ORIGINAL ARTICLE

Roxadustat for Anemia in Patients with Kidney Disease Not Receiving Dialysis

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ABSTRACT

BACKGROUND

Roxadustat (FG-4592) is an oral inhibitor of hypoxia-inducible factor (HIF) prolyl hydroxylase that stimulates erythropoiesis and regulates iron metabolism. In phase 2 studies involving patients with chronic kidney disease, roxadustat increased levels of endogenous erythropoietin to within or near the physiologic range, along with increasing hemoglobin levels and improving iron homeostasis. Additional data are needed regarding the efficacy and safety of roxadustat for the treatment of anemia in patients with chronic kidney disease who are not undergoing dialysis.

METHODS

In this phase 3 trial conducted at 29 sites in China, we randomly assigned 154 patients with chronic kidney disease in a 2:1 ratio to receive roxadustat or placebo three times a week for 8 weeks in a double-blind manner. All the patients had a hemoglobin level of 7.0 to 10.0 g per deciliter at baseline. The randomized phase of the trial was followed by an 18-week open-label period in which all the patients received roxadustat; parenteral iron was withheld. The primary end point was the mean change from baseline in the hemoglobin level, averaged over weeks 7 through 9.

RESULTS

During the primary-analysis period, the mean (±SD) change from baseline in the hemoglobin level was an increase of 1.9±1.2 g per deciliter in the roxadustat group and a decrease of 0.4±0.8 g per deciliter in the placebo group ($P<0.001$). The mean reduction from baseline in the hepcidin level (associated with greater iron availability) was 56.14±63.40 ng per milliliter in the roxadustat group and 15.10±48.06 ng per milliliter in the placebo group. The reduction from baseline in the total cholesterol level was 40.6 mg per deciliter in the roxadustat group and 7.7 mg per deciliter in the placebo group. Hyperkalemia and metabolic acidosis occurred more frequently in the roxadustat group than in the placebo group. The efficacy of roxadustat in hemoglobin correction and maintenance was maintained during the 18-week open-label period.

CONCLUSIONS

In Chinese patients with chronic kidney disease who were not undergoing dialysis, those in the roxadustat group had a higher mean hemoglobin level than those in the placebo group after 8 weeks. During the 18-week open-label phase of the trial, roxadustat was associated with continued efficacy. (Funded by FibroGen and FibroGen [China] Medical Technology Development; ClinicalTrials.gov number, NCT02652819.)

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Chronic kidney disease is a global public health challenge that affects approximately 10% of the population worldwide, including 120 million people in China.[1] Anemia (defined as a hemoglobin level of <10.0 g per deciliter) is a complication of chronic kidney disease that is associated with increased risks of death and complications.[2,3] Worldwide, among patients with chronic kidney disease who are not undergoing dialysis, anemia remains undertreated because of delayed referral to nephrologists[4] and concern about the safety of erythropoiesis-stimulating agents.[5-7]

In China, this situation is reflected by low hemoglobin levels in patients who initiate dialysis, with mean levels of 7.3 g per deciliter reported in Guangzhou, 8.2 g per deciliter in Beijing, and 7.7 g per deciliter in Shanghai.[8,9] Among the patients who initiated dialysis in rural China, those with a mean (±SD) hemoglobin level of 5.9±4.7 g per deciliter had twice the rates of heart failure and death as those living in urban areas, who had a mean level of 8.4±4.5 g per deciliter; in these two groups, rates of heart failure were 34.4% and 16.2%, respectively, and rates of death were 42.9% and 21.9%, respectively.[10]

There is evidence that when anemia is effectively treated in patients with chronic kidney disease, transfusion rates are reduced and clinical outcomes are improved.[2,11-15] Undertreatment of anemia is associated with increased rates of hospitalization, transfusion,[16] and death.[17-19] However, the package inserts of erythropoiesis-stimulating drugs manufactured in the United States include a statement that practitioners should consider initiating the drug in adults with chronic kidney disease who are not undergoing dialysis only when the hemoglobin level is less than 10 g per deciliter and consider reducing or interrupting the dose if the hemoglobin level exceeds 10 g per deciliter.[20]

Roxadustat (FG-4592, FibroGen) is a hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor that stabilizes HIF-α subunits, which results in increased HIF transcriptional activity. Increased transcriptional activity leads to functional activation of early-response target genes encoding proteins such as erythropoietin, erythropoietin receptor, enzymes of heme biosynthesis, and proteins that promote iron absorption and transport, which results in coordinated erythropoiesis. Intermittent increases in HIF activity with small-molecule HIF prolyl hydroxylase inhibitors may constitute an innovative approach to the treatment of anemia. In phase 2 studies, roxadustat increased endogenous erythropoietin within or near the physiologic range, increased hemoglobin levels, and improved iron homeostasis.[21-25] We now report the results of a phase 3 trial of roxadustat (FGCL-4592-808) in China involving patients with chronic kidney disease who were not undergoing dialysis.

METHODS

TRIAL DESIGN AND OVERSIGHT

The design called for an initial 8-week, double-blind, placebo-controlled phase in which we compared roxadustat with placebo for the treatment of anemia in patients with chronic kidney disease who were not undergoing dialysis. After the initial phase, all the patients who continued in the trial received roxadustat during an 18-week open-label phase. The trial was conducted in accordance with the principles of the Declaration of Helsinki, Chinese Good Clinical Practice, and the International Conference on Harmonization E6 guidelines.

The first two authors designed the trial in collaboration with representatives of the sponsor, FibroGen; company representatives were responsible for the collection and analysis of the data. All the authors contributed to the analysis and interpretation of the data and to the conduct of the trial, along with having full access to the data and analyses and full review of the manuscript. All the authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol (available with the full text of this article at NEJM.org).

POPULATION

Eligible patients were between the ages of 18 and 75 years, had chronic kidney disease of stage 3 to 5, and were not currently undergoing dialysis. None of the patients had received erythropoiesis-stimulating agents for at least 5 weeks before randomization. During screening, the mean of the two most recent hemoglobin values was in the range of 7.0 g per deciliter to less than 10.0 g per deciliter in all the patients. (Details regarding inclusion and exclusion criteria are provided in Table S1 in the Supplementary Appendix, available at NEJM.org.)

TREATMENT

Eligible patients were randomly assigned in a 2:1 ratio to receive oral roxadustat or placebo three times a week for 8 weeks; all the patients were subsequently eligible to receive roxadustat during the 18-week open-label phase of the trial. Randomization was performed centrally and was stratified according to the use or nonuse of an erythropoiesis-stimulating agent within 12 weeks before randomization and according to the estimated glomerular filtration rate (GFR) (<20 ml or ≥20 ml per minute per 1.73 m^2 of body-surface area). Patients initiated roxadustat according to a weight-based starting dose of 70 mg (in patients weighing 40 to <60 kg) or 100 mg (in patients weighing ≥60 kg). The dose of roxadustat was escalated every 4 weeks to maintain a hemoglobin level ranging from 10.0 to 12.0 g per deciliter (Table S2 in the Supplementary Appendix). The adjustment of the placebo dose was carried out in the same manner.

After the initial 8-week randomized phase, all the patients were invited to receive roxadustat according to the same regimen in the open-label phase. Rescue therapy — which included blood transfusion, intravenous iron, the use of erythropoiesis-stimulating agents, or any combination of the three therapies — was offered to patients with a hemoglobin level of less than 8.0 g per deciliter and to those with a hemoglobin level of less than 9 g per deciliter who had a confirmed decrease from baseline of more than 1.0 g per deciliter.

END POINTS

The primary end point was the mean change from baseline in the hemoglobin level during weeks 7 to 9 among all the patients who had undergone randomization and who had a baseline and post-baseline hemoglobin measure (intention-to-treat population). Secondary end points for the initial phase included the percentage of patients who had a response to a trial regimen, which was defined as an increase from baseline of at least 1.0 g per deciliter in the hemoglobin level at week 9; the percentage of patients with a mean hemoglobin level of at least 10.0 g per deciliter during weeks 7 to 9; the percentage of patients who had a hemoglobin level of at least 10.0 g per deciliter at week 9 along with an increase from baseline of at least 1.0 g per deciliter (among those with a baseline value of ≥8.0 g per deciliter) or along with an increase of at least 2.0 g per deciliter (among those with a baseline hemoglobin value of <8.0 g per deciliter); the percentage of patients who received rescue therapy at week 9; and the mean change from baseline in total cholesterol and low-density lipoprotein (LDL) cholesterol at weeks 7 to 9. (A full listing of secondary end points is provided in the protocol.)

We obtained information with respect to adverse events at each visit using open-ended questions. Investigators were asked to record abnormal, clinically significant laboratory results, physical examination findings, and electrocardiographic results as adverse events if such findings were deemed to meet the criteria for adverse events.

STATISTICAL ANALYSIS

We estimated that the enrollment of 150 patients would provide the trial with a power of at least 90% to show a between-group difference in the primary end point of 1.0 g per deciliter and a common standard deviation of 1.5 at a two-sided significance level of less than 0.05, as determined with the use of Student's t-test. In comparing the primary end point, we used a mixed-effects repeated-measures model that included data from all visits by patients during the initial randomized phase, with covariates that included trial agent, trial visit, interaction between trial agent and visit, corresponding baseline value, baseline estimated GFR, and use or nonuse of erythropoiesis-stimulating agents within 12 weeks before randomization. We used the same mixed-effects repeated-measures model to calculate P values and two-sided 95% confidence intervals for the between-group difference in least-squares means. We performed an analysis of covariance to estimate and compare the difference between the groups in the change from baseline in the hemoglobin level, with missing data handled with the use of multiple imputations in a sensitivity analysis.

During the randomized phase of the trial, we also used the mixed-effects repeated-measures model to perform analyses of secondary end points, including the change from baseline in iron biomarkers and total and LDL cholesterol levels at weeks 7 to 9. We performed an analysis of covariance to calculate the change from baseline in hepcidin at week 9. We used Fisher's exact test to analyze the percentage of patients who had a response to a trial regimen and Cox proportion-

al-hazards regression to compare the time until the receipt of rescue therapy and the percentage of patients who received such therapy at week 9, after adjustment for the baseline hemoglobin level, baseline estimated GFR, and the use or nonuse of an erythropoiesis-stimulating agent within 12 weeks before randomization. All the analyses were performed in the intention-to-treat population and the per-protocol population; the latter consisted of all the patients who had undergone randomization and received at least 2 weeks of a trial regimen, who had a baseline and a postbaseline hemoglobin measurement, and who did not have any important protocol violations. We report the values for the secondary analyses as point estimates and 95% confidence intervals. The confidence intervals have not been adjusted for multiple comparisons, so inferences drawn from them may not be reproducible. All the analyses that are presented were performed in the intention-to-treat population unless otherwise specified. The end-point analyses for the open-label phase of the trial were similar to those performed during the randomized phase.

RESULTS

CHARACTERISTICS OF THE PATIENTS

From December 2015 through September 2016, a total of 154 patients (102 in the roxadustat group and 52 in the placebo group) underwent randomization (Fig. S1 in the Supplementary Appendix). Of these patients, 2 did not receive a trial regimen, leaving 152 in the safety population. One patient in the safety population took one dose of placebo and was lost to follow-up, which left an intention-to-treat population of 151. A total of 131 patients completed the 8-week treatment period (87 in the roxadustat group and 44 in the placebo group).

The baseline characteristics were similar in the two groups (Table 1). The mean baseline hemoglobin level was 8.9±0.8 g per deciliter in the roxadustat group and 8.9±0.7 g per deciliter in the placebo group. Of note, 82 of 152 patients (54%) had a transferrin saturation of 20% or more, and 58 patients (38%) had a ferritin level of 200 μg per liter or more.

RANDOMIZED PHASE

Efficacy End Points

During the primary-analysis period, the mean change from baseline in the hemoglobin level was an increase of 1.9±1.2 g per deciliter in the roxadustat group and a decrease of 0.4±0.8 g per deciliter in the placebo group, for a between-group difference of 2.2 g per deciliter (95% confidence interval [CI], 1.9 to 2.6; P<0.001) (Fig. 1A, and Table S3 in the Supplementary Appendix). A sensitivity analysis performed with multiple imputations showed a similar between-group difference in the change from baseline of 2.3 g per deciliter (95% CI, 1.9 to 2.7) in the hemoglobin level.

By week 9, a hemoglobin response (i.e., an increase of ≥1.0 g per deciliter from baseline) occurred in 85 of 101 patients (84%) in the roxadustat group and in none of 50 patients in the placebo group, for a between-group difference of 84 percentage points (95% CI, 75 to 91). Similarly, at weeks 7 to 9, a mean hemoglobin level of at least 10.0 g per deciliter was reported in 68 patients (67%) in the roxadustat group and in 3 patients (6%) in the placebo group, for a between-group difference of 61 percentage points (95% CI, 47 to 72). A hemoglobin level of at least 10.0 g per deciliter and an increase from baseline of at least 1.0 g per deciliter in patients with a baseline hemoglobin level of 8.0 g per deciliter or more or an increase of at least 2.0 g per deciliter in patients with a baseline hemoglobin level of less than 8.0 g per deciliter at week 9 was reported in 76 patients (75%) in the roxadustat group and in no patients in the placebo group, for a between-group difference of 75 percentage points (95% CI, 65 to 83). Rescue therapy was administered to 3 patients (3%) in the roxadustat group and 6 patients (12%) in the placebo group (hazard ratio, 0.11; 95% CI, 0.02 to 0.51).

Hepcidin and Iron Levels

At baseline, the mean hepcidin level was 95.89±72.40 ng per milliliter in the roxadustat group and 114.71±85.72 ng per milliliter in the placebo group. (In patients with anemia who have a high hepcidin level, a reduction is typically associated with greater iron availability.) At week 9, the reduction from baseline was 56.14±63.40 ng per milliliter and 15.10±48.06 ng per milliliter, respectively, for a between-group difference of −49.77 ng per milliliter (95% CI, −66.75 to −32.79) (Fig. 1B).

Among patients in the roxadustat group, the serum iron level was clinically stable during the randomized phase and did not differ significantly from the level in the placebo group, despite

Table 1. Characteristics of the Patients at Baseline (Safety Population).*

Characteristic	Roxadustat (N=101)	Placebo (N=51)
Age — yr	54.7±13.3	53.2±13.1
Male sex — no. (%)	36 (36)	20 (39)
Hemoglobin		
Mean — g/dl	8.9±0.8	8.9±0.7
<8.0 g/dl — no. (%)	17 (17)	7 (14)
≥8.0 g/dl — no. (%)	84 (83)	44 (86)
History of diabetes mellitus — no. (%)	22 (22)	16 (31)
History of hypertension — no. (%)	89 (88)	41 (80)
Estimated GFR		
Mean — ml/min/1.73 m^2	16.5±8.0	14.5±7.6
<10 ml/min/1.73 m^2 — no. (%)	18 (18)	19 (37)
≥10 and <20 ml/min/1.73 m^2 — no. (%)	54 (53)	21 (41)
≥20 ml/min/1.73 m^2 — no. (%)	29 (29)	11 (22)
Transferrin saturation		
Mean — %	20.6±9.2	23.0±11.1
<20% — no. (%)	49 (49)	21 (41)
≥20% — no. (%)	52 (51)	30 (59)
Ferritin		
Mean — μg/liter	191.4±200.5	266.2±236.7
<100 μg/liter — no. (%)	42 (42)	14 (27)
≥100 and <200 μg/liter — no. (%)	24 (24)	14 (27)
≥200 μg/liter — no. (%)	35 (35)	23 (45)
C-reactive protein — no. (%)		
≤ULN of 4.9 mg/liter	89 (88)	46 (90)
>ULN of 4.9 mg/liter	12 (12)	5 (10)
Blood pressure — mm Hg		
Systolic	133.8±14.7	135.4±18.0
Diastolic	79.9±9.5	80.7±10.9
Cholesterol		
Total — mg/dl	172.8±45.8	181.4±49.0
LDL — mg/dl	97.8±34.0	105.2±42.2
HDL — mg/dl	49.9±14.6	48.6±16.3
Ratio of LDL to HDL	2.09±0.90	2.30±0.99
Oral iron supplementation during yr before randomization — no. (%)	40 (40)	24 (47)

* Plus–minus values are means ±SD. The analysis of the baseline data was performed in the safety population because the intention-to-treat population included only the patients who had a baseline and postbaseline hemoglobin measurement, as defined in the protocol. Of the 154 patients who underwent randomization, 2 patients (1 in each group) did not receive a dose of the trial agent, so they were not included in the safety population. There were no significant differences between the groups except in the category of patients who had an estimated glomerular filtration rate (GFR) of less than 10 ml per minute per 1.73 m^2 of body-surface area (P=0.03) and in the category of ferritin (P=0.04). Percentages may not total 100 because of rounding. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, and ULN upper limit of the normal range.

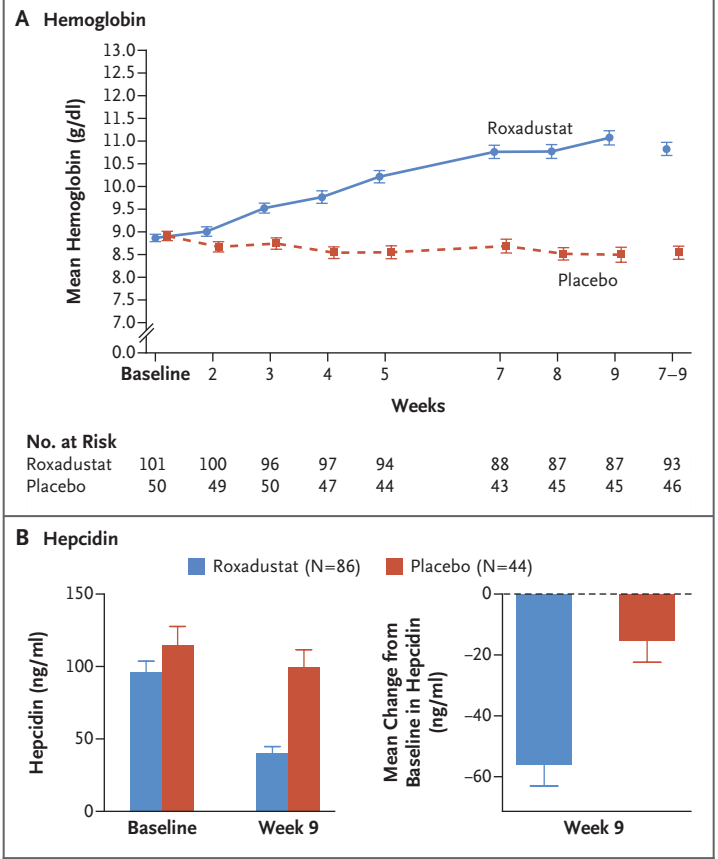

Figure 1. Hemoglobin and Hepcidin Levels.

Shown are the mean hemoglobin levels (Panel A) and mean hepcidin levels and the change from baseline (Panel B) during the 8-week double-blind period. The least-squares mean difference in hemoglobin values was 1.9±0.2 g per deciliter (95% confidence interval [CI], 1.4 to 2.4); the least-squares mean difference in hepcidin values was −49.77 (95% CI, −66.75 to −32.79). In Panel A, the average for weeks 7 through 9 (the measure that was used in the primary end point) is shown to the right of the graph. In Panel B, hepcidin measurements were not available for one patient in the roxadustat group. The error bars in the two panels indicate standard errors.

robust erythropoiesis (Table 2). In the roxadustat group, transferrin levels and total iron binding capacity increased, with a temporary decrease in the transferrin saturation from 20.6% to 15.6% at week 9 during a period of increased iron utilization in which the mean increase in hemoglobin was 1.9 g per deciliter. During the open-label phase, the transferrin saturation increased to 22.1% at week 27 during hemoglobin maintenance. In the placebo group, iron levels and related measures on average were stable during the randomized phase.

Cholesterol Levels

At baseline, the mean total cholesterol level was 172.8±45.8 mg per deciliter (4.5±1.2 mmol per liter) in the roxadustat group and 181.4±49.0 mg per deciliter (4.7±1.3 mmol per liter) in the placebo group. At week 9, the decrease in the total cholesterol level was 40.6 mg per deciliter (1.0 mmol per liter) in the roxadustat group and 7.7 mg per deciliter (0.2 mmol per liter) in the placebo group, for a between-group difference of −32.9 mg per deciliter (−0.9 mmol per liter; 95% CI, −1.1 to −0.6). At baseline, the mean LDL cholesterol level was 97.8±34.0 mg per deciliter (2.5±0.9 mmol per liter) in the roxadustat group and 105.2±42.2 mg per deciliter (2.7±1.0 mmol per liter) in the placebo group, with decreases of 25.3 mg per deciliter (0.7 mmol per liter) and 5.8 mg per deciliter (0.1 mmol per liter), respectively, at week 9, for a between-group difference of −21.2 mg per deciliter (−0.5 mmol per liter; 95% CI, −0.8 to −0.3) (Fig. S2 in the Supplementary Appendix).

Safety and Adverse Events

During the randomized phase, at least one adverse event was reported in 69 of 101 patients (68%) in the roxadustat group (14.4 patient-years) and in 38 of 51 patients (75%) in the placebo group (7.4 patient-years). Hyperkalemia and metabolic acidosis were reported more often in the roxadustat group than in the placebo group (in 16 patients [16%] in the roxadustat group and in 4 patients [8%] in the placebo group) (Table 3). On the basis of central laboratory measurements obtained at baseline (week 1) and at weeks 5 and 9, the percentages of patients in the roxadustat group who had an elevated potassium level (>5.5 mmol per liter) in the double-blind phase were 19% (19 of 101 patients) at baseline and 20% (17 of 87 patients) at 9 weeks; in the placebo group, the percentages were 12% (6 of 51 patients) at baseline and 11% (5 of 45 patients) at 9 weeks (Table S4 and Figs. S3 and S4 in the Supplementary Appendix). In the two groups, the mean potassium levels as reported by the central laboratory did not change significantly from baseline (4.98±0.64 mmol per liter at baseline and 4.96±0.68 mmol per liter at 9 weeks in the roxadustat group and 5.03±0.47 mmol per liter and 4.98±0.54 mmol per liter, respectively, in the placebo group) (Fig. S3 in the Supplementary Appendix). One patient in each group discontin-

Table 2. Change from Baseline in Serum Iron Measurements (Intention-to-Treat Population).*

Trial Group and Timeline	Transferrin	Total Iron-Binding Capacity	Transferrin Saturation	Ferritin	Iron
	g/liter	*μmol/liter*	%	*μg/liter*	*μmol/liter*
Roxadustat					
Baseline	2.18±0.48	54.64±11.98	20.6±9.2	191.4±200.5	10.69±3.93
Wk 9	2.89±0.71	72.49±17.75	15.6±10.8	98.0±146.7	10.47±6.36
Change	0.73±0.48	18.20±11.96	–5.2±10.4	–93.3±146.3	–0.24±6.31
Placebo					
Baseline	2.08±0.49	52.08±12.33	23.2±11.1	271.1±236.3	11.36±4.58
Wk 9	2.07±0.46	51.80±11.41	21.4±8.2	243.0±209.8	10.78±3.89
Change	–0.01±0.39	–0.33±9.72	–1.7±9.2	–21.9±115.5	–0.64±4.36
Between-group difference in change					
Least-squares mean ±SE	0.75±0.08	18.89±2.07	–4.3±1.6	–102.2±20.4	0.24±0.97
95% CI	0.59 to 0.92	14.79 to 22.98	–7.4 to –1.1	–142.6 to –61.7	–1.67 to 2.15

* Plus–minus values are means ±SD unless otherwise stated. Included in this analysis were 85 patients in the roxadustat group and 43 in the placebo group for whom data were available. To convert the values for iron to micrograms per deciliter, divide by 0.1791.

ued participation in the trial because of hyperkalemia. Local laboratory values were not collected.

In the roxadustat group, the percentages of patients with a serum bicarbonate level of 21 mmol per liter or less were 92% at baseline and 91% at 9 weeks. In the placebo group, the percentages were 96% at baseline and 89% at 9 weeks (Table S4 in the Supplementary Appendix).

Serious adverse events, which were consistent with those generally seen in patients with chronic kidney disease, were reported in 9 patients (9%) in the roxadustat group and in 6 patients (12%) in the placebo group (Table 3). There were no deaths during the randomized phase of the trial.

An increase in the level of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) occurred in 2 patients in the roxadustat group and 1 patient in the placebo group (2% in each group). In the roxadustat group, 1 patient who had a grade 1 elevation in ALT and AST had a spontaneous normalization in the level without any change in the drug regimen; a second patient had a grade 2 elevation in ALT and AST that was reported 2 days after receipt of the last dose of roxadustat during the trial while the patient was receiving concomitant medications known to be associated with an elevation in liver enzyme levels.

OPEN-LABEL PHASE

After the initial randomized phase of the trial, 87 patients in the roxadustat group and 44 patients in the placebo group entered the 18-week open-label phase in which all the patients received roxadustat; of these 131 patients, 98 completed the open-label phase. Among the patients who had initially received roxadustat, hemoglobin levels remained stable during the open-label phase, with an overall increase from baseline of 1.9±1.3 g per deciliter by weeks 23 through 27 (Fig. S5 in the Supplementary Appendix). Of these patients, 71 of 85 patients (84%) had a hemoglobin level of 11.0 g per deciliter or more during the 26-week treatment period, and 62 (73%) had a hemoglobin level of 10.0 g per deciliter or more during weeks 23 through 27. Among the patients who had initially received placebo, the mean hemoglobin level increased from baseline by 2.0±1.5 g per deciliter after crossover to receive roxadustat; 31 of 43 patients (72%) had a hemoglobin level of more than 11.0 g per deciliter, and 37 (86%) had a hemoglobin level of 10.0 g per deciliter or more during weeks 23 through 27.

Lipid values decreased among the patients who had initially received placebo, making this subgroup clinically similar to the entire cohort at the end of the open-label period (Fig. S6 in the Sup-

Table 3. Adverse Events (Safety Population).

Adverse Event	Roxadustat (N=101)	Placebo (N=51)
	no. of patients (%)	
Any adverse event*	37 (37)	25 (49)
Anemia	0	3 (6)
Diarrhea	0	3 (6)
Peripheral edema	7 (7)	3 (6)
Pyrexia	2 (2)	3 (6)
Upper respiratory tract infection	5 (5)	4 (8)
Hyperkalemia	16 (16)	4 (8)
Metabolic acidosis	12 (12)	1 (2)
Gout	1 (1)	3 (6)
Back pain	0	3 (6)
Dizziness	1 (1)	4 (8)
Hypertension	6 (6)	2 (4)
Any serious adverse event	9 (9)	6 (12)
Anemia	0	1 (2)
Coronary artery disease	0	1 (2)
Gastrointestinal hemorrhage	1 (1)	0
Acute cholecystitis	0	1 (2)
Cholelithiasis	0	1 (2)
Lung infection	1 (1)	1 (2)
Hyperkalemia	2 (2)	0
Hypokalemia	1 (1)	0
Metabolic acidosis	1 (1)	0
End-stage renal disease	1 (1)	0
Chronic glomerulonephritis	1 (1)	0
Azotemia	0	1 (2)
Renal impairment	0	1 (2)
Dysfunctional uterine bleeding	0	1 (2)
Acute respiratory failure	0	1 (2)
Rash	1 (1)	0
Hypertension	1 (1)	0

* Listed in this category are adverse events that occurred in at least 5% of the patients in either group during the double-blind 8-week period that included 14.4 patient-years in the roxadustat group and 7.4 patient-years in the placebo group. Adverse events were coded as preferred terms in the *Medical Dictionary for Regulatory Activities*, version 19.1.

plementary Appendix). Adverse events and serious adverse events reflected events that had occurred in the double-blind phase. Hyperkalemia was reported in 23 patients and metabolic acidosis in 14 patients during 46.7 patient-years in the open-label phase.

There were two deaths during the open-label phase. In one case, a 69-year-old woman with a history of hypertension, coronary heart disease, and stroke had a sudden loss of consciousness at home on day 129; no other information was available. In the second case, a 60-year-old woman had a urinary tract obstruction caused by bilateral renal calculi; after undergoing ureterolithotomy and placement of a double J stent, the patient died from massive retroperitoneal hemorrhage on day 65.

DISCUSSION

In this phase 3 trial, 154 patients with anemia associated with chronic kidney disease who were not undergoing dialysis were randomly assigned to receive roxadustat or placebo for an 8-week double-blind period. The primary efficacy analysis showed a significantly larger increase in the hemoglobin level from baseline over weeks 7 to 9 in the roxadustat group than in the placebo group (an increase of 1.9±1.2 g per deciliter vs. a decrease of 0.4±0.8 g per deciliter). Similarly, other hemoglobin end points, such as the percentage of patients who had a hemoglobin response (i.e., an increase of ≥1.0 g per deciliter from baseline) or who did not receive rescue therapy, were greater in the roxadustat group than in the placebo group. In spite of the robust erythropoiesis and the restriction of intravenous administration of iron in the roxadustat group, serum iron levels remained stable. We found that in addition to the erythropoietic effects of roxadustat, the drug was associated with reduced levels of hepcidin and cholesterol. After the initial randomized phase of the trial, patients who had initially received roxadustat maintained stable hemoglobin levels during the open-label phase. Patients who had initially received placebo also had a correction in hemoglobin levels after open-label crossover to roxadustat, with efficacy values paralleling those in patients who had initially received roxadustat.

We speculate that the stability of serum iron levels in the roxadustat group may have been driven by reductions in hepcidin levels, which permitted the gut absorption of iron and improved the release of macrophage iron onto transferrin.[26] Previous studies involving patients with chronic kidney disease who were not undergoing dialysis have shown that roxadustat increased hemoglobin levels with stable serum iron levels, despite robust erythropoiesis in the absence of intravenous ad-

ministration of iron.[23,25] In our trial, initial measures of iron suggested adequate baseline iron stores in only half the patients. Despite the absolute need for iron for erythropoiesis, roxadustat therapy corrected anemia and maintained hemoglobin levels in spite of lower transferrin saturation and progressive reduction in ferritin levels with only oral iron in moderate doses. Serum iron, the more important component of the plasma iron content, can remain constant or increase even if the level of carrier protein increases. In this trial and in the phase 2 studies of roxadustat,[25] transferrin levels increased in patients receiving roxadustat but not in those receiving placebo. This increase is probably a direct effect of the stabilization in the HIF level by roxadustat. The gene encoding transferrin is a well-characterized HIF target, since it contains two HIF binding sites in its 5′ enhancer region.[27] Serum hepcidin levels were reduced in the patients who received roxadustat. Hepcidin, a key regulator of iron absorption and mobilization from hepatocytes and macrophages, is down-regulated by hypoxia and HIF stabilization, which increases the synthesis of iron transport proteins and intestinal iron absorption.[28,29] Maintenance of total serum iron levels permits adequate iron delivery and avoidance of functional iron deficiency. This factor may indicate the need to reconsider the threshold of iron measures below which patients are considered to have iron depletion in order to determine which level will be most useful if HIF prolyl hydroxylase inhibitors become clinically available in the future.

In our trial, total cholesterol levels decreased by 23% during the initial 8 weeks of roxadustat therapy. The ability of roxadustat to lower cholesterol levels may be mediated, in part, by HIF-dependent effects on acetyl coenzyme A that are required for the first step of cholesterol synthesis[30] and on the degradation of 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate-limiting enzyme in cholesterol synthesis.[31,32] Among patients with chronic kidney disease, a high total cholesterol level is a major risk factor for cardiovascular disease.[33] There is evidence that statins reduce the risk of cardiovascular disease among patients with chronic kidney disease who are not undergoing dialysis.[34]

The frequencies of hyperkalemia and metabolic acidosis that were reported as adverse events were higher in the roxadustat group than in the placebo group. Central laboratory measurements of both conditions, which were monitored twice during the double-blind phase, were similar in the two groups, with similar changes from baseline to the end of the open-label phase. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest that patients with chronic kidney disease who have a serum bicarbonate level of less than 22 mmol per liter (associated with metabolic acidosis) should begin oral bicarbonate supplementation to maintain a serum bicarbonate level within the normal range.[35] In a similar study involving patients with chronic kidney disease receiving dialysis, hyperkalemia was reported as an adverse event more often in patients treated with roxadustat than in those treated with epoetin alfa.[36] It should be noted that our findings are limited by the small sample size and short trial duration relative to the ongoing large, international, phase 3 studies (ClinicalTrials.gov numbers, NCT01750190, NCT02052310, and NCT02273726).

Our data indicate that during the initial 8-week period, roxadustat was more effective than placebo in correcting anemia in this phase 3 trial involving patients with chronic kidney disease who were not undergoing dialysis. Hemoglobin levels were maintained during the subsequent 18-week open-label treatment period.

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APPENDIX

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