

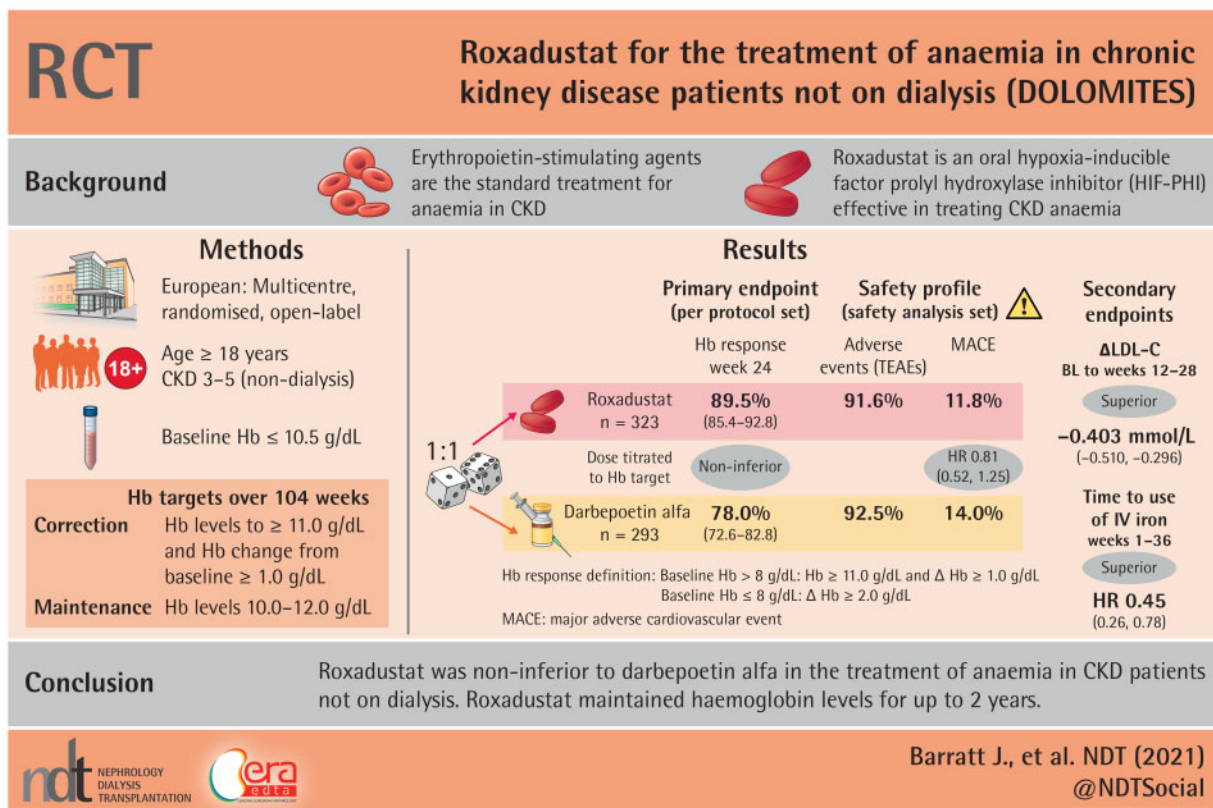
Roxadustat for the treatment of anaemia in chronic kidney disease patients not on dialysis: a Phase 3, randomized, open-label, active-controlled study (DOLOMITES)

Jonathan Barratt¹, Branislav Andric², Avtandil Tataradze³, Michael Schömig⁴, Michael Reusch⁵, Udaya Valluri⁶ and Christophe Mariat⁷

¹Department of Cardiovascular Sciences, University of Leicester, Leicester, UK, ²Health Center Krusevac, Krusevac, Serbia, ³National Center of Urology, Tbilisi, Georgia, ⁴Dialysis Center Heilbronn, Heilbronn, Germany, ⁵Astellas Pharma Europe B.V., Leiden, The Netherlands, ⁶Astellas Pharma Global Development, Inc., Northbrook, IL, USA and ⁷CHU St Etienne, Service Nephrologie Dialyse Transplantation, St Etienne, France

Correspondence to: Jonathan Barratt; E-mail: jb81@le.ac.uk

GRAPHICAL ABSTRACT



ABSTRACT

Background. Roxadustat, an orally administered hypoxia-inducible factor prolyl hydroxylase inhibitor, is being evaluated for treatment of anaemia of chronic kidney disease (CKD).

Methods. This randomized, open-label, active-controlled Phase 3 study compared roxadustat versus darbepoetin alfa (DA) in non-dialysis-dependent (NDD) CKD patients with anaemia for ≤ 104 weeks. Doses were titrated to correct and maintain haemoglobin (Hb) within 10.0–12.0 g/dL. The primary endpoint was Hb response in the full analysis set, defined as Hb ≥ 11.0 g/dL and Hb change from baseline (BL; CFB) ≥ 1.0 g/dL in patients with BL Hb > 8.0 g/dL or CFB ≥ 2.0 g/dL in patients with BL Hb ≤ 8.0 g/dL during the first 24 weeks of treatment without rescue therapy (non-inferiority margin, -15%). Key secondary endpoints included change in low-density lipoprotein (LDL), time to first intravenous (IV) iron use, change in mean arterial pressure (MAP) and time to hypertension occurrence. Adverse events were assessed.

Results. Of 616 randomized patients (roxadustat, 323; DA, 293), 424 completed treatment (roxadustat, 215; DA, 209). Hb response with roxadustat was non-inferior to DA (roxadustat: 256/286, 89.5% versus DA: 213/273, 78.0%, difference 11.51%, 95% confidence interval 5.66–17.36%). Roxadustat maintained Hb for up to 2 years. Roxadustat was non-inferior to DA for change in MAP and time to occurrence of hypertension and superior for change in LDL and time to first IV iron use. Safety profiles were comparable between groups. Findings suggest that there was no difference between groups regarding the composite endpoints major adverse cardiovascular events (MACEs) and MACE+ [MACE: 0.81 (0.52–1.25), $P = 0.339$; MACE+: 0.90 (0.61–1.32), $P = 0.583$].

Conclusions. Roxadustat is a viable option to treat anaemia in NDD CKD patients maintaining Hb levels for up to 104 weeks.

Keywords: anaemia, chronic kidney disease, erythropoietin, haemoglobin

INTRODUCTION

Anaemia of chronic kidney disease (CKD) leads to impaired renal oxygen sensing and may be caused by reduced erythropoiesis, functional iron deficiency and inflammation [1, 2]. Oral or intravenous (IV) iron, alongside erythropoiesis-stimulating agents (ESAs), are foundational CKD anaemia treatments; however, only 28–57% of non-dialysis-dependent (NDD) CKD Stages 3–5 patients with haemoglobin (Hb) levels < 10 g/dL are treated in the 3 months following Hb measurement [3]. Furthermore, high-dose ESAs pose safety concerns, including increased cardiovascular risk, in some patients [4–6], indicating that alternative therapies may be needed.

Roxadustat is a first-in-class oral hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor (PHI) approved for anaemia treatment in dialysis-dependent (DD) and NDD CKD in China and Japan. Through the reversible inhibition of HIF-PH, roxadustat stimulates an erythropoietic response that includes the increase of plasma-endogenous erythropoietin levels, regulation of iron transporter proteins and reduction of hepcidin. These results in improved iron bioavailability, increased Hb production and increased red cell mass [7].

The safety and efficacy of roxadustat in achieving and maintaining Hb target levels have been demonstrated in multiple Phase 3 studies assessing DD [8–12] and NDD [13–16] CKD patients from China, Japan and Europe. DOLOMITES is the first large, Phase 3 study to compare the efficacy, safety and tolerability of roxadustat with darbepoetin alfa (DA) for treatment of anaemia in NDD CKD patients.

MATERIALS AND METHODS

Study design

This was a Phase 3, multicentre, randomized, open-label, active-controlled study conducted at 200 study centres, primarily located in Europe, from March 2014 to June 2018 (EudraCT number: 2013-000951-42; ClinicalTrials.gov Identifier:

KEY LEARNING POINTS

What is already known about this subject?

- erythropoiesis-stimulating agents (ESAs), such as darbepoetin alfa (DA), are foundational in treating anaemia of chronic kidney disease (CKD) and are generally considered effective treatments; however, concerns regarding their efficacy, safety and tolerability in some patients suggest that there is a need for novel treatment options.

What this study adds?

- roxadustat was non-inferior to DA in achieving Hb response during the first 24 weeks of treatment without rescue therapy and superiority of roxadustat to DA was demonstrated for decrease in low-density lipoprotein from baseline to Weeks 12–28 and lower incidence rate for first use of intravenous iron during Weeks 1–36.

What impact this may have on practice or policy?

- roxadustat is a viable alternative to ESAs for anaemia treatment in non-dialysis-dependent CKD patients.

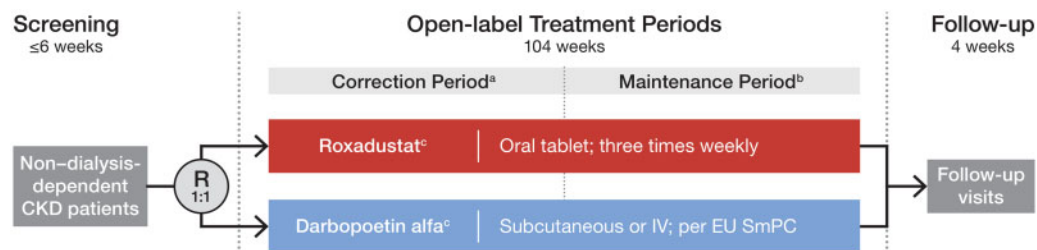


FIGURE 1: Study flow chart. After a ≤ 6 -week screening period, eligible patients were randomized (1:1) to receive roxadustat or DA for up to 104 weeks during the treatment period. An initial correction period^a to achieve Hb ≥ 11.0 g/dL and Hb CFB ≥ 1.0 g/dL occurred in both groups. This was followed by a maintenance period^b with dosing aimed at achieving Hb levels between 10.0 and 12.0 g/dL. Initial DA dosing^c was weight-based. During a 4-week follow-up period, anaemia treatment was at the discretion of study investigators.

NCT02021318). After a ≤ 6 -week screening period, eligible patients were randomized (1:1) to receive roxadustat or DA for up to 104 weeks during the treatment period. An initial correction period to achieve Hb ≥ 11.0 g/dL and Hb change from baseline (BL; CFB) ≥ 1.0 g/dL (measured at two consecutive visits separated by ≥ 5 days) occurred in both groups. This was followed by a maintenance period with dosing aimed at achieving Hb levels between 10.0 and 12.0 g/dL. During a 4-week follow-up period, anaemia treatment was at the discretion of study investigators (Figure 1).

Two substantial protocol amendments occurred. The first amendment (18 May 2015) changed: (i) dosing frequency during the maintenance period from three times weekly (TIW), two times weekly or once weekly to TIW only; (ii) initial roxadustat dose from 70, 100 and 150 mg to 70 and 100 mg; (iii) maximum dose from 3.5 to 3.0 mg/kg and maximum absolute dose from 400 to 300 mg; and (iv) randomization ratio from 2:1 to 1:1. The second amendment (31 March 2016): (i) changed Hb value assessments during the screening period from three to two and mean Hb entry threshold from ≤ 10.0 to ≤ 10.5 g/dL; (ii) removed any inclusion criteria related to ferritin ≥ 100 ng/mL and transferrin saturation (TSAT) $\geq 20\%$ at screening; and (iii) excluded patients that investigators deemed close to initiating renal replacement therapy, including dialysis and renal transplantation.

This study was conducted in accordance with the ethical principles of the declaration of Helsinki, Good Clinical Practice and International Committee on Harmonization guidelines, and applicable laws and regulations. The protocol was approved by each Institutional Review Board. All patients provided written informed consent.

Study population

Patients aged ≥ 18 years with Stages 3–5 CKD who were not receiving dialysis, had an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² and had the mean of the two most recent Hb values at screening (obtained at least 4 days apart) ≤ 10.5 g/dL with a difference between the two measurements of ≤ 1.0 g/dL were eligible. Patients with a history of cancer or prior anaemia treatment with ESA or IV iron within 12 or 6 weeks prior to randomization, respectively, were excluded. Complete inclusion and exclusion criteria are reported in the [Supplementary Methods](#).

Study drug administration

A block randomization schedule was generated with patients randomized to roxadustat or DA according to stratification factors (region; Hb values at screening; history of cardiovascular, cerebrovascular or thromboembolic diseases; and eGFR values at screening). Each site was given the next available randomization number in sequential order through the interactive response technology system, which also completed randomization generation and treatment assignments.

Roxadustat was self-administered orally TIW at any time of day, with or without food and with an initial weight-based dose (weight ≥ 45.0 to ≤ 70.0 kg, roxadustat 70 mg; weight > 70.0 to ≤ 160.0 kg, roxadustat 100 mg). Dose adjustments were permitted every 4 weeks, beginning Week 4, to maintain Hb between 10 and 12 g/dL and were conducted in accordance with pre-specified rules ([Supplementary data, Tables S1 and S2](#)). During the treatment period, a dose reduction was required if the rate of Hb rise exceeded 2 g/dL within 4 weeks, and dosing was interrupted if Hb was ≥ 13 g/dL.

Initial DA doses were weight-based (per the Summary of Product Characteristics) and administered as a single subcutaneous or IV injection (0.45 μ g/kg weekly or 0.75 μ g/kg every other week). All DA administrations were conducted by the investigator during the first 36 weeks of treatment, after which patients or caregivers could administer them. Dose adjustments were conducted in accordance with the Summary of Product Characteristics. If the Hb rise exceeded 2.0 g/dL in 4 weeks, the dose was reduced by $\sim 25\%$. Dosing days and times remained consistent throughout the study for roxadustat and DA.

Oral iron was recommended in the roxadustat group to support erythropoiesis and as the first-line treatment for iron deficiency (ferritin < 100 ng/mL or TSAT $< 20\%$). IV iron was allowed if criteria were met: inadequate Hb response after at least two dose increases or the maximum dose limit was reached and iron deficiency or intolerance to oral iron. In the DA group, oral or IV iron was required for ferritin < 100 ng/mL or TSAT $< 20\%$. The route of iron administration was left to the investigator's discretion, where IV iron was administered per local practice guidelines.

Endpoints and assessments

The primary study endpoint was Hb response, defined as Hb ≥ 11.0 g/dL and Hb CFB ≥ 1.0 g/dL in patients with BL Hb > 8.0 g/dL or Hb CFB ≥ 2.0 g/dL in patients with BL

Table 1. Key secondary efficacy endpoints

Number	Endpoint	Analysis method (analysis set)	Test
1	Hb CFB to the average of Weeks 28–36 without use of rescue therapy within the 6 weeks prior to and during the 8-week evaluation period	MMRM (PPS)	Non-inferiority
2	Change in LDL from BL to the average of Weeks 12–28	MMRM (FAS)	Superiority
3	Time to first use of IV iron during Weeks 1–36	Stratified Cox proportional hazards (FAS)	Superiority
4	Change in SF-36 PF sub-score from BL to the average of Weeks 12–28 ^a	MMRM (PPS)	Non-inferiority
5	Change in SF-36 VT sub-score from BL to the average of Weeks 12–28 ^a	MMRM (PPS)	Non-inferiority
6	Change in MAP (mmHg) from BL to Weeks 20–28	MMRM (PPS)	Non-inferiority
7	Time to first occurrence of hypertension ^b during Weeks 1–36	Stratified Cox proportional hazards (PPS)	Non-inferiority

All the analyses compared roxadustat versus DA.

^aScore range: 0–100; higher scores indicate better health status. US-normalized values were used for the analysis where the scores normed to the US population have a mean of 50 and SD of 10.

^b≥20 mmHg SBP increase and SBP ≥170 mmHg; or ≥15 mmHg DBP increase and DBP ≥110 mmHg.

DBP, diastolic blood pressure; MMRM, mixed model of repeated measures method; SBP, systolic blood pressure.

Hb ≤8.0 g/dL, measured at two consecutive visits, ≥5 days apart, during the first 24 weeks of treatment and without receiving rescue therapy [defined as red blood cell (RBC) transfusion for all patients or DA for roxadustat-treated patients]. A subgroup analysis of this primary endpoint was performed; subgroups were pre-defined based on the key BL demographics and disease characteristics (including factors used in stratification for randomization). Likewise, several sensitivity analyses were conducted.

Key secondary endpoints, tested in a hierarchical sequence, are detailed in [Table 1](#). The Short Form-36 (SF-36) health survey questionnaire is a tool to assess health-related quality of life and comprises eight domains. The SF-36 physical functioning (PF; SF-36 PF) sub-score from PF domain (10 items) and the Vitality (VT) sub-score from VT domain (4 items) are included in the hierarchical testing.

Additional secondary endpoints included time to achieve the first Hb response, as defined by the primary endpoint; occurrence of hospitalizations; occurrence and time to first use of RBC transfusions; treatment compliance (defined as the dispensed amount minus the returned amount relative to the prescribed dose × 100) and CFB in serum ferritin, TSAT, iron, HbA1c level, fasting blood glucose, eGFR and urine albumin/creatinine ratio. Visits and assessments conducted during the study are reported in [Supplementary data, Table S3](#).

Safety

Safety was assessed by monitoring treatment-emergent adverse events (TEAEs) and adjudicated events, including major adverse cardiovascular events (MACEs), MACE+ and individual cardiovascular events, as well as vital signs and clinical laboratory results. MACE was defined as the composite of death, non-fatal myocardial infarction and/or stroke, and MACE+ was defined as the composite of death, myocardial infarction, stroke, and/or hospitalization for unstable angina and/or congestive heart failure. An Independent Review Committee was established to adjudicate cardiovascular events in a blinded manner. Two primary adjudicators reviewed the data, and in the case of a disagreement, the committee chair made the final determination.

Statistical methods

Sample size. The primary endpoint was analysed using the per protocol set (PPS). Assuming 80% of randomized patients would be included in the PPS, randomization of 570 patients would result in approximately 456 patients being analysed. This would provide ≥98% power to demonstrate non-inferiority using a margin for the difference of proportions of 15% for roxadustat versus DA for the primary endpoint assuming at least 80% of patients in both treatment groups achieved a response. Additional details are in the [Supplementary Methods](#).

Analysis populations. The full analysis set (FAS) included all randomized patients who received one or more doses of study drug and had one or more post-dose Hb assessments. The PPS included all FAS patients who met no PPS exclusion criteria ([Supplementary data, Table S4](#)). The safety analysis set consisted of all randomized patients who received one or more doses of study drug.

Statistical analysis

A Miettinen and Nurminen approach was used to compare the proportion of responders in the roxadustat and DA groups, adjusting for covariates (region; BL Hb; history of cardiovascular, cerebrovascular or thromboembolic diseases; and BL eGFR). Non-inferiority was demonstrated if the lower limit of the two-sided 95% confidence interval (CI) for the difference in the proportions of responders between the roxadustat and DA groups was more than –15%. All key secondary efficacy endpoints were tested in a hierarchical fixed sequence. To compare the roxadustat versus DA groups for adjudicated events, hazard ratios (HRs) and 95% CIs were calculated from a Cox regression model stratifying for region and history of cardiovascular disease, and adjusted for age, BL Hb and BL log-transformed eGFR as continuous covariates. All data processing and analyses were performed using SAS[®] version 9.3.

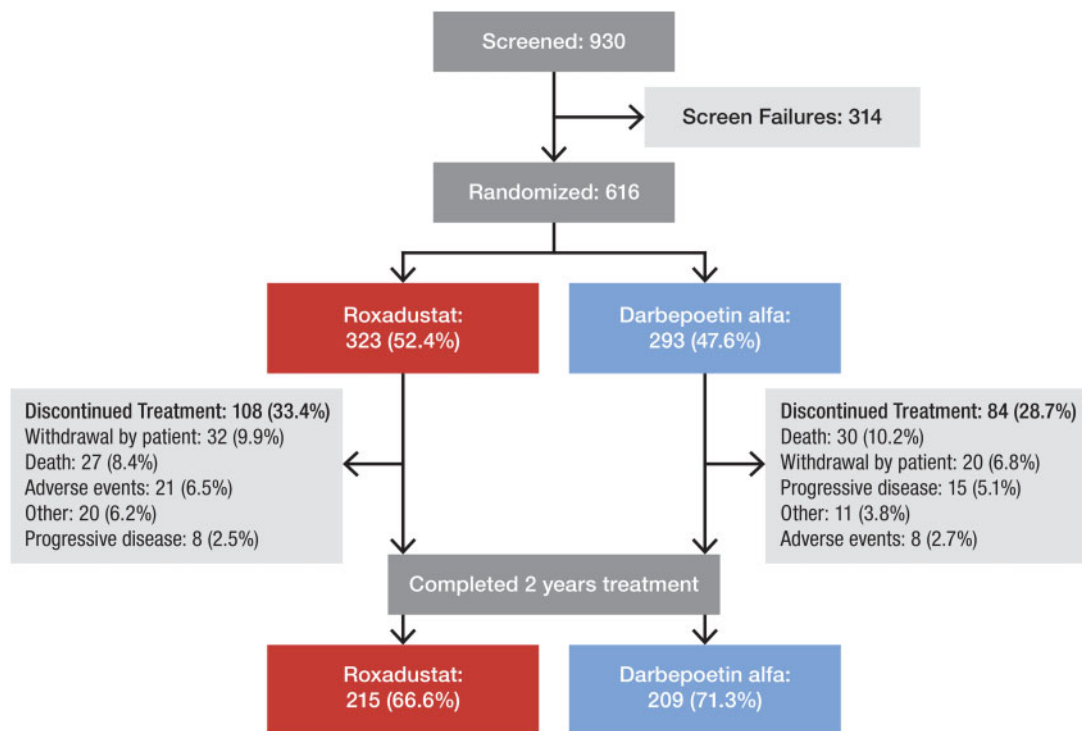


FIGURE 2: Patient disposition. Of 930 patients who signed informed consent, 616 were randomized (roxadustat, $n = 323$; DA, $n = 293$). A total of 424 [roxadustat group, $n = 215$ (66.6%); DA group, $n = 209$ (71.3%)] patients completed 2 years of treatment, whereas 33.4 and 28.7% of patients discontinued treatment in the roxadustat and DA groups, respectively.

Table 2. Subject disposition at Week 24 (safety analysis set)

Parameters	Roxadustat ($n = 323$)	DA ($n = 293$)	Total ($n = 616$)
Patients treated, n (%)	323 (100.0)	293 (100.0)	616 (100.0)
Completed treatment, n (%)	0	1 (0.3)	1 (0.2)
Discontinued treatment early, n (%)	32 (9.9)	27 (9.2)	59 (9.6)
Treatment ongoing, n (%)	291 (90.1)	265 (90.4)	556 (90.3)
Reasons for discontinuation, n (%)			
AE	6 (1.9)	2 (0.7)	8 (1.3)
Death	6 (1.9)	8 (2.7)	14 (2.3)
Non-compliance to protocol	3 (0.9)	0	3 (0.5)
Physician decision	4 (1.2)	1 (0.3)	5 (0.8)
Withdrawal by subject	13 (4.0)	15 (5.1)	28 (4.5)
Other	0	1 (0.3)	1 (0.2)

RESULTS

Patient disposition

Of the 930 patients who signed informed consent, 616 were randomized (roxadustat, $n = 323$; DA, $n = 293$). A total of 424 [roxadustat group, $n = 215$ (66.6%); DA group, $n = 209$ (71.3%)] patients completed 2 years of treatment, whereas 33.4 and 28.7% of patients discontinued treatment in the roxadustat and DA groups, respectively. Primary reasons for discontinuation in the roxadustat and DA groups were death [$n = 27$ (8.4%) versus $n = 30$ (10.2%)], withdrawal by patient [$n = 32$ (9.9%) versus $n = 20$ (6.8%)], progressive disease [$n = 8$ (2.5%) versus $n = 15$ (5.1%)] and AEs [$n = 21$ (6.5%) versus $n = 8$

(2.7%)] (Figure 2). Treatment discontinuation rates during the first 24 weeks of treatment were lower than discontinuation rates for the entire study duration and were comparable between roxadustat and DA (9.9% and 9.2%, respectively) (Table 2). In both groups, few patients were lost to follow-up (roxadustat: $n = 3$, 0.9%; DA: $n = 3$, 1.0%). Patient demographics and BL characteristics were comparable between groups. Most patients were randomized in central and eastern Europe. BL eGFRs were generally low with 30% of patients in both groups in Stage 5 CKD. Patients in the roxadustat group more frequently had eGFR < 10 mL/min/1.73 m² (17.6% versus 12.6%) (Table 3). History of ischaemic stroke, cerebrovascular accident and cerebral haemorrhage was comparable between patient

Table 3. Demographics and BL characteristics (safety analysis set)

Parameter	Roxadustat (n = 323)	DA (n = 293)	Total (N = 616)
Sex, male, n (%)	145 (44.9)	129 (44.0)	274 (44.5)
Race, n (%)			
White	306 (94.7)	281 (95.9)	587 (95.3)
Black	8 (2.5)	2 (0.7)	10 (1.6)
Asian	9 (2.8)	10 (3.4)	19 (3.1)
Age, mean (SD), years	66.8 (13.6)	65.7 (14.4)	66.3 (14.0)
Weight, mean (SD), kg	76.90 (16.33)	78.39 (17.68)	77.61 (16.99)
BMI, kg/m ²	27.95 (5.76)	28.74 (6.06)	28.33 (5.92)
Region, n (%)			
Western Europe and Israel	99 (30.7)	85 (29.0)	184 (29.9)
Central and Eastern Europe	224 (69.3)	208 (71.0)	432 (70.1)
Country, n (%)			
UK	37 (11.5)	24 (8.2)	61 (9.9)
Croatia	33 (10.2)	40 (13.7)	73 (11.9)
Serbia	25 (7.7)	23 (7.8)	48 (7.8)
Russian Federation	23 (7.1)	25 (8.5)	48 (7.8)
Czech Republic	21 (6.5)	12 (4.1)	33 (5.4)
Germany	20 (6.2)	17 (5.8)	37 (6.0)
Other	164 (50.8)	152 (51.9)	316 (51.2)
Hb, mean (SD), g/dL	9.55 (0.75)	9.55 (0.69)	–
LDL ^a , mean (SD), mg/dL, n	100.6 (40.0), 322	102.8 (39.8), 292	–
CKD aetiology, n (%)			
Diabetic nephropathy	109 (33.7)	98 (33.4)	207 (33.6)
Hypertensive nephropathy	92 (28.5)	87 (29.7)	179 (29.1)
Pyelonephritis	33 (10.2)	36 (12.3)	69 (11.2)
PKD	25 (7.7)	23 (7.8)	48 (7.8)
CKD stage ^b , n (%)			
3	72 (22.3)	62 (21.2)	134 (21.8)
4	155 (48.0)	143 (48.8)	298 (48.4)
5	96 (29.7)	88 (30.0)	184 (29.9)
eGFR, mL/min/1.73 m ²			
Mean (SD)	20.31 (11.49)	20.34 (10.73)	–
Median (min, max)	17.50 (3.1, 67.1)	18.50 (3.3, 64.8)	–
eGFR (mL/min/1.73 m ²), n (%)			
<10	57 (17.6)	37 (12.6)	94 (15.3)
≥10 to <15	74 (22.9)	71 (24.2)	145 (23.5)
≥15 to <30	133 (41.2)	136 (46.4)	269 (43.7)
≥30	59 (18.3)	49 (16.7)	108 (17.5)
hs-CRP, mg/L			
Mean (SD)	7.12 (10.52)	9.90 (21.56)	–
Median (min, max)	2.99 (0.1, 61.5)	3.39 (0.1, 241.1)	–
hs-CRP, n (%)			
≤ULN	209 (65.3)	177 (60.4)	386 (63.0)
>ULN	111 (34.7)	116 (39.6)	227 (37.0)
Missing	3 (0.9)	0	–
Iron repletion at BL, n (%)			
Ferritin ≥100 ng/mL and TSAT ≥20%	182 (56.3)	152 (51.9)	334 (54.2)
Iron parameters at BL ^a , mean (SD)			
Ferritin (pmol/L)	525.34 (519.53)	505.68 (466.90)	–
Median (min, max)	375.25 (15.28, 4986.09)	395.47 (6.52, 3588.46)	–
TSAT (%)	24.0 (10.1)	23.2 (10.6)	–
Median (min, max)	23.5 (5, 57)	22.0 (3, 64)	–
Serum iron (µmol/L)	11.28 (4.67)	10.70 (4.33)	–
Median (min, max)	10.80 (2.80, 43.50)	10.30 (1.40, 29.70)	–
Blood pressure, mean (SD), mmHg			
Systolic	137.17 (15.17)	137.53 (14.84)	–
Diastolic	74.88 (9.96)	75.24 (10.44)	–
History of cardiovascular, cerebrovascular or thromboembolic diseases, n (%)	152 (47.1)	142 (48.5)	294 (47.7)
History of ischaemic stroke, n (%)	0	1 (0.6)	1 (0.3)
History of cerebrovascular accident, n (%)	15 (8.9)	12 (7.2)	27 (8.1)
History of cerebral haemorrhage, n (%)	1 (0.6)	3 (1.8)	4 (1.2)

Continued

Table 3. Continued

Parameter	Roxadustat (n = 323)	DA (n = 293)	Total (N = 616)
History of specific cardiovascular medical conditions (≥10% of patients overall) ^c , n (%)			
Acute myocardial infarction	28 (16.7)	22 (13.2)	50 (14.9)
Angina pectoris	34 (20.2)	28 (16.8)	62 (18.5)
Cardiac failure chronic	69 (41.1)	65 (38.9)	134 (40.0)
Myocardial ischaemia	19 (11.3)	19 (11.4)	38 (11.3)
Treatment history for anaemia ^d , n (%)	210 (65.0)	207 (70.6)	417 (67.7)
ESA	22 (6.8)	17 (5.8)	39 (6.3)
IV iron	47 (14.6)	39 (13.3)	86 (14.0)
Oral iron	142 (44)	155 (52.9)	297 (48.2)
Vitamin B12	21 (6.5)	17 (5.8)	38 (6.2)
Folate	39 (12.1)	53 (18.1)	92 (14.9)
Blood transfusion	15 (4.6)	12 (4.1)	27 (4.4)
Other	12 (3.7)	9 (3.1)	21 (3.4)
Previous statin treatment, n (%)	158 (48.9)	148 (50.5)	306 (49.7)
Atorvastatin	116 (35.9)	96 (32.8)	212 (34.4)
Fluvastatin	3 (0.9)	1 (0.3)	4 (0.6)
Pitavastatin	0	1 (0.3)	1 (0.2)
Pravastatin	6 (1.9)	5 (1.7)	11 (1.8)
Rosuvastatin	17 (5.3)	22 (7.5)	39 (6.3)
Simvastatin	20 (6.2)	28 (9.6)	48 (7.8)

Data are reported as mean (SD) unless otherwise indicated.

^aData from the FAS.

^bCKD stage as reported by the investigator.

^cPatients may have reported more than one cardiovascular event.

^dMore than one treatment for anaemia may have been reported for a subject.

BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein; ULN, upper limit of normal.

groups. Concomitant medications are summarized in [Supplementary data, Table S5](#). There were no apparent differences between groups for previous statin use.

Treatment exposure and compliance

The median treatment duration was comparable between groups (roxadustat: 103.7 weeks, min, max: 0.4, 106.1; DA: 100.1 weeks, min, max: 0.1, 105.3). The mean [standard deviation (SD)] weekly dose consumed was 223.20 (127.43) mg in the roxadustat group and 33.39 (22.80) µg in the DA group. Among patients who had one or more dose changes during the correction period (roxadustat, *n* = 236; DA, *n* = 212), the mean (SD) numbers of dose changes per patient in the roxadustat and DA groups were 1.9 (1.4) and 2.9 (2.6), respectively, and during the maintenance period (roxadustat, *n* = 294; DA, *n* = 260) were 9.4 (4.2) and 9.0 (5.3), respectively. During the correction period, numerically fewer patients in the roxadustat group had dose decreases (roxadustat: *n* = 116, 35.9%; DA: *n* = 132, 45.1%) with similar rates of dose holds (roxadustat: *n* = 41, 12.7%; DA: *n* = 31, 10.6%). The mean (SD) treatment compliance was similar between groups [99.56% (3.75) versus 98.93% (3.38)].

Primary efficacy endpoint

In the PPS, among patients who had not received rescue therapy, roxadustat was non-inferior to DA for achieving Hb response during the first 24 weeks (89.5% versus 78.0%, difference of proportion 11.51%, 95% CI 5.66, 17.36) ([Table 4](#)). Mean Hb levels are shown in [Figure 3](#). Subgroup analyses

were consistent with the results of the primary analysis for non-inferiority of roxadustat to DA ([Table 4](#)). Likewise, in a sensitivity analysis of the primary efficacy endpoint following the implementation of protocol version 2.0, among patients who had not received rescue therapy, roxadustat was non-inferior to DA for achieving Hb response during the first 24 weeks (88.5% versus 77.2%, difference of proportion 11.19%, 95% CI 4.67, 17.72) ([Supplementary data, Figure S1](#)).

Key secondary efficacy endpoints

Non-inferiority of roxadustat to DA was demonstrated for Hb CFB to Weeks 28–36, CFB to Weeks 12–28 in the SF-36 PF and SF-36 health survey VT (SF-36 VT) sub-scores, CFB in Weeks 20–28 in mean arterial pressure (MAP) and time to first hypertension occurrence during Weeks 1–36. Superiority of roxadustat to DA was demonstrated for decrease in low-density lipoprotein (LDL) from BL to Weeks 12–28 and lower incidence rate for first use of IV iron during Weeks 1–36 ([Table 5](#)).

In the FAS, few patients used IV iron during Weeks 1–36 (roxadustat: *n* = 20, 6.2%; DA: *n* = 37, 12.7%). In these patients, the mean (SD) monthly dose of IV iron during Weeks 1–36 was 34.74 (29.96) mg and 69.59 (67.34) mg in the roxadustat and DA groups, respectively. Concomitant use of oral preparations of bivalent (roxadustat: 43.7%; DA: 49.8%) and trivalent (roxadustat: 35.3%; DA: 44.7%) iron was lower in roxadustat-treated patients. The LDL levels were comparable at BL between groups but were lower in the roxadustat group throughout the treatment period ([Figure 4](#)). In roxadustat-treated patients, slight

Table 4. Hb response during the first 24 weeks of treatment (PPS)^a

	Roxadustat (n = 286)	DA (n = 273)	Between-group difference of patients achieving the defined response (%) (95% CI)
Patients achieving tde defined response ^b	256 (89.5)	213 (78.0)	11.51 (5.66, 17.36)
95% CI	85.4, 92.8	72.6, 82.8	
Subgroup analyses—patients achieving the defined response ^b			
Sex, n (%)			
Male	116 (92.1)	99 (81.8)	10.25 (1.91, 18.58)
Female	140 (87.5)	114 (75.0)	12.50 (3.92, 21.08)
Age, years, n (%)			
<65	95 (86.4)	81 (77.9)	8.48 (−1.76, 18.71)
65–74	66 (89.2)	61 (77.2)	11.97 (0.33, 23.62)
≥75	95 (93.1)	71 (78.9)	12.83 (2.75, 22.92)
BL eGFR, mL/min/1.73 m ² , n (%)			
<15	105 (89.0)	78 (75.7)	14.50 (4.63, 24.37)
≥15	151 (89.9)	135 (79.4)	10.02 (2.66, 17.37)
Iron status, n (%)			
Ferritin ≥100 ng/mL and TSAT ≥20%	159 (96.4)	118 (84.3)	12.08 (5.41, 18.75)
Ferritin <100 ng/mL or TSAT <20%	97 (80.2)	95 (71.4)	8.14 (−1.97, 18.26)
BL hs-CRP, n (%)			
≤ULN	173 (91.5)	132 (78.1)	13.43 (6.04, 20.82)
>ULN	82 (85.4)	81 (77.9)	7.53 (−3.12, 18.18)

^aA generalized linear model as an approximation for the Miettinen and Nurminen method, adjusted for stratification factors (actual), was used to estimate the difference of proportions and 95% CI.

^bResponse was defined as Hb ≥11.0 g/dL and Hb change ≥1.0 g/dL if BL Hb >8.0 g/dL; or change ≥2.0 g/dL if BL Hb ≤8.0 g/dL at two consecutive visits separated by ≥5 days, without having received rescue therapy.

Rescue therapy was defined as RBC transfusion for all patients or DA for roxadustat-treated patients.

hs-CRP, high-sensitivity C-reactive protein; ULN, upper limit of normal.

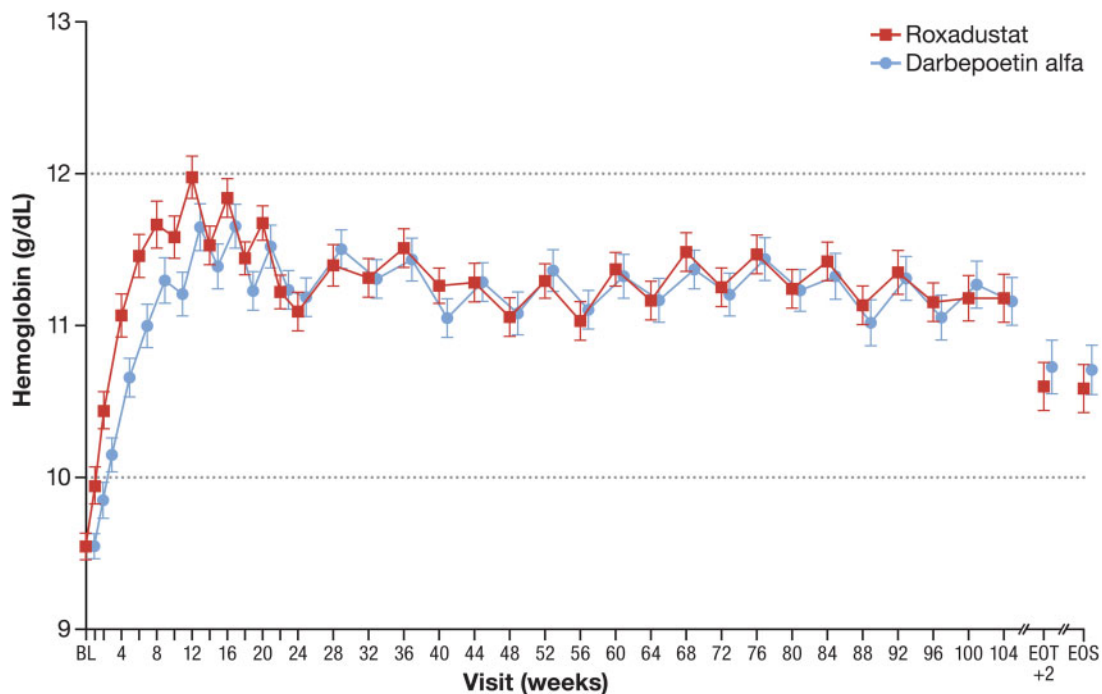


FIGURE 3: Mean (95% CI) levels of Hb (PPS). Mean Hb levels are shown with dotted lines in reference to the aim of achieving Hb levels between 10.0 and 12.0 g/dL. EOT, end of treatment; EOS, end of study.

decreases were seen in high-density lipoprotein (HDL) cholesterol [mean (SD) CFB at Week 36: roxadustat: −0.13 (0.32) mmol/L; DA: −0.01 (0.25) mmol/L] and, subsequently, in the LDL/HDL cholesterol ratio [mean (SD) CFB at Week 36: roxadustat: −0.03 (0.95); DA: 0.04 (0.93)].

At Week 24, in the FAS, 88.2% of patients in the roxadustat group and 77.4% in the DA group achieved Hb response. The time to achieve the first Hb response was shorter and the HR of the incidence rate was favourable in the roxadustat group (Supplementary data, Table S7). There was no difference

Table 5. Results for the key secondary efficacy endpoints

Endpoint	Analysis method (analysis set)	Test passed	Statistics (units)	Result (95% CI)	P-value ^a	Non-inferiority margin
Hb CFB to the average of Weeks 28–36 ^b	MMRM (PPS)	Non-inferiority	Difference between LSM (g/dL)	0.015 (–0.131, 0.162)	NA	–0.75
Change in LDL from BL to the average of Weeks 12–28	MMRM (FAS)	Superiority	Difference between LSM (mmol/L)	–0.403 (–0.510, –0.296)	<0.001	NA
Time to first use of IV iron during Weeks 1–36	Stratified Cox proportional hazards (FAS)	Superiority	HR of incidence rates	0.45 (0.26, 0.78)	0.004	NA
Change in SF-36 PF sub-score from BL to the average of Weeks 12–28 ^c	MMRM (PPS)	Non-inferiority	Difference between LSM	–1.284 (–2.423, –0.145)	NA	–3
Change in SF-36 VT sub-score from BL to the average of Weeks 12–28 ^c	MMRM (PPS)	Non-inferiority	Difference between LSM	–0.457 (–1.656, 0.742)	NA	–3
Change in MAP (mmHg) from BL to Weeks 20–28 ^d	MMRM (PPS)	Non-inferiority	Difference between LSM (mmHg)	–0.372 (–1.587, 0.842)	NA	1
Time to first occurrence of hypertension ^e during Weeks 1–36	Stratified Cox proportional hazards (PPS)	Non-inferiority	HR of incidence rates	0.83 (0.56, 1.22)	0.336	1.3

All the analyses compared roxadustat versus DA.

^aP-values are presented for superiority test only; for superiority tests, the null hypothesis was rejected if the upper bound of the 95% CI of difference of LSM was below 0.

^bNon-inferiority was concluded if the lower bound of the 95% CI of the difference of LSM was more than –0.75.

^cNon-inferiority was concluded if the lower bound of the 95% CI of the difference of LSM was more than –3.

^dNon-inferiority was concluded if the upper bound of the 95% CI of the difference of LSM was <1 mmHg.

^eNon-inferiority was declared if the upper bound of the 95% CI was <1.3.

MMRM, mixed model of repeated measures method; NA, not applicable.

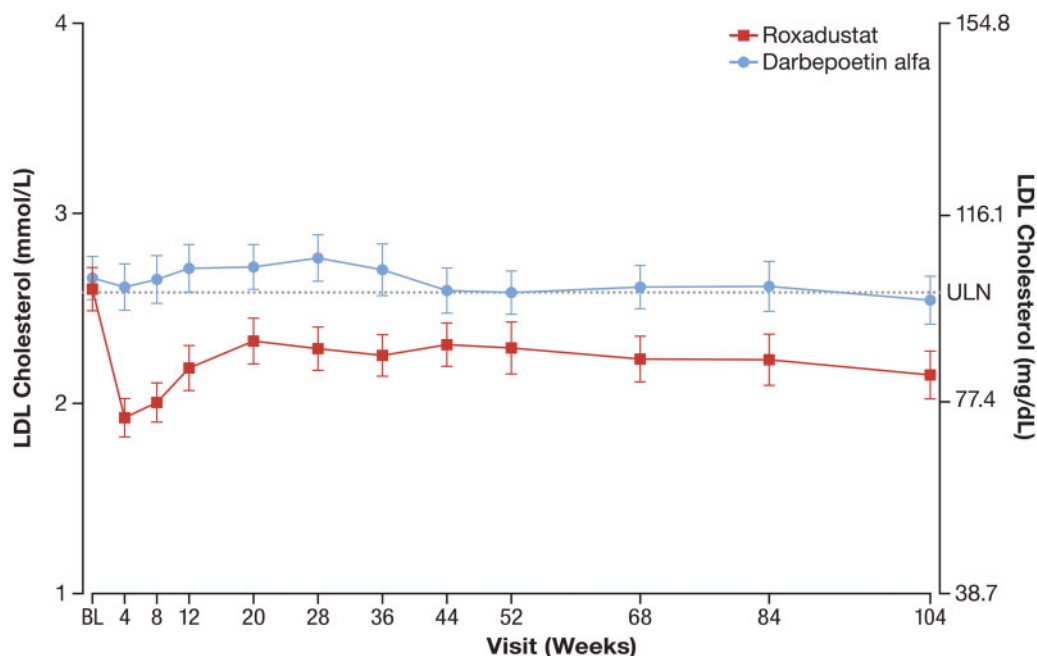


FIGURE 4: Mean (95% CI) levels of LDL by visit (FAS). BL LDL levels were comparable between groups, but patients in the roxadustat group had LDL levels below the upper limit of normal (ULN) and lower than the DA group throughout the treatment period.

between treatment groups in time to first use of RBC transfusion [subjects with RBC transfusion (FAS): roxadustat, $n = 38$ (11.8%); DA, $n = 28$ (9.6%); roxadustat HR = 1.30, 95% CI 0.79, 2.11; $P = 0.300$]. Similarly, there was no difference between treatment groups in time to first use of rescue therapy, defined as RBC transfusion for all patients or DA for roxadustat-treated patients [subjects with rescue therapy (FAS):

roxadustat, $n = 46$ (14.3%), 8 (2.5%) of whom received ESA as a rescue therapy; DA, $n = 28$ (9.6%); roxadustat HR = 1.59, 95% CI 0.99, 2.54; $P = 0.055$]. The levels of serum ferritin, TSAT and iron were comparable between treatment groups throughout the study (Figure 5, Table 6; Supplementary data, Figure S2).

In the FAS, the estimated annualized eGFR values over time were comparable between treatment groups [least squares

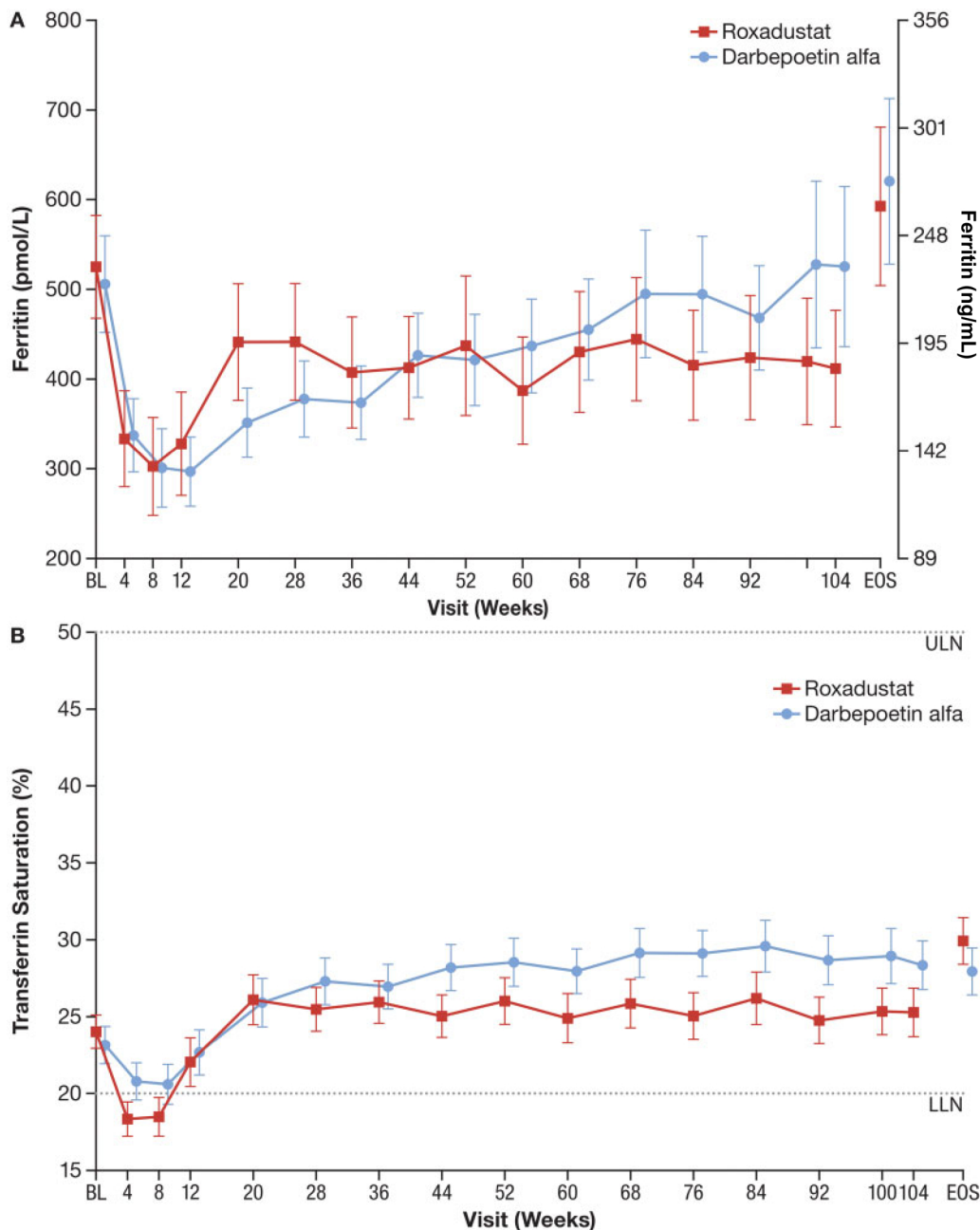


FIGURE 5: Mean (95% CI) levels of serum ferritin (A) and TSAT (B) by visit (FAS). The serum ferritin levels were comparable between the treatment groups beginning at BL and continuing throughout the end of the study (EOS). The TSAT percentages were comparable between the treatment groups beginning at BL and continuing throughout the EOS, rising above the lower limit of normal between Weeks 8 and 12 and never approaching the upper limit of normal (ULN).

mean (LSM) difference: $-0.05 \text{ mL/min}/1.73 \text{ m}^2$, 95% CI $-0.93, 0.82$, $P = 0.902$]. Likewise, the time to start of chronic dialysis or renal transplant was similar between groups (HR = 1.00, 95% CI 0.76, 1.31; $P = 0.990$).

Safety

TEAE occurrence was comparable between the roxadustat (91.6%) and DA (92.5%) groups, whereas TEAEs leading to treatment withdrawal were more frequent with roxadustat (7.7% versus 3.8%) (Table 7; Supplementary data, Tables S7 and S8). TEAEs that occurred during the safety-emergent period and led to death at any time occurred in 10.5 and 11.6%

of patients in the roxadustat and DA groups, respectively (Table 7).

Common TEAEs in both groups included end-stage renal disease, hypertension, decreased eGFR, peripheral oedema, hyperkalaemia and nausea. Peripheral oedema, hyperphosphataemia and dyspnoea occurred more frequently in the roxadustat group and end-stage renal disease, hypertension, hyperkalaemia and urinary tract infection occurred more frequently in the DA group (Supplementary data, Table S7). For all TEAEs, the difference in the incidence between treatment groups was $<5\%$. Serious TEAEs occurring during the study are reported in Table 8.

Table 6. Levels of serum ferritin, TSAT and serum iron—CFB (FAS)

Iron parameters, mean (SD)	Roxadustat	DA
Ferritin (pmol/L) at BL	525.34 (519.53)	505.68 (466.90)
CFB at Week 36	-131.80 (355.46)	-120.42 (362.08)
CFB at Week 52	-93.07 (521.43)	-72.38 (459.34)
CFB at Week 104	-89.28 (476.17)	26.45 (730.13)
CFB at EOS	78.58 (680.52)	119.16 (697.39)
TSAT (%) at BL	24.0 (10.1)	23.2 (10.6)
CFB at Week 36	1.6 (12.0)	3.9 (11.5)
CFB at Week 52	1.3 (11.8)	5.2 (13.2)
CFB at Week 104	0.5 (11.9)	5.0 (13.3)
CFB at EOS	5.3 (12.3)	4.7 (13.9)
Serum iron (µmol/L) at BL	11.28 (4.67)	10.70 (4.33)
CFB at Week 36	1.93 (6.96)	1.71 (5.09)
CFB at Week 52	1.12 (5.86)	2.18 (6.23)
CFB at Week 104	0.61 (6.19)	1.44 (5.72)
CFB at EOS	2.03 (6.70)	1.37 (5.98)

EOS, end of study.

Table 7. Overview of TEAEs^a (safety analysis set)

Event	Roxadustat (n = 323)	DA (n = 293)
TEAE	296 (91.6)	271 (92.5)
Serious TEAE	209 (64.7)	181 (61.8)
TEAE leading to withdrawal of treatment	25 (7.7)	11 (3.8)
TEAE leading to death ^b	34 (10.5)	34 (11.6)
TEAE NCI CTC grades 3 or higher	181 (56.0)	164 (56.0)
Death during the safety-emergent period	30 (9.3)	31 (10.6)

Data are reported as n (%).

^aAEs during the safety-emergent period [evaluation period from the date of first drug intake up to the minimum between (analysis date of last dose + 28 days + x), end of study visit or date of death, with x corresponding to additional days based on the last dosing frequency.

^bTEAEs occurring during the safety-emergent period and leading to death at any time.

NCI CTC, National Cancer Institute—Common Terminology Criteria for AEs.

The HR (95% CI) for the composite endpoints MACE and MACE+ for both the safety-emergent period analysis [MACE: 0.81 (0.52–1.25), P = 0.339; MACE+: 0.90 (0.61–1.32), P = 0.583; Table 9] and on-study analysis [MACE: 0.89 (0.60–1.33), P = 0.574; MACE+: 0.93 (0.65–1.32), P = 0.682; Supplementary data, Table S9] showed favourable trends for roxadustat; however, these analyses were not sufficiently powered to demonstrate non-inferiority or superiority.

DISCUSSION

Roxadustat was as effective as DA in increasing Hb levels without rescue therapy at 24 weeks, which aligns with previous findings [14, 17, 18]. In this study, Hb levels were higher in the roxadustat group versus the DA group for ~20 weeks before becoming similar in both treatment groups and maintaining within 10.0–12.0 g/dL for up to 2 years. Previously, among Japanese NDD CKD patients not receiving ESAs, the Hb response rate from BL to Week 24 was 94.9% in roxadustat-treated patients [13]. When roxadustat was compared with

Table 8. Incidence of common (≥1% in any treatment group) serious TEAEs (safety analysis set)

MedDRA version 20.0 preferred term	Roxadustat (n = 323)	DA (n = 293)
Overall	209 (64.7)	181 (61.8)
Anaemia	5 (1.5)	6 (2.0)
Acute myocardial infarction	5 (1.5)	8 (2.7)
Bradycardia	4 (1.2)	1 (0.3)
Cardiac arrest	3 (0.9)	3 (1.0)
Cardiac failure	12 (3.7)	10 (3.4)
Cardiac failure acute	3 (0.9)	6 (2.0)
Cardiac failure congestive	2 (0.6)	10 (3.4)
Coronary artery disease	1 (0.3)	3 (1.0)
Death ^a	5 (1.5)	4 (1.4)
General physical health deterioration	1 (0.3)	4 (1.4)
Cholecystitis acute	0	3 (1.0)
Clostridium difficile colitis	1 (0.3)	3 (1.0)
Device related infection	3 (0.9)	4 (1.4)
Gangrene	4 (1.2)	0
Gastroenteritis	3 (0.9)	3 (1.0)
Influenza	2 (0.6)	4 (1.4)
Osteomyelitis	1 (0.3)	3 (1.0)
Peritonitis	1 (0.3)	3 (1.0)
Pneumonia	21 (6.5)	14 (4.8)
Pyelonephritis acute	1 (0.3)	7 (2.4)
Sepsis	7 (2.2)	9 (3.1)
Staphylococcal sepsis	4 (1.2)	0
Urinary tract infection	7 (2.2)	3 (1.0)
Urinary tract infection bacterial	5 (1.5)	1 (0.3)
Urosepsis	2 (0.6)	3 (1.0)
Arteriovenous fistula thrombosis	9 (2.8)	5 (1.7)
eGFR decreased	26 (8.0)	25 (8.5)
Dehydration	3 (0.9)	7 (2.4)
Fluid overload	4 (1.2)	1 (0.3)
Hyperkalaemia	7 (2.2)	6 (2.0)
Basal cell carcinoma	4 (1.2)	0
Ischaemic stroke	0	3 (1.0)
Syncope	6 (1.9)	3 (1.0)
Transient ischaemic attack	4 (1.2)	3 (1.0)
Acute kidney injury	7 (2.2)	7 (2.4)
Azotaemia	1 (0.3)	3 (1.0)
End-stage renal disease	108 (33.4)	106 (36.2)
Dyspnoea	6 (1.9)	0
Pleural effusion	2 (0.6)	4 (1.4)
Pulmonary hypertension	1 (0.3)	3 (1.0)
Pulmonary oedema	4 (1.2)	2 (0.7)
Deep vein thrombosis	4 (1.2)	1 (0.3)
Hypertension	8 (2.5)	5 (1.7)
Hypertensive crisis	5 (1.5)	5 (1.7)
Hypotension	4 (1.2)	2 (0.7)
Peripheral arterial occlusive disease	3 (0.9)	4 (1.4)
Peripheral ischaemia	4 (1.2)	2 (0.7)

Data are reported as n (%).

^aCause not specified.

placebo in Chinese [14] and European [15, 16] NDD CKD patients with anaemia, Hb response occurred in more roxadustat patients (75.0–86.0%), compared with placebo patients (0.0–8.5%). Additionally, roxadustat demonstrated non-inferiority for Hb maintenance rate versus DA in Japanese patients on haemodialysis [11] and versus epoetin alfa in global studies of DD patients [8].

Roxadustat was superior to DA for LDL lowering from BL to Weeks 12–28, which corroborates prior data in NDD [14, 15]

Table 9. Statistical analysis of adjudicated events during the safety-emergent period^a (safety analysis set)

Event	Roxadustat (<i>n</i> = 323), <i>n</i> (%)	DA (<i>n</i> = 293), <i>n</i> (%)	HR: roxadustat versus DA (95% CI)	P-value
MACE ^b	38 (11.8)	41 (14.0)	0.81 (0.52, 1.25)	0.339
MACE+ ^c	54 (16.7)	53 (18.1)	0.90 (0.61, 1.32)	0.583
Death ^d	29 (9.0)	31 (10.6)	0.83 (0.50, 1.38)	0.467
Myocardial infarction	11 (3.4)	10 (3.4)	0.96 (0.41, 2.27)	NS
Stroke	4 (1.2)	7 (2.4)	0.48 (0.14, 1.67)	NS
Unstable angina requiring hospitalization	0 (0.0)	1 (0.3)	–	–
Congestive heart failure requiring hospitalization	25 (7.7)	21 (7.2)	1.08 (0.60, 1.95)	NS
Deep vein thrombosis/pulmonary embolism	8 (2.5)	2 (0.7)	3.63 (0.76, 17.20)	NS
Hypertensive emergency	5 (1.5)	5 (1.7)	0.86 (0.24, 3.00)	NS

Data are reported as *n* (%).

^aIncluded the treatment period and the following 28 days.

^bDefined as death, non-fatal myocardial infarction and/or stroke.

^cDefined as death, myocardial infarction, stroke and hospitalization for either unstable angina and/or congestive heart failure.

^dOne roxadustat-treated patient had a date of death (DOD) reported as after the end of the safety-emergent period date in the adjudication database used for this table; this DOD is inconsistent with the DOD reported in the primary database, which fell within the safety-emergent period. Thus, this subject is excluded from death and/or death-related adjudicated data presented in Table 9.

NS, not significant.

and DD [8, 12] CKD patients. LDL levels remained lower with roxadustat throughout the study. The clinical significance of this lowering requires further investigation. Slight decreases in HDL cholesterol were seen in both groups. Subsequent shifts in LDL/HDL cholesterol ratio were observed, where there was a slight decrease in roxadustat-treated patients and a slight increase in DA-treated patients. Again, the clinical significance of these shifts requires further investigation.

Roxadustat was non-inferior to DA for changes in patient-reported healthcare-related quality of life measurements. However, the implications of this are hypothesis-generating since an analysis of the increase of the quality of life score during treatment was not conducted.

Roxadustat was superior to DA for time to first use of IV iron during Weeks 1–36. A lower proportion of patients required IV iron and had a lower monthly dose in the roxadustat group. Similarly, the concomitant use of oral preparations of bivalent and trivalent iron was lower in roxadustat-treated patients compared with DA-treated patients. Roxadustat improves iron absorption and mobilization from iron stores, thereby increasing erythropoiesis and maintaining Hb levels with less need for IV iron supplementation [9, 10, 13, 14]. The potential advantage of a reduced requirement for additional IV or oral iron therapy associated with roxadustat remains to be confirmed. In this study, ferritin levels decreased during the first weeks of treatment, reflecting the iron consumption necessary for erythropoiesis. The initial decrease in ferritin was most pronounced around Week 8; thereafter, ferritin levels seemed to (i) stabilize in roxadustat-treated patients and (ii) slowly increase over time in DA-treated patients. Nevertheless, ferritin levels remained comparable across both treatment groups.

The safety profiles for roxadustat and DA, used at doses required to achieve Hb 10–12 g/dL, were comparable to previous studies [14, 18, 19]. Common TEAEs in both groups included end-stage renal disease, hypertension, decreased eGFR, peripheral oedema, hyperkalaemia and nausea. TEAEs leading to

treatment withdrawal were more common with roxadustat than DA in this study. The open-label comparison of roxadustat, a novel therapy, against a well-established anaemia treatment, could have introduced a bias in AE reporting or therapy discontinuation. There was no difference between treatment groups in the occurrence of adjudicated events per an exploratory cardiovascular safety analysis, including MACE, MACE+ and death. That said, these findings should be interpreted with caution because the study was not sufficiently powered to detect superiority or non-inferiority between treatment groups. Potential risks related to angiogenesis and carcinogenesis associated with HIF stabilization have been hypothesized; however, these risks were not supported in the studied population and further study with longer follow-up is warranted before firm conclusions can be drawn. In this study, deep vein thrombosis/pulmonary embolism was the only adjudicated event with ≥1% difference in incidence between the roxadustat and DA groups. Because incidence rates were low, surveillance data or pooled data from multiple studies could identify patterns of AEs.

This study has some limitations. The use of an open-label design may have increased the risk of bias. In addition, the study population was almost entirely White and from Central or Eastern Europe, which may limit the generalizability. Furthermore, this trial was not sufficiently powered to draw final conclusions across all safety measures. While only a small portion (<8%) of the patients in this study had polycystic kidney disease (PKD) as a CKD aetiology, in-depth exams regarding renal cysts were not performed in this study; pre-clinical data suggest that cyst growth is associated with hypoxia-driven activation of the HIF pathway [20, 21]. Lastly, although post-amendment sensitivity analyses of the primary efficacy endpoint were supportive of the primary analysis, during-trial amendments to the protocol remain a possible limitation to this study.

This study suggests that roxadustat was non-inferior to DA in achieving Hb response during the first 24 weeks without rescue therapy, while having a lower IV iron supplementation

requirement due to improved iron absorption and mobilization. The safety profiles of roxadustat and DA were generally comparable over the study duration with no new safety signals observed. Consequently, roxadustat is a viable option for anaemia treatment in NDD CKD patients, maintaining Hb levels for up to 104 weeks. Furthermore, the oral route of administration for roxadustat and the lower number of injected therapies needed may represent an advantage for NDD CKD patients compared with other ESAs, such as DA.

SUPPLEMENTARY DATA

Supplementary data are available at [ndt online](https://ndt.online).

ACKNOWLEDGEMENTS

Roxadustat is being developed by FibroGen, AstraZeneca and Astellas. Medical writing/editorial support was provided by Patrick Tucker, PhD, Rosalba Satta, PhD, Drayton Hammond, PharmD and Elizabeth Hermans, PhD from Peloton Advantage, LLC an OPEN Health Company, Parsippany, NJ, and funded by the study sponsor.

FUNDING

This study was funded by Astellas Pharma, Inc.

AUTHORS' CONTRIBUTIONS

Conception and design were by M.R.; acquisition of data was carried out by J.B., M.S. and U.V.; analysis and interpretation of the data were performed by J.B., M.R. and U.V.; and drafting and critical revision of the article for important intellectual content were done by J.B., B.A., A.T., M.S., M.R., U.V. and C.M.

CONFLICT OF INTEREST STATEMENT

C.M. reports personal fees from Astellas Pharma, Inc., Novartis and Amgen and non-financial support from Astellas Pharma, Inc., Novartis, Chiesi, Amgen and Fresenius. M.R., A.T. and U.V. report being an employee of Astellas Pharma, Inc. B.A., J.B. and M.S. have nothing to disclose.

(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)

DATA AVAILABILITY STATEMENT

Researchers may request access to anonymized participant-level data, trial-level data and protocols from Astellas sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing see: <https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx>.

REFERENCES

1. Fishbane S, Spinowitz B. Update on anemia in ESRD and earlier stages of CKD: core curriculum 2018. *Am J Kidney Dis* 2018; 71: 423–435
2. Locatelli F, Fishbane S, Block GA *et al*. Targeting hypoxia-inducible factors for the treatment of anemia in chronic kidney disease patients. *Am J Nephrol* 2017; 45: 187–199
3. Wong MMY, Tu C, Li Y *et al*; The CKDopps Investigators. Anemia and iron deficiency among chronic kidney disease stages 3–5ND patients in the chronic kidney disease outcomes and practice patterns study: often unmeasured, variably treated. *Clin Kidney J* 2020; 13: 613–624
4. Pfeffer MA, Burdmann EA, Chen CY *et al*. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009; 361: 2019–2032
5. Seliger SL, Zhang AD, Weir MR *et al*. Erythropoiesis-stimulating agents increase the risk of acute stroke in patients with chronic kidney disease. *Kidney Int* 2011; 80: 288–294
6. Del Vecchio L, Locatelli F. An overview on safety issues related to erythropoiesis-stimulating agents for the treatment of anaemia in patients with chronic kidney disease. *Expert Opin Drug Saf* 2016; 15: 1021–1030
7. Gupta N, Wish JB. Hypoxia-inducible factor prolyl hydroxylase inhibitors: a potential new treatment for anemia in patients with CKD. *Am J Kidney Dis* 2017; 69: 815–826
8. Chen N, Hao C, Liu BC *et al*. Roxadustat treatment for anemia in patients undergoing long-term dialysis. *N Engl J Med* 2019; 381: 1011–1022
9. Akizawa T, Otsuka T, Reusch M *et al*. Intermittent oral dosing of roxadustat in peritoneal dialysis chronic kidney disease patients with anemia: a randomized, phase 3, multicenter, open-label study. *Ther Apher Dial* 2020; 24: 115–125
10. Akizawa T, Ueno M, Shiga T *et al*. Oral roxadustat three times weekly in ESA-naïve and ESA-converted patients with anemia of chronic kidney disease on hemodialysis: results from two phase 3 studies. *Ther Apher Dial* 2020; 24: 628–641
11. Akizawa T, Iwasaki M, Yamaguchi Y *et al*. Phase 3, randomized, double-blind, active-comparator (darbepoetin alfa) study of oral roxadustat in CKD patients with anemia on hemodialysis in Japan. *J Am Soc Nephrol* 2020; 31: 1628–1639
12. Provenzano R, Shutov E, Eremeeva L *et al*. Roxadustat for anemia in patients with end-stage renal disease incident to dialysis. *Nephrol Dial Transplant* 2021; 36: 1717–1730
13. Akizawa T, Yamaguchi Y, Otsuka T *et al*. A phase 3, multicenter, randomized, two-arm, open-label study of intermittent oral dosing of roxadustat for the treatment of anemia in Japanese erythropoiesis-stimulating agent-naïve chronic kidney disease patients not on dialysis. *Nephron* 2020; 144: 372–382
14. Chen N, Hao C, Peng X *et al*. Roxadustat for anemia in patients with kidney disease not receiving dialysis. *N Engl J Med* 2019; 381: 1001–1010
15. Coyne DW, Roger SD, Shin SK *et al*. Roxadustat for CKD-related anemia in non-dialysis patients. *Kidney Int Rep* 2021; 6: 624–635
16. Fishbane S, El-Shahawy MA, Pecoits-Filho R *et al*. Roxadustat for treating anemia in patients with CKD not on dialysis: results from a randomized phase 3 study. *J Am Soc Nephrol* 2021; 32: 737–755
17. Provenzano R, Besarab A, Sun CH *et al*. Oral hypoxia-inducible factor prolyl hydroxylase inhibitor roxadustat (FG-4592) for the treatment of anemia in patients with CKD. *Clin J Am Soc Nephrol* 2016; 11: 982–991
18. Chen N, Qian J, Chen J *et al*. Phase 2 studies of oral hypoxia-inducible factor prolyl hydroxylase inhibitor FG-4592 for treatment of anemia in China. *Nephrol Dial Transplant* 2017; 32: 1373–1386
19. Provenzano R, Besarab A, Wright S *et al*. Roxadustat (FG-4592) versus epoetin alfa for anemia in patients receiving maintenance hemodialysis: a phase 2, randomized, 6- to 19-week, open-label, active-comparator, dose-ranging, safety and exploratory efficacy study. *Am J Kidney Dis* 2016; 67: 912–924
20. Buchholz B, Eckardt KU. Role of oxygen and the HIF-pathway in polycystic kidney disease. *Cell Signal* 2020; 69: 109524
21. Kraus A, Peters DJM, Klanke B *et al*. HIF-1 α promotes cyst progression in a mouse model of autosomal dominant polycystic kidney disease. *Kidney Int* 2018; 94: 887–899

Received: 2.12.2020; Editorial decision: 10.5.2021