



A 12-Week, Double-Blind, Placebo-Controlled Trial of Ferric Citrate for the Treatment of Iron Deficiency Anemia and Reduction of Serum Phosphate in Patients With CKD Stages 3-5

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Background: Iron deficiency anemia and serum phosphate levels > 4.0 mg/dL are relatively common in chronic kidney disease stages 3 to 5 and are associated with higher risks of progressive loss of kidney function, cardiovascular events, and mortality.

Study Design: Double-blind, placebo-controlled, randomized trial.

Setting & Participants: 149 patients with estimated glomerular filtration rates < 60 mL/min/1.73 m², iron deficiency anemia (hemoglobin, 9.0-12.0 g/dL; transferrin saturation [TSAT] ≤ 30%, serum ferritin ≤ 300 ng/mL), and serum phosphate levels ≥ 4.0 to 6.0 mg/dL. Use of intravenous iron or erythropoiesis-stimulating agents was prohibited.

Intervention: Randomization to treatment for 12 weeks with ferric citrate coordination complex (ferric citrate) or placebo.

Outcomes & Measurements: Coprimary end points were change in TSAT and serum phosphate level from baseline to end of study. Secondary outcomes included change from baseline to end of treatment in values for ferritin, hemoglobin, intact fibroblast growth factor 23 (FGF-23), urinary phosphate excretion, and estimated glomerular filtration rate.

Results: Ferric citrate treatment increased mean TSAT from 22% ± 7% (SD) to 32% ± 14% and reduced serum phosphate levels from 4.5 ± 0.6 to 3.9 ± 0.6 mg/dL, while placebo exerted no effect on TSAT (21% ± 8% to 20% ± 8%) and less effect on serum phosphate level (4.7 ± 0.6 to 4.4 ± 0.8 mg/dL; between-group $P < 0.001$ for each). Ferric citrate increased hemoglobin levels (from 10.5 ± 0.8 to 11.0 ± 1.0 g/dL; $P < 0.001$ vs placebo), reduced urinary phosphate excretion 39% ($P < 0.001$ vs placebo), and reduced serum intact FGF-23 levels from a median of 159 (IQR, 102-289) to 105 (IQR, 65-187) pg/mL ($P = 0.02$ vs placebo). The incidence and severity of adverse effects were similar between treatment arms.

Limitations: The study is limited by relatively small sample size and short duration and by having biochemical rather than clinical outcomes.

Conclusions: Short-term use of ferric citrate repletes iron stores, increases hemoglobin levels, and reduces levels of serum phosphate, urinary phosphate excretion, and FGF-23 in patients with chronic kidney disease stages 3 to 5.

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INDEX WORDS: Chronic kidney disease (CKD); iron-deficiency anemia; hemoglobin; transferrin saturation (TSAT); ferric citrate coordination complex (ferric citrate); oral iron therapy; phosphate binder; iron repletion; serum phosphate; urinary phosphate excretion; fibroblast growth factor 23 (FGF-23); randomized controlled trial.

Chronic kidney disease (CKD) affects up to 13% of adults and markedly increases the risk of premature cardiovascular events.¹ Anemia is among the most common complications of CKD and is associated with mortality and cardiovascular events, even after accounting for CKD stage and other cardiovascular risk factors, including albuminuria, diabetes mellitus, smoking, and hypercholesterolemia.² Although the anemia of CKD is multifactorial in origin, 60% to 73%

of persons with an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² are iron deficient.³ Clinical practice guidelines recommend that persons with CKD and anemia (hemoglobin < 13.0 g/dL for men; < 12.0 g/dL for women) be treated with iron rather than erythropoiesis-stimulating agents (ESAs) in order to increase hemoglobin level if transferrin saturation (TSAT) is ≤ 30% and serum ferritin level is ≤ 500 ng/mL. Unfortunately, conventional oral iron formulations

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(sulfate, fumarate, and gluconate) tend to be ineffective,^{4,5} and the provision of intravenous iron and ESAs to normalize hemoglobin levels in persons with CKD stages 3 to 5 is associated with relatively high rates of adverse effects.⁶ Fewer than 1 in 5 patients with CKD currently receive ESAs prior to initiating dialysis therapy, and mean hemoglobin level for patients initiating dialysis therapy in the United States is 9.6 g/dL.¹

Serum phosphate levels > 4.0 mg/dL are associated independently with more rapid decline in kidney function,⁷ resistance to the renoprotective effects of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy,⁸ development of end-stage renal disease (ESRD),⁹ arterial calcification,¹⁰ cardiovascular events, and mortality.¹¹⁻¹³ Beginning as early as eGFR < 70 mL/min/1.73 m², bone secretion of the phosphaturic hormone fibroblast growth factor 23 (FGF-23) increases.¹⁴ Acting in concert with α -klotho, FGF-23 inhibits renal tubular phosphate reabsorption to maintain serum phosphate levels within normal limits. It also directly reduces 25-hydroxyvitamin D₃ conversion to active 1,25-dihydroxyvitamin D₃, which results in reduced intestinal calcium absorption and stimulation of parathyroid hormone, which further augments phosphate excretion.¹⁵ These compensatory initially adaptive changes in FGF-23 and parathyroid hormone levels ultimately fail, typically when eGFR declines to less than ~30 mL/min/1.73 m². Persistently elevated FGF-23 levels contribute to the development of left ventricular hypertrophy and are associated with congestive heart failure and mortality.¹⁶⁻¹⁸ Reductions in dietary phosphate intake and prescription of intestinal phosphate binders are standard recommendations for patients with ESRD when serum phosphate level is overtly elevated. It has been proposed that this approach be advanced upstream to patients with CKD stages 3 to 5 in an effort to lower phosphate, FGF-23, and parathyroid hormone levels. However, it recently has been demonstrated that neither strategy consistently reduces serum phosphate levels in randomized controlled trials when using currently available phosphate binders.^{19,20}

Ferric citrate coordination complex (ferric citrate) is an intestinal phosphate binder that has been shown previously to replete iron stores, increase hemoglobin levels, and reduce serum phosphate levels in patients with ESRD undergoing hemodialysis.²¹⁻²⁵ We designed the current trial to evaluate the safety and efficacy of ferric citrate for the treatment of iron deficiency anemia and reduction of serum phosphate levels in patients with CKD stages 3 to 5.

METHODS

This was a 12-week, multicenter, double-blind, placebo-controlled, randomized trial with eligible patients randomly assigned 1:1 to ferric citrate or matching placebo. We randomly

assigned patients by a centralized interactive voice-response system with allocation generated by an independent biostatistician. Keryx Biopharmaceuticals Inc provided active drug and matching placebo. Ferric citrate was supplied as 1-g ferric citrate caplets containing 210 mg of ferric iron. An independent data safety and monitoring board periodically reviewed clinical data throughout the trial period. The study was approved by the Liberty Institutional Review Board (DeLand, FL) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Inclusion criteria included eGFR < 60 mL/min/1.73 m², serum phosphate level \geq 4.0 to 6.0 mg/dL, serum ferritin level \leq 300 ng/mL, TSAT \leq 30%, and hemoglobin level of 9.0 to 12.0 g/dL. Exclusion criteria included use of an ESA within 4 weeks or intravenous iron within 8 weeks of screening, any known cause of anemia other than iron deficiency or CKD, symptomatic gastrointestinal bleeding, or inflammatory bowel disease. Patients who were taking phosphate binders at the time of consent were required to undergo a washout period of at least 2 weeks prior to randomization. Neither iron nor ESA use was allowed during the trial. Use of calcium for the purpose of phosphate binding was prohibited; use of calcium supplements and active or nutritional vitamin D was allowed, but no changes to dose were permitted during the study (see Table S1, available as online supplementary material). Prespecified safety end points requiring discontinuation from the study medication were 2 consecutive hemoglobin values < 9.0 g/dL or 2 consecutive serum phosphate concentrations > 6.0 mg/dL. Serious adverse events were captured from the time of consent through 30 days after the last study drug exposure.

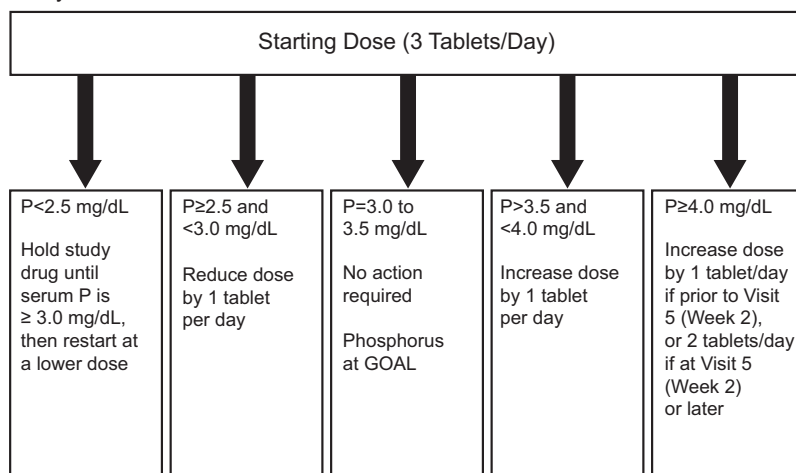
We initiated study drug (ferric citrate or placebo) at a dose of 1 caplet per meal thrice daily. We adjusted the dose based on central laboratory serum phosphate results, as shown in Fig 1A. Patients were seen by study staff at weeks 1 and 2 and subsequently at 2-week intervals.

All clinical chemistry analyses were performed by a central laboratory, PPD Central Laboratory Services, Highland Heights, KY, using a standard chemistry autoanalyzer. We conducted in-person study visits in the afternoon in a nonfasting state. FGF-23 was measured in plasma using the second-generation carboxy-terminal enzyme-linked immunosorbent assay (ELISA; Immotopics) and in serum using an ELISA against the intact protein (Kainos).

The coprimary outcomes were between-group changes in TSAT and serum phosphate levels from baseline to end of treatment. We analyzed data using a modified intention-to-treat principle, whereby all patients who were randomly assigned, received at least one dose of study medication, and had at least one postbaseline assessment were included in assessments of efficacy. Any patient who received at least one dose of study drug was included in the safety population. We conducted our primary analysis using an analysis of covariance model with treatment as a fixed effect and baseline value of the outcome analyzed as a covariate. Secondary outcomes included change from baseline to end of treatment values for ferritin, hemoglobin, intact FGF-23, urinary phosphate excretion (in milligrams per 24 hours), and eGFR. There were few missing data elements; missing laboratory data were imputed using the last-value-carried-forward method. All *P* values represent between-group comparisons in change from baseline to week 12 unless stated otherwise. To examine potential effects of the last-observation-carried-forward method on the precision and interpretation of results, we conducted prespecified companion analyses using the mixed-effect repeated-measures model.²⁶

We estimated that 110 evaluable patients would be needed to detect a between-group mean 10% \pm 5% change in TSAT and mean 0.3 \pm 0.5-mg/dL change in serum phosphate levels, with a 2-sided α of 0.05 and 80% power. We aimed to enroll 140 patients to allow for a dropout rate of ~20%. We prespecified that

A Study Medication Titration



B Patient Disposition

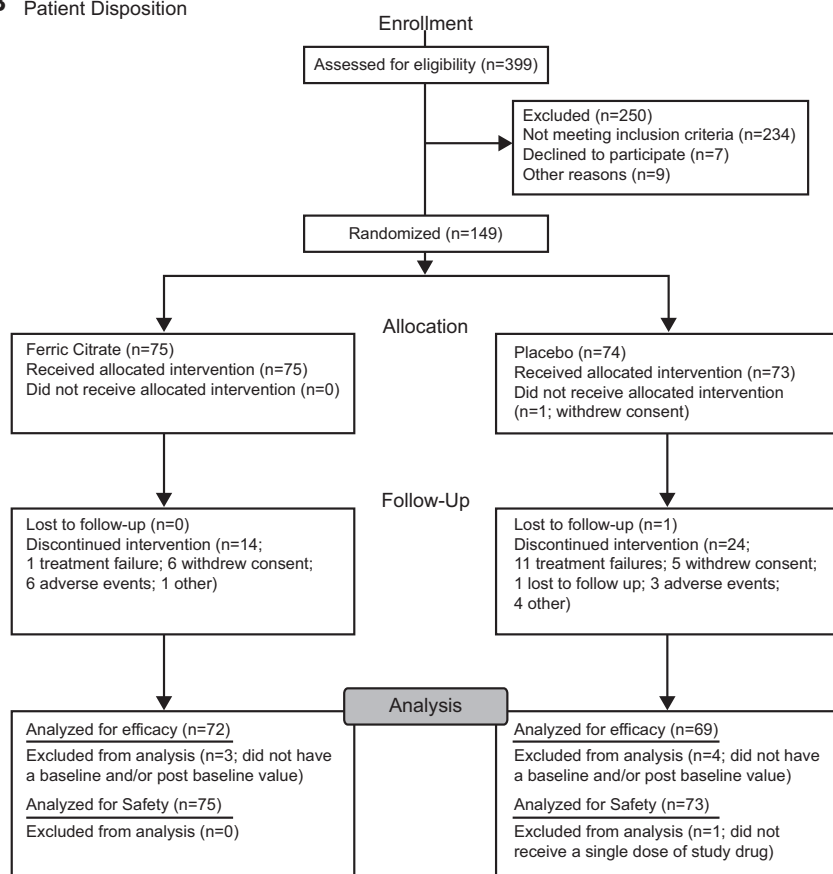


Figure 1. Study design. (A) Schematic shows study drug dose adjustments made based on laboratory serum phosphate (P) results. (B) Patient disposition.

statistically significant findings on both coprimary outcomes would be required to consider the trial as positive overall. We considered 2-sided $P < 0.05$ statistically significant, and used SAS, version 9.3 (SAS Institute Inc) to conduct all analyses. All results were verified by an independent statistician with full access to the data.

RESULTS

Patient disposition is shown in Fig 1B. Baseline characteristics were similar between treatment groups

(Table 1). Mean daily doses of study medication were 5.1 g/d (5.1 pills per day) for ferric citrate and 5.2 g/d (5.2 pills per day) for placebo. Maximum average daily doses were 9.0 and 9.3 g/d (9.0 and 9.3 pills per day) for ferric citrate and placebo, respectively. Median follow-up was 76 days with ferric citrate and 70 days with placebo. eGFRs were stable throughout the treatment period, with no significant differences between ferric citrate- and placebo-treated patients (Table S2).

Table 1. Baseline Characteristics of Study Participants

	Ferric Citrate (n = 72)	Placebo (n = 69)
Demographics		
Age (y)	66 ± 12	64 ± 14
Female sex	50 (69)	43 (62)
White	57 (79)	52 (75)
African American	15 (21)	16 (23)
Hispanic or Latino	15 (21)	21 (30)
CKD stage at baseline		
Stage 3	13 (18)	16 (23)
Stage 4	38 (53)	36 (52)
Stage 5	20 (28)	16 (23)
Weight (lb)	194 ± 47	198 ± 55
Systolic BP (mm Hg)	137 ± 21	133 ± 18
Diastolic BP (mm Hg)	71 ± 13	71 ± 10
Comorbid conditions		
Diabetes	48 (67)	49 (71)
Atherosclerotic coronary disease	19 (26)	19 (28)
Congestive heart failure	14 (19)	15 (22)
Laboratory characteristics		
Iron saturation (%)	21.6 ± 7.4	21.2 ± 8.3
Ferritin (ng/mL)	116 ± 83	110 ± 81
Hemoglobin (g/dL)	10.5 ± 0.8	10.6 ± 1.1
Phosphate (mg/dL)	4.5 ± 0.6	4.7 ± 0.6
24-h urine phosphate (mg/d)	730 ± 286	727 ± 281
Intact FGF-23 (pg/mL)	159 [102-289]	184 [111-352]
Carboxy-terminal FGF-23 (RU/mL)	377 [193-570]	436 [254-653]
eGFR (mL/min/1.73 m ²)	25.9 ± 11.5	22.6 ± 9.1
Bicarbonate (mEq/L)	21.0 ± 2.9	21.2 ± 3.3
Intact PTH (pg/mL)	97 [69-178]	135 [90-222]

Note: Values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation or median [interquartile range].

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FGF, fibroblast growth factor; PTH, parathyroid hormone.

Changes in mean TSAT (Fig 2A; Table S2) and serum phosphate values (Fig 3A; Table S2) were significantly different between ferric citrate- and placebo-treated groups (treatment-effect difference for TSAT: 11.3% [95% confidence interval (CI), 8.0%-14.7%]; for serum phosphate: -0.47 [95% CI, -0.67 to -0.26] mg/dL; *P* < 0.001 for each). TSAT increased progressively in the ferric citrate group from a baseline value of 22% ± 7% to 32% ± 14% at end of study, whereas TSAT remained stable in the placebo group, 21% ± 8% to 20% ± 8%. In the ferric citrate group, serum phosphate levels declined from a baseline of 4.5 ± 0.6 to 3.9 ± 0.5 mg/dL by week 4 and were maintained at this level throughout the duration of the 12-week study period. In the placebo group, serum phosphate levels declined from 4.7 ± 0.6 to 4.4 ± 0.8 mg/dL at week 12. Among patients who completed the 12-week study period, serum phosphate levels were reduced by 0.7 mg/dL

with ferric citrate and 0.2 mg/dL with placebo. Corresponding analyses using the mixed-effect repeated-measures model showed a change from baseline in TSAT of 10.4% ± 13.0% with ferric citrate and -0.7% ± 7.1% with placebo (between-group difference, 11.9%; *P* < 0.001); change from baseline in serum phosphate levels was -0.7 ± 0.6 mg/dL with ferric citrate and -0.2 ± 0.7 mg/dL with placebo (between-group difference, -0.5 mg/dL; *P* < 0.001).

Secondary end points of hemoglobin and serum ferritin levels are shown in Fig 2B and C and Table S2. Changes in serum ferritin levels paralleled those of TSAT, increasing steadily in the ferric citrate arm from 116 ± 83 to 189 ± 122 ng/mL while remaining unchanged (110 ± 81 to 106 ± 94 ng/mL) in patients receiving placebo (treatment-effect difference, 77.5 [95% CI, 56.2-98.7] ng/mL; *P* < 0.001). In patients receiving ferric citrate, hemoglobin levels increased from 10.5 ± 0.8 g/dL at baseline to 11.0 ± 1.0 g/dL at end of study, whereas in the placebo group, they decreased from 10.6 ± 1.1 g/dL at baseline to 10.4 ± 1.1 g/dL at end of study (treatment-effect difference, 0.6 [95% CI, 0.4-0.9] g/dL; *P* < 0.001).

Urinary phosphate and FGF-23 levels were significantly reduced in the ferric citrate group (Fig 3B and C; Table S2). In the ferric citrate group, urinary phosphate excretion was reduced by 39%, whereas levels were unchanged in the placebo group (between-group difference, -286.8 [95% CI, -379.2 to -194.4] mg/d; *P* < 0.001). Treatment with ferric citrate decreased median serum FGF-23 levels from 159 (interquartile range [IQR], 102-289) pg/mL at baseline to 105 (IQR, 65-187) pg/mL at end of study, while in placebo-treated patients, median serum FGF-23 concentrations decreased from 184 (IQR, 111-352) to 148 (IQR, 101-330) pg/mL (between-group difference, -125.3 [95% CI, -228.1 to -22.6] pg/mL; *P* = 0.02). Results with carboxy-terminal FGF-23 were consistent with those seen when intact FGF-23 was assayed (Fig 3D).

We prespecified an on-trial hemoglobin level < 9.0 g/dL or phosphate level > 6.0 mg/dL as treatment failures. Treatment failure occurred in one patient in the ferric citrate arm (low hemoglobin) and 11 patients treated with placebo (9, low hemoglobin; 2, high phosphate). No patient developed symptomatic hypophosphatemia or elevations in liver enzyme levels. There were 2 instances of isolated serum phosphate level < 2.5 mg/dL, which were asymptomatic and resolved prior to the next laboratory assessment. Changes in all other biochemical parameters are shown in Table S2.

A full listing of all treatment-emergent adverse events occurring at ≥2% incidence is shown in Table S3. Serious adverse events occurred in 8% of

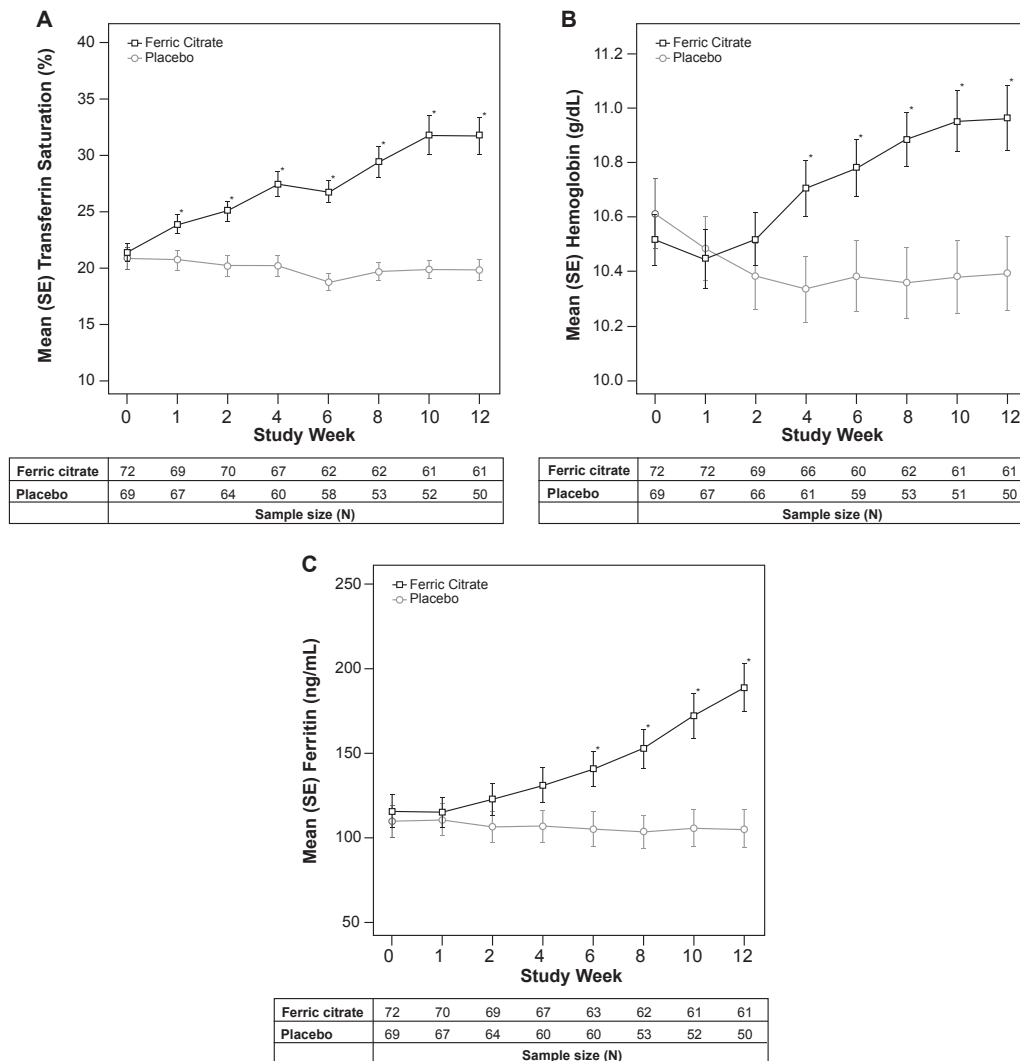


Figure 2. Primary and secondary iron-related end points: (A) transferrin saturation, (B) hemoglobin, and (C) ferritin values. Data represent mean (standard error [SE]) using the modified intention-to-treat treatment group. **P* < 0.05 using Wilcoxon rank sum test.

ferric citrate–treated and 12% of placebo-treated patients, while adverse events resulting in study drug withdrawal occurred in 13% and 11%, respectively. There were no related serious adverse events. Two patients died; both had been randomly assigned to placebo. Forty-eight of 52 ferric citrate–treated patients with adverse events (92%) had events deemed to be of mild (*n* = 28) or moderate (*n* = 20) severity. Most were gastrointestinal in nature, with 24 events of discolored feces (32%), 15 events of diarrhea (20%), and 14 events of constipation (19%).

DISCUSSION

These results demonstrate that short-term use of ferric citrate effectively repleted iron stores, increased hemoglobin levels, and reduced serum phosphate and FGF-23 levels when given to patients with CKD stages 3 to 5 and iron deficiency anemia. Historically, oral iron therapy has been at best modestly effective in repleting iron

stores or providing adequate iron to support hemato- poiesis in iron-deficient patients with CKD. Although the current trial was placebo controlled, the observed increase in hemoglobin levels of 0.5 g/dL over 12 weeks is substantially higher than that seen with ferrous sulfate (0.2 g/dL) or ferrous fumarate (0.1 g/dL) in prior studies and is similar to that seen when patients with CKD stages 3 to 5 are administered large doses of intravenous iron sucrose (0.5 g/dL), sodium ferric gluconate (0.4 g/dL), or ferumoxytol (0.6 g/dL) without a concomitant ESA.²⁷⁻²⁹

A sizeable fraction of patients with CKD stages 3 to 5 warrant treatment with iron, yet are untreated due to perceived risks and logistical challenges associated with administering intravenous iron in outpatient settings.⁴ Intravenous iron may exacerbate oxidative stress, increase inflammation, decrease immune function, and increase risk of microbial infection in patients with CKD.³⁰ A multivariable-adjusted analysis of 117,050

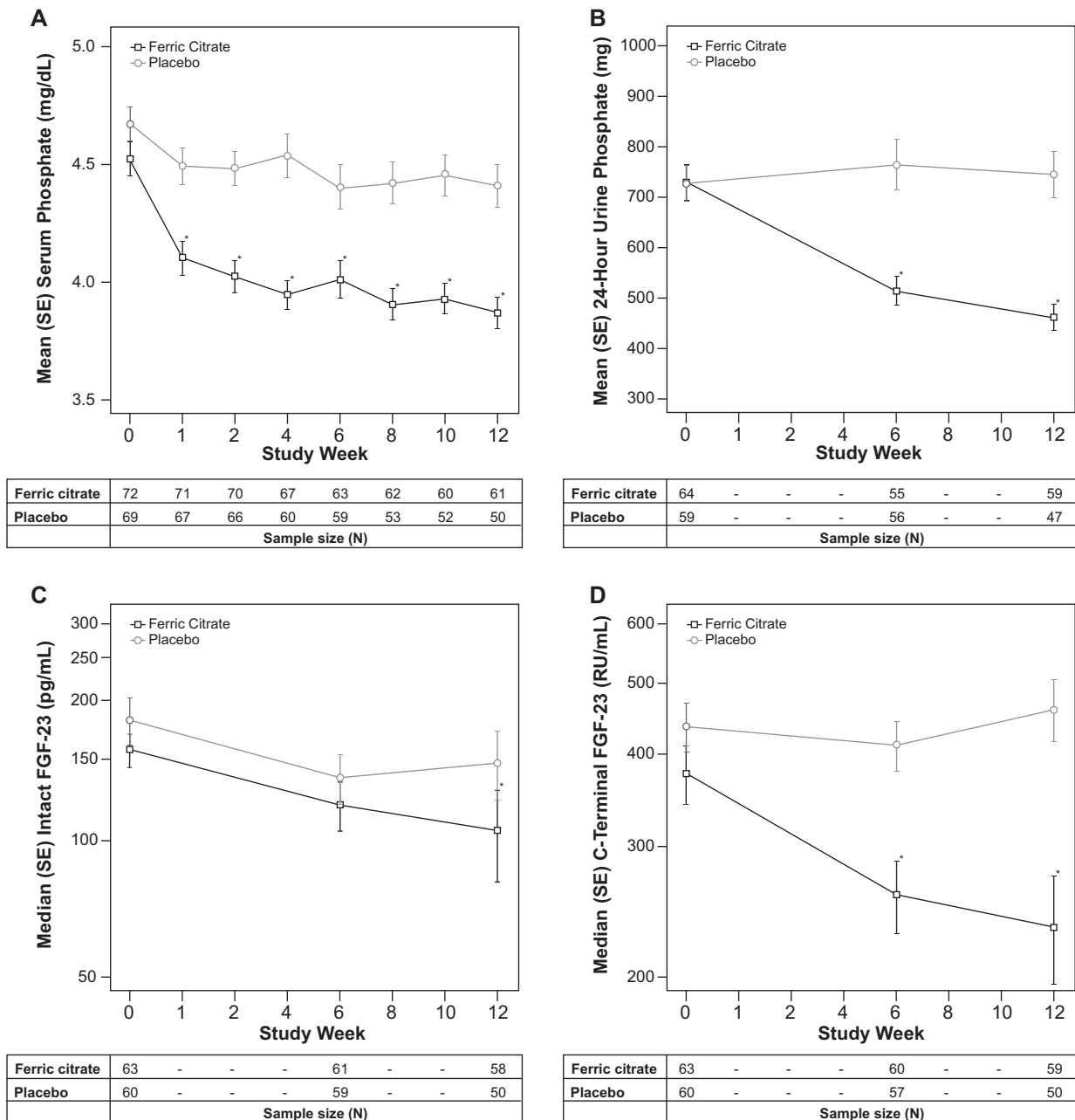


Figure 3. Primary and secondary phosphate-related end points: (A) serum phosphate (mg/dL), (B) urine phosphate (mg/24 h), (C) intact fibroblast growth factor 23 (FGF-23; pg/mL), and (D) carboxy-terminal FGF-23 (RU/mL). Data represent mean (standard error [SE]) or median (SE) using the modified intention-to-treat treatment group. **P* < 0.05 using Wilcoxon rank sum test.

patients on hemodialysis therapy described a higher risk of infection-related hospitalization and infection-related mortality with bolus intravenous iron dosing,³¹ and a recent comparison of 2 different intravenous iron compounds in CKD stages 3 to 5 demonstrated that both intravenous iron formulations were associated with hypotension and hypersensitivity reactions, risks that appear to be common to all intravenous iron formulations.⁶ As a result of these limitations, many patients with CKD stages 3 to 5 develop progressive anemia and some are started on treatment with ESAs despite

insufficient iron stores, which limits ESA efficacy (and efficiency). In a large, event-driven, randomized, placebo-controlled trial in patients with type 2 diabetes mellitus and eGFRs of 20 to <60 mL/min/1.73 m² targeting normal hemoglobin concentrations, darbepoetin showed no difference compared with placebo on a composite cardiovascular end point and nominally significant increases in risks of stroke and venous thromboembolism.³² We acknowledge that unlike ESAs, no long-term outcomes-driven trial has examined the safety and efficacy of oral or intravenous iron

formulations in CKD stages 3 to 5. We demonstrate that during a 12-week study period, ferric citrate safely provided clinically effective iron repletion, presumably without bypassing the normal physiologic regulation of intestinal iron uptake. It is notable that the benefits of iron repletion in patients with iron-deficiency anemia with and without CKD have been reported to extend beyond increasing hemoglobin levels, with demonstrated improvements in quality of life and functional ability.³³

The effects of ferric citrate on phosphate metabolism are particularly noteworthy when considered in the context of previous clinical trials in this area. A post hoc analysis of the MDRD (Modification of Diet in Renal Disease) Study, in which dietary protein restriction resulted in profound dietary phosphate reduction, demonstrated no reduction in serum phosphate levels.²⁰ In the Phosphate Normalization Trial, a 9-month, double-blind, randomized, placebo-controlled trial in patients with CKD stages 3 to 5 and similar inclusion and exclusion criteria as the current trial, the 3 commercially available phosphate binders, calcium acetate, lanthanum carbonate, and sevelamer carbonate, demonstrated a pooled decrease in serum phosphate levels of only 0.3 mg/dL, despite use of moderate to high doses of each drug.¹⁹ Furthermore, in the Phosphate Normalization Trial, calcium acetate therapy increased both carboxy-terminal and intact FGF-23, whereas lanthanum carbonate had no effect and sevelamer carbonate reduced only intact FGF-23 (but not carboxy-terminal FGF-23) by ~20%. In contrast, we demonstrate that ferric citrate reduced serum phosphate levels by 0.6 mg/dL and both carboxy-terminal and intact FGF-23 levels by nearly 40%.

FGF-23 is one of the key regulators of phosphate and vitamin D homeostasis.³⁴ Patients with CKD often have profound elevations in FGF-23 levels that have been associated with progressive loss of kidney function and ESRD, cardiovascular events, and mortality.^{16,35-40} In a cohort of 3,860 patients with CKD stages 2 to 4 followed up for 3.7 years, those in the highest quartile of FGF-23 levels had a nearly 4-fold increase in risk of incident congestive heart failure, consistent with the described ability of FGF-23 to directly stimulate left ventricular hypertrophy.¹⁸ The particularly robust effects of ferric citrate to lower serum FGF-23 concentrations may relate to greater intestinal phosphate binding relative to other phosphate binders. Alternatively, because iron deficiency is another important stimulus of FGF-23 transcription, ferric citrate's unique effect to simultaneously replete iron stores may explain its ability to lower FGF-23 levels to a greater extent than other binders.⁴¹

Aside from its effects on FGF-23 levels, the urine and serum phosphate-lowering effects of ferric citrate are

clinically meaningful. In the general population, higher levels of dietary phosphate intake are associated with mortality and are correlated directly with left ventricular mass by cardiac magnetic resonance imaging.^{42,43} Dietary phosphate intake is difficult to assess given the ubiquitous but mostly undocumented use of phosphate-based food additives, an emerging public health issue.⁴⁴ Therefore, urinary phosphate excretion is a useful surrogate measure of net phosphate absorption. Our finding that ferric citrate reduced urinary phosphate levels by nearly 40% demonstrates its biological effect to reduce phosphate absorption. Many, though not all, studies describe increased risk of CKD progression, cardiovascular events, and mortality in persons with serum phosphate levels > 4.0 mg/dL.^{8,45,46} A recent re-analysis of the Ramipril Efficacy in Nephropathy (REIN) trial found that patients with serum phosphate levels > 4.0 mg/dL were significantly more likely to progress to require dialysis or experience a doubling of serum creatinine level even after adjustment for iohexol-measured GFR, age, and ramipril use.⁸ In the group of patients who otherwise derived the strongest renoprotective benefit of ramipril, the effect was attenuated if serum phosphate level was 3.5 to 4.0 mg/dL and abolished if serum phosphate level was > 4.0 mg/dL.

This trial has several strengths. Patients were diverse in age, sex, race, and primary cause of CKD. Adherence was excellent, dropout rates were modest, and missing data were minimal. The trial's major limitations include its relatively small sample size, relatively short duration, and, most importantly, biochemical rather than clinical outcomes. Several other limitations warrant mention. We did not measure serum aluminum, but it should be emphasized that use of concurrent aluminum-containing phosphate binders and other medications was prohibited. Moreover, previously published clinical trials in patients on dialysis therapy receiving ferric citrate for 1 year have shown no change in serum aluminum concentrations.^{22,24} We did not capture data for dietary intake so we are unable to determine whether there were between-group differences in the intake of inorganic or organic phosphorus or other dietary parameters, including meat and other sources of iron, or in any derived estimates of dietary protein intake (eg, protein nitrogen appearance). Due to modest sample sizes, small differences in baseline characteristics between the ferric citrate and placebo groups were observed; however, we do not believe that these had a material influence on the primary or secondary outcomes of the study. Finally, this was a placebo-controlled trial, rather than a trial using an active phosphate binder and/or iron supplement control. We believe that a placebo-controlled trial provides unambiguous evidence of safety and efficacy, at least with respect to the treatment duration of 12 weeks.

However, without active controls, we are unable to determine whether ferric citrate is superior, inferior, or approximately similar to other phosphate binders or iron supplements in this patient population.

In summary, we demonstrate that short-term use of ferric citrate refills iron stores, increases hemoglobin levels, and decreases serum phosphate, urinary phosphate excretion, and FGF-23 levels in patients with CKD stages 3 to 5. Given the high prevalence of iron deficiency anemia and disorders of mineral metabolism in patients with CKD stages 3 to 5 and the demonstrated risks and limited efficacy of existing alternative therapies, ferric citrate may improve the treatment of iron deficiency anemia and disorders of mineral metabolism in these patients. Clinical trials evaluating longer-term effects of ferric citrate in patients with CKD stages 3 to 5 will be required in order to establish the role of ferric citrate in clinical practice.

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Disclosures: Drs Block and Pergola: consultant, research grant for Keryx Biopharmaceuticals Inc; Drs Chertow, Fishbane, Smits, and Wolf: consultant for Keryx Biopharmaceuticals, Inc; and Mr Shemesh: employee of and owns stock in Keryx Biopharmaceuticals Inc.

Contributions: Research idea and study design: GAB, GMC, SF, PEP; data acquisition: GAB, GMC, PEP, SS; data analysis/interpretation: GAB, GMC, SF, MR, PEP, MW, GS; statistical analysis: GAB, GMC, MW, GS. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. GAB takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

SUPPLEMENTARY MATERIAL

Table S1: Use of calcium supplements and vitamin D.

Table S2: Biochemical outcomes at baseline and end of study.

Table S3: Treatment-emergent adverse events by treatment group, body system, preferred term, and severity.

Note: The supplementary material accompanying this article (<http://dx.doi.org/10.1053/j.ajkd.2014.10.014>) is available at www.ajkd.org

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