Roxadustat Treatment of Anemia in Non-Dialysis-Dependent Chronic Kidney Disease Is Not Influenced by Iron Status

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Disclosures

- RP has consulted for AstraZeneca, DaVita; and FibroGen; received research funding from Akebia Therapeutics, AstraZeneca, FibroGen, and Nikkiso; and holds stock in DaVita.
- SF has received research funding from and consulted for Akebia Therapeutics, AstraZeneca, and FibroGen.
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- CAP has consulted for AstraZeneca, Eli Lilly and Company/Boehringer Ingelheim, FibroGen, Janssen-Cilag, and Vifor Pharma; conducted studies funded by AstraZeneca and Janssen-Cilag; and received honoraria from AstraZeneca, Eli Lilly and Company/Boehringer Ingelheim, Fibrogen, Janssen-Cilag, Novartis, and Vifor Pharma.
- MP is an employee of AstraZeneca.
- WC, KGS, KPY are employees of and hold stock in FibroGen, Inc.

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Introduction

- Transferrin saturations of less than 20% indicate impaired iron availability for hemoglobin (Hb) synthesis.[1]
- Iron deficiency can reduce the effectiveness of erythropoiesis-stimulating agents (ESAs), add to the cost of treatment, delay rehabilitation of the patient, and may lead to confusion about the responsiveness of the patient to anemia therapy.[1]
- Consequently, treatment with currently available ESAs require patients to be iron replete through oral or intravenous (IV) iron replacement prior to beginning treatment.[2]
- Oral iron supplementation is a common treatment for anemia of non-dialysis-dependent (NDD) chronic kidney disease (CKD), where approximately 40% of patients are iron non-replete.[2]

1. Eschbach JW, et al. *Ann Intern Med*. 1989;111:992–1000. 2. Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Anemia in Chronic Kidney Disease: https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-Anemia-Guideline-English.pdf.

Introduction

- Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that promotes erythropoiesis and improves bioavailability of iron.[1]
- Roxadustat is approved in China to treat anemia in patients with dialysis-dependent (DD)-CKD and NDD-CKD, and in Japan for DD-CKD.
- This analysis of pivotal phase 3 studies explored the efficacy of roxadustat in patients with NDD-CKD who were iron replete vs iron non-replete at baseline.

1. Provenzano R, *et al. Am J Kidney Dis.* 2016;67(6):912–24.

Methods
Summary of NDD-CKD Study Designs

- Data from three pivotal phase 3, randomized, double-blind, placebo-controlled studies of roxadustat for the treatment of anemia in patients with NDD-CKD were assessed individually and in the pooled population by iron status.

	OLYMPUS (Study 001)	ANDES (Study 060)	ALPS (Study 608)
Key eligibility criteria	• Stage 3–5 CKD • Hb <10 g/dL • No ESA ≤6 wk prior to randomization • Ferritin ≥50 ng/mL • TSAT ≥15% • No RBCT ≤6 wk	• Stage 3–5 CKD • Hb ≤10 g/dL • No ESA ≤12 wk prior to randomization • Ferritin ≥30 ng/mL • TSAT ≥5% • No RBCT ≤8 wk	• Stage 3–5 CKD • Hb ≤10 g/dL • No ESA ≤12 wk prior to randomization • Ferritin ≥30 ng/mL • TSAT ≥5% • No RBCT ≤8 wk
Randomized (N)	2781[a]	922	597[b]
Design	• 1:1 randomization • Double-blind • Roxadustat vs placebo	• 2:1 randomization • Double-blind • Roxadustat vs placebo	• 2:1 randomization • Double-blind • Roxadustat vs placebo
Mean drug exposure	• Roxadustat, 19.6 mo • Placebo, 15.2 mo	• Roxadustat, 96.9 wk • Placebo, 64.5 wk	• Roxadustat, 63.1 wk • Placebo, 51.0 wk

[a]In study 001, 20 patients were excluded from statistical analysis because of system technical issues and major good clinical practice (GCP) violations. [b]In study 608, 3 patients were excluded from statistical analysis because of GCP violations.

CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; mo, months; RBCT, red blood cell transfusion; TSAT, transferrin saturation; wk, weeks.

Methods

- In all three studies, oral iron was encouraged during the studies and IV iron was allowed as rescue.
- Iron repletion was defined as:
  - Ferritin ≥100 µg/L and TSAT ≥20% in ANDES and ALPS
  - Ferritin >100 µg/L and TSAT >20% in OLYMPUS
- Demographics and baseline characteristics, change in mean Hb from baseline, mean absolute Hb and average weekly total dose of roxadustat over time, incidence of red blood cell (RBC) transfusions, and IV iron rescue over time were evaluated using the full analysis set (FAS) population in subgroups of patients who were iron replete or iron non-replete at baseline.
- FAS consisted of all randomized/enrolled patients who received at least one dose of study drug and had baseline and at least one post-dose Hb assessment.

TSAT, transferrin saturation.

Demographics & Baseline Characteristics (1 of 2)

	Roxadustat (N=2367)		Placebo (N=1862)	
	Iron Non-replete (n=947)	Iron Replete (n=1420)	Iron Non-replete (n=748)	Iron Replete (n=1114)
Age (years), n (%)				
• 18–64	513 (54.2)	768 (54.1)	401 (53.6)	572 (51.3)
• 65–74	261 (27.6)	353 (24.9)	184 (24.6)	297 (26.7)
• ≥75	173 (18.3)	299 (21.1)	163 (21.8)	245 (22.0)
Gender, n (%)				
• Male	340 (35.9)	625 (44.0)	300 (40.1)	521 (46.8)
• Female	607 (64.1)	795 (56.0)	448 (59.9)	593 (53.2)
Race group, n (%)				
• Asian	254 (26.8)	598 (42.1)	196 (26.2)	481 (43.2)
• Black	76 (8.0)	117 (8.2)	70 (9.4)	76 (6.8)
• White	523 (55.2)	603 (42.5)	414 (55.3)	466 (41.8)
• Other	94 (9.9)	102 (7.2)	68 (9.1)	91 (8.2)
Diabetes history, n (%)				
• Yes	550 (58.1)	772 (54.4)	455 (60.8)	626 (56.2)

Note: Iron replete: TSAT ≥20% and ferritin ≥100 ng/mL.

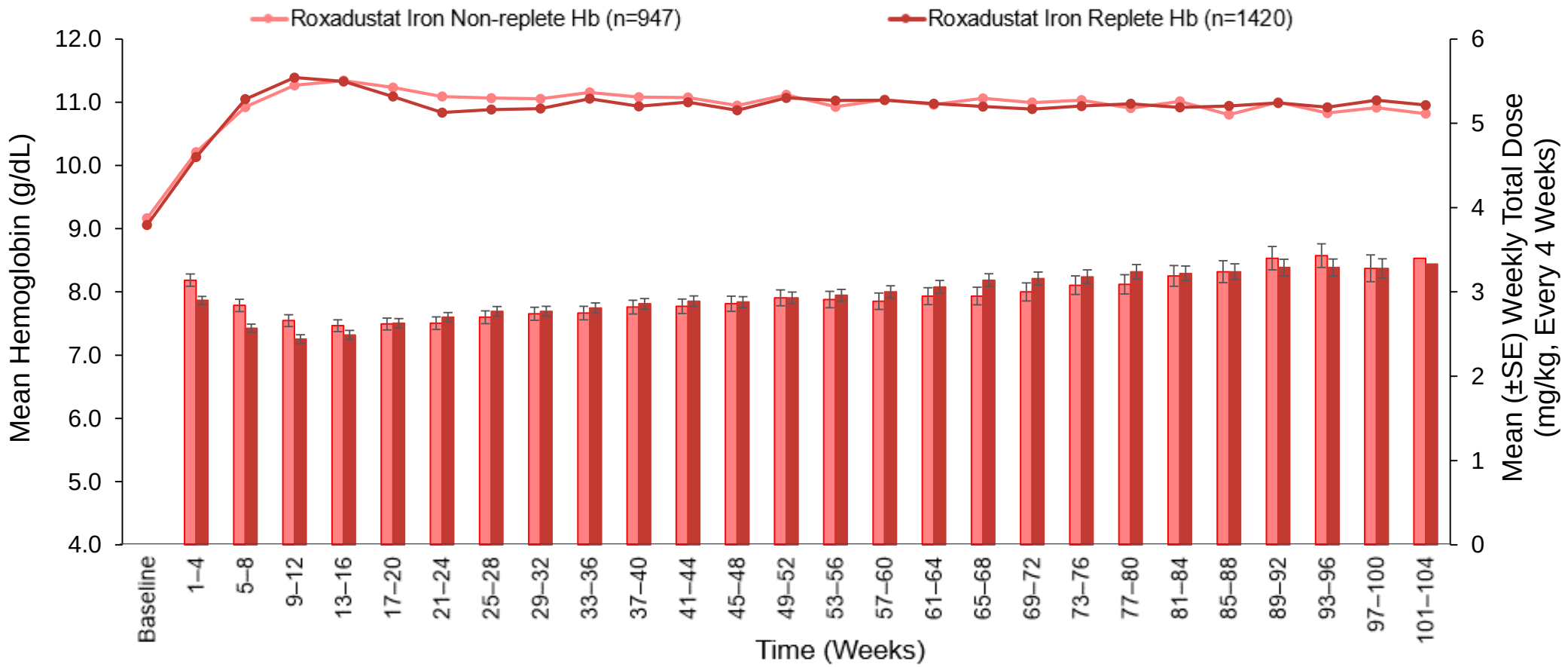
Demographics & Baseline Characteristics (2 of 2)

	Roxadustat (N=2367)		Placebo (N=1862)	
	Iron Non-replete (n=947)	Iron Replete (n=1420)	Iron Non-replete (n=748)	Iron Replete (n=1114)
Baseline Hb (g/dL), n, (%)				
• <8	68 (7.2)	131 (9.2)	46 (6.1)	114 (10.2)
• ≥8	879 (92.8)	1289 (90.8)	702 (93.9)	1000 (89.8)
Baseline eGFR (mL/min/1.73 m^2)				
• n	947	1420	748	1114
• Mean (SD)	21.28 (12.531)	18.70 (10.729)	21.88 (12.558)	18.87 (11.044)
Serum hepcidin (µg/L)				
• n	670	960	431	656
• Mean (SD)	74.38 (80.399)	143.00 (106.158)	72.26 (72.003)	154.75 (111.940)
Baseline hs-CRP (mg/L), n, (%)				
• ≤ULN	442 (46.7)	771 (54.3)	305 (40.8)	549 (49.3)
• >ULN	274 (28.9)	249 (17.5)	180 (24.1)	175 (15.7)
• Missing	231 (24.4)	400 (28.2)	263 (35.2)	390 (35.0)
Baseline MCV (fL)				
• n	428	568	228	279
• Mean (SD)	94.66 (6.652)	96.53 (7.504)	95.41 (6.324)	95.93 (7.594)

Note: Iron replete: TSAT ≥20% and ferritin ≥100 ng/mL.

eGFR, estimated glomerular filtration rate; Hb, hemoglobin; hs-CRP, high-sensitivity C-reactive protein; MCV, mean corpuscular volume; SD, standard deviation; ULN, upper limit of normal.

Mean Absolute Hb Levels and Roxadustat Dose Over Time



- In the overall NDD-CKD population, mean Hb and average weekly total dose of roxadustat by every 4 weeks up to Week 104 were similar in both iron non-replete and iron replete patients at baseline.

Note: Iron Replete: TSAT ≥20% and ferritin ≥100 ng/mL.
Hb, hemoglobin; SE, standard error.

Change in Mean Hb by Baseline Iron Repletion Status in Roxadustat-treated Patients (ITT)

Study	Sample Size	Mean (SD) Baseline Hb (g/dL)	Adjusted LS Mean Change From Baseline in Hb
OLYMPUS (Study 001)[a]	• Overall = 1384 • Iron replete = 782 • Iron non-replete = 552	9.11 (0.73)	1.75 (0.03)[b] 1.71 (0.04)[b] 1.76 (0.05)[b]
ANDES (Study 060)	• Overall = 616 • Iron replete = 366 • Iron non-replete = 241	9.10 (0.75)	2.02 (0.04)[b] 1.98 (0.05)[b] 2.10 (0.07)[b]
ALPS[a] (Study 608)	• Overall = 391 • Iron replete = 204 • Iron non-replete = 187	9.08 (0.76)	1.99 (1.82, 2.16)[c] 1.97 (1.74, 2.20)[c] 1.99 (1.69, 2.29)[c]
Pooled	• Overall = 2391 • Iron replete = 1433 • Iron non-replete = 956	9.10 (0.74)	1.94 (0.02)[d] 1.94 (0.03)[d] 1.94 (0.03)[d]

- Changes in mean Hb (g/dL) from baseline were similar in both iron non-replete and iron replete patients at baseline across all three individual NDD-CKD studies.

[a]For 060 and 608 iron replete was defined as ferritin ≥100 µg/L and TSAT ≥20%, for 001, iron replete was defined as ferritin >100 µg/L and TSAT >20%

[b]LS mean change from baseline to average during Weeks 28–52 (±SE) in the ITT population for overall results; LS mean change from baseline to average during Weeks 28–36 (±SE) in the FAS population for baseline iron subgroup results.

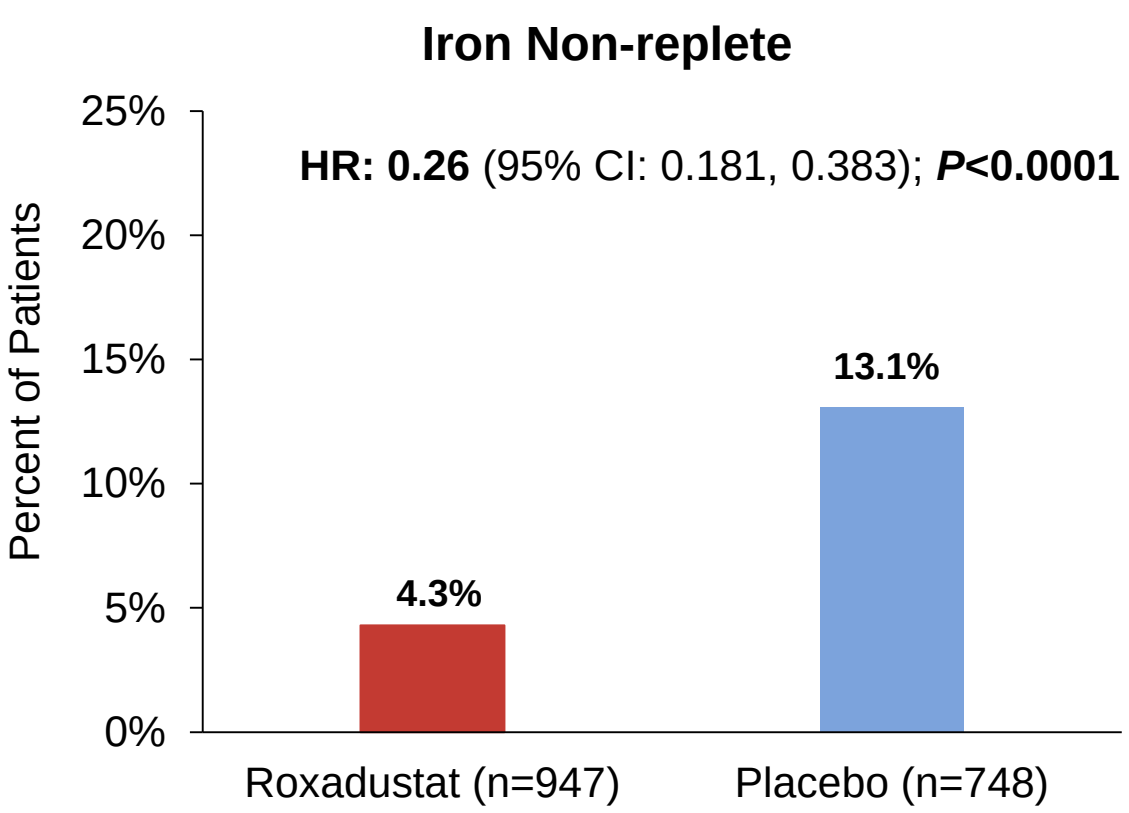
[c]LS mean change from baseline to average Hb during Weeks 28–36 (95% CI) in the all-randomized population.

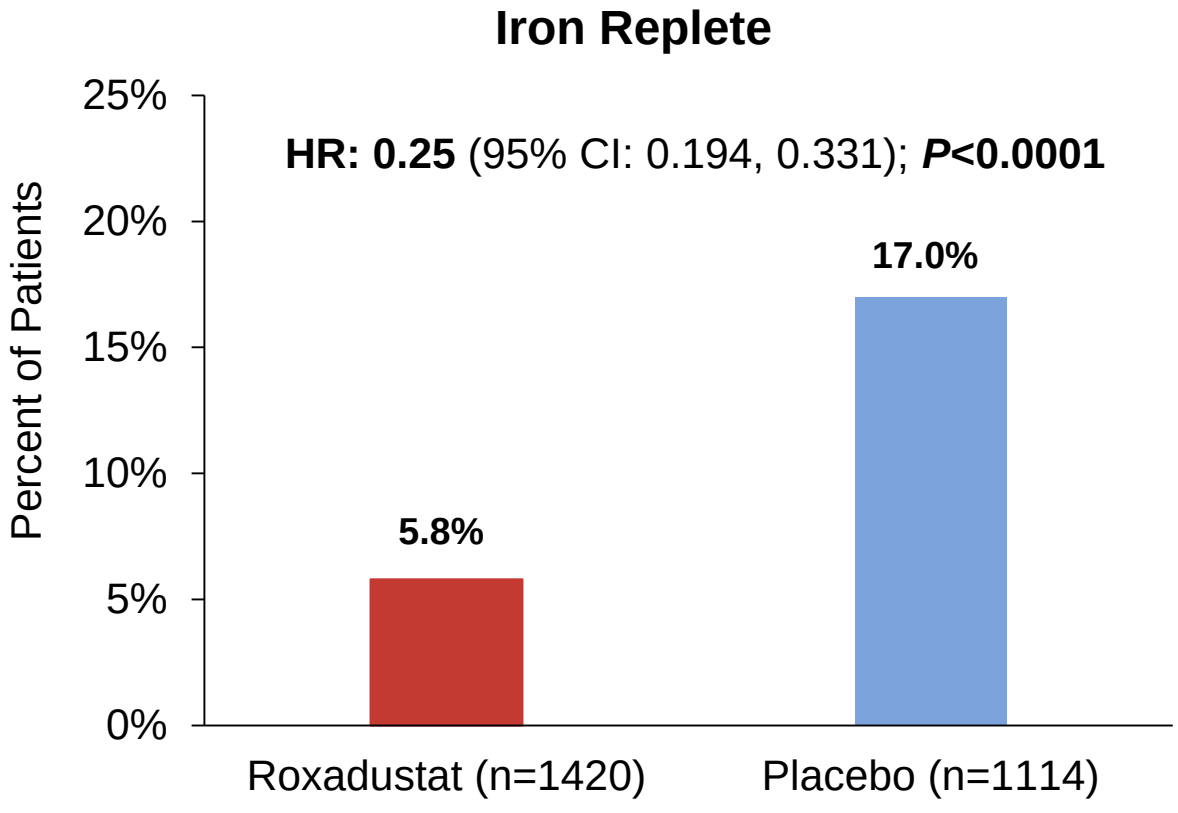
[d]LS mean change from baseline to average Hb during Weeks 28–52 (±SE) in the ITT population for overall and baseline iron subgroup results.

Note: LS mean was derived using the multiple imputation strategy by combining the results of the ANCOVA model with baseline Hb and baseline eGFR as covariates, and study, treatment, study-by-treatment interaction, region (US, Europe, Other), subgroup, subgroup-by-treatment interaction, and history of cardiovascular/cerebrovascular/thromboembolic diseases (yes vs no) as fixed effects.

ANCOVA, analysis of covariance; CI, confidence interval; FAS, full analysis set; Hb, hemoglobin; ITT, intent-to-treat; LS, least squares; SD, standard deviation.

Proportion of Patients With RBC Transfusion in the First 52 Weeks

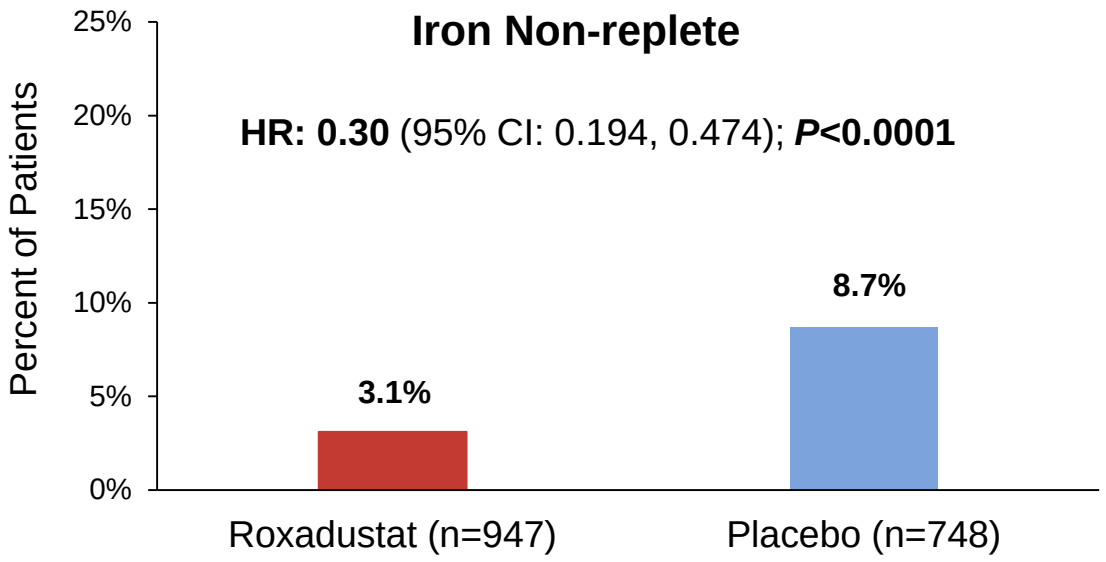


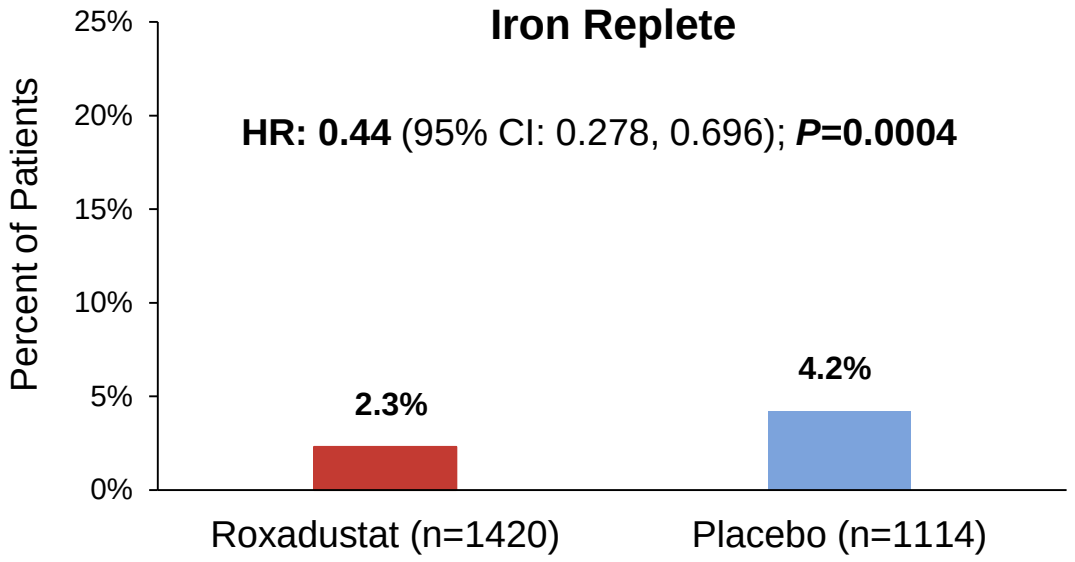


Note: *P* value was calculated from a stratified Cox proportional hazards model adjusting for baseline Hb, baseline eGFR, and treatment, stratified by study, baseline iron status, and history of cardiovascular/cerebrovascular/thromboembolic diseases (yes vs no). Iron Replete: TSAT ≥20% and ferritin ≥100 ng/mL.

CI, confidence interval; HR, hazard ratio; RBC, red blood cell.

Proportion of Patients With IV Iron Rescue in the First 52 Weeks





- In the overall NDD-CKD population, roxadustat significantly reduced the incidence of RBC transfusions and IV iron rescue therapy in the first 52 weeks compared with placebo in both iron non-replete and iron replete patients.
- Additionally, in roxadustat-treated patients, there was no clinically meaningful difference in the requirement for RBC transfusion or IV iron rescue among those who were iron replete vs non-replete.

Note: *P* value was calculated from a stratified Cox proportional hazards model adjusting for baseline Hb, baseline eGFR, and treatment, stratified by study, baseline iron status, and history of cardiovascular/cerebrovascular/thromboembolic diseases (yes vs no). Iron Replete: TSAT ≥20% and ferritin ≥100 ng/mL.

CI, confidence interval; HR, hazard ratio.

Conclusions

- Roxadustat increased and maintained Hb in patients with anemia of NDD-CKD using similar doses regardless of iron status at baseline.
- Further, roxadustat reduced the risk of RBC transfusions and IV iron rescue compared with placebo regardless of iron status at baseline.