Subgroup Analyses of Efficacy of Roxadustat for Treatment of Anemia in Patients With Non-Dialysis-Dependent Chronic Kidney Disease

Daniel W. Coyne,[1] Mohamed A. El-Shahawy,[2] Roberto Pecoits-Filho,[3,4] Hakan M. Gürcan,[5] Tyson T. Lee,[5] Elise Hardy,[6] and Peony Yu[5]

[1]Washington University School of Medicine, St. Louis, MO, USA; [2]Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; [3]Arbor Research Collaborative for Health, Ann Arbor, MI, USA; [4]School of Medicine, Pontifical Catholic University of Paraná, Paraná, Brazil; [5]FibroGen, Inc., San Francisco, CA, USA; [6]AstraZeneca, Gaithersburg, MD, USA

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.
- To explore the similarity or consistency of treatment effects, clinically relevant subgroups of patients with NDD-CKD were selected on the basis of demographic, disease, and clinical (including important comorbid) characteristics.

Methods

- Pooled 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.
- Data from clinically relevant subgroups were analyzed for mean change from baseline (CFB) in hemoglobin (Hb) averaged over Weeks 28–52 regardless of rescue therapy (primary US Food and Drug Administration [FDA] efficacy endpoint), Hb response rate for the first 24 weeks censoring for rescue therapy (primary EU European Medicines Agency [EMA] efficacy endpoint), proportion of patients who received rescue therapy, and proportion of patients who received red blood cell (RBC) transfusion in the first 52 weeks.
- Treatment-emergent adverse events (TEAE) were monitored.

Summary of Study Design: NDD Studies

	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; NDD, non-dialysis-dependent; TSAT, transferrin saturation; wk, weeks.

- Demographics, baseline characteristics, and change in mean Hb from baseline were evaluated using the intent-to-treat (ITT; all randomized patients) population, as per FDA. Patients (%) with Hb response and rescue treatment (RBC transfusions, erythropoiesis-stimulating agent [ESA] use, and intravenous [IV] iron administration) were analyzed using the full analysis set (FAS; all randomized patients who received ≥1 dose of study drug and had baseline and ≥1 post-dose Hb assessment) per EMA.
- Efficacy analysis, ITT: treatments compared by combining analysis of covariance (ANCOVA) results from a multiple imputation method for missing Hb values, adjusted for baseline Hb and estimated glomerular filtration rate (eGFR) as covariates, and study, treatment, study-by-treatment interaction, region, and history of cardiovascular (CV) diseases as fixed effects.
- Efficacy analysis, FAS: incidence rate difference (95% confidence interval [CI]) for the first 24 treatment weeks was computed using a Cochran–Mantel–Haenszel (CMH) test. Response was defined as Hb ≥11.0 g/dL and Hb increase from baseline ≥1.0 g/dL, if baseline Hb >8.0 g/dL, or an Hb increase of ≥2.0 g/dL if baseline Hb ≤8 g/dL. Hb values under the influence of rescue therapy were censored for up to 6 weeks.
- Rescue treatment analysis, FAS: incidence rate (95% CI) difference was determined for incidence and risk of RBC transfusion using a Cox proportional hazards model.
- Safety was evaluated using the safety analysis set (all patients who received study drug).
- All analyses were performed using SAS® Version 9.1.3 or higher.

Baseline Characteristics

- In total, 4277 patients with NDD-CKD were randomized to treatment (2391 roxadustat and 1886 placebo).
- Baseline characteristics were generally well-balanced between treatment groups.

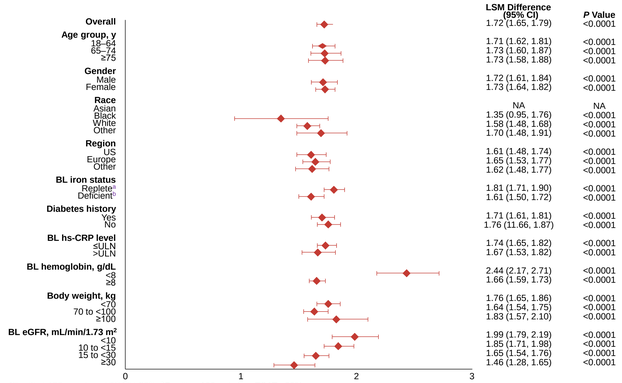
Demographics & Baseline Characteristics, ITT

	Roxadustat (n=2391)	Placebo (n=1886)
Age, mean (SD), years	61.9 (14.1)	62.7 (14.0)
Age group, n (%)		
18–64	1292 (54.0)	986 (52.3)
65–74	621 (26.0)	484 (25.7)
≥75	478 (20.0)	416 (22.1)
Sex, n (%)		
Female	1417 (59.3)	1054 (55.9)
Race group, n (%)		
Asian	863 (36.1)	689 (36.5)
Black	198 (8.3)	146 (7.7)
White	1134 (47.4)	892 (47.3)
Other	196 (8.2)	159 (8.4)
Diabetes history, n (%)		
Yes	1337 (55.9)	1096 (58.1)
Hb, mean (SD), g/dL	9.1 (0.74)	9.1 (0.73)
<8, n (%)	204 (8.5)	164 (8.7)
≥8, n (%)	2187 (91.5)	1722 (91.3)
eGFR, mL/min/1.73 m^2		
Mean (SD)	19.7 (11.6)	20.0 (11.8)
Median (min–max)	16.9 (1.6–68.2)	17.0 (2.6–75.2)
Serum hepcidin, μg/L		
n	1635	1087
Mean (SD)	114.7 (102.0)	122.0 (106.0)
Median (min–max)	87.8 (0.8-705.3)	97.6 (1.0-803)
Baseline hs-CRP, n (%)		
≤ULN	1222 (51.1)	855 (45.3)
>ULN	526 (22.0)	357 (18.9)
Missing	643 (26.9)	674 (35.7)
MCV, fL		
n	1002	508
Mean (SD)	95.69 (7.2)	95.68 (7.0)
Median (min–max)	95.9 (66.4–122.0)	95.95 (68.7–112.5)
TSAT, %		
Mean (SD)	28.2 (11.9)	28.9 (12.4)
Median (min–max)	26.3 (0.0–100.0)	27.0 (2.0–98.0)
Ferritin, mean (SD), ng/mL	263.2 (295.34)	266.3 (444.6)
<100, n (%)	657 (27.5)	523 (27.7)
100–< 400, n (%)	1286 (53.8)	1017 (53.9)
≥400, n (%)	446 (18.7)	345 (18.3)

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

Results

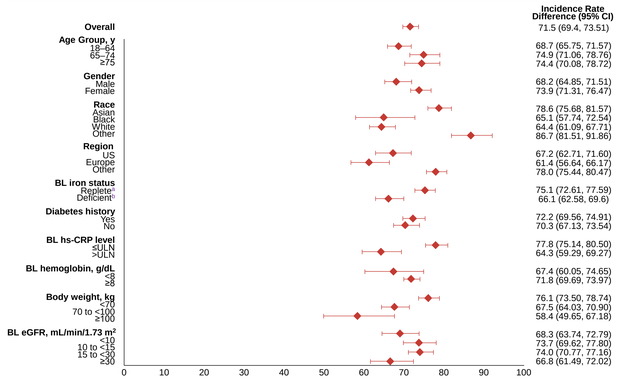
Mean CFB in Hb (g/dL) Averaged Over Weeks 28–52, ITT



[a]Ferritin ≥100 ng/mL and TSAT ≥20%. [b]Ferritin <100 ng/mL or TSAT <20%.
BL, baseline; CFB, change from baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate; hs-CRP, C-reactive protein; NA, not applicable; TSAT, transferrin saturation; ULN, upper limit of normal.

- Mean (SD) CFB in Hb averaged over Weeks 28–52, regardless of rescue therapy, was 1.85 (0.94) vs 0.13 (1.01) g/dL in the roxadustat and placebo groups, respectively (least squares mean [LSM] difference: 1.72 [95% CI: 1.65, 1.79; *P*<0.0001]).
- The results of all subgroup analyses were consistent with the result of primary efficacy analysis for the FDA.

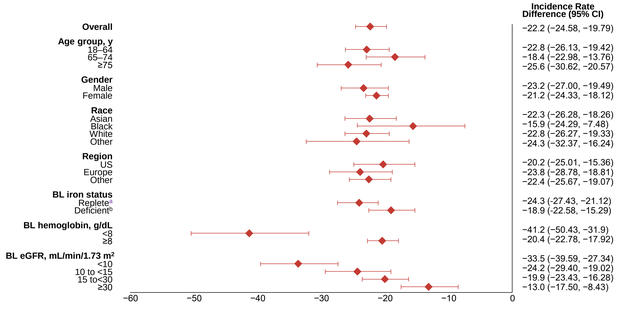
Hb Response, First 24 Weeks, FAS



[a]Ferritin ≥100 ng/mL and TSAT ≥20%. [b]Ferritin <100 ng/mL or TSAT <20%.
BL, baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set; hs-CRP, high-sensitivity C-reactive protein; TSAT, transferrin saturation; ULN, upper limit of normal.

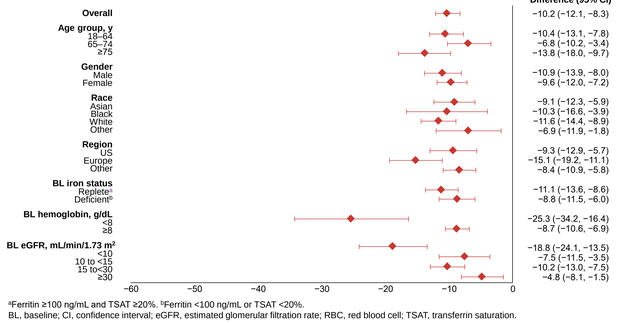
- A significantly larger percentage of roxadustat-treated patients showed an Hb response in the first 24 weeks of treatment compared with placebo-treated patients (80.2% vs 8.7%; *P*<0.001) (incidence rate difference: 71.5 [95% CI: 69.4, 73.5]).
- The results of all subgroup analyses were consistent with the results of primary efficacy analyses for EMA.

Rescue Treatment in the First 52 Weeks, FAS



[a]Ferritin ≥100 ng/mL and TSAT ≥20%. [b]Ferritin <100 ng/mL or TSAT <20%.
BL, baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set; TSAT, transferrin saturation.

RBC Transfusions in the First 52 Weeks, FAS



[a]Ferritin ≥100 ng/mL and TSAT ≥20%. [b]Ferritin <100 ng/mL or TSAT <20%.
BL, baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate; RBC, red blood cell; TSAT, transferrin saturation.

- The percentage of patients that received an RBC transfusion during the first 52 weeks of treatment was 5.2% for roxadustat vs 15.4% for placebo, respectively (incidence rate difference: −10.2 [95% CI: −12.1, −8.3]).
- Subgroup analyses of all rescue treatments and RBC transfusions alone in the first 52 weeks were consistent with the primary analysis results. Roxadustat significantly reduced the need for rescue therapy use and RBC transfusions in the NDD-CKD population up to Week 52 compared with placebo, particularly in patients with baseline Hb <8 g/dL and baseline eGFR <10 mL/min/1.73 m^2.

Adverse Event Summary, OT+28

- The incidence of TEAEs was generally similar between the treatment groups. Overall, 89.4% of patients in the roxadustat group and 85.4% in the placebo group experienced at least 1 TEAE during the treatment period and within 28 days (OT+28) of the last dose of study medication.

Conclusion

- The efficacy of roxadustat vs placebo in achieving larger mean CFB in Hb level and reducing the overall number of patients receiving rescue therapy as well as RBC transfusions was consistent across a wide range of subgroups in the NDD-CKD population.

Disclosures: This study was sponsored and funded by FibroGen, Inc, AstraZeneca, and Astellas Pharma. Tracey Fine of FibroGen, Inc., provided medical writing support for this presentation. Editorial support was provided by Ashfield Healthcare Communications, which was funded by FibroGen, Inc. All authors met the ICMJE authorship criteria. No honoraria or payments were made for authorship. DWC has consulted for AstraZeneca, FibroGen, Fresenius Medical Care-Renal Therapies Group, Otsuka Pharmaceutical, Reata Pharmaceuticals, and Vifor Pharma; and received research support from GlaxoSmithKline. MAE-S has received consulting fees and research support from AstraZeneca. RP-F has consulted for and received honoraria from Akebia Therapeutics, AstraZeneca, Fresenius Medical Care, Novo Nordisk, and Retrophin; and conducted studies funded by Amgen, AstraZeneca, Baxter, Bayer, Fresenius Medical Care, Janssen, and Lilly. HMG, TTL, and PY are employees of and hold stock in FibroGen, Inc. EH is an employee of and holds stock in AstraZeneca.
References: 1. Provenzano R, et al. *Am J Kidney Dis*. 2016;67(6):912–24.
Clinical Trial ID: NCT02174627, NCT01750190, and NCT01887600.

Presented: The American Society of Nephrology Kidney Week 2020; October 22–25, 2020.

To obtain a PDF of this poster:
- Scan the QR code or
- Visit: http://roxadustatscientificexhibit.com/abstracts4