The ASCEND-NHQ trial found positive effects of daprodustat on hemoglobin and quality of life in patients with non-dialysis-dependent chronic kidney disease

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The ASCEND-NHQ trial evaluated the effects of daprodustat on hemoglobin and the Medical Outcomes Study 36-item Short Form Survey (SF-36) Vitality score (fatigue) in a multicenter, randomized, double-blind, placebo-controlled trial. Adults with chronic kidney disease (CKD) Stages 3–5, hemoglobin 8.5–10.0 g/dl, transferrin saturation 15% or more, and ferritin 50 ng/ml or more without recent erythropoiesis-stimulating agent use were randomized (1:1) to oral daprodustat or placebo to achieve and maintain target hemoglobin of 11–12 g/dl over 28 weeks. The primary endpoint was the mean change in hemoglobin between baseline and the evaluation period (Weeks 24–28). Principal secondary endpoints were proportion of participants with a 1 g/dl or more increase in hemoglobin and mean change in the vitality score between baseline and Week 28. Outcome superiority was tested (one-sided alpha level of 0.025) among 614 randomized participants. The adjusted mean change in hemoglobin from baseline to the evaluation period was greater with daprodustat (1.58 vs 0.19 g/dl). The adjusted mean treatment difference (AMD) was significant at 1.40 g/dl (95% confidence interval 1.23, 1.56). A greater proportion of participants receiving daprodustat showed a significant 1 g/dl or more increase in hemoglobin from baseline (77% vs 18%). The mean SF-36 Vitality score increased by 7.3 and 1.9 points with daprodustat and placebo, respectively; a significant 5.4 point Week 28 ADM increase. Adverse event rates were similar (69% vs 71%); relative risk 0.98, (95% confidence interval 0.88, 1.09). Thus, in participants with CKD Stages 3–5, daprodustat resulted in a significant increase in hemoglobin and improvement in fatigue without an increase in the overall frequency of adverse events.

Kidney International (2023) ■, ■–■; https://doi.org/10.1016/j.kint.2023.02.019

KEYWORDS: anemia of CKD; chronic kidney disease; daprodustat; fatigue; HIF-PHI; quality of life

Lay Summary

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Anemia frequently develops among patients with chronic kidney disease (CKD), and its severity increases as kidney function declines. Mild anemia contributes to the symptom burden of patients with advanced CKD, particularly causing or exacerbating fatigue and dyspnea.[1,2] Early placebo-controlled trials of recombinant human erythropoietin (rhEPO) showed substantial anemia improvement and reductions in rates of red blood cell transfusion among transfusion-dependent patients with advanced CKD or end-stage kidney disease. Increases in hemoglobin (Hb) with rhEPO were accompanied by amelioration of fatigue, physical symptoms, and physical function, compared with placebo or the untreated comparator group in these small, randomized studies.[3–5] However, in the few sizeable, blinded studies that systematically evaluated the effects of treating anemia in CKD with erythropoiesis-stimulating agents (ESAs) in patients with non–dialysis dependent CKD, the benefits to health-related

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Received 27 July 2022; revised 18 January 2023; accepted 7 February 2023

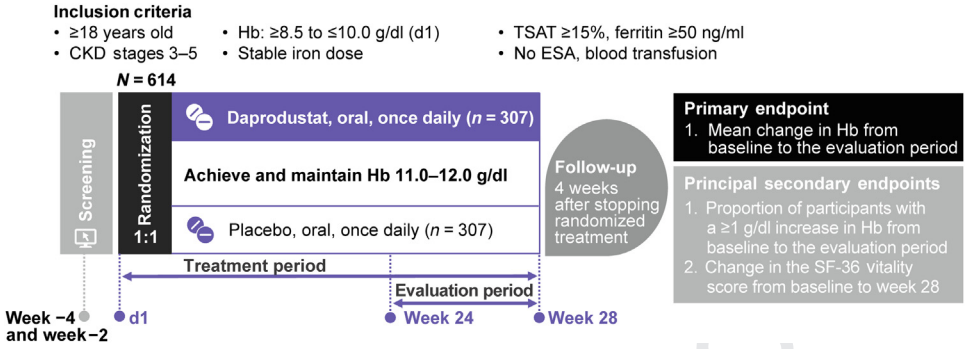

Figure 1 | Study design overview. CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; SF-36, Medical Outcomes Study 36-item Short Form Survey; TSAT, transferrin saturation. Q19

quality of life (HRQoL), including those relating to fatigue and physical functioning, were smaller and inconsistent.[6–8] Thus, significant uncertainty remains about HRQoL benefits of ESA treatment in nondialysis patients with CKD with mild anemia.

Recently, a novel class of medications, known as hypoxia inducible factor (HIF) stabilizers or prolyl hydroxylase inhibitors, has been developed and tested in large clinical trials of participants with anemia in CKD. These agents inhibit the degradation of HIF, activating various genes, including the erythropoietin gene that stimulates endogenous erythropoietin production. HIF–prolyl hydroxylase inhibitors have several potential advantages over traditional ESAs in that they are administered orally and may lead to a stable increase in plasma erythropoietin concentration.[9] Oral anemia treatment is particularly convenient for non-dialysis-dependent patients and those on home dialysis, but it requires adherence to taking oral medication, which has been shown to be suboptimal in patients with CKD.[10] The choice of injectable versus oral therapy should thus be part of shared decision- making of patients and their physicians. Multiple clinical trials have demonstrated that HIF–prolyl hydroxylase inhibitors are efficacious in treating anemia related to CKD, but the effect of HIF-prolyl hydroxylase inhibitors on HRQoL has not been widely evaluated.[11–15] The Anemia Studies in CKD: Erythropoiesis via a Novel Prolyl Hydroxylase Inhibitor Daprodustat in Non-Dialysis (ND) Participants Evaluating Hemoglobin and Quality of Life (ASCEND-NHQ) trial was designed to investigate the effects of daprodustat on Hb and fatigue experienced by patients with anemia related to CKD.

METHODS

Study design

ASCEND-NHQ was a phase 3, multicenter, randomized, double-blind, placebo-controlled study (NCT03409107) conducted in 142 centers across 14 countries. The study consisted of 4 weeks of screening, 28 weeks of treatment, and a follow-up visit at 4–6 weeks. Following screening, participants were randomized 1:1 to daprodustat or placebo. Daprodustat or placebo was dosed daily and titrated to achieve and maintain Hb 11–12 g/dl. This target range, which is consistent with European guidelines,[16,17] was selected, as prior studies have shown that achieving an Hb level in the 11–12 g/dl range is associated with the greatest incremental gain in HRQoL.[18] Outcomes for the primary and principal secondary endpoints were assessed during weeks 24–28. An overview of the study design is shown in Figure 1.

Study population

Adults with CKD stages 3–5 with anemia related to the CKD were eligible for inclusion. Anemia was defined as a Hb level of 8.5–10.5 g/dl at screening and 8.5–10.0 g/dl on day 1, based on a point-of-care system using venous blood (HemoCue). Participants had not been Q13 treated with ESAs, i.v. iron, or blood transfusion in the 8 weeks prior to screening, and from screening to day 1. They were required to have a transferrin saturation of ≥15%, and a ferritin level ≥50 ng/ml at screening, and either no receipt of oral iron or a <50% change in oral iron dose between screening and day 1. The screening period thus ensured stable Hb levels without use of ESAs or significant change in iron use prior to randomization. The complete list of inclusion and exclusion criteria is provided in the Supplementary Methods. The study was approved by institutional review boards Q14 or ethics committees at all study sites, and all participants provided written informed consent.

Randomization and intervention

Participants who successfully completed the screening period were randomized 1:1 to oral daprodustat or oral placebo on day 1. Randomization was stratified by region and performed centrally using interactive response technology. Participants were blinded to HemoCue Hb values.

The starting dose of daprodustat or placebo was based on the HemoCue Hb level on day 1 (4 mg daily if the Hb level was 8.5–<9.0 g/dl; 2 mg daily if the Hb level was 9.0–10.0 g/dl). The dose was titrated as needed at week 2 and week 4, and every 4 weeks thereafter until week 24, to achieve and maintain an Hb level of 11–12 g/dl. Dose adjustments were made by the interactive response technology system based on the HemoCue Hb level. The dosing algorithm is described in Supplementary Table S1. Participants were allowed to take oral iron, but i.v. iron was used only among participants intolerant of oral iron or for rescue.

ESAs, i.v. iron, and blood transfusion were considered rescue therapies. Details of the rescue algorithm are provided in Supplementary Table S2.

Participants continued study treatment until the end of the 28-week treatment period, unless they developed a protocol-defined criterion for stopping study treatment, as detailed in the Supplementary Methods.

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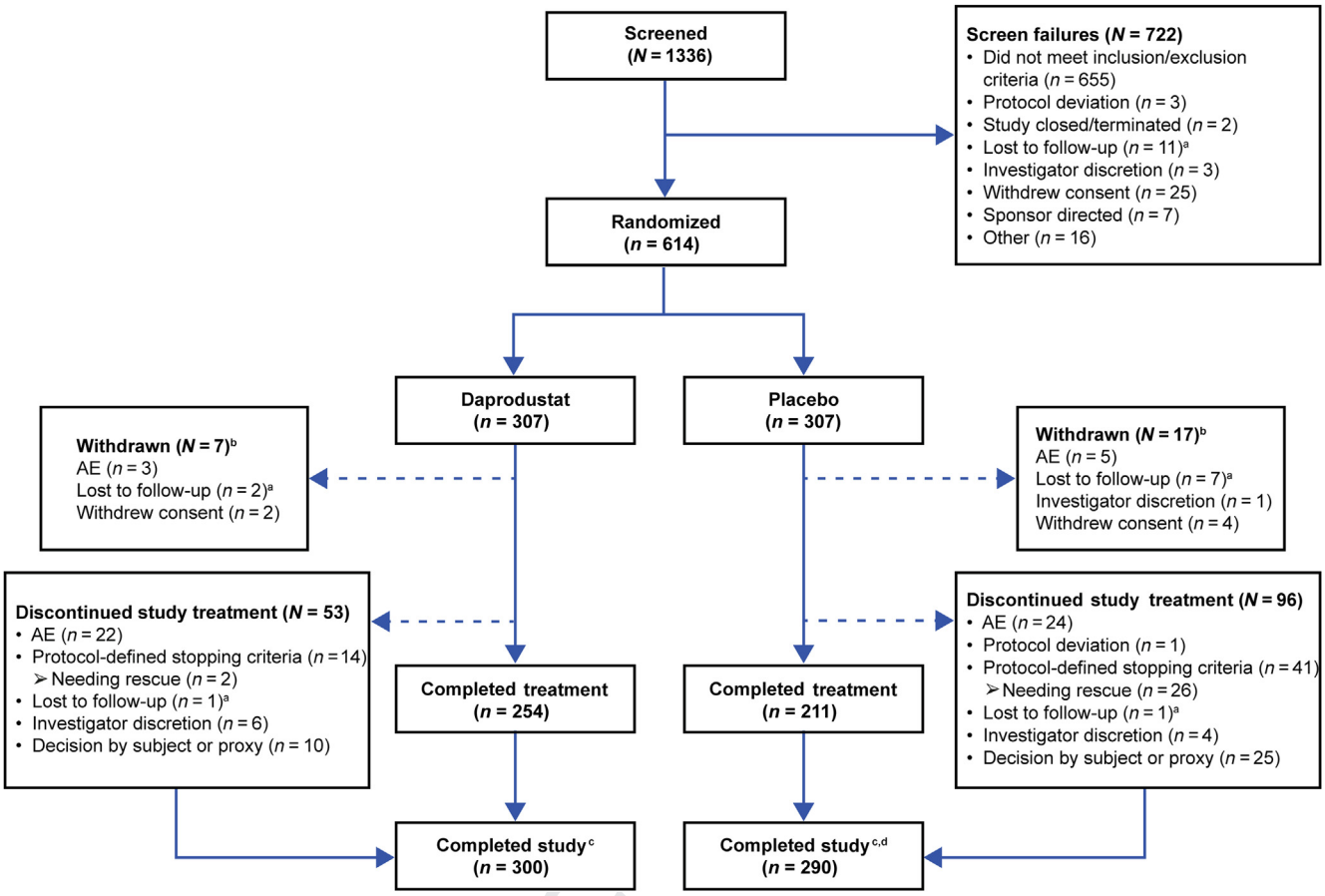

Figure 2 | Consolidate Standards of Reporting Trials (CONSORT) diagram. [a]Reason for being lost to follow-up was not reported. [b]Participants who were withdrawn are a subset of those who had treatment discontinued, and reason for withdrawal and treatment discontinuation may be different. [c]Participants who completed the study include the following: (i) those who completed 28-week treatment; (ii) those who continued in the study to week 28 after permanently discontinuing study treatment; and (iii) those who died while in the study. [d]Includes 2 participants who died while undergoing study treatment. AE, adverse event.

Study procedures

Most laboratory data, including hematology, serum creatinine concentration, and iron panels, were collected at baseline, and at weeks 4, 16, and 28. HemoCue Hb level and central laboratory Hb level were measured at every visit from screening at week 4 to week 28. Sites used the HemoCue Hb level to determine study eligibility and dose titration at study visits, whereas central laboratory Hb levels were used to ascertain study endpoints. The Medical Outcomes Study 36-item Short Form Survey, version 2 (SF-36) and other HRQoL questionnaires were administered prior to other study procedures at the baseline and weeks 8, 12, and 28 study visits. The SF-36 includes 8 domains including the "vitality" domain (Vitality), which measures fatigue by assessing if an individual feels full of life, has a lot of energy, feels worn out, or feels tired. The SF-36 had a 1-week recall period.

Study endpoints

The primary endpoint was the adjusted mean change in Hb level from baseline to the evaluation period (EP; weeks 24–28). The first principal secondary endpoint was the proportion of participants with a ≥1 g/dl increase in Hb level from baseline to the EP. The second principal secondary endpoint was the change in the SF-36 Vitality score (0–100) from baseline to week 28. The primary and principal secondary endpoints were evaluated for significance in a hierarchical manner.

The rest of the secondary endpoints were not adjusted for multiplicity, and nominal *P* values are reported. Other secondary endpoints related to Hb included the proportion of participants with a mean Hb level of 11–12 g/dl, and the percentage of time with Hb in the target range during the EP, as well as the percentage needing rescue therapy and the time to needing rescue. An additional secondary fatigue endpoint was the proportion of participants with a ≥6-point increase in the SF-36 Vitality score between baseline and week 28. Changes in blood pressure were evaluated as secondary endpoints, and changes in antihypertensive medications were evaluated as exploratory endpoints. Time to first blood transfusion, time to first rhEPO, iron usage during the study, changes in iron parameters, and mean changes in other domains of the SF-36 were all exploratory endpoints.

Safety endpoints included the frequency of adverse events (AEs), potential adverse events of special interest, and serious adverse events, and although the study was not powered to detect this endpoint, the first occurrence of an adjudicated major adverse cardiovascular event (MACE), defined as a composite of all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke. The MACE follow-up period began at randomization and ended at study

Table 1 | Baseline demographic and clinical characteristics

Characteristic	Daprodustat $n = 307$	Placebo $n = 307$
Age, yr	66.0 (56.0–75.0)	67.0 (59.0–77.0)
Age category, yr		
<65	135 (44)	121 (39)
65–<75	82 (27)	96 (31)
≥75	90 (29)	90 (29)
Gender		
Female	176 (57)	178 (58)
Male	131 (43)	129 (42)
Ethnicity		
Hispanic or Latino	104 (34)	103 (34)
Not Hispanic or Latino	203 (66)	204 (66)
Race		
American Indian or Alaska Native	34 (11)	34 (11)
Asian	30 (10)	28 (9)
Black or African American	44 (14)	47 (15)
Native Hawaiian or other Pacific Islander	0	1 (<1)
White	197 (64)	195 (64)
Mixed race	2 (<1)	2 (<1)
Region		
Asia Pacific	19 (6)	20 (7)
Eastern Europe	60 (20)	58 (19)
Western Europe/Canada/Australia	57 (19)	58 (19)
Latin America	85 (28)	85 (28)
US	86 (28)	86 (28)
Weight, kg		
<75	157 (51)	150 (49)
≥75	150 (49)	157 (51)
History		
Stroke	28 (9)	19 (6)
MI	27 (9)	29 (9)
Diabetes	187 (61)	188 (61)
Heart failure	54 (18)	52 (17)
Thromboembolic events	16 (5)	18 (6)
Smoking history		
Never smoked	199 (65)	201 (65)
Current smoker	16 (5)	21 (7)
Former smoker	92 (30)	84 (27)
Missing	0	1 (<1)
Baseline Hb, g/dl	9.80 (9.30–10.10)	9.70 (9.20–10.10)
Baseline Hb, g/dl		
<9	28 (9)	46 (15)
≥9 and <10	168 (55)	151 (49)
≥10 and ≤11	106 (35)	99 (32)
>11	5 (2)	11 (4)
CKD stage: eGFR in ml/min per 1.73 m^2		
Stage 2: ≥ 60	3 (<1)	2 (<1)
Stage 3: 30 to <60	92 (30)	87 (28)
Stage 4: 15 to <30	139 (45)	137 (45)
Stage 5: <15	73 (24)	81 (26)
Iron repletion status		
TSAT ≥15% and ferritin ≥50 ng/ml	281 (92)	283 (92)
TSAT ≥20% and ferritin ≥100 ng/ml	194 (63)	203 (66)
hsCRP, mg/l	2.30 (0.90–6.20)[a]	2.80 (1.10–6.75)[b]
Blood pressure, mm Hg		
Systolic	136.0 (125.0–147.0)	134.0 (125.0–146.0)
Diastolic	74.0 (68.0–81.0)	75.0 (68.0–81.0)
Mean arterial pressure	95.3 (87.0–103.3)	94.7 (86.7–101.7)
ACEI/ARB use		
No	233 (76)	228 (74)
Yes	74 (24)	79 (26)

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; MI, myocardial infarction; TSAT, transferrin saturation.
[a]Data from $n = 302$.
[b]Data from $n = 300$.
Values are n (%), or median (IQR).

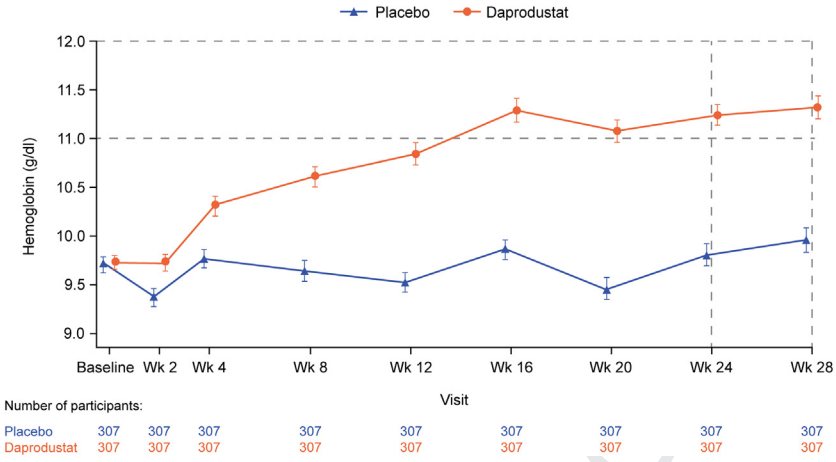

Figure 3 | Postrandomization hemoglobin level by visit (intent-to-treat [ITT] population). Error bars indicate 95% confidence interval. Dashed vertical lines represent the evaluation period (week 24 to week 28). The horizontal reference lines indicates the hemoglobin target range (11–12 g/dl). Observed on- and off-treatment and imputed hemoglobin values. Wk, week.

completion or withdrawal, with the exception of death, which was included in the analysis even if it was reported after this time.

Statistical analysis

Primary analyses were based on the intent-to-treat population, defined as all randomized participants regardless of whether they took the study drug, with groups based on randomized treatment assignment. For the primary and principal secondary endpoints, we used hierarchical testing with a 1-sided type 1 error of 0.025. Analyses of primary and secondary Hb outcomes included on- and off-treatment Hb values as well as imputed Hb values derived from multiple imputation under a missing-not-at-random assumption. The SF-36 Vitality score outcomes were also based on the intent-to-treat population, but only on-treatment observed scores, along with imputed values, were used for participants that were off-treatment or had missing values. Imputed values were derived from multiple imputation under a missing-at-random assumption. For all endpoints, superiority required a 1-sided $P < 0.025$. See the Supplementary Methods and Supplementary Table S3 for further details on imputation methodology and statistical analysis.

We performed prespecified subgroup analyses by age, gender, race, ethnicity, weight, baseline Hb, iron status, comorbidities including diabetes and heart failure, and high-sensitivity C-reactive protein category. Additional supportive analyses for the primary and principal secondary Hb endpoints were performed using evaluable Hb (defined as on-treatment values that were not taken within 8 weeks following a blood transfusion or ESA treatment) without imputation. Supportive analyses for the change in SF-36 Vitality score included one analysis that included only on-treatment scores without imputation, and another that included on- and off-treatment scores without imputation. For safety endpoints, groups were defined based on actual treatment received (safety population), except for MACE endpoints, which were assessed using the intent-to-treat population.

Power calculations were based on the change in the SF-36 Vitality score. We estimated that 600 participants would need to be randomized to have 540 participants with evaluable SF-36 Vitality score data, providing 79% power to detect a 5-point difference in mean change between groups on the SF-36 Vitality score, assuming a within-group SD of 21 points, and a 1-sided alpha level of 0.025.[19] The primary endpoint had >99% power to detect a 1.00-g/dl difference between groups for the change in Hb level from baseline to the EP, assuming a between-participant SD of 1.5 g/dl and a 1-sided alpha of 0.025.

RESULTS

Study participants

A total of 1336 participants were assessed for eligibility; 722 (54%) failed screening because they did not meet eligibility criteria ($n = 655$) or because they were excluded or dropped out between screening and randomization ($n = 67$). The remaining 614 participants, recruited between March 5, 2018 and January 29, 2020, were randomized 1:1, with 307 participants assigned to each group (Figure 2). Of the 614 randomized participants, 98% (300 of 307) in the daprodustat group and 94% (290 of 307) in the placebo group completed the study. A total of 83% of participants (254 of 307) in the daprodustat group and 69% (211 of 307) in the placebo group completed the 28-week treatment period without permanently stopping the study drug. A protocol-defined stopping criterion was the most frequent reason for treatment discontinuation in the placebo group, and placebo participants more frequently discontinued study treatment due to needing rescue.

Baseline demographic and clinical characteristics of study participants are shown in Table 1. The daprodustat and placebo groups were largely similar across baseline characteristics, although some numerical differences occurred, such as mean age 1-year older, higher mean high-sensitivity C-reactive protein levels, and a greater proportion of participants with an Hb level <9.0 g/dl in the placebo group.

The median central laboratory Hb level overall was 9.70 g/dl, with generally higher values than those in the HemoCue Hb results; therefore, 174 participants (28%) had a baseline central laboratory Hb level >10.0 g/dl even though they met eligibility criteria on the basis of a HemoCue Hb level in the range 8.5–10.0 g/dl on day 1. Iron preparations (oral or i.v.)

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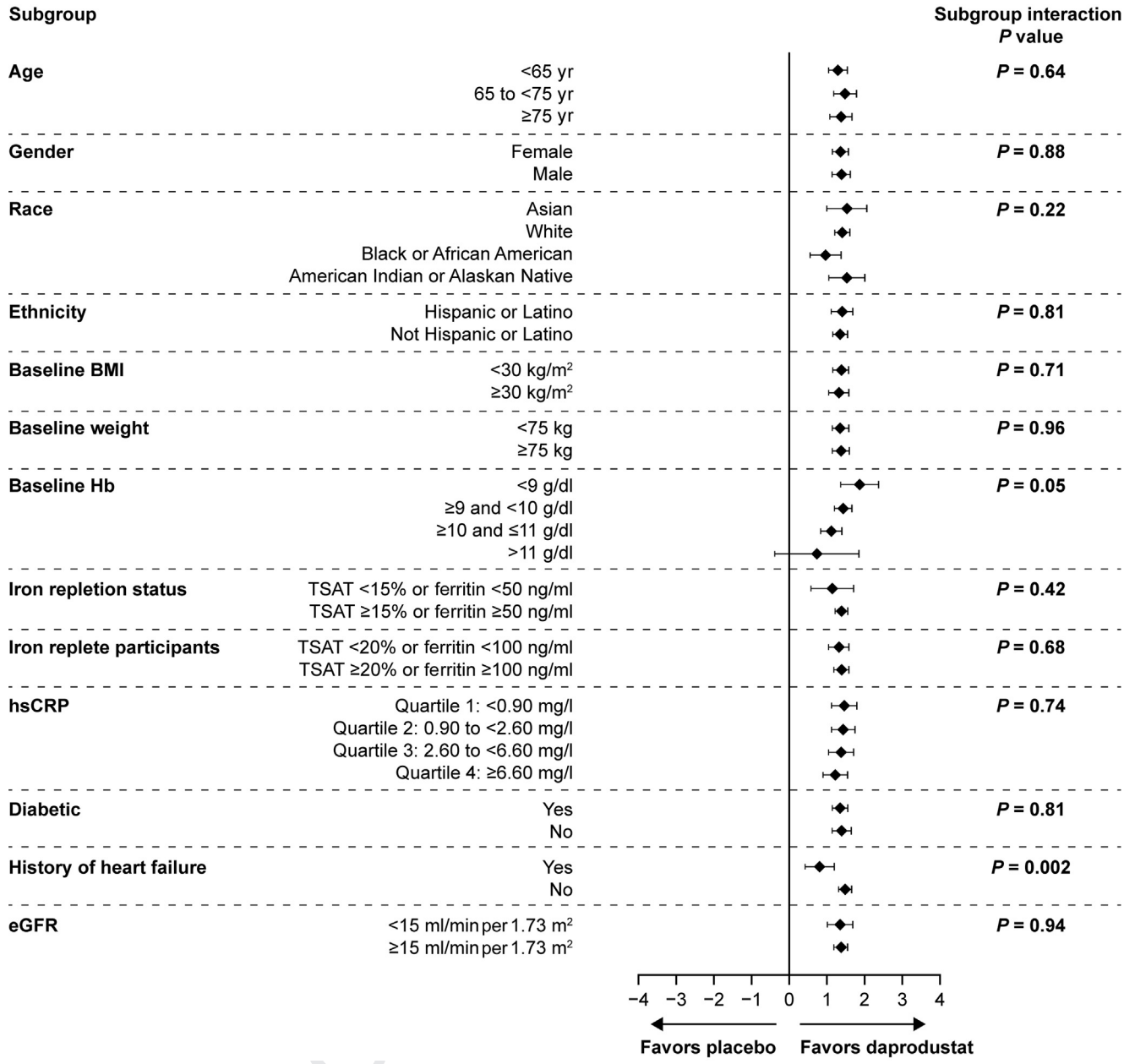

Figure 4 | Forest plot of adjusted mean difference of postrandomization hemoglobin (Hb) level change from baseline to the evaluation period across subgroups. Observed on- and off-treatment and imputed Hb values. BMI, body mass index; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; hsCRP, high-sensitivity C-reactive protein; TSAT, transferrin saturation.

were used in 147 participants (48%) in the placebo group and 131 participants (43%) in the daprodustat group prior to enrollment in the study.

Hemoglobin and iron-related endpoints

The primary endpoint, adjusted mean change in Hb level from baseline to the EP, was greater in the daprodustat group (1.58 g/dl) than in the placebo group (0.19 g/dl). The adjusted mean treatment difference (AMD) between the daprodustat and placebo groups was 1.40 g/dl (95% confidence interval [CI]: 1.23, 1.56; 1-sided $P < 0.0001$). Separation of mean Hb level between daprodustat and placebo was observed within 4 weeks of initiating treatment and continued through week 28 (Figure 3). Mean Hb values in the daprodustat group were in the Hb target range (11–12 g/dl) during the EP. In the primary analysis, imputed Hb values were used for 16% of participants in the daprodustat group (4% had 1 missing Hb value, and 12% had 2 missing Hb values during the EP) and 22% of participants in the placebo group (9% had one missing Hb value, and 13% had 2 missing Hb values during the EP). See Supplementary Table S4 for the reasons Hb values were missing. Evaluable Hb level by visit is shown in Supplementary Figure S1. The AMD using evaluable Hb without imputation was 1.47 g/dl (95% CI: 1.32, 1.63; 1-sided

Table 2 | Hb- and transfusion-related secondary endpoints (ITT population)

XXX	Daprodustat (n = 307)		Placebo (n = 307)
Participants with mean EP Hb level 11–12 g/dl			
n (%)	132 (52)		17 (8)
Difference in response rate [daprodustat – placebo], % (95% CI)		45 (37, 52)	
1-sided *P* value		< 0.0001	
Evaluable Hb within Hb 11–12 g/dl target range during EP			
Mean % time	50.1		8.2
Treatment difference [daprodustat – placebo], % (95% CI)		38.8 (25.0, 54.6)	
1-sided *P* value		< 0.0001	
Participants discontinuing randomized treatment due to meeting rescue criteria			
n (%)	2 (<1)		26 (8)
Incidence rate per 100 PY	1.33		18.88
Hazard ratio (95% CI)		0.07 (0.02, 0.30)	
1-sided *P* value		0.0002	
On-treatment blood transfusions			
Received transfusion, *n* (%)	4 (1)		15 (5)
Time to first transfusion, median d	106		60
On-treatment rhEPO use			
Received rhEPO, *n* (%)	9 (3)		22 (7)
Time to first rhEPO, median d	148		115

CI, confidence interval; EP, evaluation period; Hb, hemoglobin; ITT, intent-to-treat; PY, patient-years; rhEPO, recombinant human erythropoietin.

$P < 0.0001$). Overall, the results of subgroup analyses were consistent with the primary analysis with little or no heterogeneity among subgroups (Figure 4), except for baseline Hb, for which the mean treatment difference was greater among participants with a lower baseline Hb level (Supplementary Table S5).

A significantly larger proportion of participants in the daprodustat group (77%) compared with the placebo group (18%) had an Hb level increase of ≥1 g/dl from baseline to the EP. The difference in response rate (daprodustat–placebo) was 56% (95% CI: 49%, 63%; 1-sided $P < 0.0001$). In a supportive analysis that used evaluable Hb without imputation, the difference in response rate was 65% (95% CI: 58%, 72%; 1-sided $P < 0.0001$). The results of subgroup analyses were consistent with the primary analysis except for the extremes of baseline Hb level (<8.5 g/dl, >11 g/dl), for which the number of participants was too low to calculate a response rate (Supplementary Figure S2).

A smaller proportion of participants in the daprodustat group met rescue criteria ($n = 3$; <1%) compared with the placebo group ($n = 32$; 10%). Four participants in the daprodustat group received a blood transfusion while on treatment, compared with 15 in the placebo group, and 9 participants in the daprodustat group received rhEPO while on treatment compared with 22 in the placebo group. Secondary efficacy endpoints are presented in Table 2. Serum iron and total iron binding–capacity levels increased over the course of treatment in the daprodustat group, whereas transferrin saturation levels initially decreased before returning toward baseline (Figure 5). Ferritin and hepcidin levels also decreased in the daprodustat group over the treatment period. All iron parameters were stable in the placebo group. Few participants in either group received i.v. iron during study treatment, and monthly oral iron dose was also similar between groups (Supplementary Table S6).

Fatigue and HRQoL

The mean (SD) baseline SF-36 Vitality score was comparable for the daprodustat (50.7 [21.2]) and placebo (52.2 [21.1]) groups. The adjusted mean change in the SF-36 Vitality score from baseline to week 28 was greater in the daprodustat (7.3 points) group than in the placebo group (1.9 points). The AMD was 5.4 points (95% CI: 2.2, 8.6; 1-sided $P = 0.0005$; Figure 6). In the primary analysis, which included observed on-treatment scores and imputed values for participants with scores that were measured off treatment and those with missing scores, 32% and 38% of participants in the daprodustat and placebo groups, respectively, had one or more imputed values. See Supplementary Table S7 for the timing and reasons for missing SF-36 values that required imputation based on a *post hoc* analysis.

Results of prespecified supportive analyses without imputed values were consistent with the primary analysis. In the on-treatment analysis, the adjusted mean change was 7.4 points in the daprodustat group and 2.4 points in the placebo group, with an AMD of 5.0 (95% CI: 1.7, 8.2; 1-sided $P = 0.0013$). Supplementary Figure S3 shows the change in the SF-36 Vitality score based on observed, on-treatment values. The on- and off-treatment analysis included observed SF-36 Vitality scores for 78% and 79% of participants in the daprodustat and placebo groups, respectively. The adjusted mean change was 7.0 points in the daprodustat group, and 1.8 points in the placebo group, with an AMD of 5.2 (95% CI: 2.2, 8.3; 1-sided $P = 0.0004$).

Overall, the results of subgroup analyses were consistent with the primary analysis with little or no heterogeneity among subgroups. In the subgroup by baseline Hb level, the AMD of 7.44 points was numerically higher for those with baseline Hb level <9.0 g/dl, but the CI was wider, and the difference was similar for those with baseline Hb level of 9–10 g/dl (5.25 points) and 10–11 g/dl (6.01 points). The

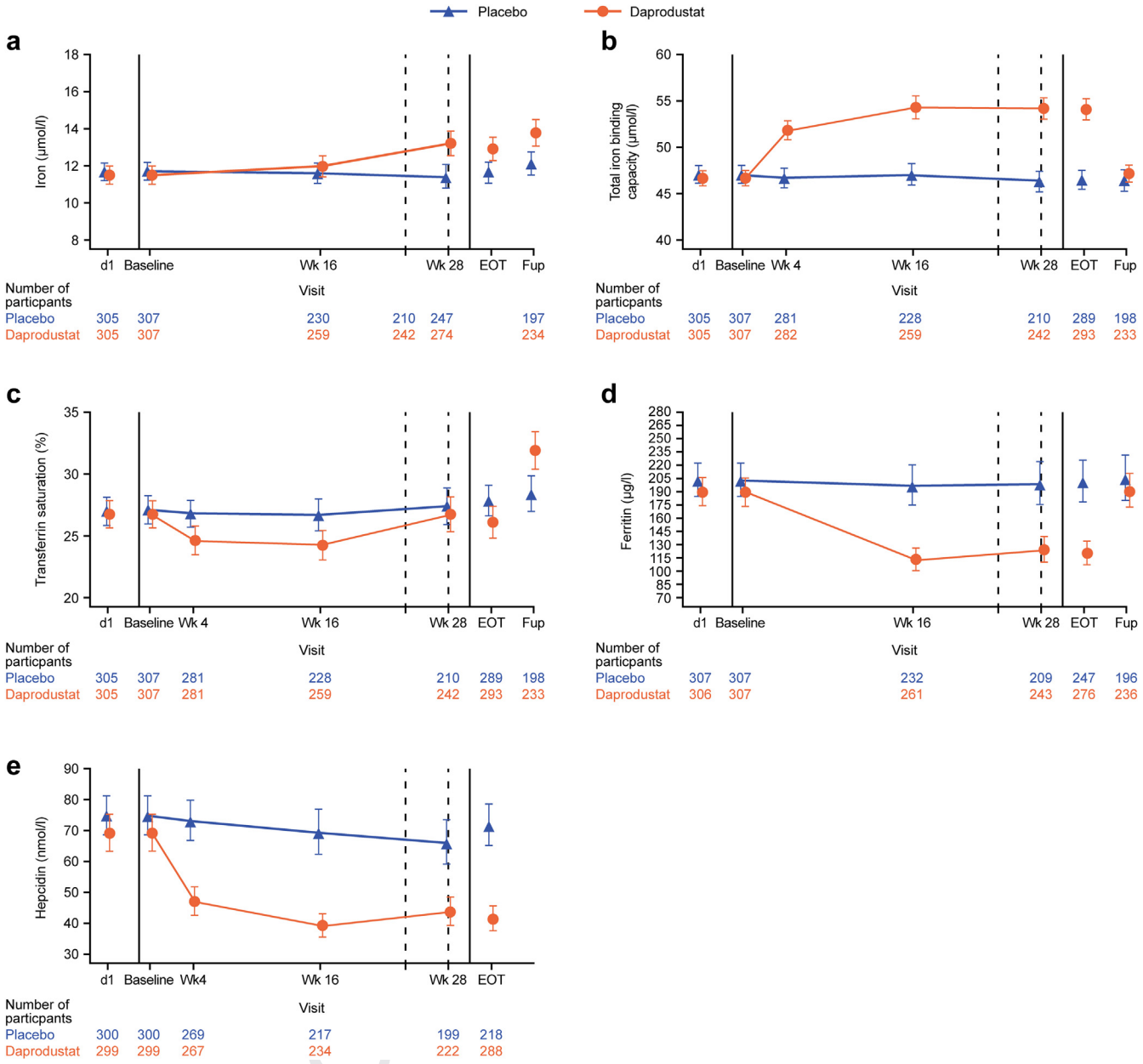

Figure 5 | Serum iron parameters by visit. (**a**) Iron; (**b**) total iron binding capacity; (**c**) transferrin saturation; (**d**) ferritin; (**e**) hepcidin. Data are presented as mean and 95% confidence interval. Dashed vertical lines represent the evaluation period (week 24 to week 28). Baseline is defined as the latest pre-dose measurement on or before the randomization date. End of treatment (EOT) was the latest value on or before the treatment stop day + 1 day. Fup, follow-up; Wk, week.

AMD was in favor of daprodustat for all subgroups tested, except for the group with baseline Hb level >11 g/dl, which had very few participants (Figure 7).

The distribution of change in SF-36 Vitality scores from baseline to week 28 shows the variation across participants in both treatment groups (Figure 8). More participants in the daprodustat group (58%) had an improvement in the SF-36 Vitality score of ≥6 points from baseline at week 28 than those in the placebo group (40%). The difference in response rate was 13% (95% CI: 4%, 22%; 1-sided P = 0.0049). Participants treated with daprodustat had greater numeric improvements at week 28 for all SF-36 domains compared to those treated with placebo (Supplementary Table S8).

Safety

The proportion of participants with any treatment-emergent AE was similar among the daprodustat and placebo groups (69% vs. 71%, respectively: Table 3). The most commonly reported AEs (≥5%) were diarrhea, hypertension, and peripheral edema. The proportion of participants discontinuing study treatment prematurely secondary to an AE was similar

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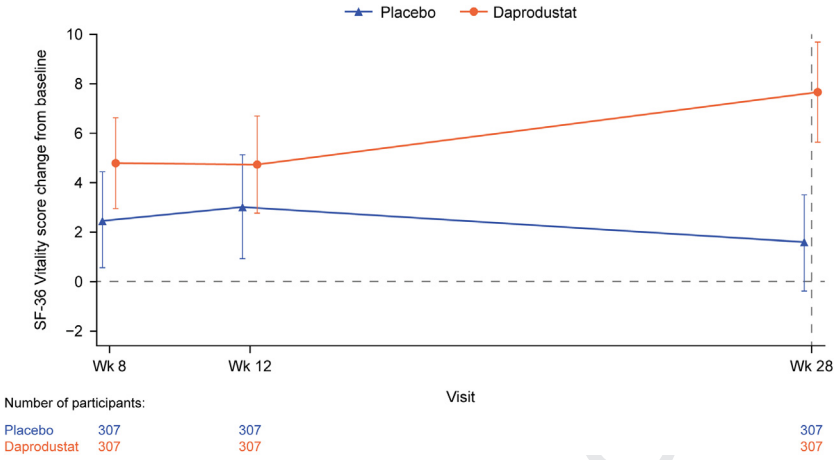

Figure 6 | Change in on-treatment observed and imputed Medical Outcomes Study 36-item Short Form Survey (SF-36) Vitality score from baseline (intent-to-treat population). Error bars indicate 95% confidence intervals. Wk, week.

in the daprodustat ($n = 22$; 7%) and placebo ($n = 24$; 8%) groups (Figure 2). The proportion of participants with potential AEs of special interest was generally similar between the treatment groups for each category of AEs of special interest. The most frequent AEs of special interest category was worsening of hypertension (daprodustat: $n = 31$ [10%]; placebo: $n = 26$ [8%]; Supplementary Table S9).

The proportion of participants with any treatment-emergent serious adverse events was similar among the daprodustat and placebo groups (20% and 22%, respectively; Supplementary Table S10). First occurrence of adjudicated MACE was similar among the daprodustat and placebo groups over the MACE follow-up period (Table 4). The results of the blood pressure–related endpoints are shown in Supplementary Table S11.

DISCUSSION

In this randomized, double-blind, placebo-controlled trial, daprodustat increased Hb level by 1.40 g/dl (95% CI: 1.23, 1.56) more than placebo on average ($P < 0.0001$) over 28 weeks, demonstrating that daprodustat is superior to placebo in increasing Hb level among participants with CKD stages 3–5 who do not require dialysis. Improvement in Hb level with daprodustat was accompanied by a lower proportion of participants needing rescue, blood transfusions, or ESAs, compared with that in the placebo group. The daprodustat group also had a greater mean change from baseline in the SF-36 Vitality score, compared with that in the placebo group (treatment difference 5.4 [95% CI: 2.2, 8.6]), a difference that was statistically significant. A greater proportion of participants in the daprodustat group experienced a clinically meaningful increase in SF-36 Vitality score of ≥6 points (58% vs. 40% of those in the placebo group). This endpoint was included because clinically important differences in quality-of=life (QoL) measures are usually based on analyses of within-patient changes rather than the mean difference between treatment groups. The threshold of 6 points was selected *a priori* based on prior studies that have estimated the minimally important difference or clinically important difference in SF-36 Vitality score to be between 5 and 6 points, and on an anchor-based minimally clinically important difference estimation indicating that 6 points is the most appropriate threshold among patients with CKD.[20–22] A 6-point improvement in SF-36 Vitality score is also equivalent to a 1-level improvement (6.25 points) in any 1 of the 4 questions within the SF-36 Vitality domain; therefore, this level of improvement would signify a patient shifting from feeling worn out "most of the time" to feeling worn out "some of the time."

Although treatment of severe anemia among patients with non-dialysis-dependent CKD improves QoL, no clear HRQoL evidence supports current guidelines that suggest treatment when Hb level is <10 g/dl.[17,23] Early rhEPO trials, in which participants started with Hb levels in the range of 6 to 7 g/dl and experienced large increases in Hb level, showed clear improvements in HRQoL, specifically decreases in fatigue or increases in energy level.[3–5] In contrast, a population with CKD, type 2 diabetes, and baseline Hb level ≤11.0 g/dl in the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) study,[7] in which participants who received darbepoetin alfa achieved a median Hb level of 12.5 g/dl, and participants receiving placebo achieved a median Hb level of 10.6 g/dl, the difference in the mean change in SF-36 Vitality score was neither statistically nor clinically significant (5.3 ± 20 vs. 4.2 ± 19 for darbepoetin alfa vs. placebo). A small but nominally significant difference was found in the proportion of participants with a ≥5-point increase in SF-36 Vitality score (54% for darbepoetin alfa vs. 49% placebo). Participants in the placebo group had greater i.v. iron utilization (20.4% vs. 14.8%) and received more red blood cell transfusions (24.5% vs. 14.8%) than those in the darbepoetin alfa group, leading to a rise in Hb level that likely contributed to the improvement in the SF-36 Vitality score in the placebo group.[7,24] Furthermore, the more detailed analysis of QoL in the Trial to Reduce Cardiovascular Events with Aranesp Therapy by Lewis *et al.* notes that the evidence supporting

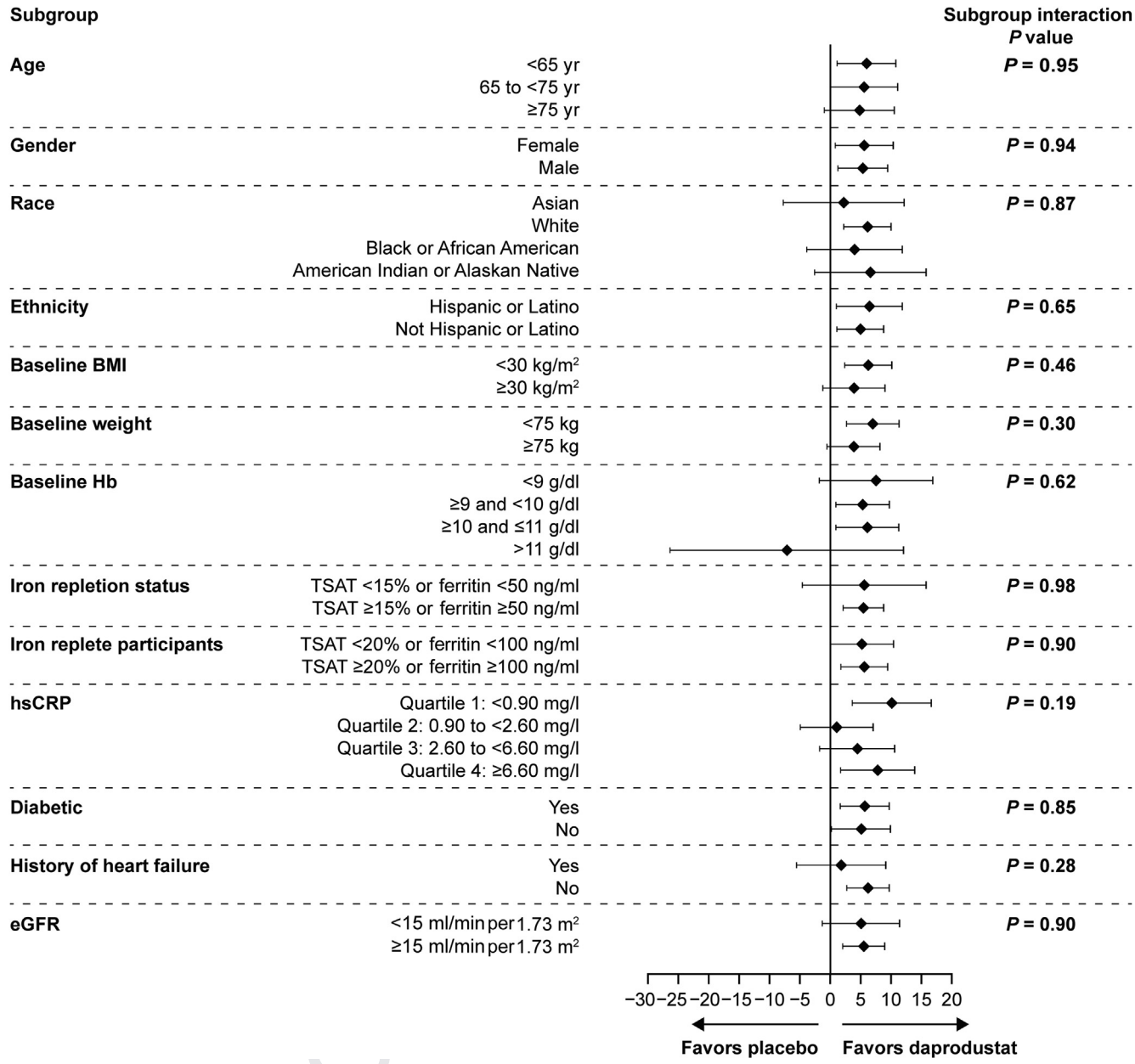

Figure 7 | Forest plot of adjusted mean difference of the change from baseline to week 28 in on-treatment observed and imputed Medical Outcomes Study 36-item Short Form Survey (SF-36) Vitality score across subgroups defined at baseline. BMI, body mass index; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; hsCRP, high-sensitivity C-reactive protein; TSAT, transferrin saturation.

improvement in HRQoL is mixed, as the improvement in some domains was of modest clinical significance, and no consistent improvement was observed in the SF-36 Vitality and Physical Function domains.[7] The Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) and the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) studies evaluated the effect of ESA treatment on HRQoL, but the results of these trials are not comparable to those of the ASCEND-NHQ, as these studies had no placebo group, were open-label, and targeted an Hb level of >13 g/dl.[6,8] The ASCEND-NHQ results are potentially important because they demonstrate that a clinically meaningful improvement in fatigue can be achieved using daprodustat, compared with placebo, in a non-dialysis-dependent CKD population with baseline central laboratory Hb level in the 9–11 g/dl range. However, no conclusion can be made as to whether this meaningful change in quality of life is due to daprodustat specifically or rather the availability of an appropriate anemia treatment to address energy and fatigue level associated with anemia of CKD.

Despite some numerical differences in baseline characteristics such as age, Hb levels, and high-sensitivity C-reactive protein levels between the 2 treatment groups, the consistent improvement in the SF-36 Vitality score seen with

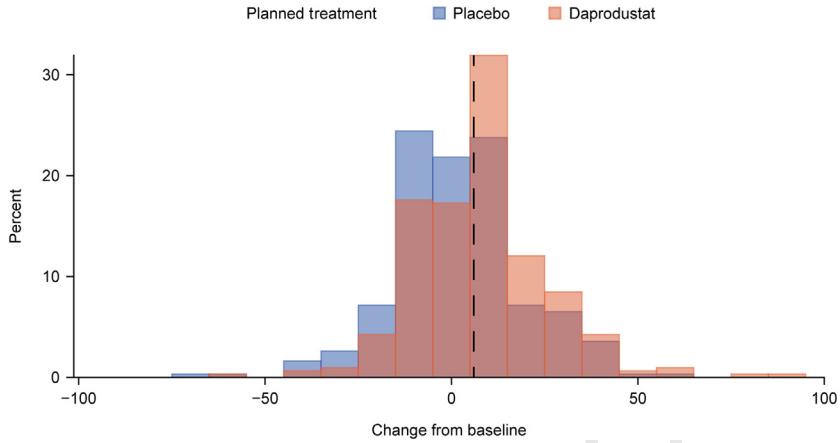

Figure 8 | Histogram of on-treatment observed and imputed Medical Outcomes Study 36-item Short Form Survey (SF-36) Vitality score change from baseline at week 28, 0–100 scoring. Vertical dashed line represents change from baseline of 6 points. Figure was created *post hoc*.

daprodustat in the subgroup analyses suggests that the baseline differences did not bias the SF-36 Vitality score results. Effects of daprodustat on Hb level and the SF-36 Vitality score were similar across subgroups defined by age, sex, race, ethnicity, high-sensitivity C-reactive protein level, and other characteristics. The increase in Hb level was greater among participants whose Hb level was lower at baseline, but the increase in Hb level did not differ among those who were iron replete or deficient at baseline. For the SF-36 Vitality score, the consistency of effects across age, sex, and race is notable because prior studies have shown that women and older individuals with CKD have lower SF-36 Vitality scores than men and younger patients.[24] Daprodustat also improved the SF-36 Vitality score to a similar degree among participants whose Hb level was <10 g/dl at baseline and those whose Hb level was between 10 and 11.0 g/dl, so no clear association was present between achieved Hb level and change in SF-36 Vitality score. Furthermore, no difference was present in receipt of oral or i.v. iron between the daprodustat and placebo groups during the study period that might explain the difference in fatigue. Thus, participants with various demographic and laboratory characteristics reported a decrease in fatigue.

A major strength of ASCEND-NHQ is its placebo-controlled, double-blinded study design. Blinding of study participants and investigators to study treatment and patient-reported outcome results is particularly important when assessing HRQoL because these endpoints might be

Table 3 | AEs summary in safety population[a] Q22

Event type	Daprodustat (n = 308)		Placebo (n = 306)		
	n (%)	Rate per 100 PY[b] (exposure in PY)	n (%)	Rate per 100 PY[b] (exposure in PY)	Daprodustat vs. placebo RR (95% CI)
Treatment-emergent AE	213 (69)	266.96 (79.79)	216 (71)	285.95 (75.54)	0.98 (0.88, 1.09)
Treatment-emergent SAE	62 (20)	45.43 (–)	68 (22)	53.90 (–)	0.91 (0.67, 1.23)
Treatment-emergent Fatal SAE	4 (1)	2.69 (148.84)	7 (2)	5.11 (137.04)	N/A
Participants with any event	**213 (69)**	**266.96 (79.79)**	**216 (71)**	**285.95 (75.54)**	**0.98 (0.88, 1.09)**
Diarrhea	25 (8)	17.61 (141.95)	17 (6)	12.83 (132.48)	1.46 (0.81, 2.65)
Hypertension	23 (7)	16.00 (143.77)	16 (5)	11.93 (134.07)	1.43 (0.77, 2.65)
Peripheral edema	12 (4)	8.24 (145.55)	21 (7)	16.00 (131.23)	0.57 (0.28, 1.13)
Fatigue	2 (<1)	1.35 (147.99)	15 (5)	11.19 (134.05)	0.13 (0.03, 0.57)
Urinary tract infection	13 (4)	8.99 (144.62)	15 (5)	11.31 (132.61)	0.86 (0.42, 1.78)
Nausea	14 (5)	9.64 (145.26)	5 (2)	3.67 (136.18)	2.78 (1.01, 7.63)
Arthralgia	9 (3)	6.14 (146.53)	13 (4)	9.81 (132.49)	0.69 (0.30, 1.59)
Anemia	3 (<1)	2.02 (148.51)	12 (4)	8.81 (136.22)	0.25 (0.07, 0.87)
Headache	12 (4)	8.25 (145.44)	8 (3)	5.95 (134.49)	1.49 (0.62, 3.59)
Nasopharyngitis	11 (4)	7.57 (145.39)	9 (3)	6.69 (134.59)	1.21 (0.51, 2.89)
Upper respiratory tract infection	8 (3)	5.42 (147.50)	11 (4)	8.16 (134.79)	0.72 (0.29, 1.77)

AE, adverse event; CI, confidence interval; N/A, not applicable; PY, patient-year; RR, relative risk; SAE, serious AE.
[a]The safety population included 306 participants in the placebo group and 308 in the daprodustat group, because 1 participant in the placebo group received daprodustat 10 mg for 1 month at the week-4 visit and was therefore included in the daprodustat group in the safety population.
[b]Calculated as 100 X (number of participants with events/PY).
Common treatment-emergent AEs occurring in >3% of the safety population are listed.
Bold data indicate xxx. Q23

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Table 4 | First adjudicated MACE in ITT population

MACE	Daprodustat $n = 307$	Placebo $n = 307$
First occurrence	15 (4.9)	19 (6.2)
All-cause mortality	10 (3.3)	15 (4.9)
Nonfatal myocardial infarction	4 (1.3)	4 (1.3)
Nonfatal stroke	1 (0.3)	0

ITT, intent-to-treat; MACE, major adverse cardiovascular event.
Values are *n* (%).

susceptible to bias.[24] However, the study also has limitations that should be acknowledged. The primary analysis of mean change in the SF-36 Vitality score included imputed values for approximately one-third of participants who discontinued treatment prior to week 28 or had missing values, and the primary analysis of mean change in Hb level from baseline to the EP included imputed values for approximately one-fifth of participants who had missing values. However, supportive analyses that did not include imputed values were consistent with the primary analyses. The study population did not include a substantial proportion of patients with severe anemia; approximately one-third of participants had a central laboratory Hb level ≥10 g/dl at baseline. Furthermore, this trial targeted an Hb level of 11–12 g/dl—which is an approved target for ESAs in some parts of the world, such as the European Union[25]—in order to show that Hb level improvement leads to improved HRQoL outcomes in line with the current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines,[23] which suggest that some patients have improvements in QoL at a higher Hb level and that therapy may be started at levels above 10.0 g/dl. The inclusion criterion of transferrin saturation ≥15% and ferritin ≥50 ng/ml could have allowed enrollment of participants with iron deficiency, according to current guidelines.[23] However, the randomized design of the study resulted in similar iron parameters in the treatment arms. Differences in iron sufficiency are therefore unlikely to explain the difference in QoL observed, particularly as most patients were iron replete at baseline. The SF-36 Vitality score was assessed only at baseline and weeks 8, 12, and 28, and the improvement in SF-36 Vitality score was not observed until week 28, despite an increase in Hb level that occurred earlier. However, the mean Hb level was not in the target range until week 16 in the daprodustat group. Finally, although procedures were in place to ensure that participants remained blinded to their Hb values, some participants could have become aware of their Hb levels at some point during the study, which in turn could have influenced their responses to the HRQoL questionnaires.

In conclusion, use of daprodustat resulted in a significant increase in Hb and a reduction in the need for rescue treatment with ESA or transfusion. Participants who were assigned to daprodustat experienced a significant decrease in fatigue. Participants who received daprodustat did not generally experience more AEs than did those who received placebo.

DISCLOSURE

KLJ reports consultancy fees from GSK and is an associate editor of the *Journal of the American Society of Nephrology*. AKS reports consultancy fees from GSK, Zydus, and Bayer, and honoraria from Nephrology Times. ICM reports research grants, consultancy fees, and honoraria from GSK and Vifor Pharma. RDL reports grants and personal fees from Bristol Myers Squibb and Pfizer; personal fees from Boehringer Ingelheim and Bayer AG; and research grants from Amgen Inc., GSK, Medtronic PLC, and Sanofi Aventis. GTO reports consultancy fees from GSK, Roche, AbbVie, and AstraZeneca; royalties or licenses from UpToDate and Elsevier Barcelona; honoraria from GSK, Amgen, and AstraZeneca; meeting and/or travel support from KDIGO Controversies Conference and GSK; and a leadership/fiduciary role in the *Mexican Board of Nephrology* and the *Mexican Kidney Foundation*. CPK reports consultancy fees from GSK, Abbott, Akebia, AstraZeneca, Bayer, Cara Therapeutics, Boehringer Ingelheim, CSL Behring, Tricida, Reata, Rockwell, Takeda, and Vifor; royalties from UpToDate and Springer; meeting and travel support from Bayer, AstraZeneca, Reata, and Tricida; participation fees from AstraZeneca and Bayer; and a leadership/fiduciary role in the *International Society of Renal Nutrition and Metabolism*. VJ reports consultancy fees from GSK; grants from Baxter Healthcare, GSK and NephroPlus; honoraria from Baxter Healthcare, AstraZeneca, and Boehringer Ingelheim; and board participation fees from Zydus Cadilla; and is a past president of the *International Society of Nephrology*. SJ reports consultancy and advisory board fees from GSK. DCW reports honoraria and/or consultancy fees from AstraZeneca, Amgen, Astellas, Bayer, Boehringer Ingelheim, GSK, Jansen, Merck Sharp and Dohme, Mundipharma, Napp, Pharmacosmos, Reata, Tricida, and Vifor Fresenius. ARC, MS, TK, ACL, PB are employees of and stockholders in GSK. RRC is an employee of GSK and stockholder in GSK and Pfizer.

BC, RI, and TO were employees of and stockholders in GSK at the time of the study.

DATA STATEMENT

Within 6 months post-US and European Union regulatory approval and publication of this study, anonymized individual participant data, the annotated case report form, protocol, reporting and analysis plan, data set specifications, raw dataset, analysis-ready dataset, and clinical study report will be available for research proposals approved by an independent review committee. Proposals should be submitted to either ViVli Center for Global Clinical Research or www.clinicalstudydatarequest.com. A data access agreement will be required.

ACKNOWLEDGMENTS

Editorial support with writing assistance, assembling figures, grammatical editing and referencing was provided by Jonathan Plumb, PhD, of Fishawack Indicia Ltd, UK, part of Fishawack Health, and was funded by GSK. The ASCEND-NHQ study (study ID: 205270; clinicaltrials.gov: NCT03409107) was funded by GSK. The study funders had a role in study design, data collection, data analysis, data interpretation, and writing of the article.

AUTHOR CONTRIBUTIONS

The first draft of the article was prepared by the first author, who had unrestricted access to the data, and it was reviewed and edited by all the authors. All authors agreed to submit the article for publication and all vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods: inclusion criteria; exclusion criteria; protocol defined criteria for stopping study treatment; multiple imputation methodology.

Supplementary Table S1. Dosing algorithm.

Supplementary Table S2. Rescue algorithm.

Supplementary Table S3. Statistical analyses of efficacy endpoints.

Supplementary Table S4. Reasons for missing hemoglobin values requiring imputation in the primary hemoglobin analysis (intent-to-treat [ITT] population).

Supplementary Table S5. Summary of postrandomization hemoglobin change from baseline to the evaluation period per baseline hemoglobin group.

Supplementary Table S6. On-treatment iron use to week 28 (intent-to-treat [ITT] population).

Supplementary Table S7. *Post hoc* summary of imputed and missing data for Medical Outcomes Study 36-item Short Form Survey (SF-36) Vitality score analysis.

Supplementary Table S8. Baseline and change from baseline in the on-treatment observed scores for for Medical Outcomes Study 36-item Short Form Survey (SF-36) domains (0–100 scoring).

Supplementary Table S9. Overview of treatment-emergent adverse events of special interest in safety population.

Supplementary Table S10. Summary of serious treatment-emergent adverse events in safety population.

Supplementary Table S11. Blood pressure results (intent-to-treat [ITT] population).

Supplementary Figure S1. Evaluable haemoglobin (Hb) by visit (intent-to-treat [ITT] population) created *post hoc*. Error bars indicate 95% confidence interval. Dashed vertical lines represent the evaluation period (EP; week 24 to week 28). The horizontal reference lines in the figures represent the Hb target range (11–12 g/dl). Evaluable values are on-treatment values that are not taken within the 8 weeks following a red blood cell or whole blood transfusion or a postrandomization nonrandomized erythropoiesis-stimulating agents (ESA) treatment. Wk, week. Note: Figure was created *post hoc* based on prespecified analyses of evaluable Hb by visit.

Supplementary Figure S2. Forest plot of difference in response rate from the analysis of participants with postrandomization haemoglobin (Hb) increase of ≥1.0 g/dl across subgroups. Observed on and off-treatment and imputed Hb values. BMI, body mass index; eGFR, estimated glomerular filtration rate; hsCRP, high-sensitivity C-reactive protein; TSAT, transferrin saturation.

Supplementary Figure S3. Observed Medical Outcomes Study 36-item Short Form Survey (SF-36) Vitality score (on-treatment) change from baseline. Error bars indicate 95% confidence interval. Observed on-treatment SF-36 Vitality scores. Wk, week. Note: Figure created *post hoc* based on prespecified analysis of change from baseline in observed (on-treatment) SF-36 Vitality subscore values.

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