The Effect of Roxadustat on Blood Pressure Relative to Placebo or Epoetin Alfa in the Phase 3 Trials

Tak Mao Chan,[1] Roberto Pecoits-Filho,[2,3] Anjay Rastogi,[4] Pablo E. Pergola,[5] Jacqueline G. Nolen,[6] Ming Zhong,[6] Lynda Szczech,[6] Kin-Hung P. Yu[6]

[1]University of Hong Kong, Queen Mary Hospital, Pok Fu Lam, Hong Kong SAR, China; [2]Arbor Research Collaborative for Health, Ann Arbor, MI, USA; [3]Pontificia Universidade Catolica do Parana Departamento de Medicina, Curitiba, PR, Brazil; [4]University of California at Los Angeles, Los Angeles, CA, USA; [5]Renal Associates, PA, San Antonio, TX, USA; [6]FibroGen, Inc., San Francisco, CA, 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.
- Hypertension is a common cause of CKD, and the prevalence of hypertension increases as CKD progresses.[2]
- Because erythropoiesis-stimulating agents have been associated with increases in blood pressure,[3] this analysis of pivotal phase 3 studies explored the hypertensive effects of roxadustat in patients with either NDD-CKD or DD-CKD.

Methods

- Data from three pivotal, phase 3, randomized, double-blind, placebo-controlled studies of roxadustat in patients with NDD-CKD and three pivotal, phase 3, open-label, epoetin alfa–controlled studies of roxadustat in patients with DD-CKD, including those new to dialysis (incident dialysis–dependent [ID]; on dialysis for ≤4 months) or on maintenance dialysis (stable dialysis–dependent [SDD]; on dialysis for >4 months) were assessed.

Summary of NDD-CKD Study Designs

	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, 50.96 wk

[a]In study 001, 20 patients were excluded from the statistical analysis because of system technical issues and major good clinical practice (GCP) violations. [b]In study 608, 3 patients were excluded from the statistical analysis because of GCP violations.
CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; mo, months; NDD, non-dialysis-dependent; RBCT, red blood cell transfusion; TSAT, transferrin saturation; wk, weeks.

Summary of DD-CKD Study Designs

	ROCKIES (Study 002)	SIERRAS (Study 064)	HIMALAYAS (Study 063)
Key eligibility criteria	• ID + stable DD (HD/PD) • Hb <12 g/dL if on ESA or Hb <10 g/dL if not on ESA for ≥4 wk before first visit • Ferritin ≥100 ng/mL • TSAT ≥20% • No RBCT ≤8 wk	• ID + stable DD (HD/PD) • Stable DD: Hb ≥9.0 to ≤12.0 g/dL; on ESA ≥8 wk • ID: Hb ≥8.5 to ≤12.0 g/dL; on ESA ≥4 wk • Ferritin ≥100 ng/mL • TSAT ≥20% • No RBCT ≤8 wk	• ID (HD/PD) • Hb ≤10 g/dL • On ESA ≤3 wk within the past 12 wk • Ferritin ≥100 ng/mL • TSAT ≥20% • No RBCT ≤8 wk
Randomized (N)	2133[a]	741	1043
Design	• 1:1 randomization • Open-label, active controlled • Roxadustat vs epoetin alfa	• 1:1 randomization • Open-label, active controlled • Roxadustat vs epoetin alfa	• 1:1 randomization • Open-label, active controlled • Roxadustat vs epoetin alfa
Mean drug exposure	• Roxadustat, 20.6 mo • Epoetin alfa, 23.2 mo	• Roxadustat, 88.1 wk • Epoetin alfa, 107.1 wk	• Roxadustat, 89.0 wk • Epoetin alfa, 96.0 wk

[a]In Study 002, 27 patients were excluded from the statistical analysis because of major good clinical practice violations or technical issues.
CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; DD, dialysis-dependent; Hb, hemoglobin; HD, hemodialysis; ID, incident dialysis; mo, months; PD, peritoneal dialysis; RBCT, red blood cell transfusion; TSAT, transferrin saturation; wk, weeks.

- Data in patients with NDD-CKD were censored after dialysis initiation (NDD-NDD).
- Demographics and baseline characteristics were evaluated using the intent-to-treat (all randomized patients) population.
- 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) was used to evaluate:
  - Mean change from baseline (CFB) in mean arterial pressure (MAP) averaged over Weeks 20–28 in patients with either NDD-NDD-CKD or SDD-CKD and over Weeks 8–12 in patients with ID-CKD.
  - Time to first exacerbation of hypertension (systolic blood pressure [SBP] ≥170 mmHg or diastolic blood pressure [DBP] ≥110 mmHg and an increase from baseline of ≥20 mmHg in SBP or ≥15 mmHg in DBP).
- Incidence rate of adjudicated hypertensive emergency (defined per Medical Dictionary for Regulatory Activities code) was analyzed using the safety analysis set (all patients who received study drug). Events were reported by treating physicians and adjudicated by an independent review committee.

Baseline Characteristics

Demographics & Baseline Characteristics: Patients With NDD-CKD

	Roxadustat (n=2391)	Placebo (n=1886)
Age (years), n (%)		
18–64	1292 (54.0)	986 (52.3)
65–74	621 (26.0)	484 (25.7)
≥75	478 (20.0)	416 (22.1)
Gender, n (%)		
Male	974 (40.7)	832 (44.1)
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)
Iron repletion status, n (%)		
TSAT ≥20% & ferritin ≥100 ng/mL	1433 (59.9)	1127 (59.8)
TSAT <20% or ferritin <100 ng/mL	956 (40.0)	755 (40.0)
Missing	2 (0.1)	4 (0.2)
eGFR, mean (SD), mL/min/1.73 m^2	19.7 (11.6)	20.0 (11.8)
MAP, mean (SD)	94.1 (8.7)	94.3 (8.7)
Receiving ACE inhibitor, n (%)	310 (13.0)	179 (9.5)
CVD, n (%)	763 (31.9)	611 (32.4)

Data derived from the intent-to-treat population (all randomized patients).
ACE, angiotensin-converting enzyme; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure; NDD-CKD, non-dialysis-dependent chronic kidney disease; SD, standard deviation; TSAT, transferrin saturation.

- Of the 4277 patients with NDD-CKD randomized in the three pivotal phase 3 studies, 4270 received study treatment and were evaluated in this analysis (2386 roxadustat and 1884 placebo).

Demographics & Baseline Characteristics: Patients With DD-CKD

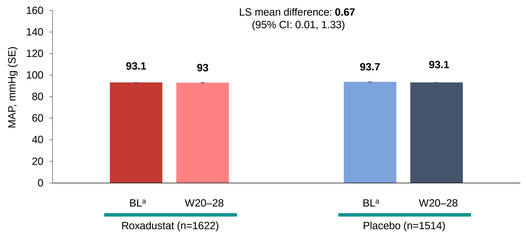
	ID-CKD		SDD-CKD	
	Roxadustat (n=760)	Epoetin Alfa (n=770)	Roxadustat (n=1183)	Epoetin Alfa (n=1177)
Age (years), n (%)				
18–64	570 (75.0)	584 (75.8)	862 (72.9)	836 (71.0)
65–74	132 (17.4)	129 (16.8)	222 (18.8)	219 (18.6)
≥75	58 (7.6)	57 (7.4)	99 (8.4)	122 (10.4)
Gender, n (%)				
Male	461 (60.7)	464 (60.3)	660 (55.8)	684 (58.1)
Female	299 (39.3)	306 (39.7)	523 (44.2)	493 (41.9)
Race group, n (%)				
Asian	116 (15.3)	127 (16.5)	156 (13.2)	137 (11.6)
Black	67 (8.8)	67 (8.7)	283 (23.9)	297 (25.2)
White	508 (66.8)	505 (65.6)	669 (56.6)	677 (57.5)
Other	69 (9.1)	71 (9.2)	75 (6.3)	66 (5.6)
Iron repletion status, n (%)				
TSAT ≥20% & ferritin ≥100 ng/mL	603 (79.3)	608 (79.0)	1087 (91.9)	1084 (92.1)
TSAT <20% or ferritin <100 ng/mL	155 (20.4)	162 (21.0)	92 (7.8)	89 (7.6)
Missing	2 (0.3)	0	4 (0.3)	4 (0.3)
MAP, mean (SD)	99.5 (10.3)	99.1 (10.1)	99.6 (11.3)	99.2 (11.4)
Receiving ACE inhibitor, n (%)	131 (17.2)	129 (16.8)	113 (9.6)	103 (8.8)
CVD, n (%)	290 (38.2)	291 (37.8)	548 (46.3)	547 (46.5)

Data derived from the intent-to-treat population (all randomized patients).
ACE, angiotensin-converting enzyme; CVD, cardiovascular disease; DD-CKD, dialysis-dependent chronic kidney disease; ID-CKD, incident dialysis–dependent chronic kidney disease; MAP, mean arterial pressure; SD, standard deviation; SDD, stable dialysis–dependent; TSAT, transferrin saturation.

- Of the 3890 patients with DD-CKD randomized in the three pivotal phase 3 studies, 3880 received study treatment and were evaluated in this analysis (1940 roxadustat and 1940 epoetin alfa). Of these, 1526 patients were new to dialysis (ID-CKD) and 2354 were on maintenance dialysis (SDD-CKD).

Results

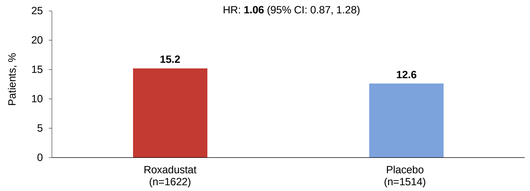
MAP (mmHg) in the NDD-NDD Population



[a]Baseline MAP was defined as the last MAP value prior to the first dose of study treatment.
Treatment comparison was made using a mixed model of repeated measurements with baseline Hb, baseline eGFR, and baseline MAP as covariates, and study, treatment, visit, visit-by-treatment interaction, study-by-treatment interaction, history of cardiovascular/cerebrovascular/thromboembolic diseases (yes vs no), and region (USA vs Europe vs other) as fixed effects. Analysis 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; CI, confidence interval; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; LS, least squares; MAP, mean arterial pressure; NDD-NDD, non-dialysis-dependent patients with data censored after dialysis initiation; SE, standard error; W, weeks.

- The mean (± standard deviation [SD]) MAP CFB over Weeks 20–28 in patients in the NDD-NDD population was 0.19 (8.54) mmHg for roxadustat vs −0.24 (8.24) mmHg for placebo (least squares [LS] mean [95% CI] difference: 0.67 [0.01, 1.33]); this difference was not considered clinically meaningful.

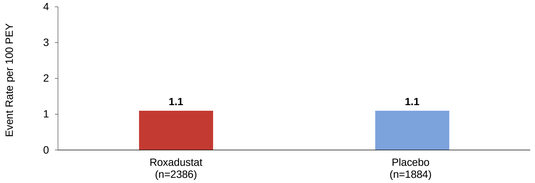
Incidence of and Time to First Exacerbation of Hypertension in the NDD-NDD Population



Treatment comparison was made using a Cox proportional hazards model adjusted for baseline Hb, baseline eGFR, baseline SBP, baseline DBP, study, treatment, region (USA vs Europe vs other), and history of cardiovascular/cerebrovascular/thromboembolic diseases (yes vs no). Analysis 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).
CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HR, hazard ratio; NDD-NDD, non-dialysis-dependent patients with data censored after dialysis initiation; SBP, systolic blood pressure.

- A total of 15.2% of patients in the NDD-NDD population administered roxadustat and 12.6% of those administered placebo experienced exacerbation of hypertension. The hazard ratio for time to first exacerbation of hypertension was 1.06 (95% CI: 0.87, 1.28).

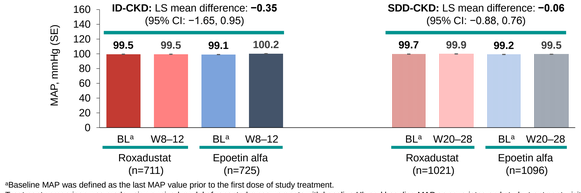
Adjudicated Hypertensive Emergency in the NDD-NDD Population



Data are follow-up–adjusted incidence rates which were calculated as follows: (100 × number of patients with the event)/PY, where PY is equivalent to (first event occurrence or censor date - first dose date + 1) / 365.25. Analysis performed on the safety analysis set (patients who received ≥1 dose of study drug) including on-treatment 28 day (treatment period and within 28 days of the last dose of study medicine) data plus long-term follow up.
NDD-NDD, non-dialysis dependent patients with data censored after dialysis initiation; PEY, patient exposure–years.

- In the NDD-NDD population, the follow-up adjusted incidence rate of adjudicated hypertensive emergency was 1.1 per 100 patient-years for both roxadustat and placebo.

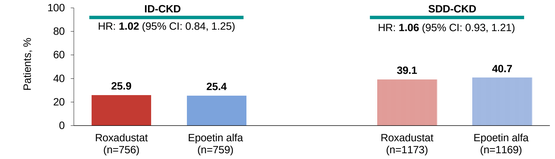
MAP (mmHg) in the DD Population



[a]Baseline MAP was defined as the last MAP value prior to the first dose of study treatment.
Treatment comparison was made using a mixed model of repeated measurements with baseline Hb and baseline MAP as covariates and study, treatment, visit, visit-by-treatment interaction, study-by-treatment interaction, and history of cardiovascular/cerebrovascular/thromboembolic diseases (yes vs no) as fixed effects. The comparison in the SDD-CKD population also included mean prescribed baseline epoetin alfa dose or equivalent (≤150 vs >150 IU/kg/week) as a fixed effect. 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; CI, confidence interval; Hb, hemoglobin; ID-CKD, incident dialysis-dependent chronic kidney disease; LS, least squares; MAP, mean arterial pressure; SE, standard error; SDD-CKD, stable dialysis–dependent chronic kidney disease; W, weeks.

- The mean (±SD) MAP CFB over Weeks 8–12 in ID-CKD patients was −0.05 (9.00) mmHg for roxadustat vs +1.0 (9.24) mmHg for epoetin alfa (LS mean [95% CI] difference: −0.35 [−1.65, 0.95]). The corresponding values over Weeks 20–28 for SDD-CKD patients were 0.01 (10.10) and 0.45 (10.06) mmHg, respectively (LS mean [95% CI] difference: −0.06 [−0.88, 0.76]).

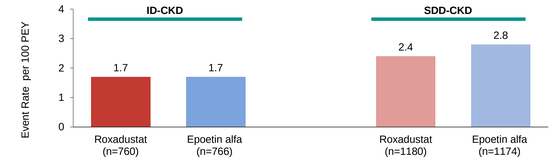
Incidence of and Time to First Exacerbation of Hypertension in the DD Population



Treatment comparison was made using a Cox proportional hazards model adjusted for baseline Hb, baseline SBP, baseline DBP, study, treatment, and history of cardiovascular/cerebrovascular/thromboembolic diseases (yes vs no). The comparison in the SDD-CKD population also adjusted for mean prescribed baseline epoetin alfa dose or equivalent (≤150 vs >150 IU/kg/week). 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). CI, confidence interval; DBP, diastolic blood pressure; Hb, hemoglobin; HR, hazard ratio; ID-CKD, incident dialysis–dependent chronic kidney disease; SBP, systolic blood pressure; SDD-CKD, stable dialysis–dependent chronic kidney disease.

- Among ID-CKD patients administered roxadustat vs epoetin alfa, the hazard ratio for time to first exacerbation of hypertension was 1.02 (95% CI: 0.84, 1.25). The corresponding value among SDD-CKD patients was 1.06 (95% CI: 0.93, 1.21).

Adjudicated Hypertensive Emergency in the DD Population



Data are the number of events per 100 PEY, which were calculated as follows: (100 × number of patients with the event)/PEY, where PEY is equivalent to (last dose date − first dose date + 1) / 365.25 days. Events reported during the treatment period and within 7 days of the last dose of study medication are captured. Analysis performed on the safety analysis set (patients who received ≥1 dose of study drug).
ID-CKD, incident dialysis–dependent chronic kidney disease; PEY, patient exposure–years; SDD-CKD, stable dialysis–dependent chronic kidney disease.

- In both ID-CKD and SDD-CKD patients, the exposure-adjusted incidence rates of adjudicated hypertensive emergency were similar for roxadustat and epoetin alfa.

Conclusion

- These pooled analyses of pivotal phase 3 data across a continuum of patients with CKD and anemia found no clinically meaningful effect of roxadustat on blood pressure, exacerbation of hypertension, or the incidence of adjudicated hypertensive emergency vs placebo in NDD-NDD patients or vs epoetin alfa in DD patients.

Disclosures: This study was sponsored and funded by FibroGen, Inc., AstraZeneca, and Astellas Pharma. Medical writing support for this presentation 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. TMC is an employee of the University of Hong Kong; has consulted for Novartis, Visterra, and UCB Biosciences; and received research funding from Astellas Pharma and Baxter. RP-F has consulted for and received honoraria from Akebia Therapeutics, AstraZeneca, Fresenius Medical Care, Novo Nordisk, and Retrophin; conducted studies funded by Amgen, AstraZeneca, Baxter, Bayer, Fresenius Medical Care, Janssen, and Lilly. AR has consulted for AstraZeneca and received research funding from AstraZeneca and GlaxoSmithKline. PEP received research support and consulting fees from AstraZeneca. JGN, MZ, LS, and KPY are employees of and hold stock in FibroGen, Inc.

References: 1. Provenzano R, et al. *Am J Kidney Dis*. 2016;67(6):912–24. 2. Rao MV, et al. *Am J Kidney Dis*. 2018;51(S2):S30–7. 3. Palmer SC, et al. *Cochrane Database Syst Rev*. 2014;2014(12):CD010590.

Clinical Trial ID: NCT02174627, NCT01750190, NCT01887600, NCT02174731, NCT02273726, and NCT02052310.

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/abstracts13