

Roxadustat for anemia in patients with end-stage renal disease incident to dialysis

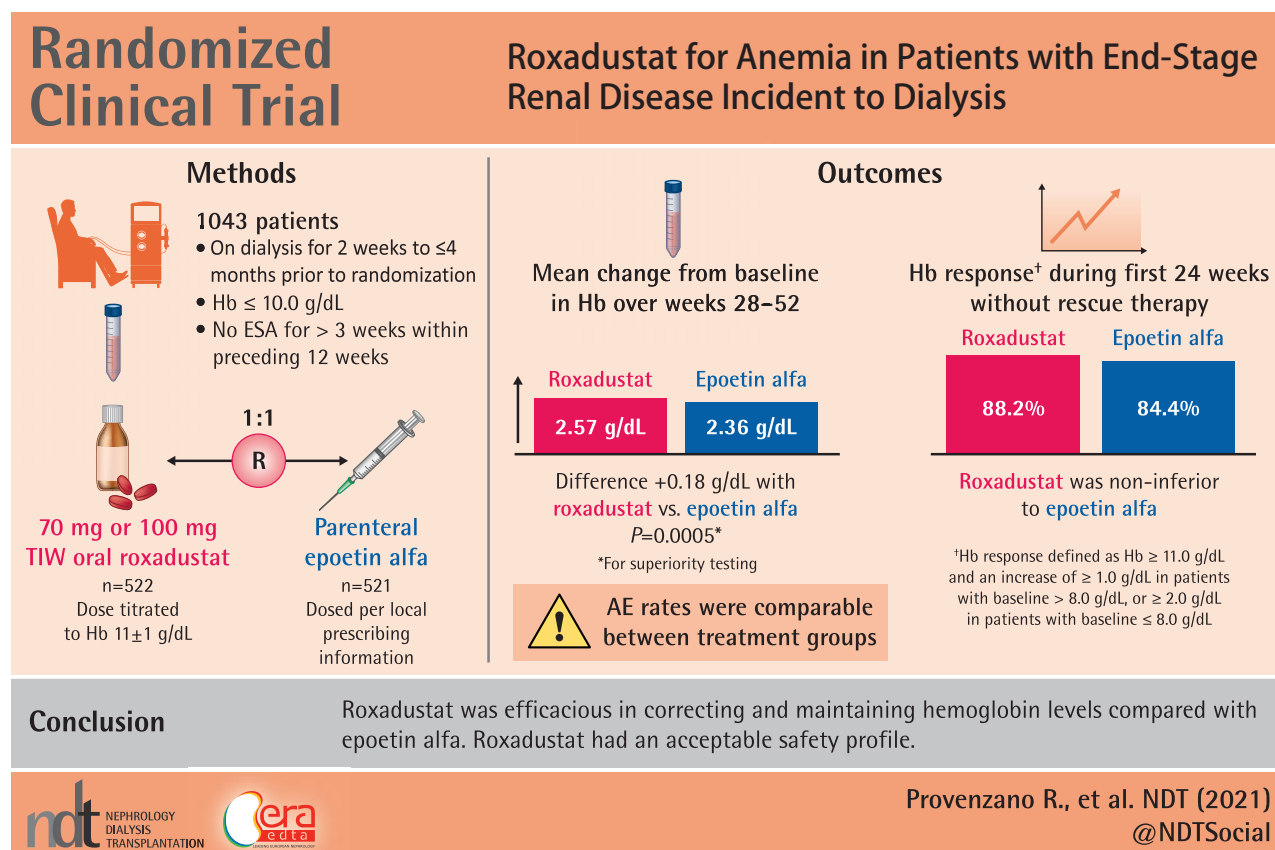
Robert Provenzano¹, Evgeny Shutov², Liubov Eremeeva³, Svitlana Korneyeva⁴, Lona Poole⁵, Gopal Saha⁵, Charles Bradley⁵, Meray Eyassu⁵, Anatole Besarab⁶, Robert Leong⁵, Cameron S. Liu⁵, Thomas B. Neff^{5,†}, Lynda Szczech⁵ and Kin-Hung P. Yu⁵

¹Wayne State University School of Medicine, Detroit, MI, USA, ²Botkins Hospital, Moscow, Russia, ³LLC Fresenius Medical Care Kuban, Krasnodar, Russia, ⁴Zaporizhzhya Regional Clinical Hospital, Zaporizhzhia, Ukraine, ⁵FibroGen Inc., San Francisco, CA, USA and ⁶Stanford University School of Medicine, Stanford, CA, USA

Correspondence to: Kin-Hung P. Yu; E-mail: roxadustat.author@fibrogen.com

[†]Deceased.

GRAPHICAL ABSTRACT



ABSTRACT

Background. We evaluated the efficacy and safety of roxadustat versus epoetin alfa for the treatment of chronic kidney disease-related anemia in patients new to dialysis.

Methods. HIMALAYAS was a Phase 3, open-label, epoetin alfa-controlled trial. Eligible adults were incident to hemodialysis/peritoneal dialysis for 2 weeks to ≤ 4 months prior to randomization and had mean hemoglobin (Hb) ≤ 10.0 g/dL. Primary endpoints were mean Hb (g/dL) change from baseline averaged over Weeks 28–52 regardless of rescue therapy [non-inferiority criterion: lower limit of 95% confidence interval (CI) for treatment difference > -0.75] and percentage of patients achieving an Hb response between Weeks 1 and 24 censored for rescue therapy (non-inferiority margin for between-group difference -15%). Adverse events were monitored.

Results. The intent-to-treat population included patients randomized to roxadustat ($n = 522$) or epoetin alfa ($n = 521$). Mean (standard deviation) Hb changes from baseline averaged over Weeks 28–52 were 2.57 (1.27) and 2.36 (1.21) in the roxadustat and epoetin alfa groups. Roxadustat was non-inferior [least squares mean difference: 0.18 (95% CI 0.08, 0.29)] to epoetin alfa. Percentages of patients with an Hb response were 88.2% and 84.4% in the roxadustat and epoetin alfa groups, respectively. Roxadustat was non-inferior to epoetin alfa [treatment-group difference 3.5% (95% CI -0.7% , 7.7%)]. Adverse event rates were comparable between treatment groups.

Conclusions. Roxadustat was efficacious for correcting and maintaining Hb levels compared with epoetin alfa. Roxadustat had an acceptable safety profile.

Keywords: anemia, dialysis, efficacy, roxadustat, HIF-PHI

ADDITIONAL CONTENT

An author video to accompany this article is available at: https://academic.oup.com/ndt/pages/author_videos.

INTRODUCTION

Chronic kidney disease (CKD) is a growing public health problem, with a global prevalence of $\sim 13\%$. The prevalence of anemia increases as CKD progresses, and is experienced by $> 90\%$ of patients on dialysis [1]. Globally, there were ~ 2.5 million patients on dialysis in 2016. In 2016, there were $> 124\,000$ newly reported cases of end-stage renal disease (ESRD) in the USA alone, with an incidence of 373/million/year [2]. Globally, it is estimated that 2 million people have kidney failure, with rates increasing 5–7% per year [3]. While the mortality rate for people requiring dialysis is more than an order of magnitude higher than the general population [4], it is highest among patients newly initiating dialysis (the incident population). Mortality rates during the first 2 months of dialysis are twice as high as rates 8–12 months later [5, 6]. Patients incident to dialysis require the highest doses of erythropoiesis-stimulating agents (ESAs), likely related to systemic inflammation [7]. To date, the impact of anemia therapies during this highly vulnerable time for patients on dialysis has not been studied in a clinical trial.

The pathogenesis of anemia is multifactorial, and impaired oxygen-dependent regulation of erythropoiesis contributes to inadequate erythropoietin production [8–10]. The standard of care for CKD-related anemia among patients requiring dialysis is treatment with an ESA, intravenous (IV) iron supplementation and/or red blood cell (RBC) transfusion [11]. ESAs correct anemia in patients with CKD; however, trials have shown that the use of ESAs to target normal or near-normal hemoglobin (Hb) levels increases cardiovascular (CV) disease risk [12–15], which led to safety warnings on ESA product labels [16]. During the past decade, this guidance has led to decreases in achieved Hb levels and increases in RBC transfusions [17]. These trends highlight the need for new therapies for CKD-related anemia.

In the past decade, the role of hypoxia-inducible factor (HIF), the body's main oxygen tension sensor [18], in mediating Hb response has been documented. Roxadustat (FG-4592) is a potent, reversible HIF prolyl hydroxylase (HIF-PH) inhibitor in development to treat CKD-related anemia [19]. HIF-PH enzymes modify HIF- α transcription factors, targeting them for degradation. Roxadustat prevents these enzymes from modifying HIF- α proteins, and stabilized HIF- α proteins dimerize with HIF- β to function as transcription factors that activate expression of erythropoietin and genes encoding proteins involved in iron metabolism [19–22]. Roxadustat transiently increases endogenous erythropoietin levels, with peak increases 8–12 h post-dose in healthy volunteers and patients with CKD [23]. Weight-based doses of roxadustat increase Hb in a dose-dependent manner and without the need for routine IV iron supplementation [19, 24–29]. Roxadustat also decreases cholesterol levels [19, 24–29]. Phase 3 trials of roxadustat led to its approval to treat anemia in non-dialysis-dependent and dialysis-dependent patients with CKD in China and Japan [26, 27, 30–32].

Clinically, it is important to study patients with CKD-related anemia incident to dialysis (ID-CKD), because anemia therapy may be started with the initiation of dialysis. This approach enables an unbiased comparison between roxadustat and the current standard of care in settings consistent with clinical practice. Moreover, patients with ID-CKD are generally ESA naïve, so both roxadustat and epoetin alfa groups started treatment at the same time and underwent dose titration. Because patients with ID-CKD have the highest mortality risk [29], they are a sample that does not exclude the highly vulnerable subgroups of patients that experience premature mortality. We report the results of HIMALAYAS (Safety and Efficacy Study for Treatment of Anemia in ESRD Newly Initiated Dialysis Patients), a Phase 3 trial comparing roxadustat versus epoetin alfa in patients with ID-CKD.

MATERIALS AND METHODS

Overall study design

HIMALAYAS was a randomized, open-label, active-controlled, Phase 3 trial evaluating the efficacy and safety of roxadustat for the treatment of CKD-related anemia in patients with ID-CKD in 19 countries in the USA, Europe, South America and Asia (NCT02052310). The protocol was approved by local

KEY LEARNING POINTS

What is already known about this subject?

- patients who newly initiate dialysis are a highly vulnerable subgroup with the greatest risk for morbidity and mortality during the first year on dialysis. Studying patients new to dialysis obviates the bias associated with studying only erythropoiesis-stimulating agent (ESA)-experienced patients on stable dialysis, who are most often studied;
- clinical evaluation of patients newly initiating dialysis allows assessment of the effects of roxadustat on the universe of patients affected by chronic kidney disease (CKD) before vintage (time on dialysis) modifies the cohort; and
- it is anticipated that most patients starting therapy on a newly approved agent would be patients not previously treated with an ESA, so the population newly initiating dialysis likely best represents the anticipated real-world population following approval of a novel agent.

What this study adds?

- this is the first study of a novel hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitor reporting the clinical outcomes for treatment of patients newly initiating dialysis with CKD-related anemia;
- in patients who have recently initiated dialysis, roxadustat was successful in increasing hemoglobin levels when compared with epoetin alfa; and
- roxadustat and epoetin alfa had comparable, acceptable safety profiles.

What impact this may have on practice or policy?

- the HIMALAYAS study was the pivotal trial submitted for US Food and Drug Administration and European Union European Medicines Agency approval of roxadustat for the treatment of CKD-related anemia in CKD patients; and
- if approved, roxadustat will be the first-in-class HIF-PH inhibitor for the treatment of CKD-related anemia, and will provide another treatment option.

regulatory authorities and/or ethics committees and was conducted in accordance with the tenets of the declaration of Helsinki [33] and with local regulatory and ethics requirements.

The sponsor (FibroGen) designed the trial, provided financial support and was responsible for data collection and analysis. All authors had full access to study data and analyses, approved the final draft of the manuscript and signed off on its accuracy. A FibroGen employee wrote the first draft of the manuscript. All authors reviewed the manuscript and vouched for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Study participants

Eligible patients were aged ≥ 18 years and were on hemodialysis or peritoneal dialysis for ESRD for 2 weeks to ≤ 4 months prior to randomization. Mean Hb level (from the last two predialysis screening assessments) was ≤ 10.0 g/dL. Patients who received ESAs for >3 weeks within the preceding 12 weeks at the time informed consent was obtained were excluded. A complete list of the inclusion and exclusion criteria is provided in [Supplementary data, Table S1](#). All patients provided written informed consent prior to study participation.

Randomization

Patients were randomly assigned (1:1) to open-label, oral roxadustat or parenteral epoetin alfa thrice weekly to the time of study completion. Randomization was performed centrally in sequence, stratified by geography (USA versus ex-USA);

baseline Hb levels (≤ 8.0 versus >8.0 g/dL) and CV, cerebrovascular and/or thromboembolic medical history. Automated randomization and treatment assignments were performed using an Interactive Voice and Web Response System. Details are provided in the [Supplementary data](#).

Interventions

Roxadustat was supplied by the sponsor; epoetin alfa was supplied from commercial sources as the standard of care. The starting dose of roxadustat was 70 mg (patients weighing ≤ 70 kg) or 100 mg (patients weighing >70 –160 kg). Epoetin alfa was dosed according to the country-specific product labeling [e.g. Package Insert, Summary of Product Characteristics ([Supplementary data, Table S2](#))]. Patients on hemodialysis were required to use IV epoetin alfa; patients on peritoneal dialysis were allowed to use subcutaneous epoetin alfa, at the discretion of the Investigator. A roxadustat-specific dosing algorithm was used to correct and maintain Hb level ([Supplementary data, Table S3](#)). The roxadustat algorithm was based on the cumulative dosing experience from previous Phase 2 studies with an expected population distribution for Hb of 11 ± 1 g/dL. The algorithm and dosing instructions in the local package labeling reflect past experience with ESAs and may not have the same Hb goal. Thus, overall treatment strategies, not drug doses, were compared. Scheduled visits were weekly for the first 4 weeks, every 2 weeks until Week 24 and then every 4 weeks until the end of treatment.

All patients were encouraged to take oral iron as the first-line iron supplementation; the dose and frequency were at the discretion of the Investigator. IV iron was allowed in both treatment groups if, in the opinion of the Investigator, the patient's Hb had not responded adequately, and the patient was considered iron deficient [i.e. ferritin <100 ng/mL and transferrin saturation (TSAT) <20%]. Treatment with study drug continued during IV iron administration and IV iron was discontinued once the patient was iron replete (defined as ferritin \geq 100 ng/mL and TSAT \geq 20% as per the US package insert for epoetin alfa) [16].

Rescue therapy included RBC transfusion, ESAs or a combination. For roxadustat-treated patients, the use of ESAs was not permitted unless the patient's Hb had not responded after two or more dose increases, if the maximum dose was reached, other causes for the lack of an Hb response were excluded and reduction of alloimmunization in transplant-eligible patients was a goal.

Outcomes

The primary US efficacy endpoint was mean Hb change from baseline to Weeks 28–52 regardless of rescue therapy. The primary European Union (EU) efficacy endpoint was the proportion of patients achieving an Hb response at two consecutive visits (\geq 5 days apart) during Weeks 1–24, censored for rescue therapy within 6 weeks of the Hb response. An Hb response was defined as achieving an Hb level \geq 11.0 g/dL with an increase from baseline \geq 1.0 g/dL (patients with baseline >8.0 g/dL) or \geq 2.0 g/dL (patients with baseline \leq 8.0 g/dL).

A key US secondary efficacy endpoint was the percentage of patients that achieved an Hb response at two consecutive visits (\geq 5 days apart) during the first 24 weeks of treatment without rescue therapy within 6 weeks of the Hb response. A key EU secondary efficacy endpoint was the mean Hb change from baseline averaged over Weeks 28–52 without rescue therapy within 6 weeks of and during Weeks 28–52 of treatment. For both, secondary efficacy endpoints included: mean change from baseline in low-density lipoprotein (LDL) cholesterol averaged over Weeks 12–24, mean change from baseline in Hb levels averaged over Weeks 18–24 in patients with baseline high-sensitivity C-reactive protein (hs-CRP) levels higher than the upper limit of normal (>ULN), mean monthly IV iron use per patient during Weeks 28–52, time to first transfusion during treatment, mean change in mean arterial pressure (MAP) averaged over Weeks 8–12 and time to first exacerbation of hypertension [i.e. systolic blood pressure (SBP) \geq 170 mmHg and SBP increase from baseline \geq 20 mmHg, or diastolic blood pressure (DBP) \geq 100 mmHg and DBP increase from baseline \geq 15 mmHg during Weeks 28–52].

Additional efficacy endpoints included measurements of hepcidin and iron indices at baseline and follow-up. Sensitivity analyses included subgroups categorized by important baseline demographic and clinical characteristics.

Safety measures included reported treatment-emergent adverse events (AEs) (TEAEs), treatment-emergent serious AEs (TESAEs), vital signs, electrocardiograms, clinical laboratory values and physical examinations. These were assessed during treatment and for 28 days after the last dose of study drug in the

safety population (SAF; all randomized patients who received one or more dose of study drug). If the treatment received was different from that randomly assigned, the treatment received was analyzed. Additionally, safety data for the pre-specified populations of all dialysis and incident dialysis patients in the roxadustat Phase 3 development program are in press [34] or are published elsewhere [35].

Statistical analysis

Details regarding the determination of sample size are provided in the [Supplementary data](#). The US primary efficacy endpoint analysis was conducted on the intent-to-treat (ITT) population (all randomized patients); secondary efficacy endpoint analyses were performed on the full analysis set (FAS; all randomized patients who received one or more dose of study drug and had one or more post-dose Hb assessment). For the EU primary and secondary efficacy endpoints, analyses were conducted on the FAS. Analyses for non-inferiority were conducted on the per-protocol set (PPS; all FAS patients who received \geq 8 weeks of treatment had one or more post-dose Hb assessment and were without major protocol violations).

For the primary efficacy analyses, a multiple imputation (MI) analysis of covariance (ANCOVA) model was used, including terms for treatment group, baseline Hb and stratification factors [except screening Hb (\leq 8.0 versus >8.0 g/dL)]. At least 600 patients provided \geq 99% power to assess non-inferiority of roxadustat versus epoetin alfa for the US primary efficacy endpoint, assuming a treatment group difference (roxadustat – epoetin alfa) of -0.30 g/dL, a non-inferiority margin for this difference of -0.75 g/dL and a standard deviation (SD) of 1.25 g/dL. For the EU primary efficacy endpoint, the study provided \geq 99% power to demonstrate statistical non-inferiority of roxadustat versus epoetin alfa, assuming an 80% response rate for both treatment groups and a non-inferiority margin of -15% for the between-group difference (roxadustat – epoetin alfa). Additional details are provided in the [Supplementary data](#).

The analyses of secondary efficacy endpoints were adjusted for multiple comparisons using fixed-sequence testing procedures ([Supplementary data, Table S4](#)). Analyses for the additional efficacy endpoints were not adjusted for multiple comparisons; P-values are provided for reference. Point estimates and 95% confidence intervals (CIs) without P-values are reported. All statistical analyses were performed using SAS[®] version 9.1.3 or higher. All statistical analyses were performed by the study sponsor.

RESULTS

Participants

The trial was conducted between February 2014 and September 2018. A total of 1043 patients were randomized (roxadustat = 522, epoetin alfa = 521). The percentages of patients that discontinued treatment were comparable in the roxadustat and epoetin alfa groups. AEs and/or death were the primary causes of discontinuation in both groups ([Figure 1](#)). The mean and median durations of exposure were 89.0 and 84.4 weeks in the roxadustat and 96.0 and 95.7 weeks in the

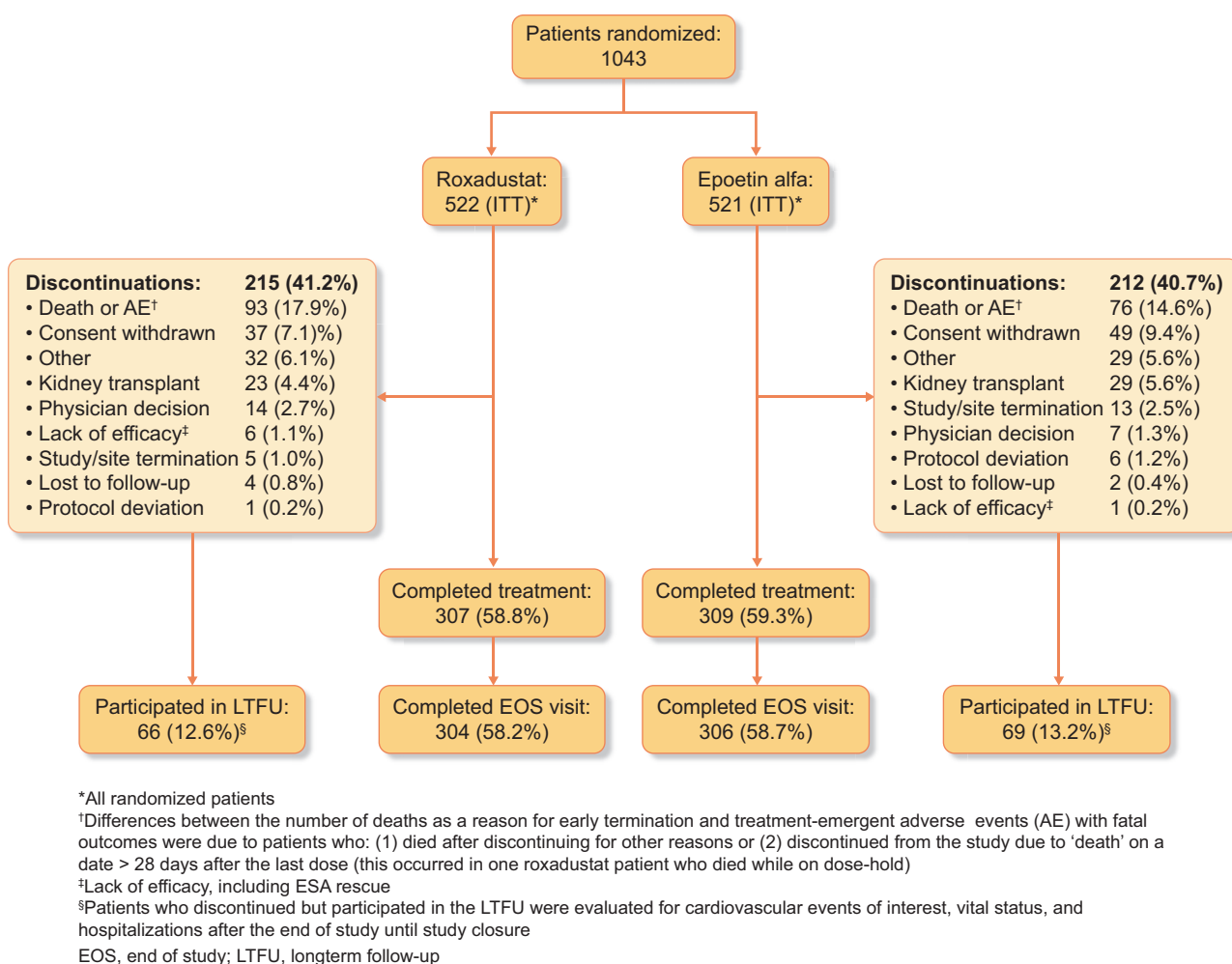


FIGURE 1: CONSORT flow diagram.

epoetin alfa group. Baseline demographic and clinical characteristics were comparable between treatment groups. Mean baseline Hb levels were 8.4 and 8.5 g/dL in the roxadustat and epoetin alfa groups, respectively (Table 1).

Primary efficacy endpoints

Mean (SD) changes in Hb (g/dL) from baseline averaged over Weeks 28–52 regardless of rescue therapy were 2.57 (1.27) and 2.36 (1.21) in the roxadustat and epoetin alfa groups, respectively [least squares mean (LSM) difference 0.18 (95% CI 0.08, 0.29)]. Roxadustat met the non-inferiority criterion (i.e. lower limit of 95% CI >−0.75) (Table 2). The treatment strategy for roxadustat versus epoetin alfa achieved numerically higher Hb levels at the administered doses used for roxadustat and epoetin alfa accounting for the doses of IV iron and number of blood/RBC transfusions; the lower limit of the 95% CI for the treatment difference was >0 ($P = 0.0005$). Figure 2A shows mean Hb values through Week 52.

Subgroup analyses of the US primary efficacy endpoint demonstrated non-inferiority versus epoetin alfa, consistent with the results of primary analysis (Supplementary data, Figure S1).

The percentage of patients achieving an Hb response during the first 24 weeks of treatment censored for rescue therapy within 6 weeks of the response in the roxadustat and epoetin alfa groups was 88.2% and 84.4% (Table 2). Roxadustat met the non-inferiority criterion, as the treatment difference [3.5% (95% CI −0.7, 7.7)] was >−15%. At each time point evaluated and based on the doses administered for roxadustat and epoetin alfa, more patients in the roxadustat versus epoetin alfa group achieved an Hb response (Figure 2B).

Secondary efficacy endpoints

Based on the doses administered for roxadustat and epoetin alfa for the US key secondary endpoint, the percentage of patients achieving an Hb response in the roxadustat and epoetin alfa groups was 84.3% and 79.5%. Roxadustat met the non-inferiority criterion, as the treatment difference was 4.3% (95% CI −0.1%, 8.7%), and the lower limit of the 95% CI was >−15% (Table 3). For the EU key secondary endpoint, mean changes from baseline in Hb averaged over Weeks 28–52 were 2.62 versus 2.44 in the roxadustat versus epoetin alfa group, respectively [LSM difference 0.16 (95% CI 0.03, 0.30);

Table 1. Baseline demographic and clinical characteristics (ITT)

Characteristic	Roxadustat (n = 522)	Epoetin alfa (n = 521)
Age, mean (SD), year ^a	53.8 (14.7)	54.3 (14.6)
Male sex, n (%)	309 (59.2)	307 (58.9)
Race, no. (%)		
White	415 (79.5)	400 (76.8)
Black	44 (8.4)	50 (9.6)
Asian	43 (8.2)	51 (9.8)
Other	20 (3.8)	20 (3.8)
Weight, mean (SD), kg	76.0 (18.5)	76.7 (19.1)
Hb, mean (SD), g/dL	8.4 (1.0)	8.5 (1.0)
Hb distribution, n (%)		
≤8.0 g/dL	166 (31.8)	157 (30.1)
>8.0 g/dL	356 (68.2)	364 (69.9)
CRP distribution, n (%)		
≤ULN	289 (55.4)	289 (55.5)
>ULN	228 (43.7)	226 (43.4)
Missing	5 (1.0)	6 (1.2)
Dialysis method, n (%)		
Hemodialysis	469 (89.8)	462 (88.7)
Peritoneal dialysis	53 (10.2)	58 (11.1)
Duration of dialysis, mean (SD), weeks	10.1 (3.9)	10.2 (3.6)
Total cholesterol, mean (SD), mg/dL	184.6 (45.8)	185.3 (43.9)
LDL cholesterol, mean (SD), mg/dL	109.1 (38.8)	109.2 (35.9)
Ferritin, mean (SD), ng/mL	441.4 (337.0)	437.4 (311.4)
TSAT, mean (SD), %	27.0 (9.3)	27.6 (8.9)
Iron repletion status, n (%)		
Ferritin ≥100 ng/mL and TSAT ≥20%	406 (77.8)	406 (77.9)
Ferritin <100 ng/mL or TSAT <20%	116 (22.2)	115 (22.1)
Diabetes, n (%)	205 (39.3)	204 (39.2)
CV history, n (%)		
Hypertension	505 (96.7)	504 (96.7)
Congestive heart failure	132 (25.3)	136 (26.1)
Myocardial infarction (STEMI or NSTEMI)	33 (6.3)	33 (6.3)
Stroke	41 (7.9)	43 (8.3)

NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction. ^aAge was calculated in years from birthdate to date of informed consent.

$P = 0.0148$]. Roxadustat met the non-inferiority criterion, as the lower limit of the 95% CI was > -0.75 g/dL (Table 3).

At baseline, mean (SD) LDL cholesterol (mg/dL) was 109.1 (38.8) and 109.2 (35.9) in the roxadustat and epoetin alfa groups, respectively. Roxadustat patients showed a consistent decrease in LDL cholesterol from baseline through the first 4 weeks; levels remained low through Week 48 (Figure 3). From Weeks 12 to 24, mean (SD) changes from baseline were -23.8 (30.0) versus -5.4 (26.2) in the roxadustat versus epoetin alfa group, respectively [LSM difference: -18.3 (95% CI $-21.45, -15.23$); $P < 0.0001$]. A larger percentage of patients in the roxadustat versus the epoetin alfa group achieved the LDL target of <100 mg/dL [65.9% versus 44.2%; odds ratio 3.12 (95% CI 2.32, 4.19)].

Post hoc analysis of other lipid parameters [i.e. total cholesterol, high-density lipoprotein (HDL) cholesterol, LDL:HDL ratio, non-HDL cholesterol, triglycerides] showed decreases in the roxadustat versus epoetin alfa group through Week 48 (Supplementary data, Table S5). Mean (SD) changes from baseline in total cholesterol were 32.5 (37.7) and 6.06 (31.42) in the roxadustat and epoetin alfa group, respectively [LSM difference: -26.54 (95% CI $-30.44, -22.63$)]. Although HDL cholesterol

levels decreased, an improvement in the LDL:HDL ratio was observed.

In patients with hs-CRP $>ULN$, mean (SD) changes from baseline in Hb (mg/dL) averaged over Weeks 18–24 were 2.34 (1.26) versus 2.48 (1.27) in the roxadustat versus epoetin alfa group, respectively [LSM difference 0.02 (95% CI $-0.17, 0.22$)]. Roxadustat was non-inferior to epoetin alfa. Roxadustat dose requirements were similar in patients with hs-CRP $>ULN$ and those with hs-CRP $\leq ULN$. Both subgroups achieved comparable Hb levels (Figure 4). In contrast, mean epoetin alfa doses required to maintain similar Hb levels, averaged over the first 52 weeks of treatment, were higher in patients with baseline hs-CRP $>ULN$ versus those with hs-CRP $\leq ULN$ (137.4 versus 122.3 IU/kg) (Figure 4). The between-subgroup difference was -15.1 IU/kg (95% CI $-26.4, -3.8$; $P = 0.0088$).

Mean monthly IV iron use (mg) per patient-exposure month during Weeks 1–28 was significantly lower in the roxadustat versus epoetin alfa group (LSM difference -30.79 (95% CI $-44.45, -17.13$)) (Table 4). Mean monthly IV iron use per patient-exposure month during Weeks 28–52 was significantly lower in the roxadustat versus epoetin alfa group [LSM difference -4.38 (95% CI $-20.71, 11.95$); $P = 0.00028$]. In the roxadustat and epoetin alfa groups, 83.7% and 85.4% of patients, respectively, received oral iron between Weeks 28 and 52. *Post hoc* analysis of mean (SD) oral iron use (mg/month) during this time period showed no statistically significant difference between the roxadustat [4873 (5582)] and epoetin alfa groups [4561 (5850)] [LSM difference 290.68 (95% CI $-463.21, 1044.57$); $P = 0.13$].

The non-inferiority criterion was not met for roxadustat for transfusions [7.3% (4.3 per 100 patient exposure years, PEY) and 6.4% (3.5 per 100 PEY); $P = 0.3284$ in roxadustat and epoetin alfa arms, respectively] as the upper limit of the 95% CI for the hazard ratio (HR) was >1.8 (Table 5). Thus, the fixed-sequence testing procedure was stopped.

At baseline, both treatment groups had comparable mean MAP (mmHg) of ~ 99 . Mean changes from baseline averaged over Weeks 8–12 were -0.12 and 1.15 in the roxadustat and epoetin alfa group [LSM difference -1.15 (95% CI $-2.09, -0.20$)]. Fourteen percent of roxadustat- and 15.2% of epoetin alfa-treated patients experienced an exacerbation of hypertension during treatment. The incidence rate (per 100 PEY) for time to first exacerbation of hypertension was 16.9 for roxadustat and 17.9 for epoetin alfa. Roxadustat met the non-inferiority criterion for this endpoint, as the upper limit of the 95% CI of the HR was <1.8 [HR 0.93 (95% CI 0.68, 1.28)].

Additional efficacy endpoints

At baseline, mean hepcidin levels were comparable and decreased similarly in both treatment groups at Week 4 (Figure 5A). By Week 44, the magnitude of the reduction was maintained in the roxadustat group, while levels trended toward baseline in the epoetin alfa group (Table 6).

Serum ferritin levels were gradually reduced in both treatment groups at all post-dosing time points (Table 6 and Figure 5B).

At baseline, mean (SD) serum iron levels (μ g/dL) were 64.41 (24.24) and 65.52 (24.15) in the roxadustat and epoetin alfa

Table 2. Primary efficacy endpoint results

USA: Change from baseline in Hb averaged over Weeks 28–52 regardless of rescue therapy ^a (ITT)						
	Roxadustat (<i>n</i> = 522)		Epoetin alfa (<i>n</i> = 521)		Treatment difference	P-value
	Observed values	Change from baseline ^b	Observed values	Change from baseline ^b		
Baseline Hb, mean (SD), g/dL	8.43 (1.04)	–	8.46 (0.96)	–	–	–
Weeks 28–52 Hb, mean (SD), g/dL	11.00 (0.82)	2.57 (1.27)	10.83 (0.88)	2.36 (1.21)	–	–
Treatment comparison ^c	–	–	–	–	–	–
LSM (SEM)	–	2.38 (0.04)	–	2.20 (0.04)	0.18 (0.05)	0.0005
95% CI	–	2.30, 2.46	–	2.12, 2.28	0.08, 0.29	–

EU: Percentage of patients with an Hb response during the first 24 weeks of treatment censored for rescue therapy ^d (PPS)			
	Roxadustat (<i>n</i> = 490)	Epoetin alfa (<i>n</i> = 468)	Response rate difference (95% CI) ^e
Patients with response, <i>n</i> (%) ^f	432 (88.2)	395 (84.4)	
95% CI ^g	85.0, 90.9	80.8, 87.6	3.5 (–0.7, 7.7)

SEM, standard error of the mean.

^aHb values under the influence of a rescue therapy were not censored. Intermittent missing Hb data were imputed for each treatment relying on non-missing data from all patients within each treatment group using the Markov Chain Monte Carlo imputation model. Monotone missing data were imputed by regression from its own treatment group.

^bBaseline Hb was defined the mean of up to four last central laboratory values before the first dose of study drug.

^cTreatment comparison was made using the MI strategy by combining the results of ANCOVA model with baseline Hb as a covariate, and treatment, region and CV/cerebrovascular/thromboembolic medical history (yes versus no) as factors.

^dHb values under the influence of rescue therapy (RBC transfusion or ESA) were censored up to 6 weeks.

^e95% CI was derived from the Miettinen and Nurminen approach [36] adjusting for randomization stratification factors.

^fDefined as patients who achieved an Hb response (i.e. achieving an Hb level ≥ 11 g/dL and an increase from baseline ≥ 1.0 g/dL in patients with baseline Hb > 8 g/dL or an increase ≥ 2.0 g/dL in patients with baseline Hb ≤ 8.0 g/dL) at two consecutive visits at least 5 days apart during the first 24 weeks of treatment without rescue therapy within 6 weeks of the response.

^g95% CIs were derived using the exact method of Clopper and Pearson [37] for each treatment group.

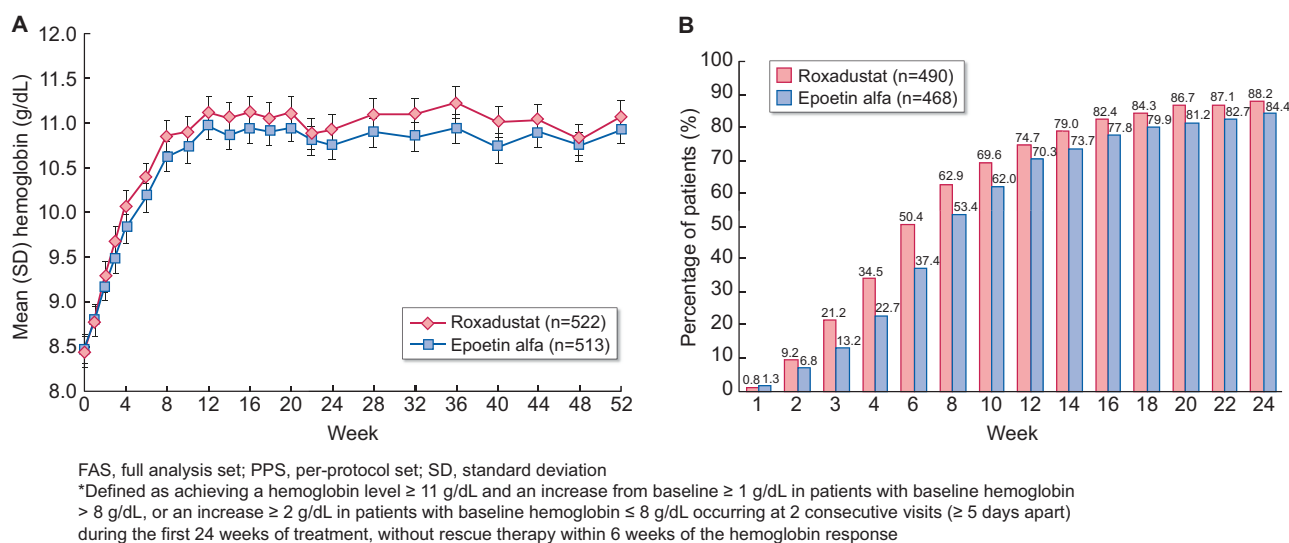


FIGURE 2: Hb levels from baseline to Week 52 (FAS) (A); cumulative percentage of patients that achieved an Hb response* during the first 24 weeks of treatment (PPS) (B).

groups (Figure 5C). At Week 4, iron levels remained stable in the roxadustat group and declined significantly in the epoetin alfa group. By Week 44, the LSM treatment difference was 6.86 (95% CI 2.43, 11.30) ($P = 0.0024$). Total iron-binding capacity (TIBC; $\mu\text{g/dL}$) also was similar between treatment groups at baseline; in the roxadustat and epoetin alfa groups, mean (SD) changes from baseline to Week 44 were 40.31 (51.89) and 2.74 (42.62) in the roxadustat and epoetin alfa groups, respectively [LSM difference 33.73 (95% CI 27.77, 39.70); $P < 0.0001$].

TSAT was clinically stable in both treatment groups, resulting in a non-statistically significant between-group difference at Week 52 (Table 6 and Figure 5D).

Safety

More than 85% of patients in the roxadustat and epoetin alfa groups experienced one or more TEAE during treatment (Table 7). The most frequently reported TEAE in the roxadustat group was hypertension, which occurred in 19.0% of patients in

Table 3. Key secondary efficacy endpoint results

USA: Patients (%) with Hb response ^a during the first 24 weeks censored for rescue therapy ^b (ITT)						
	Roxadustat (<i>n</i> = 552)		Epoetin alfa (<i>n</i> = 521)		Response rate difference (95% CI) ^c	
Patients with response, <i>n</i> (%)	440 (84.3)		414 (79.5)		4.3 (−0.1, 8.7)	
95% CI ^d	80.9, 87.3		75.7, 82.9			
EU: Hb change from baseline averaged over Weeks 28–52 censored for rescue therapy ^e (PPS)						
	Roxadustat (<i>n</i> = 490)		Epoetin alfa (<i>n</i> = 468)		Treatment difference	P-value
	Observed values	Change from baseline ^f	Observed values	Change from baseline ^f		
Baseline Hb, g/dL, mean (SD)	8.43 (1.04)		8.43 (0.96)		–	–
Hb over Weeks 28–52, g/dL, mean (SD)	11.04 (0.91)	2.62 (1.29)	10.88 (0.89)	2.44 (1.21)	–	–
Treatment comparison ^g	–	–	–	–	–	–
LSM (SEM)	2.49 (0.05)	–	2.32 (0.05)	–	0.16 (0.07)	0.0148
95% CI	2.39, 2.58	–	2.23, 2.42	–	0.03, 0.30	–

^aDefined as patients who achieved an Hb response at two consecutive visits (≥ 5 days apart) during the first 24 weeks of treatment without rescue therapy. Patients who dropped out or received rescue therapy before or on the date of the second consecutive Hb value were classified as non-responders. An Hb response was defined as: Hb ≥ 11.0 g/dL and Hb increase from baseline by ≥ 1.0 g/dL in patients with baseline Hb > 8.0 g/dL or increase in Hb ≥ 2.0 g/dL in patients with baseline Hb ≤ 8.0 g/dL.

^bHb values under the influence of a rescue therapy (RBC transfusion or ESA) were censored up to 6 weeks.

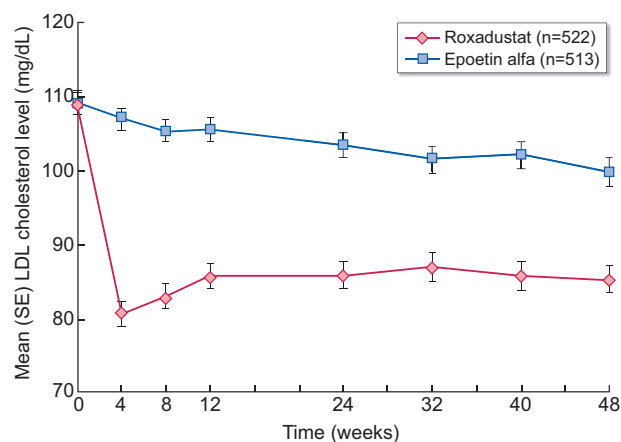
^c95% CI was derived using the Miettinen and Nurminen approach [36] adjusting for randomization stratification factors.

^d95% CIs were derived using the exact method of Clopper and Pearson [37] for each treatment group.

^eHb values under the influence of a rescue therapy (roxadustat: RBC transfusion or ESA; epoetin alfa: RBC transfusions) were censored up to 6 weeks.

^fBaseline Hb was defined the mean of up to four last central laboratory values before the first dose of study treatment.

^gTreatment comparison was made using an mixed model of repeated measures with baseline Hb as a covariate, and treatment, visit, visit-by-treatment interaction and randomization stratification factors except mean qualifying screening Hb (≤ 8.0 versus > 8.0 g/dL) as fixed effects.

**FIGURE 3: LDL cholesterol levels from baseline to Week 48 (FAS).**

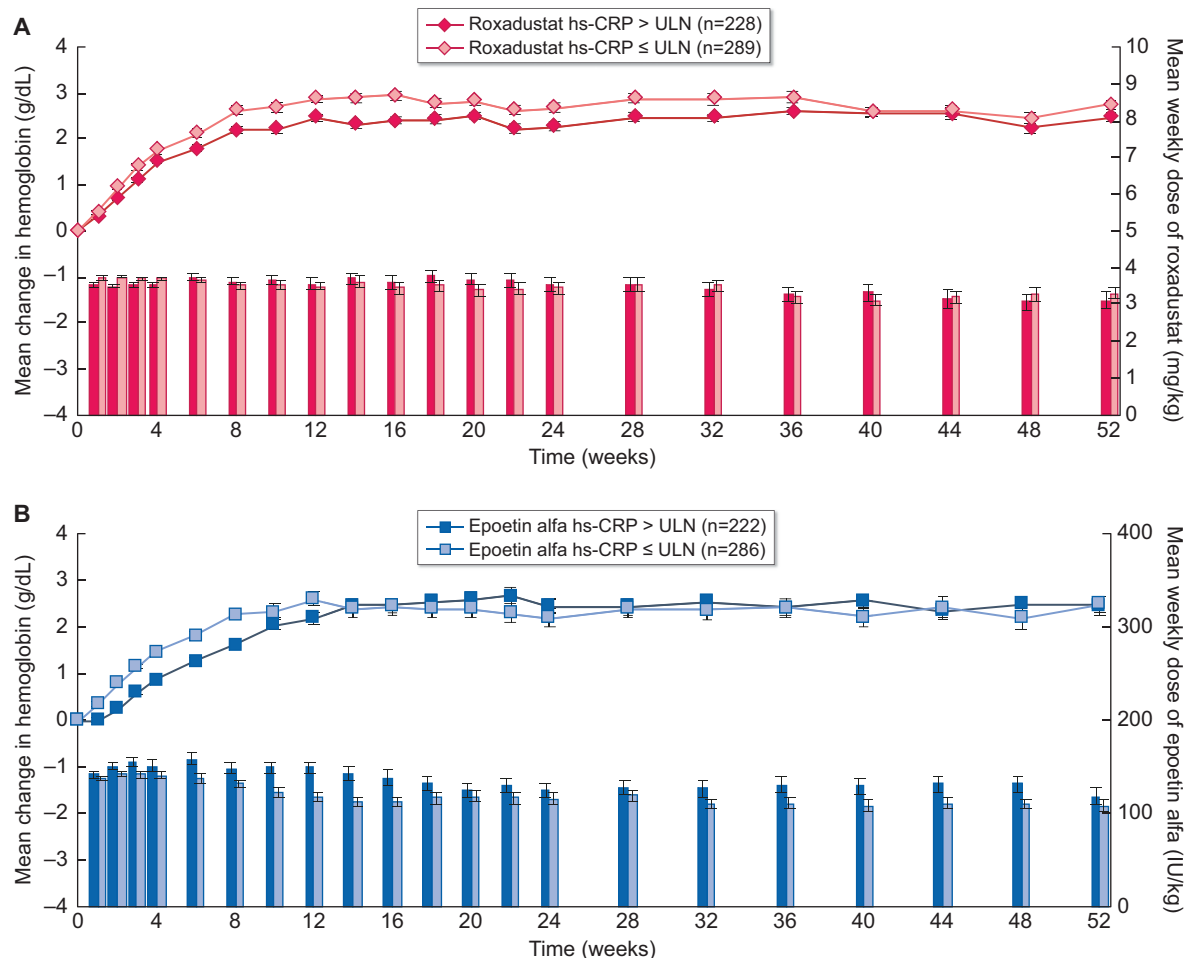
the roxadustat group and 17.0% in the epoetin alfa group. Hyperkalemia rates were lower in the roxadustat versus epoetin alfa group (5.0% versus 7.0%). In the roxadustat and epoetin alfa groups, 44.8% and 42.2%, respectively, experienced one or more TESAE during treatment (Table 8). There were 63 (12.1%) fatal TEAEs in the roxadustat group and 59 (11.4%) in the epoetin alfa group.

DISCUSSION

The HIMALAYAS Phase 3 trial compared the efficacy and safety of roxadustat, an oral HIF-PH inhibitor, versus epoetin alfa for the treatment of CKD-related anemia in patients

initiating dialysis. This study demonstrated that roxadustat was non-inferior to epoetin alfa for the correction and maintenance of Hb levels. Roxadustat met both the US and EU primary endpoints for increases in Hb and percentage of patients achieving an Hb response. Additionally, this study of >1000 patients with ID-CKD represents the largest to date to examine the efficacy and safety of a treatment for CKD-related anemia in a population of highly vulnerable patients.

It is well recognized that the initiation of dialysis is associated with a high risk of morbidity and mortality. The annualized mortality rate in the first few months of dialysis can exceed 200 deaths per 1000 patient-years at risk [39]. Clinical studies



Abbreviations: FAS, full analysis set; hs-CRP, high-sensitivity C-reactive protein; ULN, upper limit of normal

FIGURE 4: Relationship between Hb changes and study drug dosing changes over the first 52 weeks stratified by C-reactive protein (FAS).

Table 4. Monthly IV iron use^a per patient-exposure month during Weeks 1–28 of treatment (FAS)

	Roxadustat (n = 522)	Epoetin alfa (n = 513)	Treatment difference (Roxadustat – epoetin alfa)
IV iron, mg, mean (SD)	58.14 (110.58)	88.67 (122.49)	–
Median (range)	0.00 (0, 938.8)	42.86 (0, 800.0)	–
Treatment comparison ^b			–
LSM (SEM)	88.14 (6.08)	118.93 (6.17)	–30.79 (6.96)
95% CI	76.21, 100.06	106.83, 131.03	–44.45, –17.13
P-value ^c			<0.00001

^aMonthly iron use for each patient: total IV iron (mg)/[(last visit date – first dose date of study medication in the period + 1)/28].

^bTreatment comparison was made using an ANCOVA model with baseline iron repletion status, treatment and randomization stratification factors as fixed effects.

^cBased on Koch *et al.* [38] stratified rank ANCOVA analysis, stratified by iron repletion status and randomization stratification factors, except mean qualifying screening Hb (≤ 8.0 versus >8.0 g/dL) and considering baseline Hb as a covariate for the between-group comparison.

in the ID-CKD population are essential because their results can be generalized to the real-world setting of initiating a new anemia management strategy and reflect a comparison of treatments prior to a population becoming stabilized on one treatment and being subject to a transition to another. Roxadustat is also being studied in patients not selected for their recent initiation of dialysis (prevalent patients). The HIMALAYAS study of

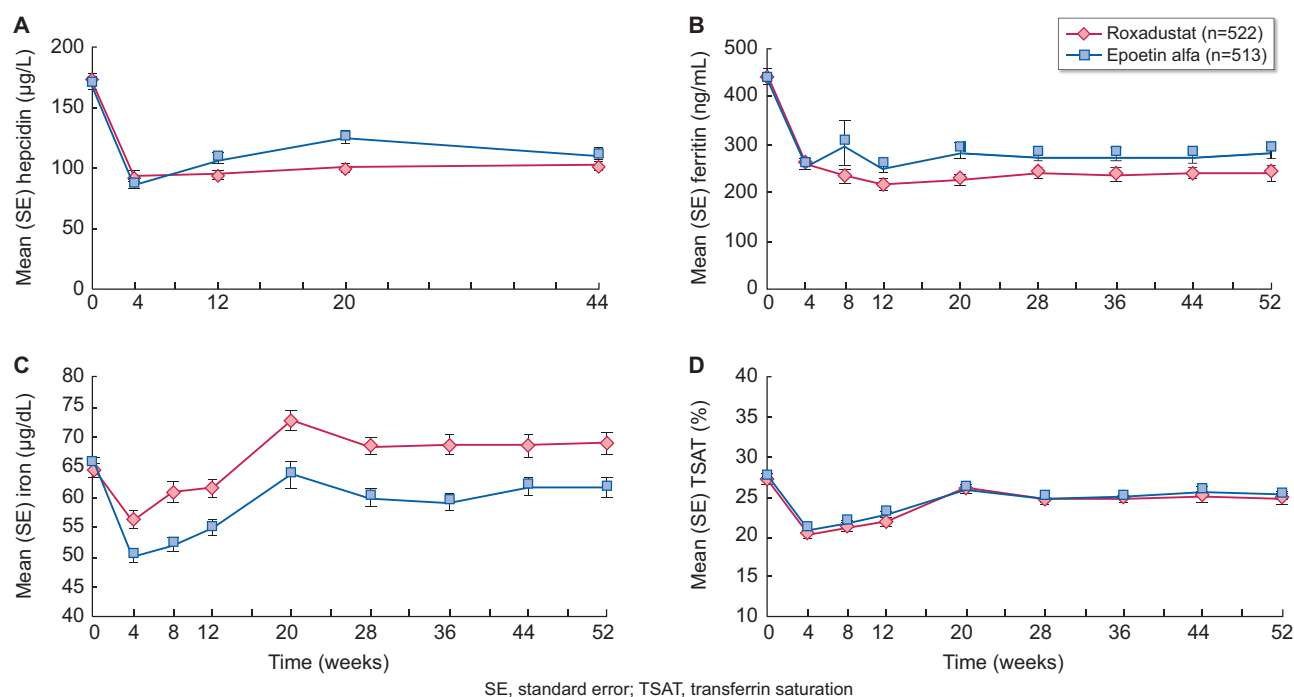
incident patients is complemented by the SIERRAS trial (Evaluation of Efficacy and Safety of Roxadustat in the Treatment of Anemia in Stable Dialysis Subjects; NCT02273726), which also compared roxadustat with epoetin alfa and will be published separately.

In general, levels of all components of fractionated lipid measures decreased with roxadustat versus epoetin alfa,

Table 5. Time to first RBC transfusion during treatment (FAS)

Population	Roxadustat (<i>n</i> = 522)	Epoetin alfa (<i>n</i> = 513)	HR (95% CI)	P-value ^a
Patients with events ^b , <i>n</i> (%)	38 (7.3)	33 (6.4)	–	–
Patients censored ^c , <i>n</i> (%)	484 (92.7)	480 (93.6)	–	–
Median time to event ^d , weeks	NE	NE	–	–
95% CI	NE, NE	NE, NE	–	–
Total PEY ^e	890.7	951.6	–	–
Incident rate (per 100 PEY)	4.3	3.5	–	–
Treatment effect	–	–	1.26	0.3284
95% CI	–	–	0.79, 2.02	

NE, not evaluable.

^aCox proportional hazards model adjusted for baseline Hb and other stratification factors except mean qualifying screening Hb (≤ 8.0 versus >8.0 g/dL) as fixed effects.^bAny use of RBC/blood transfusion.^cPatients with no events were censored on the earliest date (i.e. last dose date, last visit date and death date).^dCalculated using Kaplan–Meier survival estimates. Medians were not calculated because $<50\%$ of patients had events.^eCalculated as: (last dose date – first dose date + 1)/365.25.**FIGURE 5: Levels of hepcidin (A), ferritin (B), iron (C) and TSAT (D) (FAS).**

including LDL and HDL, which resulted in an overall improvement in the LDL:HDL ratio.

Patients with ID-CKD require higher doses of ESAs to treat anemia, perhaps due to the greater degree of inflammation (hs-CRP $>$ ULN) and its subsequent impact on ESA responsiveness [7]. While higher doses of ESAs are associated with higher risk of CV events [15], the efficacy of roxadustat was not affected by patients' baseline hs-CRP level, and similar doses of roxadustat produced comparable Hb increases in patients with normal or higher than normal baseline hs-CRP. In contrast, epoetin alfa-treated patients with high baseline hs-CRP required higher doses to maintain comparable Hb levels. Efficacy independent of inflammation has been observed consistently in roxadustat studies, as noted in the stable dialysis trial of roxadustat conducted in China [26] and in the US-based SIERRAS trial.

Sensitivity to inflammation observed in the epoetin alfa groups in these trials is consistent with other studies demonstrating the inflammation sensitivity of ESAs [25, 29].

Inflammation results in functional iron deficiency [24]. Consistent with the known mechanism of action of roxadustat [25], hepcidin levels decreased from baseline. While the reduction of hepcidin occurred in both groups, we postulate this and other effects of roxadustat increased the mobilization of internal iron stores to enhance production of a robust RBC population. Overall, changes in iron biomarker levels showed improvement with roxadustat versus epoetin alfa. Serum iron levels maintained in the roxadustat group were higher than the epoetin alfa group; TSAT levels were comparable between the groups throughout the study, when the roxadustat group achieved larger Hb increases with less IV iron supplementation per

Table 6. Changes from baseline for hepcidin and iron-related parameters at Week 44 (FAS)

	Serum hepcidin (µg/L)		Serum ferritin (ng/mL)		TSAT (%)	
	Roxadustat (n = 522)	Epoetin alfa (n = 513)	Roxadustat (n = 522)	Epoetin alfa (n = 513)	Roxadustat (n = 522)	Epoetin alfa (n = 513)
Baseline value, mean (SD)	173.21 (120.21)	169.91 (127.98)	441.38 (337.02)	436.65 (311.67)	27.02 (9.27)	27.55 (8.90)
Patients at Week 44, n	356	372	362	381	364	383
Week-44 value, mean CFB (SD)	−67.78 (112.71)	−55.96 (135.32)	−198.47 (311.70)	−141.13 (328.52)	−1.90 (13.79)	−1.79 (13.52)
Treatment comparison ^a						
LSM (SEM)	−64.76 (4.84)	−54.06 (4.77)	−191.30 (22.00)	−130.02 (21.87)	−2.70 (0.59)	−2.22 (0.58)
95% CI	−74.25, −55.27	−63.41, −44.70	−234.44, −148.17	−172.89, −87.15	−3.87, −1.54	−3.36, −1.07
Difference (SEM)	−10.70 (6.36)		−61.29 (28.40)		−0.48 (0.79)	
95% CI	−23.17, 1.77		−116.96, −5.62		−2.04, 1.07	
P-value	0.0926		0.0310		0.5419	

	Reticulocyte Hb (pg)		Serum iron (µg/dL)		TIBC (µg/dL)	
	Roxadustat (n = 522)	Epoetin alfa (n = 513)	Roxadustat (n = 522)	Epoetin alfa (n = 513)	Roxadustat (n = 522)	Epoetin alfa (n = 513)
Baseline value, mean (SD)	31.15 (1.92)	31.24 (1.82)	64.41 (24.24)	65.52 (24.15)	241.04 (43.00)	238.06 (37.04)
Patients at Week 44, n	358	364	364	384	364	383
Week-44 value, mean CFB (SD)	0.61 (2.04)	0.40 (2.02)	4.31 (37.22)	−4.06 (34.90)	40.31 (51.89)	2.74 (42.62)
Treatment comparison ^a						
LSM (SEM)	0.43 (0.10)	0.21 (0.10)	2.14 (1.69)	−4.72 (1.66)	37.70 (2.26)	1.65 (2.23)
95% CI	0.23, 0.62	0.01, 0.40	−1.18, 5.46	−7.98, −1.46	33.28, 42.12	−2.73, 6.02
Difference (SEM)	0.22 (0.13)		6.86 (2.27)		36.05 (2.97)	
95% CI	−0.04, 0.48		2.43, 11.30		30.23, 41.87	
P-value	0.0975		0.0024		<0.0001	

^aAnalyzed using a mixed model of repeated measures with baseline as a covariate, and treatment, visit, visit-by-treatment interaction and randomization stratification factors as fixed effects. CFB, change from baseline

Table 7. TEAEs reported by ≥5% of patients in either treatment group (SAF)

Preferred term ^b	Roxadustat		Epoetin alfa	
	n = 522	PEY ^a = 890.7 events (events/100 PEY)	n = 517	PEY ^a = 951.6 events (events/100 PEY)
	n (%)		n (%)	
Hypertension	99 (19.0)	165 (18.5)	88 (17.0)	134 (14.1)
Diarrhea	72 (13.8)	112 (12.6)	38 (7.4)	56 (5.9)
Muscle spasms	60 (11.5)	106 (11.9)	39 (7.5)	65 (6.8)
Arteriovenous fistula thrombosis	59 (11.3)	80 (9.0)	46 (8.9)	69 (7.3)
Headache	57 (10.9)	88 (9.9)	44 (8.5)	66 (6.9)
Hypotension	54 (10.3)	104 (11.7)	35 (6.8)	51 (5.4)
Hyperphosphatemia	52 (10.0)	57 (6.4)	35 (6.8)	39 (4.1)
Nausea	45 (8.6)	57 (6.4)	30 (5.8)	33 (3.5)
Pneumonia	42 (8.0)	48 (5.4)	40 (7.7)	46 (4.8)
Constipation	35 (6.7)	40 (4.5)	23 (4.4)	24 (2.5)
Vomiting	32 (6.1)	45 (5.1)	17 (3.3)	23 (2.4)
Arteriovenous fistula site complication	31 (5.9)	40 (4.5)	43 (8.3)	79 (8.3)
Pruritus	30 (5.7)	36 (4.0)	22 (4.3)	26 (2.7)
Fluid overload	29 (5.6)	42 (4.7)	28 (5.4)	39 (4.1)
Cough	28 (5.4)	35 (3.9)	21 (4.1)	22 (2.3)
Dizziness	28 (5.4)	39 (4.4)	24 (4.6)	32 (3.4)
Hyperkalemia	26 (5.0)	37 (4.2)	36 (7.0)	47 (4.9)
Procedural hypotension	26 (5.0)	35 (3.9)	31 (6.0)	49 (5.1)
Hyperparathyroidism secondary	25 (4.8)	26 (2.9)	27 (5.2)	32 (3.4)
Back pain	18 (3.4)	21 (2.4)	27 (5.2)	28 (2.9)

An AE (classified by preferred term) started during the treatment period and was considered a TEAE if it was not present before to the first dose of study drug, or it was present before the first dose of study drug but increased in severity during the treatment period and up to 28 days after last dose of study drug or until the administration of another anemia drug (other than the randomized treatment).

^aPEY = (last dose date − first dose date + 1)/365.25.

^bMedical Dictionary for Regulatory Activities version 20.0.

Table 8. TESAEs^a occurring in ≥1% of patients in either treatment group (SAF)

Preferred term ^b	Roxadustat (n = 522)		Epoetin alfa (n = 517)	
	n (%)	PEY = 890.7 events (events/100 PEY ^c)	n (%)	PEY = 951.6 events (events/100 PEY ^c)
Arteriovenous fistula thrombosis	39 (7.5)	48 (5.4)	21 (4.1)	27 (2.8)
Pneumonia	30 (5.7)	30 (3.4)	26 (5.0)	30 (3.2)
Sepsis	13 (2.5)	14 (1.6)	8 (1.5)	8 (0.8)
Peritonitis	12 (2.3)	17 (1.9)	12 (2.3)	14 (1.5)
Device-related infection	9 (1.7)	9 (1.0)	3 (0.6)	3 (0.3)
Fluid overload	9 (1.7)	9 (1.0)	12 (2.3)	15 (1.6)
Hypertensive crisis	9 (1.7)	12 (1.3)	12 (2.3)	14 (1.5)
Device related sepsis	7 (1.3)	11 (1.2)	2 (0.4)	2 (0.2)
Hypotension	7 (1.3)	8 (0.9)	3 (0.6)	3 (0.3)
Septic shock	7 (1.3)	7 (0.8)	4 (0.8)	4 (0.4)
Sudden death	7 (1.3)	7 (0.8)	4 (0.8)	4 (0.4)
Acute myocardial infarction	6 (1.1)	9 (1.0)	11 (2.1)	11 (1.2)
Gangrene	6 (1.1)	6 (0.7)	6 (1.2)	6 (0.6)
Hypertension	6 (1.1)	6 (0.7)	3 (0.6)	4 (0.4)
Urinary tract infection	6 (1.1)	7 (0.8)	4 (0.8)	4 (0.4)
Arteriovenous fistula site complication	5 (1.0)	5 (0.6)	2 (0.4)	2 (0.2)
Cardiac failure congestive	5 (1.0)	6 (0.7)	7 (1.4)	9 (0.9)
Ischemic stroke	5 (1.0)	6 (0.7)	2 (0.4)	2 (0.2)
Myocardial infarction	5 (1.0)	5 (0.6)	2 (0.4)	2 (0.2)
Pancreatitis acute	5 (1.0)	6 (0.7)	0	0
Pulmonary edema	5 (1.0)	5 (0.6)	5 (1.0)	5 (0.5)
Atrial fibrillation	4 (0.8)	4 (0.4)	5 (1.0)	5 (0.5)
Cellulitis	4 (0.8)	5 (0.6)	5 (1.0)	6 (0.6)
Gastrointestinal hemorrhage	4 (0.8)	4 (0.4)	5 (1.0)	6 (0.6)
Angina unstable	3 (0.6)	3 (0.3)	5 (1.0)	5 (0.5)
Cardiac arrest	3 (0.6)	4 (0.4)	5 (1.0)	5 (0.5)
Hyperkalemia	3 (0.6)	5 (0.6)	6 (1.2)	7 (0.7)
Hemorrhagic stroke	3 (0.6)	3 (0.3)	6 (1.2)	6 (0.6)
Death	2 (0.4)	2 (0.2)	7 (1.4)	7 (0.7)
Acute pulmonary edema	1 (0.2)	1 (0.1)	6 (1.2)	6 (0.6)

^aAn AE (classified by preferred term) started during the treatment period was considered a TEAE if it was not present before the first dose of study drug, or it was present before the first dose but increased in severity during the treatment period up to 28 days after last dose or until the administration of another anemia drug (other than the randomized treatment).

^b Medical Dictionary for Regulatory Activities version 20.0.

^cPEY for each patient = (last dose date – first dose date + 1)/365.25. Event rate (per 100 PEY) = 100 × number of events/PEY.

patient treated. These data support the idea that roxadustat promotes coordinated erythropoiesis that combines the drug's favorable impact on iron mobilization with its ability to induce erythropoietin.

The overall frequency of TEAEs and TESAEs was balanced between treatment groups. Roxadustat was well tolerated, extending the safety profile beyond the 26-week treatment period conducted in the Phase 3 studies in China [26, 27]. Approximately 10% of patients discontinued therapy, with a similar number of fatal events in each group. While the reported rates of hyperkalemia were lower in the roxadustat versus epoetin alfa group, rates of arteriovenous access thrombosis were higher. The underlying mechanism of this, however, is unclear. The absence of a hyperkalemia signal in the roxadustat group was consistent with stable mean potassium levels after roxadustat therapy. While these results should be interpreted in the context of the slightly longer mean exposure time for patients in the epoetin alfa group, the reported rates were adjusted for exposure (i.e. events/100 PEY).

While this study was designed to focus on the highly vulnerable population of patients that has recently initiated dialysis, its results must be interpreted within a certain context.

Treatment of anemia can vary based on country and local practice patterns, and investigators were asked to follow the country-specific regulatory document for epoetin alfa (e.g. package insert). Therefore, point estimates for treatment differences may vary globally due to differences in epoetin alfa usage. Treatment of anemia using roxadustat was protocolized. As with all studies, the potential for volunteer bias (i.e. the Hawthorne effect) should be noted as it relates to the generalizability in clinical practice.

This Phase 3 trial in patients with ID-CKD showed that roxadustat was efficacious for correcting and maintaining Hb levels versus epoetin alfa with an acceptable safety profile.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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AUTHORS' CONTRIBUTIONS

K.-H.P.Y. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. R.P., L.P., G.S., A.B., T.B.N., L.S. and K.-H.P.Y. were responsible for concept and design. R.P., E.S., L.E., S.K., L.P., G.S., C.B., M.E., A.B., R.L., C.S.L., T.B.N., L.S. and K.-H.P.Y. were involved in the acquisition, analysis or interpretation of data. L.S. drafted the manuscript. R.P. and E.S. critically revised the manuscript for important intellectual content. C.S.L. performed statistical analysis. T.B.N. and K.-H.P.Y. obtained funding. K.-H.P.Y. provided supervision.

CONFLICT OF INTEREST STATEMENT

FibroGen employees and subcontractors had a role in study design, data collection, data analysis, data interpretation and writing of the manuscript. R.P. serves as a consultant for AstraZeneca, DaVita and FibroGen; he also owns stock in DaVita. A.B. and T.B.N. were the employees of FibroGen at the time the studies were conducted. E.S., L.E. and S.K. have no conflicts of interest to disclose. L.P., G.S., C.B., M.E., R.L., C.S.L., L.S. and K.-H.P.Y. are employees of FibroGen, Inc. and hold stock and/or stock options in FibroGen, Inc. Roxadustat is in clinical development for the treatment of CKD-related anemia in collaboration with Astellas Pharma and AstraZeneca.

(See related article by Locatelli and Vecchio. A new paradigm in treating patients with chronic kidney disease and anaemia after a journey lasting more than 35 years. *Nephrol Dial Transplant* 2021; 36: 1559–1563)

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