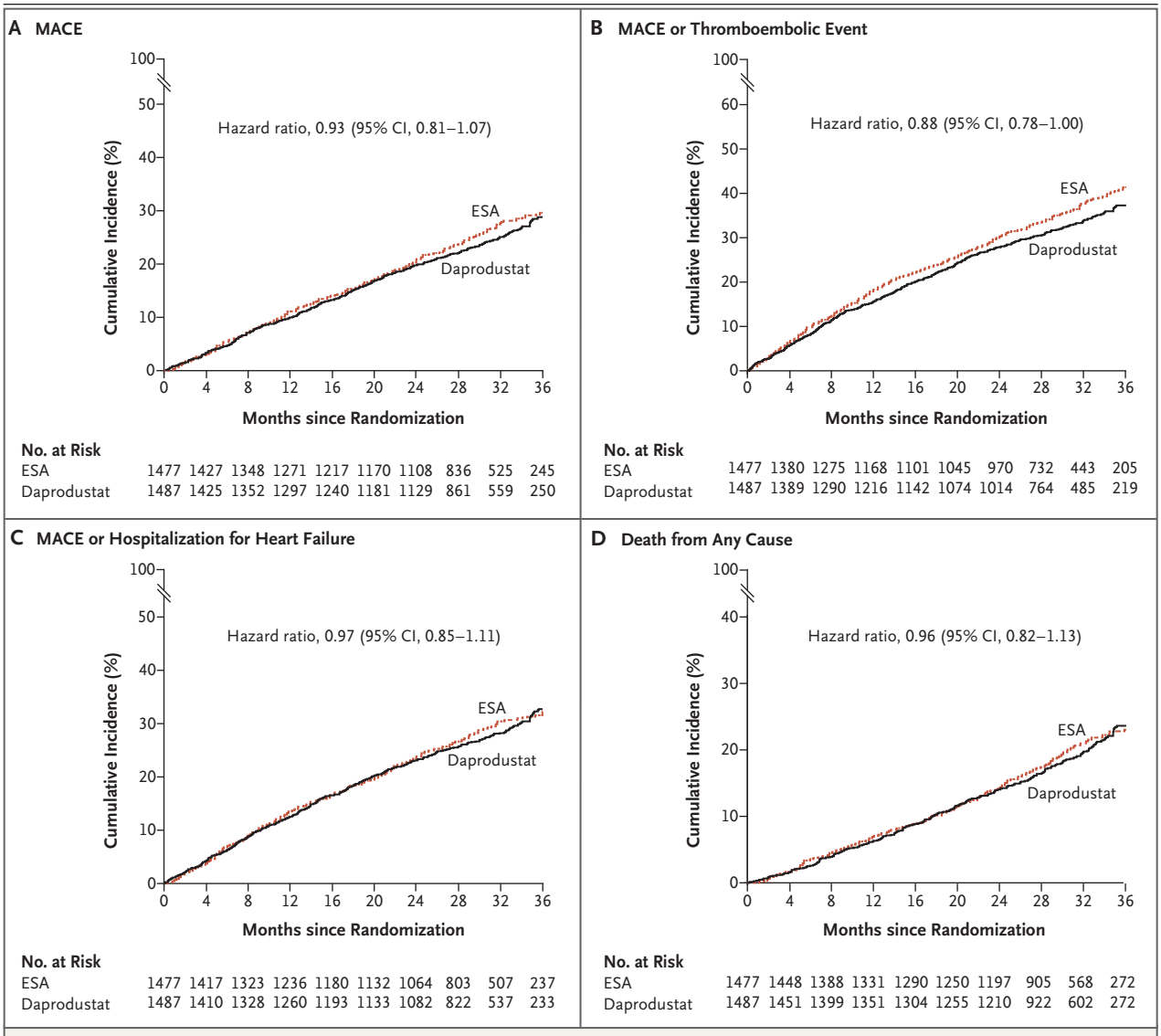

Figure 2. Kaplan–Meier Plots of Time to First Occurrence of Adjudicated Cardiovascular Events and Death from Any Cause (Intention-to-Treat Population).

Shown is the cumulative incidence of a first adjudicated major adverse cardiovascular event (MACE, a composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke) (Panel A), a first adjudicated MACE or thromboembolic event (Panel B), a first adjudicated MACE or hospitalization for heart failure (Panel C), and death from any cause (Panel D). CI denotes confidence interval.

ing the three cardiovascular principal secondary outcomes: the first occurrence of MACE (hazard ratio, 0.93; 95% CI, 0.81 to 1.07), the first occurrence of MACE or a thromboembolic event (hazard ratio, 0.88; 95% CI, 0.78 to 1.00), and the first occurrence of MACE or hospitalization for heart failure (hazard ratio, 0.97; 95% CI, 0.85 to 1.11) (Table 2 and Fig. 2). The incidence of death from any cause was similar in the two groups (hazard ratio, 0.96; 95% CI, 0.82 to 1.13) (Table S8).

The superiority test for the mean monthly dose of intravenous iron from baseline through week 52, a principal secondary outcome, was also not significant. The mean (±SE) monthly dose from day 1 to week 52 decreased to 90.8±3.3 mg in the daprodustat group and to 99.9±3.3 mg in the ESA group, for a mean difference of –9.1 mg (95% CI, –18.4 to 0.2 mg). Subgroup analyses for intravenous iron outcomes are shown in Figure S9.

Variables in iron metabolism are shown in Tables 1 and 2 and Figure S10. In the daprodustat group, the level of hepcidin decreased and

the total iron-binding capacity increased from baseline and relative to the ESA group, whereas the ferritin level decreased in both groups. Transferrin saturation levels were similar in the two groups and were slightly lower than baseline levels. Total iron levels increased slightly with daprodustat but not with ESA.

The criteria for rescue therapy (i.e., a hemoglobin level of <9 g per deciliter or transfusion of more than 2 units of packed red cells) were met by 53 patients (3.6%) in each treatment group, which resulted in permanent discontinuation of the randomized treatment. The percentage of patients who received at least one red-cell or whole-blood transfusion from day 1 through the day after discontinuation of the trial-specific dosing algorithm was 15.7% in the daprodustat group and 18.3% in the ESA group (hazard ratio, 0.86; 95% CI, 0.72 to 1.02) (Fig. S11).

ADVERSE EVENTS

Eight patients (5 in the daprodustat group and 3 in the ESA group) were excluded from the safety analyses because they did not receive the randomized treatment (Fig. S2). Serious adverse events during the trial were reported in 773 patients (52.2%) in the daprodustat group and in 748 (50.7%) in the ESA group (Table 3). The most common adverse events and serious adverse events are listed in Tables S9 and S10, respectively. There was no notable excess of any event in the daprodustat group. The incidences of prespecified adverse events of special interest — including esophageal or gastric erosions and cancers — were similar in the two treatment groups. Daprodustat had an effect on blood pressure and the use of antihypertensive medications that was similar to that with ESA therapy (Table S11).

DISCUSSION

In this international, randomized, phase 3 clinical trial, daprodustat was effective as a treatment for anemia in patients with CKD who were undergoing maintenance hemodialysis or peritoneal dialysis. Daprodustat was noninferior to ESA therapy with respect to both the change in the hemoglobin level from baseline and cardiovascular safety. These findings were consistent across predefined subgroups, as well as for the expanded definitions of MACE to include thromboembolic events and hospitalization. The safety profile of daprodustat appeared to be similar to that of ESA therapy, and no unexpected safety concerns were identified.

Our findings extend the results of previous phase 2 trials of daprodustat.[14] The effects of daprodustat on hemoglobin levels among patients receiving dialysis that we observed are also consistent with the recently published findings of a phase 3 trial of the HIF-PHI vadadustat ($INNO_2VATE$)[11] and a smaller trial of roxadustat involving patients who were undergoing dialysis in China,[15] along with pooled roxadustat data for patients undergoing dialysis.[16]

Neither the $INNO_2VATE$ trial nor the Chinese roxadustat trial included an evaluation of the rate of increase in the hemoglobin level from baseline.[11,15] In our trial, we evaluated a rapid rise in the hemoglobin level, as measured by an increase of more than 2 g per deciliter during a 4-week period. Such increases occurred infrequently and did not differ between treatment groups.

The increase in the hemoglobin level with daprodustat is most plausibly explained by our dosing protocol, which included fewer dose steps for daprodustat than for ESAs. Although we observed benefits in several variables of iron metabolism, including a reduction in serum hepcidin in patients in the daprodustat group, the observed reduction in intravenous iron was similar to that with ESA. Thus, further studies are warranted to explore the effects of daprodustat on iron kinetics and utilization. The effect of HIF-PHI agents on hepcidin has been noted previously[17,18] and confirmed observations from the 24-week daprodustat phase 2 trials[14,19] and for other HIF-PHI agents.[11,12]

We also examined the hemoglobin response in patients with ESA hyporesponsiveness, which remains a concern in managing anemia among patients who are receiving dialysis.[20] In our trial, approximately 12% of the patients were observed to have ESA hyporesponsiveness at baseline. The mean hemoglobin level remained between 10.0 to 11.5 g per deciliter in patients treated with daprodustat, regardless of whether they were hyporesponsive or had a heightened level of inflammation as measured by an elevated level of high-sensitivity C-reactive protein. Patients with ESA hyporesponsiveness who were treated with daprodustat received less intravenous iron than those who were treated with an ESA.

There were no apparent between-group differences in adverse events during the trial, including serious adverse events. In particular, we

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

Variable	Daprodustat (N=1482)		ESA (N=1474)		Relative Risk (95% CI)	P Value*
	Value	No. of Events	Value	No. of Events		
Adverse events — no. of patients (%)†						
Any adverse event	1307 (88.2)	10,501	1252 (84.9)	10,984	—	—
Any serious adverse event	773 (52.2)	2,021	748 (50.7)	2,218	—	—
Adverse events of special interest‡						
Thrombosis or tissue ischemia due to excessive erythropoiesis	20 (1.3)	30	11 (0.7)	12	1.81 (0.87–3.76)	0.11
Cardiomyopathy	15 (1.0)	16	16 (1.1)	17	0.93 (0.46–1.88)	0.85
Pulmonary-artery hypertension	9 (0.6)	9	12 (0.8)	13	0.75 (0.32–1.77)	0.50
Cancer-related death or tumor progression or recurrence	47 (3.2)	51	51 (3.5)	58	0.92 (0.62–1.35)	0.66
Esophageal or gastric erosions	60 (4.0)	75	81 (5.5)	100	0.74 (0.53–1.02)	0.06
Proliferative retinopathy, macular edema, or choroidal neovascularization	38 (2.6)	45	35 (2.4)	44	1.08 (0.69–1.70)	0.74
Exacerbation of rheumatoid arthritis	2 (0.1)	2	1 (0.1)	1	1.99 (0.18–21.91)	0.57
Worsening of hypertension	293 (19.8)	512	302 (20.5)	524	0.96 (0.84–1.11)	0.63
Median laboratory measures at wk 52 (IQR)§						
Hepcidin — ng/ml¶	124.6 (64.5–204.4)	—	156.7 (86.0–237.4)	—	—	—
Transferrin saturation — %¶	30 (24–38)	—	30 (23–38)	—	—	—
Ferritin — ng/ml¶	448 (231–772)	—	493 (261–781)	—	—	—
Total iron-binding capacity — μmol/liter¶	45 (40–51)	—	39 (35–45)	—	—	—
Total iron — μmol/liter¶	14 (11–17)	—	12 (9–15)	—	—	—
High-sensitivity C-reactive protein — mg/liter	4.4 (1.7–10.7)	—	4.0 (1.6–10.6)	—	—	—
Potassium — mmol/liter	4.9 (4.4–5.4)	—	4.9 (4.4–5.4)	—	—	—
Albumin-corrected calcium — mg/dl	9.0 (8.5–9.4)	—	9.0 (8.5–9.4)	—	—	—
Phosphate — mg/dl	5.3 (4.2–6.3)	—	5.3 (4.3– 6.3)	—	—	—
Intact parathyroid hormone — pg/ml	362.8 (189.9–627.7)	—	353.3 (188.0–631.5)	—	—	—
Total cholesterol — mg/dl¶	146.7 (117.8–175.7)	—	152.5 (123.6–181.5)	—	—	—
Low-density lipoprotein	76.8 (57.1–100.0)	—	81.9 (61.0–103.9)	—	—	—
High-density lipoprotein	38.6 (32.8–48.3)	—	42.5 (34.7–52.1)	—	—	—

* 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 a 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 associated with ESA. 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.

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

¶ Data were evaluated in the intention-to-treat population (1487 patients in the daprodustat group and 1477 patients in the ESA group).

did not observe a higher incidence of hypertension among the patients in the daprodustat group, in contrast to the incidence associated with roxadustat in the Chinese trial.[15] Although an increased incidence of hyperkalemia has previously been observed with some HIF-PHIs, we did not observe such an increase with daprodustat in our trial. We also found similar incidences of esophageal or gastric erosions and cancers in the two groups.

Our trial has several limitations. First, the open-label design among patients and investigators may have biased reporting of adverse events. Second, since HIF activates the transcription of many cytokines, some of which 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. Finally, we used epoetin alfa as the comparator for patients undergoing hemodialysis in this trial, which may limit the generalizability of our conclusions about the noninferiority of daprodustat to other ESAs.

In this trial, we found that daprodustat was noninferior to conventional ESAs in the treatment of anemia among patients with CKD who were undergoing dialysis and in the incidence of cardiovascular outcomes.

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APPENDIX

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