HIMALAYAS: A Phase 3, Randomized, Open-Label, Active-Controlled Study of the Efficacy and Safety of Roxadustat in the Treatment of Anemia in Incident-Dialysis Patients

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**Deceased*

Disclosures

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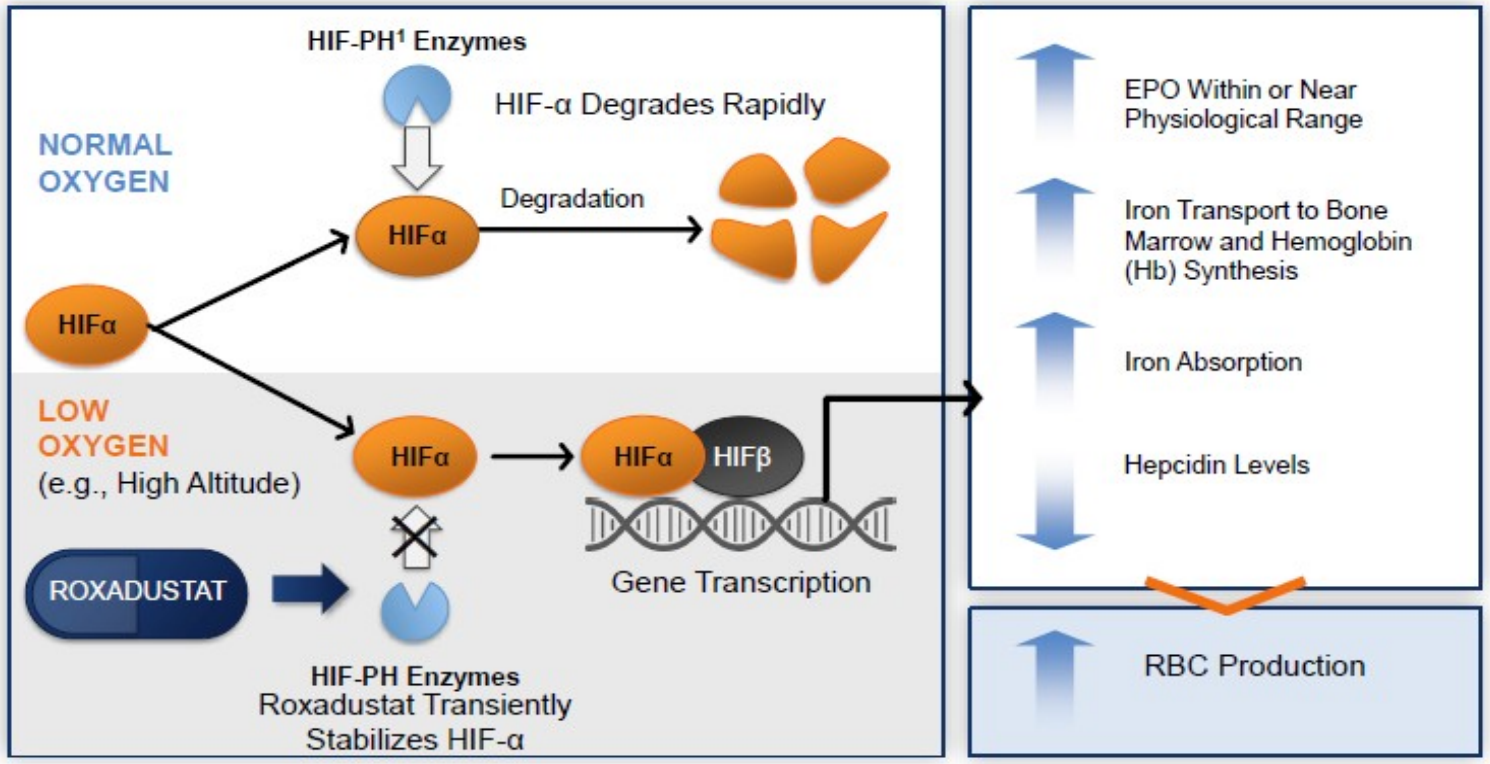
Vice President of Medical Affairs for DaVita.
Board of Directors for Nephroceuticals and Vasc-Alert

Study funding: FibroGen, AstraZeneca, Astellas

Roxadustat: Novel, First-in-class Treatment for CKD Anemia

- Roxadustat – oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI)
  - 2019 Nobel Prize winning science is the foundation of roxadustat
  - Increases hemoglobin (Hb) by mimicking the body's natural response to low oxygen
  - Studied for treatment of anemia in Stage 3 to 5 CKD patients, both on and not on dialysis
  - Approved in China: (dialysis 12/2018, not on dialysis 8/2019) and Japan: (on dialysis 9/2019)



2019 Nobel Prize In Physiology or Medicine

"for their discoveries of how cells sense and adapt to oxygen availability."

Awarded jointly to:

William G. Kaelin Jr.
Harvard University

Gregg L. Semenza
Johns Hopkins University

Peter J. Ratcliffe
Francis Crick Institute
London

[1]hypoxia-inducible factor prolyl hydroxylase (HIF-PH)

Background & Study Objective

- Phase 3 studies conducted in China and reported in *NEJM* suggest that roxadustat is efficacious and well tolerated in both dialysis-dependent (DD) and non-dialysis dependent (NDD) chronic kidney disease (CKD) patients with anemia[1-2]

- The primary objective of this Phase 3 US/EU study was to evaluate efficacy and safety of roxadustat in the treatment of CKD anemia in incident-dialysis (ID) patients vs. active control (epoetin alfa)

1. Chen et al. *N Engl J Med.* 2019; 381:1011–1022;
2. Chen et al. *N Engl J Med*. 2019; 381:1001–1010. DD, dialysis-dependent; CKD, chronic kidney disease,
 EU, European Union; HIF, hypoxia-inducible factor; ID, incident-dialysis; NDD, non-dialysis dependent, US, United States.

Roxadustat in HIMALAYAS: A Study in Incident Dialysis

Evaluate Anemia Treatment Starting Early Period of Chronic Dialysis Treatment (2 weeks to ≤4 months of dialysis initiation) & Continue for Long Term Safety Evaluation

Incident Dialysis (ID) Patients are Highly Vulnerable

- Experiencing high rates of morbidity and mortality especially as they transition through the first year of dialysis, therefore, studying the safety and efficacy of roxadustat in this subgroup is important

Enhanced generalizability given the lack of a selection bias

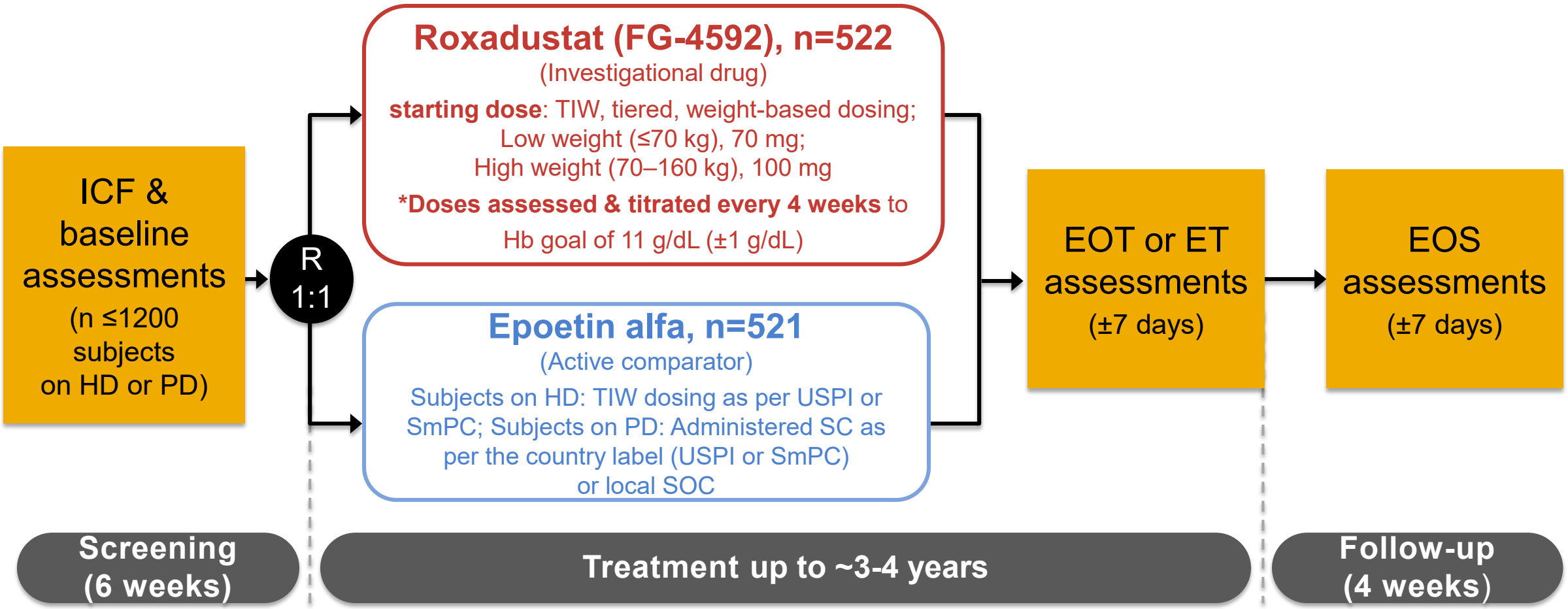
- Including a broader range of patients on dialysis, not only the previously ESA-exposed stable dialysis patient pool of "EPO and dialysis survivors."

Comparison Starting At Initial Exposure to Both Agents (Roxa & Epoetin) in Dialysis Patients

- Given that incident dialysis patients are generally ESA-naïve; roxadustat or epoetin alfa arms start treatment at the same time vs. conversion studies.

EPO, epoetin alfa; ESA, erythropoiesis-stimulating agent; ID, incident dialysis

Design: Phase 3, Multicenter, Randomized, Open-Label



*Detailed dose titration instructions similar to SIERRA study posters SA-PO227; EOS, end of study; EOT, end of treatment; ET, early termination; HD, hemodialysis; ICF, informed consent form; IV, intravenous, PD, peritoneal dialysis, SC, subcutaneous, SmPC, summary of product characteristics; SOC, standard of care; TIW, three times a week; USPI, US Package Insert;

HIMALAYAS Study Design

Key Eligibility Criteria

- ESRD receiving dialysis for 2 weeks to ≤4 months
- Baseline hemoglobin (Hb) ≤10.0 g/dL
- On ESA ≤3 weeks in the 3 months prior to screening

Primary Efficacy Endpoints

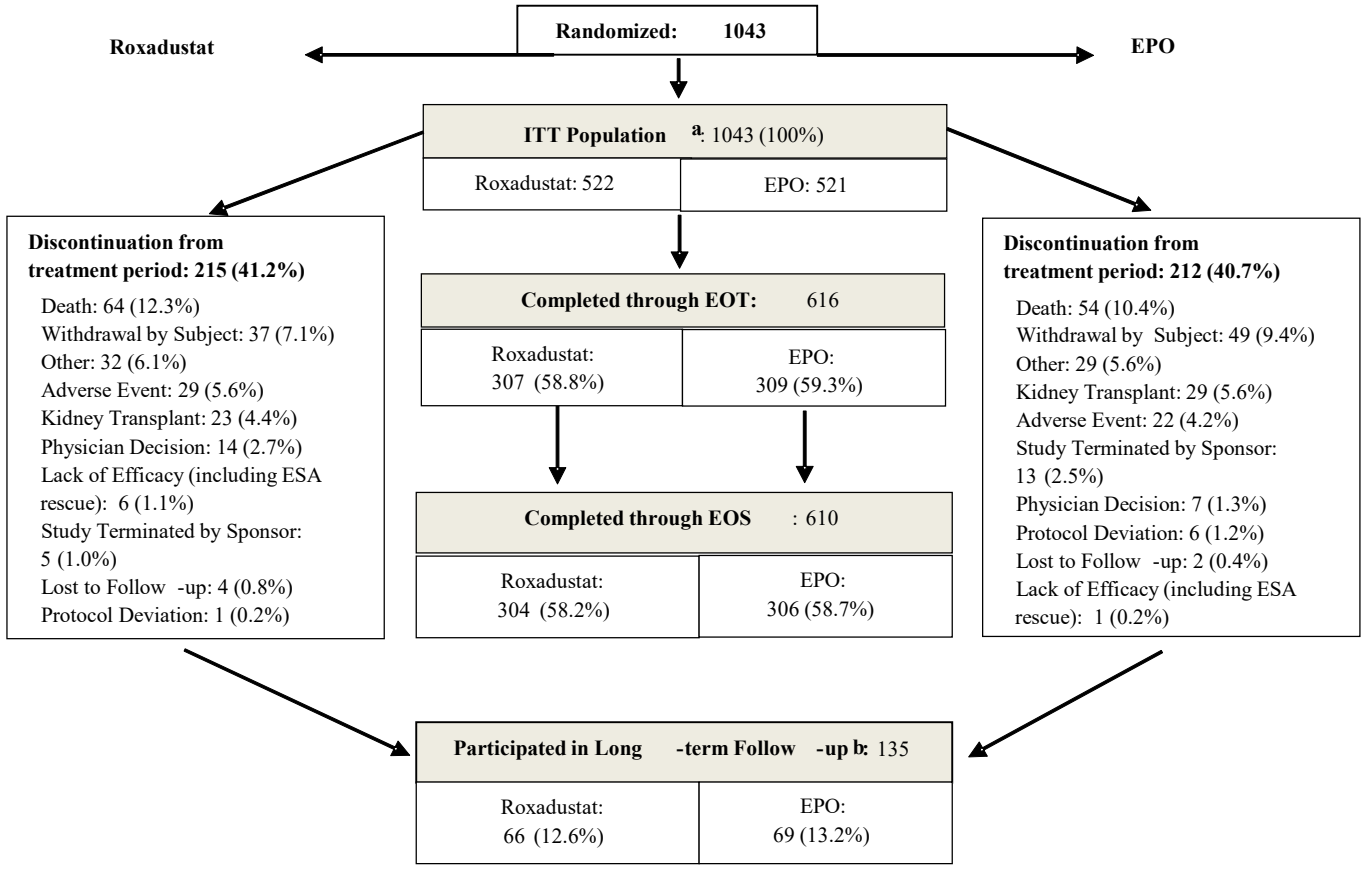
- Mean change from baseline (CFB) in Hb over weeks 28–52
- Proportion achieving an Hb response at 2 consecutive visits during the first 24 weeks (without rescue therapy for the 6 weeks prior to the assessment)
  - Hb response: Hb ≥11.0 g/dL + Hb increase from baseline (BL) by ≥1.0 g/dL (BL Hb >8.0 g/dL), or increase from BL by ≥2.0 g/dL (BL Hb ≤8.0 g/dL)

CV Safety Endpoint Analyses

- HIMALAYAS pooled with other roxadustat phase 3 dialysis studies for analyses of CV safety

BL, baseline; CFB, change from baseline; CV, cardiovascular; ESA, erythropoiesis-stimulating agent; ESRD, end-stage renal disease; Hb, hemoglobin; ID, incident dialysis

HIMALAYAS Patient Disposition



EOS = end of study; EOT = end of treatment; EPO = epoetin alfa; ESA = erythropoiesis -stimulating agent ; ITT = intent -to-treat; LTFU = long -term follow -up

Note: The percentage is calculated based on the number of randomized subjects.

a The ITT population included all randomized/enrolled subjects.

b Subjects who discontinued from study and participated in LTFU were followed for cardiovascular events of interest, vital status, and hospitalizations until EOS.

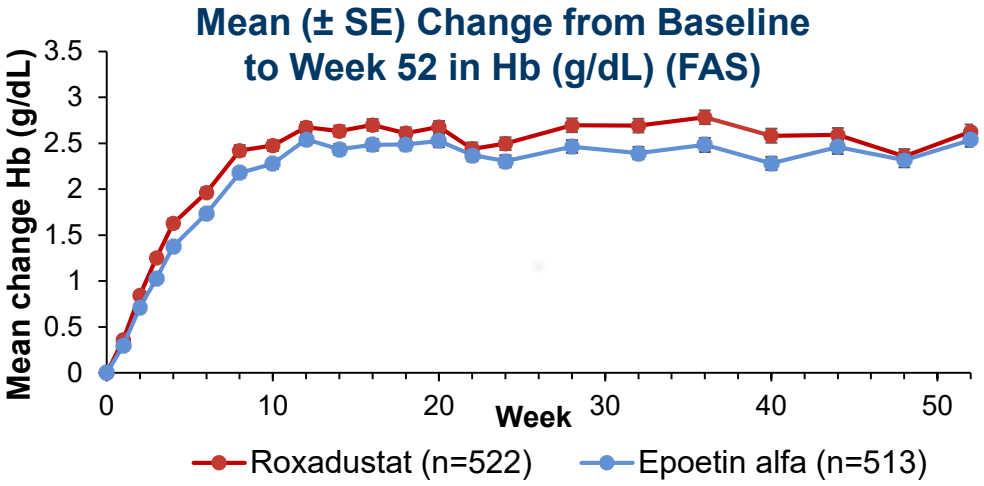
HIMALAYAS: Balanced Demographic & Baseline Values for Roxadustat vs Epoetin Alfa-Treated ID Subjects

	Roxadustat (N=522)	Epoetin alfa (N=521)
Age (years), mean (SD)	53.8 (14.74)	54.3 (14.55)
Sex, n (%)		
Male	309 (59.2)	307 (58.9)
Female	213 (40.8)	214 (41.1)
Diabetes, n (%)		
Type 1	22 (4.2)	25 (4.8)
Type 2	183 (35.1)	179 (34.4)
Dialysis modality, n (%)		
Hemodialysis	469 (89.8)	462 (88.7)
Peritoneal Dialysis	53 (10.2)	58 (11.1)
Hemoglobin (g/dL), mean (SD)	8.43 (1.044)	8.46 (0.964)
≤8.0 g/dL	166 (31.8)	157 (30.1)
>8.0 g/dL	356 (68.2)	364 (69.9)
CRP, n (%)†		
≤ULN	289 (55.4)	289 (55.5)
>ULN	228 (43.7)	226 (43.4)
ESA naïve (%)	93.7	93.9
CV history, n (%)	141 (27.0)	149 (28.6)
Ferritin (ng/mL), mean (SD)	441 (337.0)	437 (311.4)
TSAT (%), mean (SD)	27.02 (9.3)	27.56 (8.9)

- **Severe Anemia ~30% Hb <8.0 g/dL at baseline**
- **Long Treatment Duration**
  - up to **~3 years**;
  - average duration was **>1.5 years** (89 weeks)

*Iron replete defined as ferritin >100 µg/L and transferrin saturation >20%. †Epoetin alfa dialysis modality and CRP totals <100% due to missing data for some patients CRP, C-reactive protein; CV, cardiovascular; SD, standard deviation; TSAT, transferrin saturation; ULN, upper limit of normal

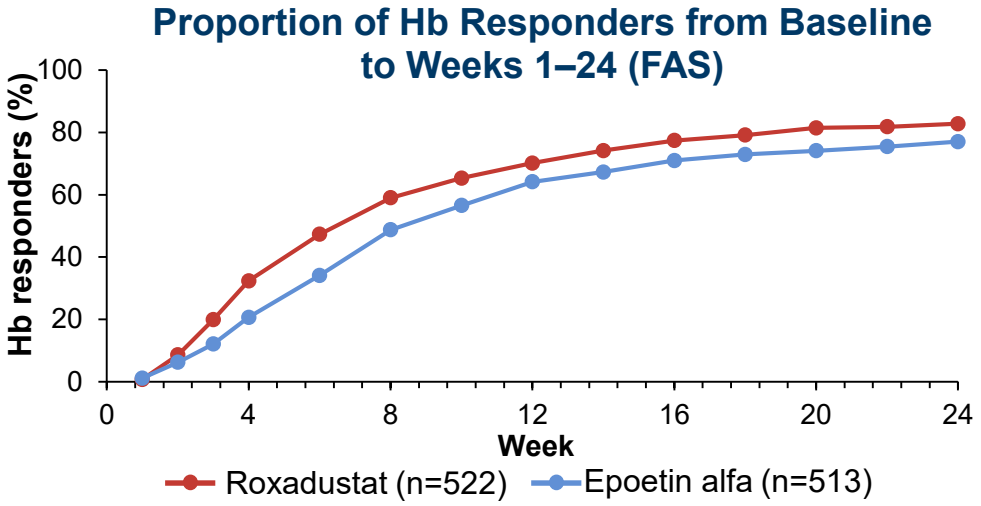
Roxadustat Met Primary Efficacy Hb Endpoints in Incident Dialysis



Mean change in Hb (g/dL) from BL to average over Weeks 28–52		LS mean difference (95% CI)
Roxadustat	2.57	0.18 g/dL (0.079, 0.287)
Epoetin alfa	2.36	

Roxadustat was non-inferior to epoetin alfa*

Roxadustat was superior to epoetin alfa (*p=0.0005*)



Proportion of subjects who achieved an Hb response†		LS mean difference (95% CI)
Roxadustat	88.2%	3.5% (-0.7%, 7.7%)
Epoetin alfa	84.4%	

Roxadustat was non-inferior to epoetin alfa

(Noninferiority margin: -15%;)

*Lower bound noninferiority margin: -0.75 g/dL. Prespecified analysis.

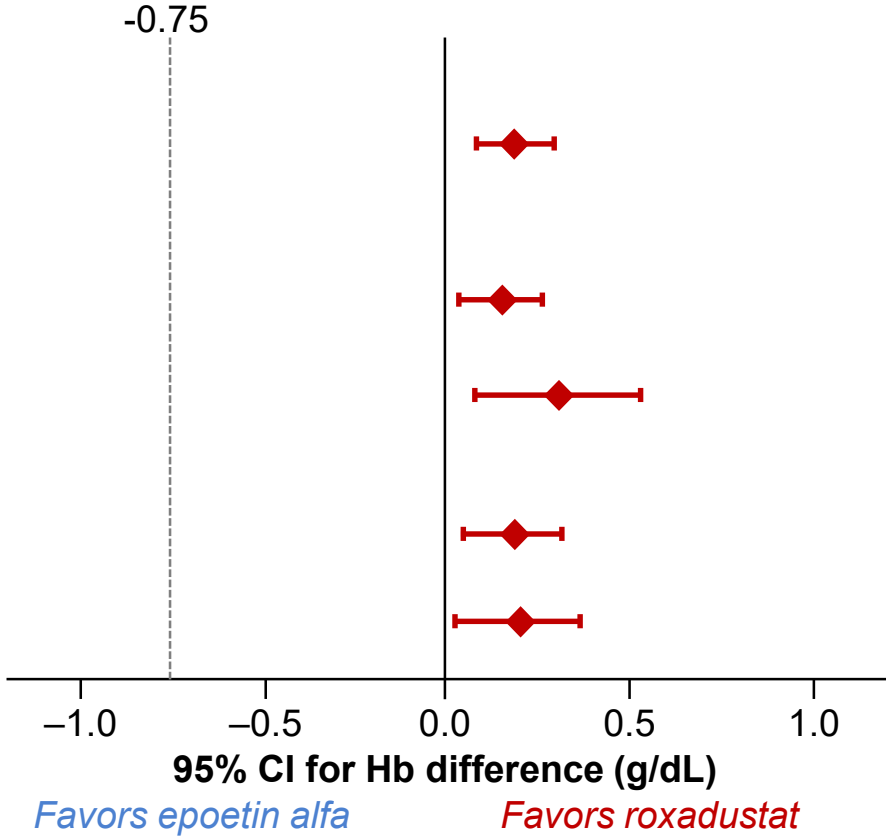
†Hb >11 g/dL and a Hb increase from baseline of 1 g/dL for baseline Hb >8 g/dL or 2 g/dL for baseline Hb <8 g/dL. BL, baseline; FAS, full analysis set; Hb, hemoglobin; LS, least squares

Roxadustat Efficacy Outcomes Were Not Affected by Baseline Iron Status or Inflammation Status

Subgroup Analyses of the Primary Efficacy Outcomes: Results Favor Roxadustat Over Epoetin alfa

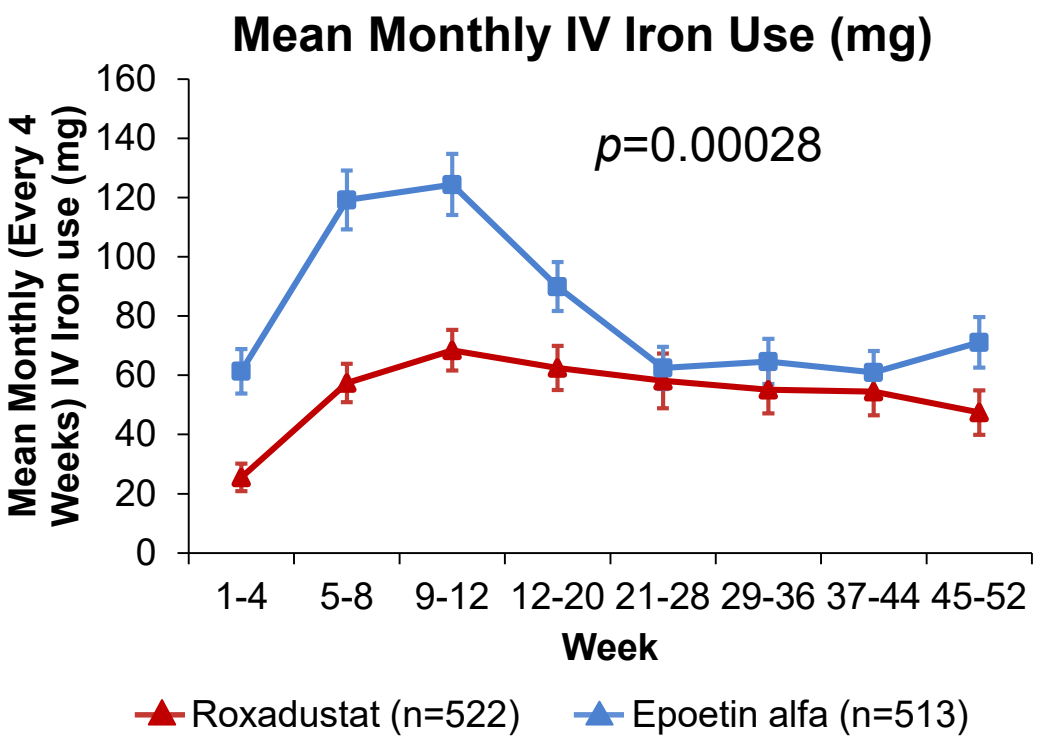
Roxadustat was superior to epoetin alfa in clinically relevant patient subsets consistent with the primary analysis

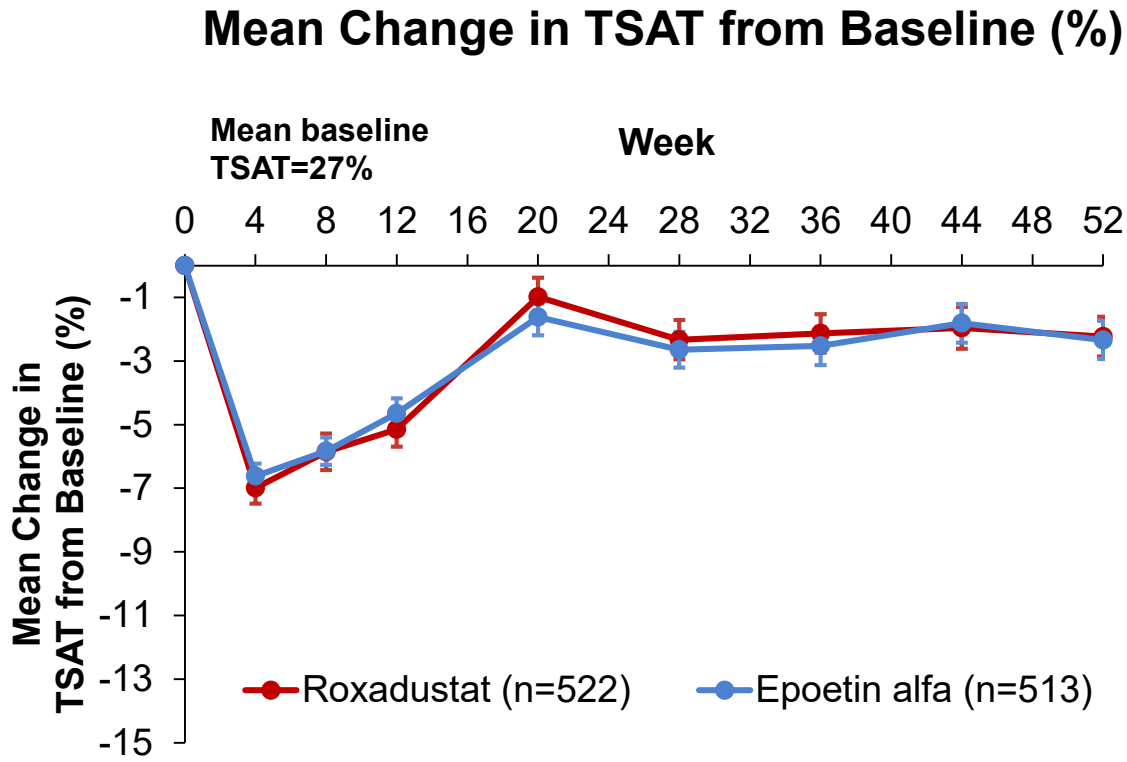
Subgroup/Value	Treatment difference* Estimate (95% CI)
Overall	**0.18 (0.079, 0.287)**
Iron repletion status	
Ferritin ≥100 ng/mL and TSAT ≥20%	0.15 (0.032, 0.266)
Ferritin <100 ng/mL or TSAT <20%	0.31 (0.084, 0.537)
CRP category†	
≤ULN	0.18 (0.045, 0.312)
>ULN	0.19 (0.021, 0.355)



*Treatment difference calculated with LS Means. †ULN is 4.9 µg/L. -0.75 mg/dL defines the prespecified threshold for the lower bound to establish non-inferiority. CI, confidence interval; CRP, C-reactive protein; SD, standard deviation; TSAT, transferrin saturation; ULN, upper limit of normal

Roxadustat Treatment Required Less IV Iron While Achieving Similar Levels of Iron Repletion





12 PEM, Patient Exposure Month; TSAT, transferrin saturation

Treatment Emergent Adverse Events

Overview

	Roxadustat (N=522)	Epoetin Alfa (N=517)
Any TEAEs, n (%)	450 (86.2)	441 (85.3)
Any TESAEs, n (%)	234 (44.8)	218 (42.2)
***Deaths, n (%)**	63 (12.1)	59 (11.4)

TEAEs reported in ≥5% of subjects in either arm

Preferred Term	Roxadustat (N=522)	Epoetin Alfa (N=517)
Hypertension	99 (19.0)	88 (17.0)
Diarrhea	72 (13.8)	38 (7.4)
Muscle spasms	60 (11.5)	39 (7.5)
Arteriovenous fistula thrombosis	59 (11.3)	46 (8.9)
Arteriovenous fistula site complication	31 (5.9)	43 (8.3)
Headache	57 (10.9)	44 (8.5)
Hypotension	54 (10.3)	35 (6.8)
Hyperphosphatemia	52 (10.0)	35 (6.8)
Nausea	45 (8.6)	30 (5.8)
Pneumonia	42 (8.0)	37 (7.7)
Constipation	34 (6.7)	23 (4.4)
Vomiting	32 (6.1)	17 (3.3)
Pruritus	30 (5.7)	22 (4.3)
Fluid overload	29 (5.6)	28 (5.4)
Cough	28 (5.4)	21 (4.1)
Dizziness	28 (5.4)	24 (4.6)
Procedural hypotension	26 (5.0)	31 (6.0)
Hyperkalemia	26 (5.0)	36 (7.0)
Hyperparathyroidism secondary	25 (4.8)	27 (5.2)
Back pain	18 (3.4)	27 (5.2)

AE, adverse event; TEAE, treatment-emergent adverse event reported during treatment+28 days post treatment followup; TESAE, treatment-emergent serious adverse event; *Deaths- Fatal TESAEs

Conclusions

Efficacy:

- Both primary efficacy endpoints were met
  - Roxadustat was non-inferior and superior to epoetin alfa in Hb change in incident dialysis patients
  - Roxadustat was non-inferior to epoetin alfa in the proportion of subjects achieving an Hb response
- Roxadustat was non-inferior to epoetin alfa among patients who were iron deplete and/or inflamed at baseline
- Roxadustat treatment reduces IV iron use while achieving similar levels of iron repletion

Safety:

- The safety profile of roxadustat in this study was consistent with results from prior roxadustat studies