Roxadustat Favorably Modifies Iron Indices in Patients With Non-Dialysis-Dependent Chronic Kidney Disease-Related Anemia

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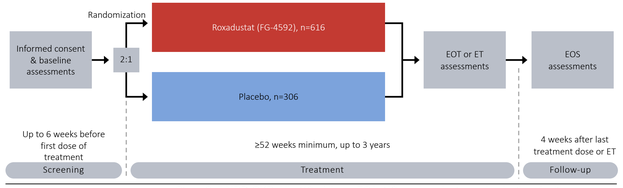
Introduction

- Roxadustat (FG-4592; ASP1517; AZD9941) is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that promotes erythropoiesis and improves iron availability.[1]
- Roxadustat is approved in China to treat anemia in patients with dialysis-dependent (DD) and non-dialysis-dependent (NDD) chronic kidney disease (CKD), and in Japan for DD-CKD.
- This pivotal phase 3 study explored the efficacy and safety of roxadustat in patients with NDD-CKD. In prior analyses, the overall exposure-adjusted safety profile of roxadustat was shown to be comparable to placebo and consistent with that expected in patients with CKD and anemia.
- Using data from this pivotal phase 3 study, we analyzed the impact of roxadustat on iron-related parameters.

Methods

- ANDES was a pivotal, phase 3, randomized, double-blind, placebo-controlled study of roxadustat in patients with NDD-CKD.
- Oral daily iron in addition to dietary intake was encouraged for all subjects unless not tolerated.
- Intravenous (IV) iron was considered rescue therapy and permitted only if the patient's Hb had not responded adequately AND ferritin was <100 ng/mL OR TSAT was < 20%.

ANDES (Study 060) Study Design



Key eligibility criteria	• Stage 3–5 NDD-CKD, Hb ≤10 g/dL, no ESA ≤12 weeks prior to randomization, ferritin ≥30 ng/mL, TSAT ≥5%, no RBCT ≤8 weeks
Mean drug exposure	• Roxadustat, 96.9 weeks • Placebo, 64.5 weeks

EOS, end of study; EOT, end of treatment; ESA, erythropoiesis-stimulating agent; ET, early termination; Hb, hemoglobin; NDD-CKD, non-dialysis-dependent chronic kidney disease; RBCT, red blood cell transfusion; TSAT, transferrin saturation.

- Demographics, baseline characteristics, and mean change from baseline (CFB) in Hb averaged over Weeks 28–52, regardless of rescue therapy, were evaluated using the intent-to-treat (all randomized patients) population, per the United States Food and Drug Administration.
- Mean CFB in iron parameters (eg, serum ferritin, transferrin saturation [TSAT], iron) and serum hepcidin at each scheduled time point up to Week 52 were evaluated using the full analysis set (all randomized/enrolled patients who received ≥1 dose of study drug and had a baseline and ≥1 post-dose Hb assessment).

Baseline Characteristics

- A total of 922 patients with NDD-CKD were randomized to this pivotal phase 3 study (616 roxadustat and 306 placebo).
- Baseline characteristics were generally comparable between patients that received roxadustat vs placebo.
- At baseline, similar proportions of patients in both treatment arms were iron-replete (roxadustat, 60.6%; placebo, 55.6%) and had C-reactive protein levels above the upper limit of normal (25.3% vs 26.5%). Mean estimated glomerular filtration rate was also comparable (21.9 vs 22.4 mL/min/1.73 m^2).

Demographics & Baseline Characteristics

	Roxadustat (n=616)	Placebo (n=306)
Age (years), n (%)		
18–64	271 (44.0)	146 (47.7)
65–74	192 (31.2)	79 (25.8)
≥75	153 (24.8)	81 (26.5)
Gender, n (%)		
Male	241 (39.1)	130 (42.5)
Female	375 (60.9)	176 (57.5)
Race group, n (%)		
Asian	310 (50.3)	151 (49.3)
Black	76 (12.3)	28 (9.2)
White	176 (28.6)	99 (32.4)
Other	54 (8.8)	28 (9.2)
Iron repletion status, n (%)		
TSAT ≥20% & ferritin ≥100 ng/mL	373 (60.6)	170 (55.6)
TSAT <20% or ferritin <100 ng/mL	241 (39.1)	134 (43.8)
Missing	2 (0.3)	2 (0.7)
Hb, mean (SD), g/dL	9.10 (0.75)	9.09 (0.69)
≤8	52 (8.4)	23 (7.5)
>8	564 (91.6)	283 (92.5)
eGFR, mean (SD), mL/min/1.73 m^2	21.9 (11.5)	22.4 (11.4)
LDL cholesterol, mean (SD), mg/dL	98.0 (39.1)	96.3 (40.0)
hs-CRP, n (%)		
≤ULN	457 (74.2)	223 (72.9)
>ULN	156 (25.3)	81 (26.5)
Missing	3 (0.5)	2 (0.7)

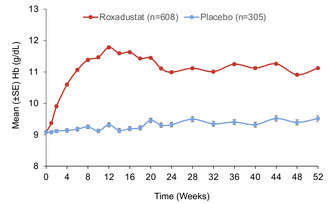
Data derived from the intent-to-treat population (all randomized patients).
eGFR, estimated glomerular filtration rate; Hb, hemoglobin; hs-CRP, C-reactive protein; LDL, low-density lipoprotein; SD, standard deviation; TSAT, transferrin saturation; ULN, upper limit of normal.

Results

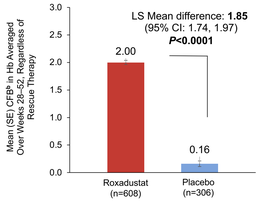
Mean Hb From Baseline to Week 52, Regardless of Rescue Therapy

A.

Hb (g/dL)	Roxadustat	Placebo
BL,[a] mean (SD)	9.09 (0.75)	9.09 (0.69)



B.



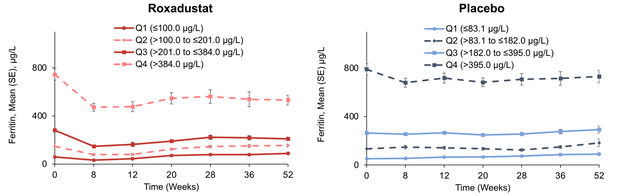
[a]Baseline Hb was defined as the mean of up to four of the last central laboratory values prior to the first dose of study treatment. [b]Data are observed plus imputed.
Figure A: analyses performed on the full analysis set (all randomized patients who received ≥1 dose of study drug and had a baseline and ≥1 post-dose Hb assessment).
Figure B: analyses performed on the intent-to-treat population (all randomized patients). Treatment comparison was made using the multiple imputation strategy by combining the results of ANCOVA 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/1.73m^2), as fixed effects.
ANCOVA, analysis of covariance; BL, baseline; CFB, change from baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; LS, least squares; SE, standard error.

- At all post-baseline time points, mean Hb levels were greater in patients with NDD-CKD administered roxadustat vs placebo.
- The mean (± standard deviation [SD]) Hb CFB over Weeks 28–52, regardless of rescue therapy, was 2.00 (0.95) g/dL for roxadustat vs 0.16 (0.90) g/dL for placebo (least squares [LS] mean standard error [SE] difference: 1.85 [0.059]; *P*<0.0001)
- Roxadustat-treated patients received lower mean (SD) dose (mg) of IV iron per patient-exposure month (roxadustat: 0.89 [7.45] vs placebo: 4.60 [28.75]); LS mean (SE) difference: -2.00 (0.79); *P*=0.0114.

Mean Levels Over Time for (A) Serum Hepcidin, (B) Serum Ferritin, (C) Serum Iron, and (D) TSAT, (E) Reticulocyte Hb Content (CHr), and (F) Total Iron Binding Capacity (TIBC)

- **Hepcidin:** Roxadustat-treated patients experienced a reduction in serum hepcidin as early as week 4, while hepcidin levels remained approximately stable in the placebo arm. Mean (±SD) changes from baseline to Week 44 for roxadustat and placebo were −22.11 (80.90) and +3.88 (80.93) µg/L, respectively (LS mean [SE] difference: −25.71 [6.53]; *P*<0.0001).
- **Ferritin:** Mean serum ferritin values decreased from baseline up to Week 52 for roxadustat, but remained approximately stable for placebo. Mean (±SD) changes from baseline to Week 44 for roxadustat and placebo were −48.43 (252.39) and +6.53 (167.89) ng/mL, respectively (LS mean [SE] difference: −57.54 [17.96]; *P*=0.0014).
- **Iron:** In roxadustat-treated patients, mean serum iron levels initially decreased from baseline up to Weeks 4–8 and then gradually increased above baseline and plateaued after Week 20. Mean serum iron levels remained approximately stable for placebo. Mean (±SD) changes from baseline to Week 44 for roxadustat and placebo were 12.63 (37.85) and 3.53 (28.51) µg/dL, respectively (LS mean [SE] difference: 8.26 [2.74]; *P*=0.0026).
- **TIBC:** By Week 44, there was a significant mean increase in TIBC among patients administered roxadustat (+35.07 µg/dL) and a small mean decrease among those administered placebo (−3.58 µg/dL). The LS mean (SE) difference was 38.65 (3.46) µg/dL (*P*<0.0001).
- **TSAT:** Mean serum TSAT (a mathematical ratio of iron and TIBC) initially decreased from baseline up to Weeks 4–8 for roxadustat and then gradually increased and plateaued after Week 20. Mean TSAT remained approximately stable for placebo. Mean (±SD) changes from baseline to Week 44 for roxadustat and placebo were 1.13% (13.42) and 1.12% (10.71), respectively (LS mean [SE] difference: −0.12 [0.94]; *P*=0.90).
- **CHr:** Among roxadustat-treated patients, reticulocyte Hb content initially decreased, but returned to baseline levels at Week 20 and gradually increased above baseline up to Week 52. The LS mean (SE) difference at Week 44 between treatments was 0.24 (0.13) pg (*P*=0.07).
- **MCV:** Mean (±SD) changes from baseline to Week 44 in mean corpuscular volume for roxadustat and placebo were 2.13 (5.31) and 0.65 (4.11) fL, respectively. The corresponding values for mean corpuscular Hb concentration were −0.28 (1.52) and −0.14 (1.35) g/dL.

Mean Serum Ferritin From Baseline to Week 52 by Baseline Serum Ferritin Quartiles



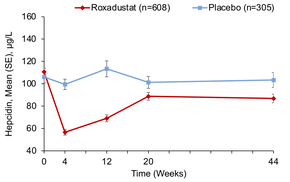
Q1	152	143	139	135	124	121	107
Q2	155	142	141	136	134	126	120
Q3	149	132	134	127	128	121	116
Q4	151	139	137	133	127	124	115

Q1	77	72	67	63	57	53	45
Q2	76	70	65	57	50	47	41
Q3	76	69	66	61	54	50	40
Q4	76	66	64	57	56	48	40

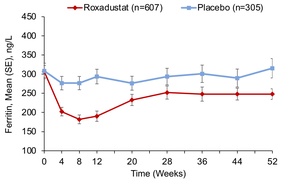
Analyses performed on the full analysis set (all randomized patients who received ≥1 dose of study drug and had a baseline and ≥1 post-dose Hb assessment).
Hb, hemoglobin; Q, quartile; SE, standard error.

- In the ferritin subgroups, mean serum ferritin levels initially decreased in the roxadustat subgroups up to Weeks 8-12 and remained lower than levels in the corresponding placebo subgroups over 52 weeks, except for the Q1 subgroup whose baseline ferritin was ≤100 ng/mL where serum ferritin levels were similar between treatment arms starting at week 20.

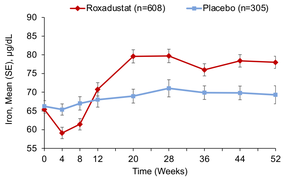
Hepcidin (µg/dL)	Roxadustat	Placebo
BL, mean (SD)	110.66 (79.08)	106.11 (90.68)



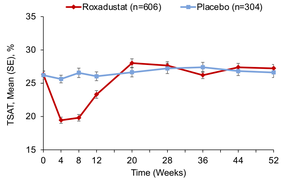
Ferritin (ng/L)	Roxadustat	Placebo
BL, mean (SD)	306.89 (388.48)	308.39 (352.51)



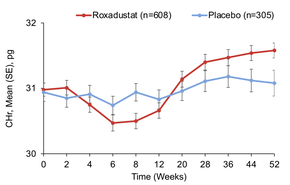
Iron (µg/dL)	Roxadustat	Placebo
BL, mean (SD)	65.54 (25.33)	66.26 (26.02)



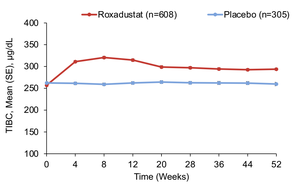
TSAT (%)	Roxadustat	Placebo
BL, mean (SD)	26.31 (10.84)	26.21 (11.30)



CHr (pg)	Roxadustat	Placebo
BL, mean (SD)	30.98 (2.47)	30.94 (2.42)



TIBC (µgd/L)	Roxadustat	Placebo
BL, mean (SD)	257.18 (50.51)	262.30 (49.64)



Analyses performed on the full analysis set (all randomized patients who received ≥1 dose of study drug and had a baseline and ≥1 post-dose Hb assessment).
BL, baseline; CHr, reticulocyte hemoglobin content; Hb, hemoglobin; SD, standard deviation; SE, standard error; TIBC, total iron binding capacity; TSAT, transferrin saturation.

Conclusion

- Roxadustat increases Hb and mean corpuscular volume without causing clinically significant changes in traditional markers of iron stores, ferritin, and TSAT as compared with placebo.
- Roxadustat increased both serum iron and transferrin, resulting in the long-term clinical stability of TSAT while increasing the absolute amount of iron available for erythropoiesis.
- Roxadustat was administered, encouraging the use of oral iron and without the routine use of IV iron.
- These findings suggest that iron is efficiently absorbed and mobilized for erythropoiesis during anemia correction and Hb maintenance in roxadustat-treated patients with NDD-CKD.

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

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