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Roxadustat for CKD-related Anemia in Non-dialysis Patients

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Introduction: Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that stimulates erythropoiesis and improves iron metabolism. We assessed the efficacy and tolerability of roxadustat in patients with chronic kidney disease (CKD)-related anemia not on dialysis.

Methods: ANDES was a global Phase 3 randomized study in which adults with stage 3–5 CKD not on dialysis received roxadustat or placebo. Patients were initially dosed thrice weekly; dose was titrated to achieve a hemoglobin level ≥11.0 g/dl, followed by titration for maintenance. The primary endpoints were change in hemoglobin (weeks 28–52) and proportion of patients achieving a hemoglobin response (hemoglobin ≥11.0 g/dl and increase ≥1.0 g/dl [baseline >8.0 g/dl], or increase ≥2.0 g/dl [baseline ≤8.0 g/dl]) (week 24). Treatment-emergent adverse events (TEAEs) and serious adverse events (TESAEs) were recorded.

Results: In roxadustat (n = 616) and placebo (n = 306) groups, hemoglobin mean (SD) change from baseline over weeks 28–52 was significantly larger for roxadustat (2.00 [0.95]) versus placebo (0.16 [0.90]), corresponding to least-squares mean difference of 1.85 g/dl (95% confidence interval [CI] 1.74–1.97; $P < 0.0001$). The proportion of patients achieving a response at week 24 was larger for roxadustat (86.0%; 95% CI 83.0%–88.7%) versus placebo (6.6%; 95% CI 4.1%–9.9%; $P < 0.0001$). The proportion of patients receiving rescue therapy at week 52 was smaller for roxadustat (8.9%) versus placebo (28.9%); hazard ratio, 0.19 (95% CI 0.14–0.28; $P < .0001$). The incidences of TEAEs and TESAEs were comparable.

Conclusion: This study showed that roxadustat corrected and maintained hemoglobin and was well tolerated in patients with CKD-related anemia not on dialysis (ClinicalTrials.gov NCT01750190).

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In patients with non–dialysis-dependent CKD (NDD-CKD), anemia is a common complication with increasing prevalence as CKD progresses, with nearly 50% of patients with stage 5 CKD having anemia.[1,2] The severity of anemia is associated with an increased risk for cardiovascular disease and death.[3,4] The current treatment for CKD-related anemia includes oral or intravenous (i.v.) iron supplementation, red blood cell (RBC) transfusions, and/or treatment with an erythropoiesis-stimulating agent (ESA) administered subcutaneously.[5]

Studies demonstrate more cardiovascular events and higher mortality rates among patients with CKD randomized to higher target hemoglobin levels with ESAs,[6–8] and consequently these products carry black box safety warnings.[9,10] Subsequent analyses demonstrated higher ESA doses, rather than achieved hemoglobin, were associated with higher risk.[11] Safer and simpler treatments for CKD-related anemia are needed.

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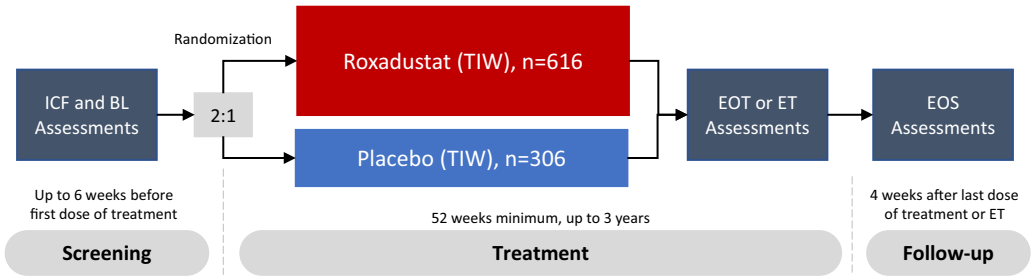


Figure 1. Study design. BL, baseline; EOS, end of study; EOT, end of treatment; ET, early termination; ICF, informed consent form; TIW, thrice weekly.

Anemia pathogenesis is multifactorial, and includes impaired oxygen-dependent regulation of erythropoiesis due to inadequate production of erythropoietin.[12–14] Hypoxia-inducible factor (HIF) is part of a system in which the prolyl hydroxylases sense oxygen[15] and is key to erythropoietic response. Roxadustat is an oral HIF prolyl hydroxylase inhibitor that stimulates erythropoiesis and improves iron metabolism. HIF stabilizers have been approved for the treatment of CKD-related anemia in China and Japan, including roxadustat, which has been approved in China[16,17] and Japan to treat anemia in patients with dialysis-dependent CKD and NDD-CKD.[18]

We evaluated the efficacy and safety of roxadustat versus placebo for the treatment of CKD-related anemia in patients with NDD-CKD.[19,20]

METHODS

Trial Design and Patients

This randomized, double-blind, placebo-controlled, Phase 3 study evaluated the efficacy and safety of roxadustat in patients with NDD-CKD and CKD-related anemia (ClinicalTrials.gov number, NCT01750190) (Figure 1). The study was conducted at 163 sites in the United States, South America, Australia, New Zealand, and Asia.

The study protocol was approved by institutional review boards and/or ethics committees. All patients provided informed consent. The study was conducted in accordance with the Declaration of Helsinki[21] and International Council for Harmonisation guidelines for Good Clinical Practice.[22]

Eligible patients were ≥18 years; had a diagnosis of stage 3–5 CKD[23] and not on dialysis, with an estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m^2; baseline hemoglobin ≤10.0 g/dl, ferritin ≥30 ng/ml, and transferrin saturation (TSAT) ≥5%. Key exclusion criteria included any ESA treatment, >1 i.v. iron dose, major cardiovascular event within 12 weeks of randomization, and RBC transfusion within 8 weeks of randomization. Complete criteria are listed in Supplementary Table S1 and sample size determination methods are described in the Supplementary Material.

Randomization and Dosing Procedures

Patients were randomly assigned (2:1) to receive oral roxadustat or matching placebo in a double-blinded manner. Randomization schedules were prospectively prepared, and automated randomization and treatment assignments were provided by an interactive web response system. Randomization was stratified by screening hemoglobin (≤8.0 vs. >8.0 g/dl); history of cardiovascular, cerebrovascular, or thromboembolic diseases; eGFR (<30 vs. ≥30 ml/min per 1.73 m^2); and region (US vs. countries outside US).

All patients were initially dosed thrice weekly based on body weight. Patients weighing 45 to <70 kg received 70 mg roxadustat or placebo, and those weighing ≥70 kg received 100 mg thrice weekly. The investigator, study site staff, patient, sponsor, and designees were all blinded to the study drug assignment, but not the dose, which was achieved by using identical roxadustat and placebo tablets. Additional dosing details are provided in Supplementary Table S2.

Efficacy Assessments

The primary efficacy endpoints were change in hemoglobin from baseline averaged over weeks 28 to 52 regardless of rescue therapy (US Food and Drug Administration submission) and the proportion of patients achieving a hemoglobin response at 2 consecutive visits ≥5 days apart during the first 24 weeks without rescue therapy (EU European Medicines Agency submission). A hemoglobin response was defined as hemoglobin ≥11.0 g/dl and an increase of ≥1.0 g/dl in patients with baseline >8.0 g/dl, or hemoglobin increase ≥2.0 g/dl in patients with baseline ≤8.0 g/dl. Rescue therapy included blood/RBC transfusion, ESA treatment, or i.v. iron. Oral iron was encouraged. Secondary efficacy endpoints are listed in Supplementary Table S3.

Additional, exploratory efficacy endpoints included the following: mean change from baseline in hemoglobin during weeks 28–36 by baseline iron

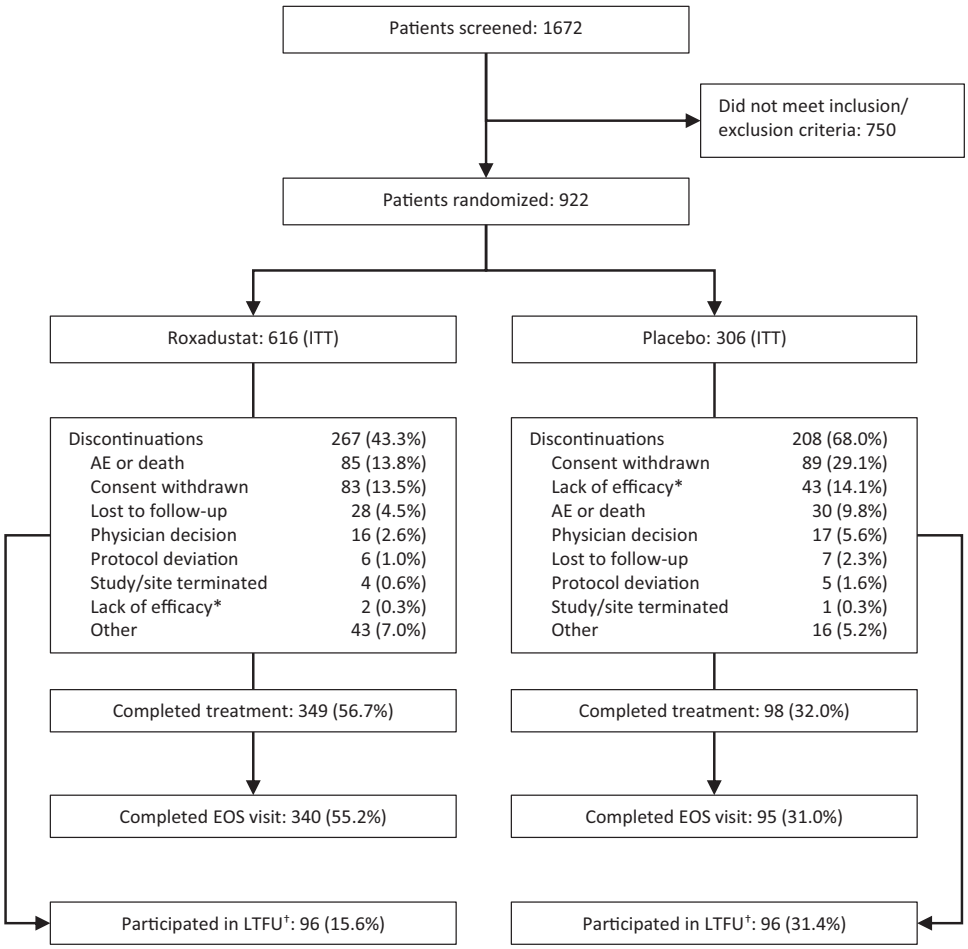


Figure 2. CONSORT flow diagram. *Including ESA rescue. †Patients who discontinued from the study and participated in the LTFU were evaluated for cardiovascular events of interest, vital status, and hospitalizations after EOS until study closure. AE, adverse event; EOS, end of study; ESA, erythropoiesis-stimulating agent; LTFU, long-term follow-up.

status regardless of rescue therapy; mean changes from baseline in serum hepcidin, iron, and other iron-related parameters, including ferritin, TSAT, and total iron-binding capacity (TIBC), total cholesterol, and low-density lipoprotein (LDL)/high-density lipoprotein ratio at each scheduled visit to week 52.

Safety

Safety measures included TEAEs and TESAEs, laboratory measures, vital signs, and electrocardiograms.

Statistical Analysis

For the US Food and Drug Administration primary endpoint, a missing-at-random-based multiple imputation analysis of covariance model tested the null hypothesis that hemoglobin changes from baseline averaged over weeks 28 to 52 regardless of rescue therapy were comparable in roxadustat and placebo patients in the intent-to-treat (ITT) population (all randomized patients). For the EU European Medicines Agency primary endpoint, a Cochran-Mantel-Haenszel model tested the null hypothesis that the percentage of patients achieving a hemoglobin response without rescue therapy would be comparable in roxadustat and placebo patients in the full analysis set (FAS; all randomized patients who received ≥1 dose of study drug with baseline and ≥1 post-dose hemoglobin). The Cochran-Mantel-Haenszel model was adjusted for stratification factors (see Supplementary Material). For both US and EU endpoints, the 2-sided alpha level of significance was $P < 0.05$.

For primary endpoints, sensitivity analyses were performed on multiple patient subgroups (see Supplementary Material). An analysis using multiple imputations was prespecified as a sensitivity analysis.

Secondary efficacy endpoints were analyzed using a fixed-sequence approach to adjust for multiplicity testing. If the null hypothesis was rejected, the superiority/noninferiority of roxadustat versus placebo was accepted, and testing progressed to the next endpoint (Supplementary Table S3).

The safety population included all randomized patients who received ≥1 dose of study drug. If the

Table 1. Baseline demographic and clinical characteristics (intent to treat)

Characteristic	Roxadustat (n = 616)	Placebo (n = 306)
Mean (SD) age, y	64.9 (12.6)	64.8 (13.2)
Median (range) age, y	66 (22–94)	66 (22–91)
Age group, *n* (%)		
18–64	271 (44.0)	146 (47.7)
65–74	192 (31.2)	79 (25.8)
≥75	153 (24.8)	81 (26.5)
Female gender, *n* (%)	375 (60.9)	176 (57.5)
Mean (SD) BMI, kg/m^2	27.4 (6.3)	27.3 (6.0)
Mean (SD) hemoglobin (g/dl)[a]	9.10 (0.75)	9.09 (0.69)
Hemoglobin (g/dl) cohort, n (%)		
≤8.0	52 (8.4)	23 (7.5)
>8.0 to ≤9.0	173 (28.1)	97 (31.7)
>9.0	391 (63.5)	186 (60.8)
Mean (SD) eGFR (ml/min per 1.73 m^2)	21.9 (11.5)	22.4 (11.4)
eGFR (ml/min/1.73 m^2)[b] cohort, n (%)		
<10	71 (11.5)	19 (6.2)
10 to <15	124 (20.1)	76 (24.8)
15 to <30	292 (47.4)	146 (47.7)
30 to <45	96 (15.6)	46 (15.0)
45 to <60	31 (5.0)	18 (5.9)
≥60	2 (0.3)	1 (0.3)
Iron repletion status, *n* (%)		
Replete: Ferritin ≥100 ng/ml and TSAT ≥20%	373 (60.6)	170 (55.6)
Not replete: Ferritin <100 ng/ml or TSAT <20%	241 (39.1)	134 (43.8)
Missing	2 (0.3)	2 (0.7)
CRP,[c] *n* (%)		
≤ULN (4.9 mg/l)	457 (74.2)	223 (72.9)
>ULN (4.9 mg/l)	156 (25.3)	81 (26.5)
Missing	3 (0.5)	2 (0.7)
Mean (SD) total cholesterol, mg/dl	174.9 (48.4)	172.5 (52.5)
Mean (SD) LDL cholesterol, mg/dl	98.0 (39.1)	96.3 (40.0)
CVD history, *n* (%)		
Hypertension	583 (94.6)	292 (95.4)
Diabetes mellitus	398 (64.6)	200 (65.4)
Stroke	56 (9.1)	26 (8.5)
CHF (NYHA 1 or 2)	51 (8.3)	24 (7.9)
MI (STEMI or NSTEMI)	31 (5.0)	21 (6.9)

BMI, body mass index; CHF, congestive heart failure; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; NYSA, New York Heart Association; SAF, safety population; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; TSAT, transferrin saturation; ULN, upper limit of normal.
[a]Defined as the mean of up to 4 of the last central laboratory values before the first dose.
[b]Defined as the mean of all available central lab values before the first dose of study drug, including the day-1 predose value.
[c]Defined as the mean of values obtained within 2 weeks before the first dose.

treatment received was different from that randomly assigned, the actual treatment received was analyzed. Because TEAE and TESAE rates were expected to be affected by between-group differences in discontinuation rates, exposure-adjusted incidence rates (patients per 100 patient exposure years [PEY]) were calculated. Descriptive statistics were used for all safety data (TEAEs, TESAEs, and deaths).

RESULTS

Patient Disposition and Baseline Characteristics

Between November 5, 2012, and September 24, 2018, 922 were randomized to receive oral roxadustat (n = 616) or placebo (n = 306); 916 patients (611 and 305) took ≥1 dose of medication. In the roxadustat group, 43.3% (267/616) of patients discontinued treatment, whereas 68.0% (208/306) of placebo-treated patients discontinued treatment (Figure 2). This between-group difference in discontinuations was largely due to the lack of efficacy among patients in the placebo group. The primary reasons for discontinuations in the placebo group were withdrawal of consent and lack of efficacy. The primary reasons for discontinuations in the roxadustat group, which occurred at lesser rates were adverse events or death and withdrawal of consent.

Baseline characteristics were balanced between groups (Table 1). Mean (SD) hemoglobin was 9.10 (0.75) and 9.09 (0.69) g/dl, and mean eGFR levels were 21.9 (11.5) and 22.4 (11.4) ml/min per 1.73 m^2, roxadustat versus placebo, respectively. Approximately 32% of patients had stage 5 CKD, and 40% of patients were not iron replete (TSAT <20% or ferritin <100 ng/ml).

Treatment duration was up to 4.5 years. The median duration of study drug exposure was 95.6 weeks in the roxadustat group and 52.1 weeks in the placebo group, resulting in an overall drug exposure three times higher for roxadustat (1134.9 vs. 377.3 PEY). The differential dropout rate manifested as early as week 8. In each baseline eGFR category, study drug discontinuation was higher in placebo- versus roxadustat-treated patients. The relative difference in discontinuation was most pronounced in those with the lowest eGFRs (Figure 3). In patients with baseline eGFR <10 ml/min per 1.73 m^2, 40 of 71 roxadustat-treated patients versus 5 of 19 placebo-treated patients were still on treatment at week 48.

Primary Efficacy Endpoints

For the US primary endpoint, the mean (SD) hemoglobin change to weeks 28 to 52 regardless of rescue therapy was larger in the roxadustat versus placebo group. The least-squares mean (LSM) between-group treatment difference (roxadustat−placebo) was 1.85 g/dl (95% CI 1.74–1.97; $P < 0.0001$) (Figure 4a). Among subgroups, the results were consistent (Supplementary Figure S1).

For the EU primary endpoint, the proportion of patients achieving a response without rescue therapy at 2 consecutive visits during the first 24 weeks was larger in the roxadustat versus placebo group (86.0% [95% CI 83.0%–88.7%] vs. 6.6% [95% CI 4.1%–

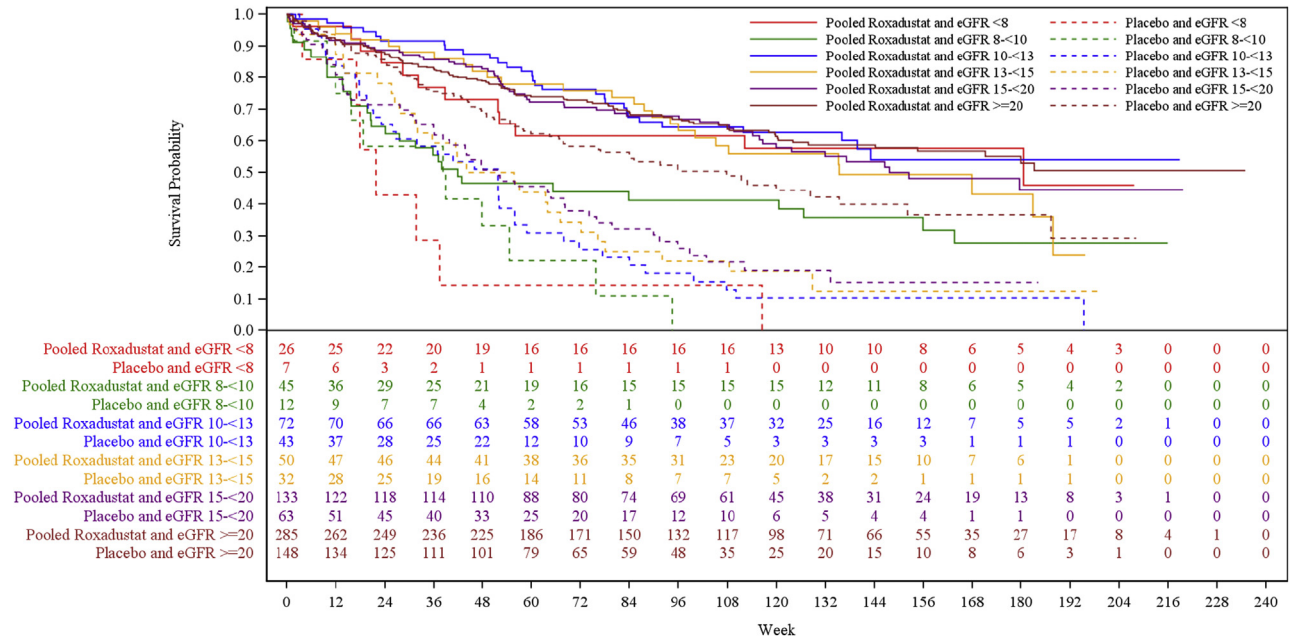
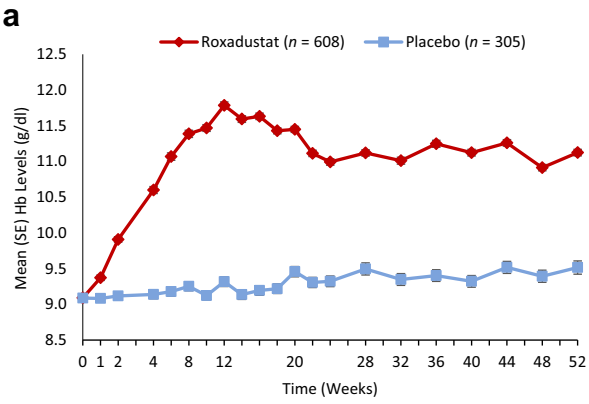


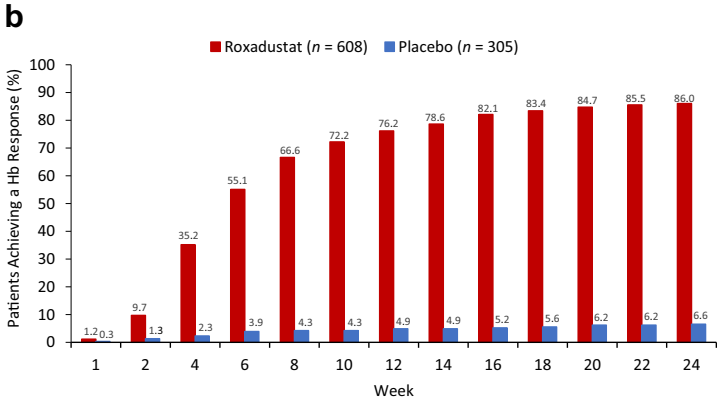
Figure 3. Percentage of patients on treatment over time by baseline estimated glomerular filtration rate (eGFR) category (safety population [SAF]).

9.9%]), with an odds ratio of 77.6 (95% CI 44.7–134.5; $P < 0.0001$) (Figure 4b). Among subgroups, the results were consistent (Supplementary Figure S2). The analyses using multiple imputations provided similar results in direction and magnitude.

Secondary Efficacy Endpoints

Mean (SD) change in hemoglobin over weeks 28 to 36 without rescue therapy within 6 weeks of and during the 8-week treatment period were 2.02 (1.07) and 0.20 (0.99) g/dl in roxadustat and placebo groups. The LSM





Changes in Hb (g/dl) from BL over W28–52 regardless of rescue therapy (ITT)

	Roxadustat		Placebo		Treatment
	Hb (O + I)	Hb Δ from BL	Hb (O + I)	Hb Δ from BL	Difference†
BL*	9.1 (0.8)		9.1 (0.7)		
W28–52	11.1 (0.7)	2.00 (0.95)	9.2 (1.1)	0.16 (0.90)	
LSM (SE)		2.02 (0.04)		0.17 (0.05)	1.85 (0.06)
(95% CI)		(1.95, 2.09)		(0.07, 0.27)	(1.74, 1.97)
P-value					<0.0001

Patients Achieving a Hb Response during first 24 weeks of treatment, censoring for rescue therapy (FAS)

	Roxadustat	Placebo	Difference (95% CI)	OR (95% CI)‡ [Roxadustat/Placebo]
Patients Achieving Response‡, n (%)	523 (86.0)	20 (6.6)	79.5 (75.6, 83.4)	77.6 (44.7, 134.5)
(95% CI)§	(83.0, 88.7)	(4.1, 9.9)		
P-value‖				<0.0001

Figure 4. Hemoglobin levels over time (a) and percentage of patients with a hemoglobin response (b). *Defined as the mean of up to 4 last central laboratory values before the first dose of study treatment. †Multiple imputation strategy by combining the results of ANCOVA model with baseline Hb and baseline eGFR as covariates, and treatment and other randomization stratification factors, except baseline Hb (≤8 vs. >8 g/dl) and eGFR (<30 vs. ≥30 ml/min per 1.73 m^2), as fixed effects. ‡Patient who achieved Hb response (central laboratory values: Hb ≥11.0 g/dl and an Hb increase from baseline by ≥1.0 g/dl in patients with baseline Hb >8 g/dl, or an increase in Hb ≥2.0 g/dl in patients with baseline Hb ≤8 g/dl) at 2 consecutive visits ≥5 days apart during the first 24 weeks of treatment without rescue therapy. Patients who dropped out or received rescue therapy before or on the date of the second consecutive Hb value were classified as nonresponders. §Based on the exact method of Clopper-Pearson. ||CMH method adjusting for all randomization stratification factors. Δ, change; ANCOVA, analysis of covariance; CMH, Cochran-Mantel-Haenszel; CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set; Hb, hemoglobin; I, imputed; ITT, intent to treat; LS, least squares; O, observed; SE, standard error; W, weeks.

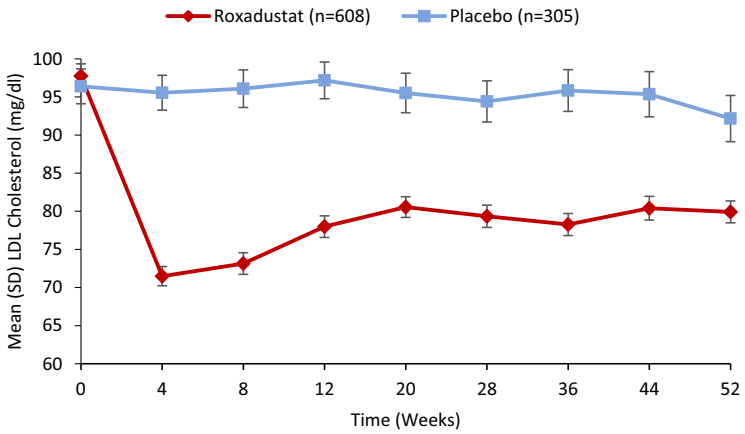


Figure 5. Low-density lipoprotein (LDL) cholesterol levels over time (full analysis set).

between-group treatment difference was 1.88 g/dl (95% CI 1.73–2.04; $P < 0.0001$).

Mean (SD) changes from baseline in hemoglobin over weeks 28 to 52 in roxadustat and placebo patients with baseline high-sensitivity C-reactive protein greater than the upper limit of normal were 2.02 (0.93) and 0.18 (0.95) g/dl, with a LSM difference of 1.90 g/dl (95% CI 1.66–2.14; $P < 0.0001$).

The proportion of patients with hemoglobin ≥10.0 g/dl over weeks 28 to 36 without rescue therapy within 6 weeks of and during the 8-week treatment period was larger in the roxadustat versus placebo group (76.8% [95% CI 73.2%–80.1%] vs. 18.4% [95% CI 14.2%–23.2%]), with an odds ratio of 15.5 (95% CI 10.79–22.19; $P < 0.0001$).

Roxadustat lowered mean LDL cholesterol at week 4, and this was sustained through week 52 (Figure 5). The mean (SD) change from baseline in LDL cholesterol over weeks 12 to 28 was −18.48 (29.60) in the roxadustat group and 0.22 (29.37) mg/dl in the placebo group, corresponding to an LSM difference of −17.26 mg/dl (95% CI −20.65 to −13.87; $P < 0.0001$). The LDL cholesterol-lowering effect of roxadustat was similar in patients taking or not taking statins (Supplementary Table S4).

A smaller proportion of patients in roxadustat versus placebo groups received rescue therapy during the first 52 weeks (8.9% vs. 28.9%) with a hazard ratio of 0.19 (95% CI 0.14–0.28; $P < 0.0001$) (Figure 6a). The percentage of patients receiving RBC transfusion during the first 52 weeks of treatment was lower in the roxadustat versus placebo group (5.6% and 15.4%), with a time to first rescue therapy use hazard ratio of 0.26 (95% CI 0.17–0.41; $P < 0.0001$ [nominal]) (Figure 6b). The percentage of patients who received i.v. iron therapy was lower in the roxadustat versus placebo group (2.5% vs. 4.9%), with a time to first i.v. iron use hazard ratio of 0.39 (95% CI 0.19–0.81) ($P = 0.011$). The percentage of patients who received ESA therapy was lower in the roxadustat versus placebo group (2.1% vs. 6.7%), with a time to first ESA therapy hazard ratio of 0.08 (95% CI 0.04–0.15) ($P < 0.0001$).

Mean (SD) changes from baseline in the Short Form-36 Vitality subscore averaged over weeks 12 to 28 were 1.90 (8.71) and 1.02 (8.33) points in the roxadustat and placebo groups, corresponding to a LSM difference of 1.22 points (95% CI 0.15–2.29; $P = 0.0259$).

There was no significant between-group difference in progression of CKD, as measured by the rate of change in eGFR over time. Therefore, the fixed-sequence testing was stopped.

Additional Efficacy Endpoints

The mean (SD) change from baseline in hemoglobin averaged over weeks 28 to 36 by baseline iron status in the roxadustat group was 2.07 (1.03) g/dl among those with baseline ferritin <100 ng/ml and/or TSAT <20% versus 1.99 (1.04) g/dl in those with baseline ferritin ≥100 ng/ml and TSAT ≥20%. Both of these results were significantly higher than the corresponding values in the placebo group (0.37 [1.05] vs. −0.02 [0.88] g/dl) ($P < 0.0001$).

At baseline, mean (SD) hepcidin levels were comparable in the roxadustat and placebo groups (110.66 [79.08] and 106.11 [90.68] μg/l). Roxadustat-treated patients experienced a lowering in serum hepcidin at week 4, which was sustained through week 44 (Figure 7a). Mean (SD) changes from baseline to week 44 in the roxadustat and placebo groups were −22.11 (80.90) and 3.88 (80.9) μg/l with an LSM difference of −25.71 μg/l (95% CI −38.52 to −12.90) (Supplementary Table S5).

At baseline, mean (SD) ferritin levels were comparable in the roxadustat and placebo groups (306.89 [388.48] and 308.39 [352.51] ng/ml; Supplementary Table S5). Through week 12, roxadustat-treated

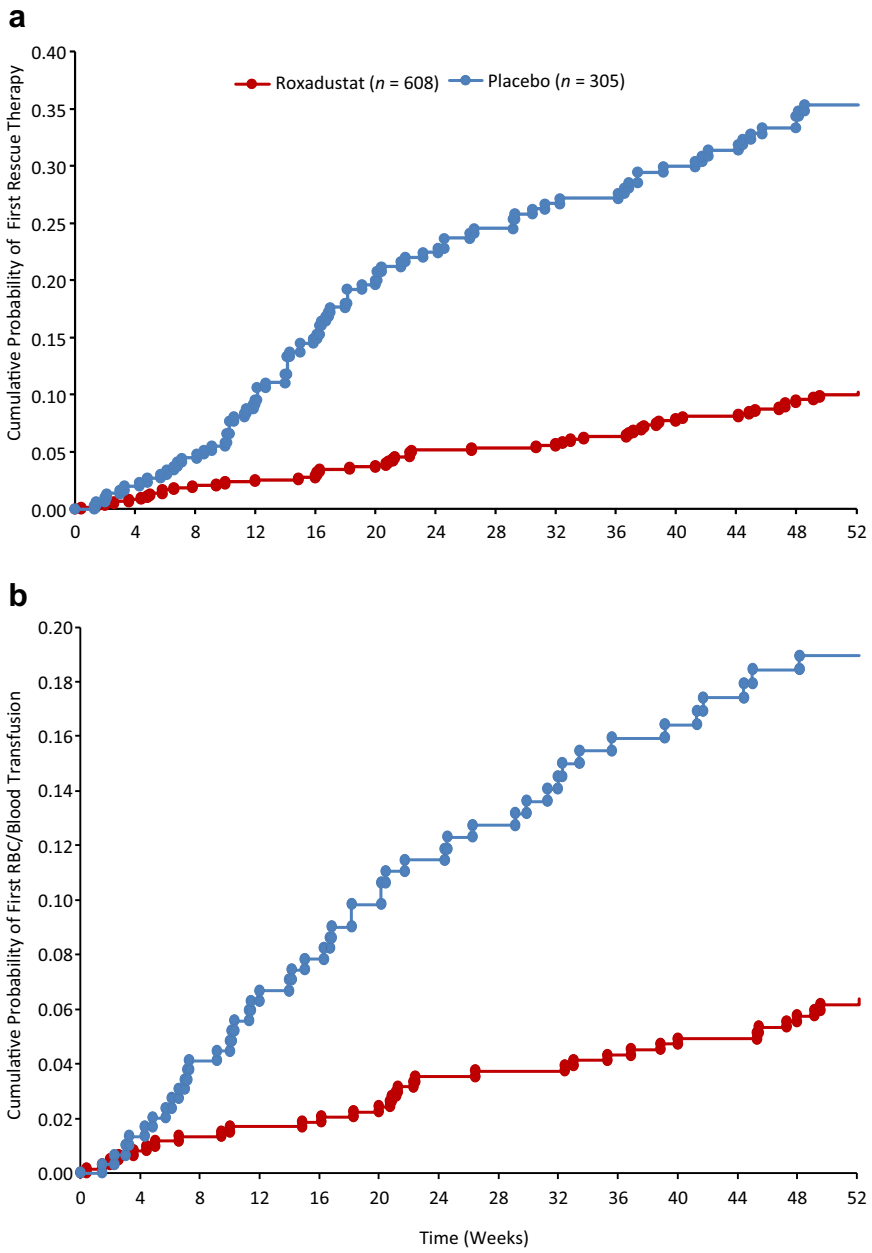


Figure 6. Time from baseline to first use of rescue therapy (a) and first blood/RBC transfusion (b). Time to first event was calculated as: (first event date or censoring date − first dose date + 1)/7. Patients were censored at last dose, week 52, last visit date, or death date, whichever occurred first, if rescue therapy after the first 52 weeks did not occur. Rescue therapy was defined as any use of RBC transfusion, ESA, or i.v. iron. Cox proportional hazards model adjusted for baseline Hb, eGFR, and other randomization stratification factors, except baseline Hb (≤8.0 vs. >8.0 g/dl) and eGFR (<30 vs. ≥30 ml/min per 1.73 m^2). eGFR, estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; i.v., intravenous; RBC, red blood cell.

patients experienced a decrease in ferritin that returned toward baseline by week 20 (Figure 7b).

At baseline, mean (SD) serum iron was comparable in the roxadustat and placebo groups (65.42 [25.05] and 66.26 [26.02] μg/dl; Supplementary Table S5). In roxadustat-treated patients, mean serum iron decreased from baseline to week 4, and then increased above baseline by 10.4 μg/dl through week 20, remaining stable through week 52 (Figure 7c). At baseline, mean (SD) TIBC also was comparable in the roxadustat and placebo groups (257.18 [50.51] and 262.30 [49.64 μg/dl]). By week 44, TIBC increased in the roxadustat group and decreased in placebo group, with a LSM difference of 38.65 (95% CI 31.86–45.45; $P < 0.0001$) (Supplementary Table S5).

At baseline, TSAT was 26% in both groups. In the roxadustat group, mean TSAT initially decreased from baseline up to weeks 4 through 8, and then gradually increased and plateaued after week 20 (Figure 7d).

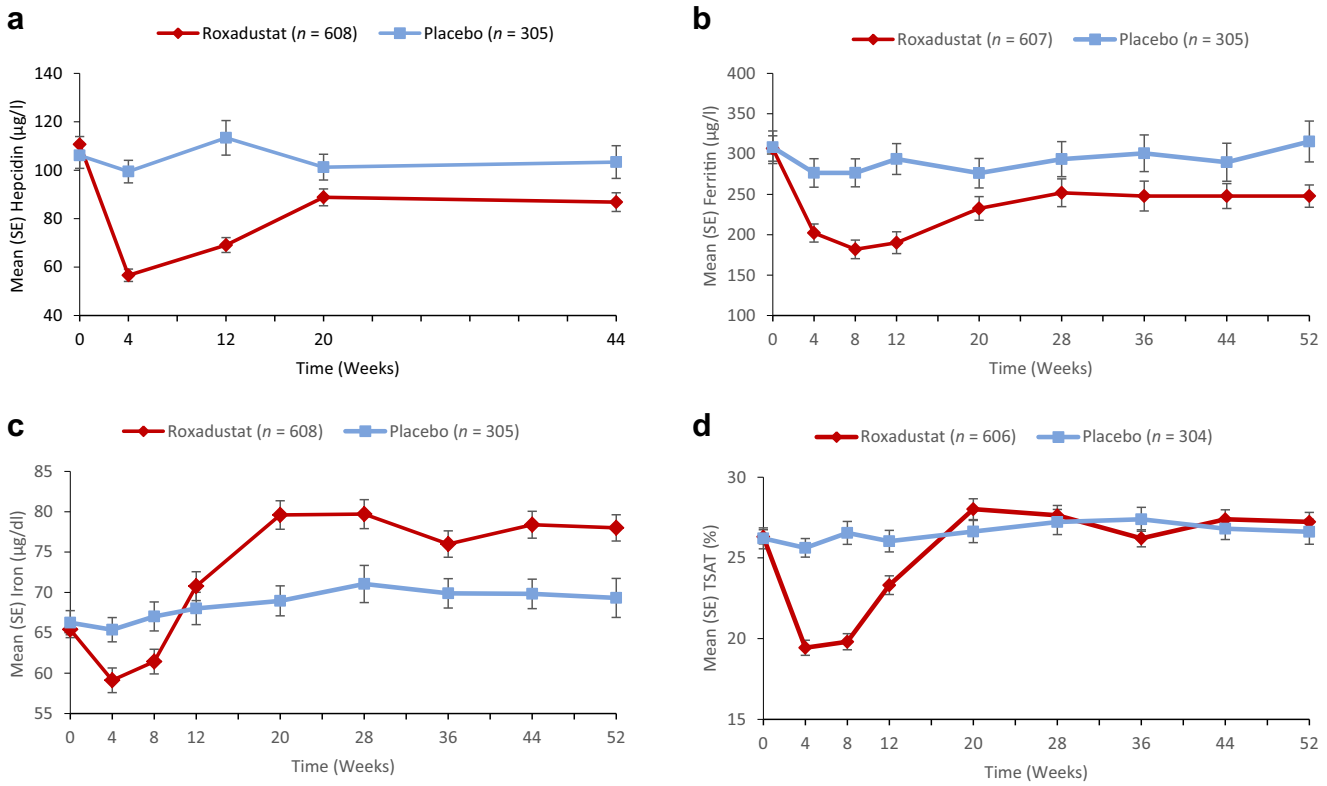


Figure 7. Levels of hepcidin (a), ferritin (b), iron (c), and TSAT (d) (full analysis set). SE, standard error; TSAT, transferrin saturation.

Total cholesterol and LDL/high-density lipoprotein ratios were reduced over time. For total cholesterol, mean (SD) changes from baseline to week 52 in roxadustat and placebo groups were −27.20 (45.79) and −3.21 (49.78) mg/dl. For the LDL/high-density lipoprotein ratio, mean (SD) changes from baseline to week 52 in roxadustat and placebo groups were −0.19 (0.91) and −0.10 (0.79) mg/dl.

Tolerability

TEAEs were reported by 92.3% (564/611) of roxadustat- and 89.5% (273/305) of placebo-treated patients, corresponding to incidence rates of 554.4 and 594.5/100 PEY. The most common TEAEs in the roxadustat or placebo group were hyperkalemia (13.6 vs. 12.5/100 PEY), constipation (12.2 vs. 10.3/100 PEY), viral upper respiratory tract infection (16.9 vs. 15.4/100 PEY), upper respiratory tract infection (12.8 vs. 18.0/100 PEY), and hypertension (11.3 vs. 10.1/100 PEY) (Table 2). The incidence rates of TESAEs were 74.2 and 66.0/100 PEY among roxadustat- versus placebo-treated patients (Table 3). Incidence rates for fatal TESAEs were 3.8 and 2.9, respectively.

Through 52 weeks of treatment, the incidence of TEAEs was comparable in roxadustat- and placebo-treated patients (87.6% and 85.9%), corresponding to incidence rates of 643.4 and 684.0, respectively. TEAEs occurring in ≥5% of patients in either treatment group are summarized in Supplementary Table S6. The incidence of TESAEs through 52 weeks of treatment was also comparable (33.2% and 29.8%), and TESAEs occurring in ≥1% of patients in either treatment group are summarized in Supplementary Table S7. Time-to-death analyses at various time points (52 weeks, 104 weeks, up to 28 days after the last dose of study drug, and including deaths during long-term follow-up) suggest there was no significant difference in mortality risk between the 2 groups.

DISCUSSION

In this ANDES Phase 3 study, roxadustat administered orally 3 times per week was superior to placebo in correcting and maintaining hemoglobin levels in patients with NDD-CKD and CKD-related anemia, with a comparable overall tolerability profile. Significant and comparable improvements in hemoglobin were observed in the iron-replete and not iron–replete subgroups (baseline ferritin <100 ng/l and/or TSAT <20%). Inflamed patients, reflected by high high-sensitivity C-reactive protein levels, are more likely to be ESA hyporesponsive and require higher ESA doses or have lower hemoglobin. In contrast, we found no significant differences in hemoglobin response or roxadustat dose in the subgroups with normal versus elevated high-sensitivity C-reactive protein levels. Nevertheless, these results should be interpreted in light of the fact that hyporesponsiveness

Table 2. Summary of TEAEs[a] occurring in ≥5% of patients in either treatment group (OT+28) (SAF)

	Roxadustat (n = 611)		Placebo (n = 305)	
Preferred term[b]	n (%)	PEY = 1134.9[c] events (per 100 PEY)	n (%)	PEY = 377.3[c] events (per 100 PEY)
Hyperkalemia	111 (18.2)	154 (13.6)	41 (13.4)	47 (12.5)
Constipation	105 (17.2)	139 (12.2)	34 (11.1)	39 (10.3)
Viral upper respiratory tract infection	98 (16.0)	192 (16.9)	40 (13.1)	58 (15.4)
Hypertension	95 (15.5)	128 (11.3)	27 (8.9)	38 (10.1)
Edema peripheral	89 (14.6)	128 (11.3)	28 (9.2)	38 (10.1)
Nausea	85 (13.9)	110 (9.7)	29 (9.5)	35 (9.3)
Upper respiratory tract infection	79 (12.9)	145 (12.8)	48 (15.7)	68 (18.0)
Diarrhea	78 (12.8)	106 (9.3)	31 (10.2)	39 (10.3)
Urinary tract infection	68 (11.1)	103 (9.1)	29 (9.5)	56 (14.8)
End-stage renal disease	67 (11.0)	74 (6.5)	18 (5.9)	18 (4.8)
Headache	66 (10.8)	99 (8.7)	26 (8.5)	31 (8.2)
Insomnia	63 (10.3)	75 (6.6)	9 (3.0)	10 (2.7)
Dizziness	58 (9.5)	85 (7.5)	32 (10.5)	35 (9.3)
Cough	57 (9.3)	71 (6.3)	28 (9.2)	33 (8.7)
Back pain	55 (9.0)	66 (5.8)	18 (5.9)	20 (5.3)
Chronic kidney disease	54 (8.8)	61 (5.4)	21 (6.9)	22 (5.8)
Pruritus	54 (8.8)	72 (6.3)	19 (6.2)	24 (6.4)
Vomiting	54 (8.8)	65 (5.7)	20 (6.6)	22 (5.8)
Hypoglycemia	53 (8.7)	69 (6.1)	15 (4.9)	17 (4.5)
Acute kidney injury	49 (8.0)	55 (4.8)	11 (3.6)	13 (3.4)
Edema	48 (7.9)	62 (5.5)	9 (3.0)	12 (3.2)
Arthralgia	45 (7.4)	50 (4.4)	24 (7.9)	27 (7.2)
Pneumonia	44 (7.2)	52 (4.6)	18 (5.9)	21 (5.6)
Decreased appetite	41 (6.7)	51 (4.5)	8 (2.6)	8 (2.1)
Muscle spasms	41 (6.7)	53 (4.7)	9 (3.0)	10 (2.7)
Hyperphosphatemia	40 (6.5)	46 (4.1)	10 (3.3)	10 (2.7)
Dyspepsia	39 (6.4)	45 (4.0)	12 (3.9)	12 (3.2)
Pain in extremity	39 (6.4)	42 (3.7)	14 (4.6)	14 (3.7)
Pyrexia	39 (6.4)	61 (5.4)	9 (3.0)	12 (3.2)
Abdominal pain	35 (5.7)	44 (3.9)	13 (4.3)	14 (3.7)
Bronchitis	34 (5.6)	44 (3.9)	13 (4.3)	16 (4.2)
Dyspnea	34 (5.6)	49 (4.3)	23 (7.5)	28 (7.4)
Cellulitis	32 (5.2)	37 (3.3)	7 (2.3)	22 (5.8)
Gout	32 (5.2)	46 (4.1)	20 (6.6)	33 (8.7)
Asthenia	31 (5.1)	35 (3.1)	11 (3.6)	11 (2.9)
Hypotension	31 (5.1)	37 (3.3)	10 (3.3)	10 (2.7)
Metabolic acidosis	29 (4.7)	31 (2.7)	18 (5.9)	20 (5.3)
Anemia	17 (2.8)	19 (1.7)	44 (14.4)	58 (15.4)

AE, adverse event; OT, on treatment; PEY, patient exposure year; SAF, safety population; TEAE, treatment-emergent adverse event.
[a]Occurred after the first dose of study drug and up to 28 days after the last dose was considered a TEAE if it was not present before the first dose of study drug, or it was present before the first dose of study drug but increased in severity during the double-blind treatment period. Patients with >1 event in a category were counted only once for that category.
[b]MedDRA (Medical Dictionary for Regulatory Activities) version 20.0.
[c]PEY = (Last Dose Date − First Dose Date + 1) / 365.25.

to ESAs is a complex topic with both acute and chronic effects. Our findings may reflect the effect of roxadustat in patients who could be hyporesponsive to ESAs to the extent that C-reactive protein is a surrogate for the hyporesponsive state.

Roxadustat reduced the use of RBC transfusion. RBC transfusions may result in complications such as volume overload, hyperkalemia, immunologically mediated transfusion reactions, iron overload, and in rare cases, transmission of infections.[5] In addition, significant costs are associated with RBC transfusions, including storage and acquisition.[24] Importantly, because of alloimmunization risks, RBC transfusion can decrease the opportunity to receive a kidney transplant. Reducing the need for transfusions with roxadustat may reduce the associated risks, lower health care costs, and preserve the opportunity for transplantation.

Roxadustat reduced mean LDL cholesterol in all patients regardless of whether they were taking statins. The LDL cholesterol-lowering effect may be mediated by HIF-dependent effects on acetyl coenzyme A that are required for the first step of cholesterol synthesis,[25] and on the degradation of 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate-limiting enzyme in cholesterol synthesis.[26,27] This may be beneficial, as

Table 3. Summary of TESAEs[a] occurring in ≥2% of patients in either treatment group (OT+28) (SAF)

	Roxadustat (n = 611)		Placebo (n = 305)	
Preferred Term[b]	n (%)	PEY = 1134.9[c] events (/100 PEY)	n (%)	PEY = 377.3[c] Events (/100 PEY)
Acute kidney injury	41 (6.7)	45 (4.0)	6 (2.0)	7 (1.9)
End-stage renal disease	34 (5.6)	36 (3.2)	10 (3.3)	10 (2.7)
Pneumonia	29 (4.7)	35 (3.1)	12 (3.9)	13 (3.4)
Chronic kidney disease	27 (4.4)	30 (2.6)	9 (3.0)	9 (2.4)
Cardiac failure congestive	23 (3.8)	25 (2.2)	5 (1.6)	5 (1.3)
Hyperkalemia	19 (3.1)	22 (1.9)	4 (1.3)	4 (1.1)
Urinary tract infection	18 (2.9)	21 (1.9)	8 (2.6)	10 (2.7)
Hyponatremia	15 (2.5)	16 (1.4)	3 (1.0)	3 (0.8)
Azotemia	13 (2.1)	13 (1.1)	5 (1.6)	5 (1.3)
Hypoglycemia	13 (2.1)	14 (1.2)	4 (1.3)	4 (1.1)
Peritonitis	13 (2.1)	14 (1.2)	1 (0.3)	1 (0.3)
Anemia	5 (0.8)	5 (0.4)	8 (2.6)	8 (2.1)
Pulmonary edema	4 (0.7)	5 (0.4)	6 (2.0)	7 (1.9)

OT, on treatment; PEY, patient exposure year; SAF, safety population; TESAE, treatment-emergent serious adverse event.
[a]Occurred after the first dose of study drug and up to 28 days after the last dose of study drug was considered a treatment-emergent adverse event (TEAE) if it was not present before the first dose of study drug, or it was present before the first dose of study drug but increased in severity during the double-blind treatment period. An adverse event that occurred more than 28 days after the last dose of study drug was not counted as a TEAE. Patients with >1 event in a category were counted only once for that category.
[b]MedDRA (Medical Dictionary for Regulatory Activities) version 20.0.
[c]PEY = (Last Dose Date − First Dose Date + 1) / 365.25; reported as an event rate per 100 PEY.

patients with CKD are more likely to die from cardiovascular events[28] than from kidney failure.

Hepcidin regulates iron absorption and mobilization of iron from hepatocytes and macrophages. Hepcidin is downregulated by hypoxia via HIF stabilization, which increases the synthesis of iron transport proteins and intestinal iron absorption,[29,30] and improves the release of macrophage iron onto transferrin.[31] Serum hepcidin levels decreased with roxadustat, which was likely due to indirect effects, including the production of erythroferrone by developing erythroblasts and normoblasts, as well as utilization of iron for hemoglobin synthesis. This study confirms the findings of previous clinical trials in patients with NDD-CKD demonstrating that roxadustat increased hemoglobin levels while maintaining stable serum iron levels, despite robust erythropoiesis, without i.v. iron.[34,35]

TSAT is a ratio of serum iron and TIBC. Although TSAT values were stable in the roxadustat and placebo groups, there was a between-group difference in the constituent components of the calculation. In the placebo group, neither serum iron nor TIBC changed. In the roxadustat group, both serum iron and TIBC[34] increased, suggesting greater iron movement through transferrin for erythropoiesis. Ferritin, which reflects intracellular iron stores and inflammation, decreased in parallel to the decline in hepcidin and the rise in serum iron. This suggests roxadustat may help mobilize iron stores previously sequestered by hepcidin and inflammation.

Largely due to worsening anemia, significantly more patients in the placebo group discontinued study participation than the roxadustat group. This is supported by the reasons behind discontinuation. This led to a significant difference in median drug exposure time between the groups, and was most pronounced in patients with the lowest baseline eGFR. The risks of morbidity and mortality and anemia severity increase as eGFR decreases, which leads to higher discontinuations in the placebo group. Thus, informative censoring may have affected the comparison between treatment groups for events such as acute kidney injury and end-stage renal disease. To reduce the effect of this bias, we provide exposure-adjusted comparisons of incidence rates for adverse events. Overall, incidence rates of the most commonly reported TEAEs and TESAEs were comparable between treatment groups. As part of the sensitivity analyses, these data also were evaluated during the first 52 weeks of treatment when the between-group differences in exposure were less disparate.

The design and results of this study should be considered relative to the current standard of care for patients with NDD-CKD. Since the completion of CHOIR,[8] CREATE,[6] and TREAT,[7] the proportion of patients treated for anemia has declined. In 2003, approximately 33% of patients received an ESA in the year before starting chronic dialysis. Largely because of ESA safety concerns, predialysis treatment with an ESA had declined to <14% by 2014.[35] Therefore, the use of placebo as a comparator more accurately reflects the current standard of care. A placebo control also provides a clearer assessment of the safety of roxadustat and its novel mechanism of action.

This trial had a larger proportion of patients with stage 4 to 5 CKD than other anemia trials. Although the

mean baseline eGFRs for patients in CHOIR and TREAT were approximately 27 and 34 ml/min per 1.73 m^2, the mean in this study was 22 ml/min per 1.73 m^2, and 32% of these patients had stage 5 CKD. This allows for the assessment of efficacy and safety in a population not previously studied with ESAs.

This Phase 3 clinical study evaluating the efficacy and safety of roxadustat versus placebo in patients with NDD-CKD and anemia included patients with more advanced CKD, more severe anemia, less iron repletion at baseline, and less concomitant i.v. iron use, compared with previous studies in this population. Treatment with roxadustat versus placebo met both primary efficacy endpoints, was superior to placebo for increasing hemoglobin, and reduced the need for blood/RBC transfusion. The overall exposure-adjusted safety profile of roxadustat was comparable to placebo and consistent with that expected in patients with CKD-related anemia.

DISCLOSURES

DWC is a consultant for FibroGen, AstraZeneca, Vifor Pharma, GSK, Akebia, and FMC-RTG. SDR has received travel fees for investigator meetings and honoraria for serving on advisory boards for FibroGen, AstraZeneca, ZS Pharma, Vifor Pharma, and Amgen. TMC is an employee of the University of Hong Kong, and he has consulted for Novartis, Visterra, and UCB Biosciences. He has received research funding from Astellas Pharma and Baxter. AAC receives research funding from FibroGen. AB is consultant to FibroGen. WC, CB, ME, RL, TL, LS, and K-HPY are employees of FibroGen, Inc. and hold stock and/or stock options in FibroGen, Inc. SGK, SKS, and MAM declared no competing interests.

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FibroGen, Inc. sponsored the study. Roxadustat is under clinical development for the treatment of CKD-related anemia in collaboration with Astellas Pharma and AstraZeneca. FibroGen employees and subcontractors had a role in study design, data collection, data analysis, data interpretation, and writing of the manuscript. All authors had full access to all of the study data and had responsibility for the decision to submit the manuscript for publication. Medical writing assistance was also provided by Linda Goldstein, PhD, CMPP from The Write Source MSC, LLC, and was funded by FibroGen.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods

Figure S1. Subgroup analysis of the primary US efficacy endpoint (ITT).

Figure S2. Subgroup analysis of the primary EU efficacy endpoint (FAS).

Table S1. Inclusion and exclusion criteria.

Table S2. Roxadustat dose adjustment algorithm.

Table S3. Fixed sequence for testing secondary efficacy endpoints.

Table S4. Change from baseline to weeks 12 to 28 in LDL cholesterol by treatment and statin use (FAS).

Table S5. Mean change from baseline for hepcidin and iron-related parameters at week 44 (FAS).

Table S6. Summary of TEAEs* occurring in ≥5% of patients in either treatment group (W52) (SAF).

Table S7. Summary of TESAEs* occurring in ≥1% of patients in either treatment group (W52) (SAF).

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