

Ferric Citrate (Auryxia) for the Treatment of Hyperphosphatemia

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INTRODUCTION

Chronic kidney disease (CKD) represents an enormous global public health concern, affecting an estimated 8% to 16% of the world's population.¹ In the U.S., data from the National Health and Nutrition Examination Survey indicate that more than 25 million Americans have CKD, defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m² or a urine albumin/creatinine ratio of 30 mg/g or higher.² According to the U.S. Renal Data System, more than 636,000 Americans were receiving treatment for end-stage renal disease (ESRD) at the end of 2012, with nearly 450,000 patients requiring dialysis and approximately 186,000 with a functioning renal transplant.³ In 2011, total Medicare expenditures for the treatment of patients with ESRD topped \$34.4 billion, with medications and estimated total net Part D payments estimated to be \$2.1 billion.²

Mineral and bone disorders in CKD patients encompass abnormalities in bone architecture, such as renal osteodystrophy, osteitis fibrosa cystica, and osteomalacia, and mineral metabolism, including hyperphosphatemia, secondary hyperparathyroidism, and impaired vitamin D activation, with or without extraskeletal calcification.⁴⁻⁶ The collective effect of these abnormalities is an increase in cardiovascu-

lar mortality related to uncontrolled hyperparathyroidism and vascular calcification.^{7,8} Controlling serum phosphate levels via use of dietary phosphate binders, along with dietary phosphate control, may help to reduce the adverse consequences of hyperphosphatemia.⁷ Phosphate binding agents work to reduce serum phosphate levels by forming an insoluble complex with dietary phosphorus in the gastrointestinal (GI) tract and allowing its elimination in the feces. Currently available phosphate binding agents include elemental compounds such as aluminum hydroxide, magnesium and calcium carbonate, calcium acetate, sucroferric oxyhydroxide, and lanthanum carbonate, and the nonelemental agent sevelamer carbonate.

In September 2014, ferric citrate (Auryxia, Keryx Biopharmaceuticals), a novel phosphate-binding agent, received Food and Drug Administration approval for the treatment of hyperphosphatemia in CKD patients on dialysis. This article will review the clinical evidence supporting the use of ferric citrate for this indication.

PHARMACOLOGY

Healthy kidneys excrete phosphate extremely efficiently, even in the setting of precipitously increased dietary intake. In CKD patients with an eGFR below 20–25 mL/min, however, phosphate excretion into the urine becomes much less predictable.⁹ In advanced renal failure, the parathyroid gland functions to compensate for impaired phosphate excretion by increasing its production and secretion of parathyroid hormone (PTH), a polypeptide responsible for maintaining calcium and phosphate homeostasis.¹⁰ Secretion of PTH serves to reduce renal phosphate reabsorption in the proximal tubule and thereby compensate for reduced excretion resulting from CKD. As CKD progresses, the increase in PTH fails to compensate for the kidneys' continual reduction in phosphate excretion. As a result, phosphate accumulates to supraphysiological levels.⁹ The

dangers of hyperphosphatemia in CKD patients on dialysis include increased risks of cardiovascular death and overall mortality, left ventricular hypertrophy, calcium-phosphate crystal formation, and a progression of kidney disease.¹¹⁻¹⁴

Strategies for lowering serum phosphate concentrations differ based upon the degree and onset of hyperphosphatemia. Current guidelines recommend first-line use of oral dietary phosphate binders to reduce phosphate concentrations in patients with eGFR values below 60 mL/min/1.73 m² through end-stage disease requiring dialysis. The serum phosphate-lowering ability of the oral phosphate binders is second only to dialysis in its effectiveness.¹⁵ This is logical, since the gut absorbs 60% to 80% of dietary phosphate and the process of phosphate absorption is nonsaturable. As a result, products that bind phosphate in the gut and reduce the percentage of dietary phosphate available for absorption have been proven effective for lowering serum phosphate in CKD patients.⁹

Ferric citrate is an oral, insoluble, aluminum-free, calcium-free, ferric iron-based phosphate binder that exerts its effects in the GI tract. After administration, the product dissociates into its ferric iron (Fe⁺³) and citrate (C₆H₄O₄⁻) components. This allows the ferric iron ion to bind multiple phosphate ions and create a ferric phosphate precipitate that is excreted in the stool, thereby reducing absorption of dietary phosphate. As with other oral phosphate binders, the resultant effect is a lowering of the serum phosphate concentration. In addition to its phosphate-lowering effects, ferric citrate provides the added benefit of improved iron parameters for CKD patients, including increases in ferritin, iron, and transferrin saturation (TSAT). The product contains 210 mg of ferric iron supplied as 1 g of ferric citrate.¹⁶

The clinician should note, however, that ferric iron must be converted in the intestinal lumen to its divalent ferrous

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(Fe⁺²) form prior to absorption in the GI tract, so absorption is expected to be limited compared with the other available oral ferrous formulations.¹⁶ The bioavailability of ferrous sulfate ranges from 10% to 35% in patients with normal iron stores to 80% to 95% in iron-deficient patients.¹⁷

PHARMACOKINETICS

Although it is known that iron is absorbed from ferric citrate, formal pharmacokinetic studies are ongoing to quantify the rate and extent of iron absorption from this formulation.

USE IN RENAL AND HEPATIC IMPAIRMENT

Under the U.S. labeling and initial FDA approval, ferric citrate is intended for use in CKD patients on dialysis. In Japan, however, this agent is approved for the treatment of hyperphosphatemia in patients with CKD, including dialysis- and nondialysis-dependent disease; this indication is also being sought in the proposal submitted to the European Medicines Agency. This medication has not been studied for use in individuals with comorbid liver disease.

CLINICAL EFFICACY

The safety and efficacy of ferric citrate as a dietary phosphate binder in CKD patients on dialysis has been evaluated in several clinical trials conducted both in the United States and abroad. The recently approved 1-g dosage form was studied in two pivotal phase 3 trials, both of which are summarized in this article. In addition, the results of three pivotal phase 3 trials, two performed in Japan and one in Taiwan, supported the eventual approval there of the drug under the brand name Riona in January 2014. Summaries of these trials are also provided in this article. The dosage form approved in Japan differs from the product available in the U.S., as Riona is a 250-mg tablet containing ferric citrate anhydrate, which provides approximately 62 mg of ferric iron per tablet. It should be reiterated that Riona is also approved for use in Japan for phosphate-lowering therapy in CKD patients not dependent upon dialysis.

U.S. Trials in Dialysis-Dependent CKD

Dwyer et al.¹⁸

In 2013, Dwyer and colleagues reported the results of a phase 3, multicenter, ran-

domized, open-label trial comparing three fixed-dose regimens of ferric citrate. Study subjects were recruited at 15 U.S. sites and assigned in a 1:1:1 ratio to receive ferric citrate in doses of 1 g, 6 g, and 8 g per day for 28 days. Subjects were eligible for the study if they were adults with ESRD on thrice-weekly hemodialysis for at least three months prior to screening. In addition, subjects must previously have been taking between three and 15 capsules/tablets daily of calcium acetate 667 mg or sevelamer hydrochloride/carbonate 800 mg, respectively. If patients were prescribed sevelamer hydrochloride 400-mg tablets, use of between six and 30 tablets per day was acceptable. Subjects also had to have a serum ferritin level of less than 1,000 mcg/L, TSAT less than 50%, and serum phosphorus level greater than or equal to 3.5 mg/dL and less than or equal to 8 mg/dL. Patients were excluded if they had a parathyroidectomy within six months of screening, an actively symptomatic GI bleed or inflammatory bowel disease, a history of malignancy within five years, previous intolerance to ferric citrate, or an absolute need for oral iron, ascorbic acid, or drugs containing calcium, magnesium, or aluminum taken with meals.

After screening and enrollment, subjects included in the study underwent a one- or two-week washout period during which their serum phosphorus levels were measured weekly. Those with serum phosphorus levels greater than 9 mg/dL after week 1 of washout were randomized immediately, whereas those with phosphorus levels between 6 and 8.9 mg/dL proceeded to week 2 of washout. Patients with serum phosphorus levels below 6 mg/dL after two weeks of washout were excluded from randomization and further study participation. Subjects included after the washout period were randomized in a 1:1:1 ratio to receive ferric citrate 1 g, 6 g, or 8 g per day. Ferric citrate was administered as 1-g tablets containing 210 mg of ferric iron. Subjects were permitted to use vitamin D analogues, cinacalcet, and calcium supplements provided that the doses of these supplements remained constant throughout the study and that calcium products were not taken with food. In addition, the use of erythropoietin-stimulating agents (ESAs) was allowed at the discretion of the investigators, as was the use of intravenous (IV) iron, which was permitted for use only in patients with ferritin and

TSAT values that were less than or equal to 1,000 mcg/L and less than or equal to 50%, respectively.

The primary efficacy endpoint was the change in serum phosphorus level from baseline to the end of the treatment period, analyzed by a regression model with dose effect as the covariate. The main secondary endpoint was the change in serum phosphorus level from baseline to the end of the treatment period with direct pairwise comparisons among all three groups. Other secondary endpoints were changes in calcium, calcium-phosphorus product, ferritin, TSAT, and bicarbonate values from baseline to the end of the treatment period.

A total of 154 patients were randomly assigned after screening; 122 (79.2%) completed the full 28 days of treatment. Of those who did not complete the full treatment period, 15 patients (9.7%) discontinued treatment but completed all study assessments, and 14 (9.1%) failed the treatment and were terminated early. Treatment failure was defined as a serum phosphorus level of 2.5 mg/dL or less after day 7 or 2.5 mg/dL or less or 9.0 mg/dL or more at day 14 or day 21. Baseline characteristics, including baseline serum phosphorus levels, were well matched among groups. Mean serum phosphorus level changes from baseline to the end of the treatment period in the 1-g, 6-g, and 8-g groups were -0.1 mg/dL, -1.9 mg/dL, and -2.1 mg/dL, respectively. It was found that the mean differences in change from baseline were significant when the 6-g and 8-g groups were compared with the 1-g group ($P < 0.001$), but the difference between the 6-g and 8-g groups was not significant when they were directly compared ($P = 0.5$). Table 1 summarizes the results of the secondary endpoint analyses. These analyses show a statistically significant difference in dose-response relating to change in ferritin concentration, TSAT, and bicarbonate concentrations. As for safety, the overall incidence in adverse effects (AEs) in the 1-g, 6-g, and 8-g groups was 66.7%, 82.7%, and 85.4%, respectively. It should be noted that the incidence of AEs related to ferric citrate, serious AEs, and AEs resulting in study-drug discontinuation increased as the dose of the study drug increased. Gastrointestinal AEs occurred in 43.1%, 42.3%, and 52.1% of patients in the 1-g, 6-g, and 8-g groups, respectively.

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Table 1 Dwyer et al.: Summary of Secondary Endpoints¹⁸

	1 g/day	6 g/day	8 g/day	P value (Dose–Response)
Calcium (mg/dL)	-0.01 ± 0.4	0.2 ± 0.5	0.4 ± 0.6	0.07
Ca x P (mg ² /dL ²)	-0.7 ± 11.6	-15.0 ± 15.4	-17.2 ± 16.9	0.1
Ferritin (mg/dL)	-14.4 ± 155.0	90.1 ± 198.6	90.2 ± 279.0	< 0.001
TSAT (%)	-0.8 ± 10.7	1.5 ± 17.0	4.4 ± 12.9	0.02
Bicarbonate (mEq/L)	0.1 ± 2.4	1.6 ± 3.1	1.5 ± 3.9	0.03

Ca x P = calcium x phosphate product; TSAT = transferrin saturation

The authors concluded that ferric citrate is efficacious as a dietary phosphate binder and that its use results in lower serum phosphorus levels in patients on dialysis. They also noted that a significant dose–response relationship was associated with the primary efficacy endpoint as well as some of the secondary efficacy endpoints when all groups were included. The difference between the 6-g and 8-g groups was not statistically significant; however, the difference was consistent with the dose–response relationship, so the difference in dose may be clinically significant in some patients.

Lewis et al.^{19,20}

The 2014 study by Lewis et al. details the findings of a sequential three-period, 58-week, phase 3 randomized controlled trial. Study subjects who were enrolled at 56 centers in the U.S. and two centers in Israel were randomized to receive either ferric citrate or an active control. The study was performed to assess the safety and efficacy of ferric citrate as a phosphate binder in 441 patients with ESRD requiring dialysis. Subjects were enrolled in the trial if they were 18 years of age or older and had ESRD on thrice-weekly dialysis (hemodialysis [HD] or peritoneal dialysis [PD]) for at least three months. Included subjects were also required to have a serum phosphorus level between 2.5 mg/dL and 8 mg/dL upon screening, as well as a serum phosphorus level of 6 mg/dL or greater after the two-week washout period. In addition, because the active drug contains ferric iron and secondary study endpoints included the drug's effects on iron parameters, patients were required to have serum ferritin levels of less than 1,000 mcg/L and a TSAT of less than 50% at screening. Finally, subjects had to be taking three to 18 pills per day of a previously approved phosphate binder

prior to enrollment and needed to have a life expectancy exceeding one year. Important exclusion criteria included parathyroidectomy within six months of screening; GI bleeding; inflammatory bowel disease; intolerance to iron-containing products, sevelamer carbonate, or calcium acetate; or an absolute requirement for oral iron, ascorbic acid, or drugs containing calcium, magnesium, or aluminum.

The study was divided into three periods: a two-week washout period, a 52-week safety assessment period (SAP), and a four-week placebo-controlled efficacy assessment period (EAP). The prestudy washout period was intended to ensure that subjects developed hyperphosphatemia and had cleared their previous phosphate binders. Following the washout period, subjects who met the inclusion criteria were randomized in a 2:1 ratio to ferric citrate or an active control and entered into the SAP. Active controls included calcium acetate 667-mg capsules and sevelamer carbonate 800-mg tablets, which could be taken individually or in combination by those assigned to the active control group at the discretion of the principal investigator. Those assigned to ferric citrate would receive six 1-g caplets daily, each containing 210 mg of ferric iron, and those assigned to one or both of the active controls would receive those medications in doses as specified by the product labeling or at the discretion of the principal investigator. Serum phosphorus and calcium levels were evaluated at least every two weeks during the first 12 weeks of the SAP and at least monthly thereafter for the remainder of the SAP. The resultant values were used to guide titration of the study drug using a predetermined, protocol-supplied titration schedule as well as the dosage of the active controls via their respective product labeling. Following the SAP, subjects

who had been assigned to receive ferric citrate were enrolled in a four-week, randomized, open-label, placebo-controlled EAP. Patients were assigned in a 1:1 ratio to receive active drug or placebo.

The primary efficacy outcome of both the 52-week SAP and the four-week EAP was the change in serum phosphorus between ferric citrate and comparator(s). Reported secondary outcome measures included differences in serum ferritin, TSAT, ESA dose, hemoglobin, and iron, phosphorus, calcium, and intact PTH (iPTH) levels between ferric citrate and the comparator(s). Safety was assessed by recording and monitoring all reported AEs. Results were reported separately for the SAP and the EAP.

After the 52-week SAP, serum phosphorus concentrations did not differ significantly among the ferric citrate and active control groups, with serum phosphorus concentrations of 5.4 ± 1.6 mg/dL (± SD) in the ferric citrate group and 5.4 ± 1.7 mg/dL and 5.3 ± 1.4 mg/dL in the sevelamer carbonate group (*P* = 0.94 compared with ferric citrate) and the calcium acetate group (*P* = 0.84 compared with ferric citrate), respectively. However, the results of the four-week EAP showed a significantly lower serum phosphorus level in the ferric citrate group versus the placebo group (mean difference ± standard error of the mean [SEM], -2.2 ± 0.2 mg/dL, *P* < 0.001). It is important to note that the baseline serum phosphorus levels prior to the start of the EAP were similar between those randomized to the ferric citrate and placebo groups. In addition, the results were unchanged after adjustment for the three baseline characteristics that were significantly different between groups (sex, ferritin, and hemoglobin). The trial also showed that ferric citrate significantly increased serum ferritin and TSAT and decreased IV iron and ESA requirements in the 52-week SAP (Table 2).

With regard to safety, the incidence of summed nonserious AEs and serious AEs between ferric citrate and active controls was similar (90.3% versus 89.3%) in the SAP. The incidence of serious adverse drug reactions (ADRs) in the SAP, however, was found to be 39.1% in the ferric citrate group and 49.0% in the active control group. No deaths throughout the entire study were deemed to result from administration of the study drug.

The authors concluded that ferric

Table 2 Lewis et al.: Iron Parameters After 52-week Safety Assessment Period, Ferric Citrate Versus Active Control^{19,20}

	Baseline Mean (SEM)		Week 52 Mean (SEM)		Week 52 Median or Cumulative Median (25 th –75 th Percentile)		ANCOVA or Wilcoxon Rank Sum Results (Ferric Citrate Versus Active Control)		
	Ferric Citrate	Active Control	Ferric Citrate	Active Control	Ferric Citrate	Active Control	Adjusted Mean Difference	95% Confidence Interval	P Value
Ferritin (ng/mL)	593 (18)	609 (26)	899 (31)	628 (31)	858 (568–1,105)	576 (333–883)	282	197 to 366	< 0.001
TSAT (%)	31.3 (0.7)	30.9 (1.0)	39.3 (1.1)	29.7 (1.0)	36.0 (27.5–47.0)	28.0 (21.0–34.5)	9.5	6.4 to 12.6	< 0.001
IV iron requirements (mg/week)	–	–	–	–	12.9 (1.0–28.9)	26.8 (13.4–47.6)	–12.5	–17.2 to –7.9	< 0.001
ESA dose (units/week)	–	–	–	–	5,303 (2,023–9,695)	6,954 (2,664–12,375)	–1,191	–2,632 to 0	0.04

ESAs = erythropoietin-stimulating agents; IV = intravenous; SEM = standard error of the mean; TSAT = transferrin saturation

citrate is effective as a dietary phosphorus binder and improves ferritin and TSAT levels and reduces IV iron and ESA requirements in patients with CKD on dialysis. The incidence of AEs was not significantly different between the two groups, although serious AEs were more common in the active control group than the ferric citrate group. Discontinuation was more common in the ferric citrate group (33%) than the active control group (23%), a finding that was assumed to relate to the occurrence of more non-serious GI AEs (such as diarrhea and bloating) in the ferric citrate group.

Japan: Trials in Dialysis-Dependent CKD Patients

Yokoyama et al.,²¹ May 2014

A trial directly comparing JTT-751 (ferric citrate anhydrate) and sevelamer hydrochloride (HCl) in HD-dependent CKD patients was published by Yokoyama et al. in May 2014. The trial was a phase 3, multicenter, randomized, active-controlled, open-label, parallel-group study. Altogether, 230 patients were recruited across 49 centers in Japan. This study included patients at least 20 years of age undergoing thrice-weekly hemodialysis for at least 12 weeks prior to study screening who had been taking a constant dose of phosphate binders for at least four weeks prior to screening or who had discontinued phosphate binders with serum phosphate concentrations between 6.1 mg/dL and 10 mg/dL and were taking constant doses of vitamin D, calcitonin, or cinacalcet preparations

for at least four weeks prior to screening. Patients were excluded if they had any active GI disease, a history of gastrectomy or enterectomy, marked constipation or a severe GI motility disorder, serum ferritin greater than 500 ng/mL or TSAT greater than 50%, corrected calcium of less than 8 mg/dL or greater than 11 mg/dL, a parathyroidectomy, or hepatic dysfunction/cirrhosis.

Included patients were entered into a two-week washout period during which any previously used phosphate binders were discontinued, followed by a 12-week treatment period. Patients were randomized to receive either JTT-751 1.5 g per day or sevelamer HCl 3 g or 6 g per day depending on serum phosphorus levels; sevelamer HCl 3 g per day was used in those with serum phosphorus concentrations of 6.1 mg/dL or more and less than 8 mg/dL, and sevelamer HCl 6 g per day was used in those with serum phospho-

rous concentrations of 8 mg/dL or more and 10 mg/dL or less. Doses of the drugs were titrated in a prespecified range: 1.5 g to 6 g per day for JTT-751 and 3 g to 9 g per day for sevelamer HCl. Discontinuation of study drugs was mandated for patients with ferritin greater than or equal to 800 ng/mL, two consecutive serum phosphate concentrations below 3 mg/dL, or two consecutive corrected calcium concentrations below 7.5 mg/dL. All patients were allowed IV iron administration at the discretion of the investigators.

The primary efficacy outcome was the relative change in serum phosphate concentrations between JTT-751 and sevelamer HCl from baseline to the end of treatment. Secondary efficacy outcomes included the change in corrected serum calcium and iPTH concentrations from baseline to the end of treatment. Serum hemoglobin, hematocrit, iron, ferritin, total iron-binding capacity (TIBC), and

Table 3 Yokoyama et al. (May 2014): Secondary Outcomes Summary²¹

	JTT-751 (n = 116)		Sevelamer HCl (n = 113)		Between-Group P Value
	Baseline	End of Treatment	Baseline	End of Treatment	
Serum iron (mcg/dL)	52.5	81.5	63.0	58.0	< 0.001
Ferritin (ng/mL)	48.2	123.0	66.9	54.7	< 0.001
TIBC (mcg/dL)	249.0	226.5	241.0	261.0	< 0.001
TSAT (%)	23.0	35.9	24.1	23.5	< 0.001
Hgb (g/dL)	10.9	11.8	10.8	10.6	< 0.001
Hct (%)	33.5	36.1	33.1	32.9	< 0.001

HCl = hydrochloride; Hct = hematocrit; Hgb = hemoglobin; TIBC = total iron binding capacity; TSAT = transferrin saturation

TSAT data were also collected throughout the trial.

The change in serum phosphate concentrations was -2.53 mg/dL in the JTT-751 group and -2.40 mg/dL in the sevelamer HCl group. The least squares mean difference between the two groups was -0.10 mg/dL (95% confidence interval [CI], -0.39 to 0.20), which showed noninferiority of JTT-751 to sevelamer. The percentage of patients reaching the normal range of serum phosphorus concentrations (defined as 3.5 – 5.5 mg/dL) was 62% in the JTT-751 group and 60% in the sevelamer group. As for secondary outcomes, JTT-751 was shown to increase serum calcium levels more than sevelamer in a statistically significant fashion ($P = 0.01$). However, this change was not deemed to be clinically meaningful by the study authors (0.32 mg/dL in the JTT-751 group versus 0.15 mg/dL in the sevelamer group). The change in iPTH concentrations was not significantly different between the JTT-751 and sevelamer groups (0.74 versus 0.73 , $P = 0.73$). Secondary endpoints are summarized in Table 3.

Safety endpoints of the trial included any clinically significant AEs. The incidence of AEs for the JTT-751 group and the sevelamer group was 73% and 74%, respectively. Serious AEs occurred in 5.2% of patients in the JTT-751 group and 2.7% of patients in the sevelamer group. GI AEs occurred in 37% of those in the JTT-751 group and 35% of those in the sevelamer group.

The authors concluded that serum phosphate concentrations declined significantly from baseline in both groups and that the intergroup difference was not significant, thus proving JTT-751 was noninferior to sevelamer HCl as a phosphate binder for HD-dependent CKD patients. They also concluded that JTT-751 led to higher hemoglobin, hematocrit, serum ferritin, and TSAT than sevelamer. In addition, it was noted that none of the patients assigned to JTT-751 had a documented ferritin concentration that exceeded levels at which clinical guidelines recommend withholding IV iron.¹⁵

Yokoyama et al.,²² July 2014

Yokoyama et al. also published the results of a long-term safety and efficacy trial of JTT-751 in July 2014. This trial was an open-label, phase 3, multicenter,

dose-titration trial that recruited subjects at 29 centers in Japan. The inclusion and exclusion criteria mirrored those of the previous trial (Yokoyama et al.,²¹ May 2014) with a few key exceptions; patients were included if they were taking a constant dose of phosphate binders and had a serum phosphorus concentration between 3.5 mg/dL and 10 mg/dL or if they were not taking phosphate binders and had a serum phosphorus concentration between 6.1 mg/dL and 10 mg/dL. The study consisted of a one-week screening period followed by a 52-week treatment period without a washout period between previous treatment modalities and study-drug initiation. The starting dose of JTT-751, 1.5 g per day, was titrated to a maximum of 6 g per day based on a prespecified titration schedule of serum phosphate concentrations. The target serum phosphate concentration for the trial was 3.5 mg/dL to 6 mg/dL.

The primary efficacy outcomes were the change in serum phosphate from baseline to the end of treatment and changes in measured and corrected serum calcium, as well as serum iPTH concentrations from baseline to the end of treatment. In addition to the data associated with the primary outcomes, iron-related tests (TIBC and TSAT), vitamin D-related tests (25-hydroxy and 1,25-dihydroxy vitamin D), bone-specific alkaline phosphatase (BAP, a bone metabolism-related test), and others were administered. Use of IV iron, vitamin D preparations, cinacalcet, and ESAs was allowed at the discretion of the investigators.

The trial included 180 patients who met all of the criteria, 128 of whom completed the full 52-week trial. All patients who received a dose of JTT-751 were included in both the safety and efficacy analyses. The change in serum phosphorus concentrations from baseline to week 12, week 28, and end of treatment was -0.52 mg/dL,

-0.35 mg/dL, and -0.24 mg/dL, respectively. The mean phosphate at the end of treatment was 5.42 mg/dL, which was within the prespecified target range of 3.5 mg/dL to 6.0 mg/dL. As for the secondary outcomes, trends in hemoglobin, hematocrit, serum iron, ferritin, and TSAT were all positive, as would be expected. Secondary outcomes unique to this study are shown in Table 4. BAP, an ectoenzyme that is anchored to the cell membranes of osteoblasts, is used for the purposes of this discussion as a biomarker for bone turnover.²⁵ Aluminum levels are of interest because the anionic component of JTT-751, citrate, has been implicated in increased aluminum absorption from the GI tract.²⁶

The safety endpoints for this trial were clinically relevant AEs determined by symptoms, physical findings, and physiological/laboratory abnormalities. After the trial's conclusion, only one severe AE was found to be related to the study drug (abdominal pain). Besides this AE, nine other AEs led to drug discontinuation, including three cases of elevated hemoglobin, two cases of diarrhea, and one case each of elevated ferritin, liver dysfunction, elevated serum aluminum, and extrasystole. All were determined to be due to the study drug's use except for the case of extrasystole. In total, 96% of the patients (173 of 180) experienced an AE, with the most common AEs being infections unrelated to study-drug use. The investigators further categorized AEs into ADRs that were deemed to be related to study-drug use. Overall, 49 of 180 patients (27%) experienced an ADR, with GI disorders being the most common complaints.

Yokoyama et al. concluded that JTT-751 effectively controlled serum phosphate concentrations in patients receiving hemodialysis during a full year of study. The researchers also found that serum calcium and iPTH concentrations

Table 4 Yokoyama et al. (July 2014): Changes in Blood Biochemical Tests²²

	Baseline	Week 12	Week 28	Week 52	EOT
BAP (mcg/L) Normal range varies widely by age/sex ²³	14.17 ± 9.86	—	17.40 ± 9.52	19.16 ± 13.83	17.77 ± 12.62
Aluminum (mcg/L) Normal range: < 30 ng/mL ²⁴	10.8 ± 5.9	11.5 ± 4.9	11.1 ± 1.18	11.5 ± 5.4	—

BAP = bone-specific alkaline phosphatase; EOT = end of treatment
Data are expressed as mean ± standard deviation (SD); P values are not presented

were maintained and that there were no meaningful changes in markers of bone turnover. In addition, although *P* values were not published, the investigators concluded that the use of JTT-751 significantly reduced IV iron and ESA usage throughout the study.

Taiwan: Trial in Hemodialysis-Dependent CKD

Lee et al.²⁷

Another study published in May 2014 detailed the results of a phase 3, randomized, double-blind, placebo-controlled study intended to assess the efficacy of ferric citrate as a phosphate binder in patients with ESRD on hemodialysis. Patients were screened at five centers in Taiwan and included in the study if they had received thrice-weekly hemodialysis for at least three months, had been on a stable dose of phosphate binders for at least one month, had hematocrit values above 20%, and had a serum calcium level between 8 mg/dL and 10.5 mg/dL. Exclusion criteria included pregnancy, lactation, GI abnormalities, congestive heart failure, diabetic gastroparesis, or clinically significant electrocardiogram (ECG) abnormalities. In addition, patients were excluded if their serum ferritin was above 800 ng/mL, if they had a history of iron allergy or hemochromatosis, or if they had an active malignancy.

Included patients were randomized in a 1:2:2 ratio to receive placebo, ferric citrate 4 g per day, or ferric citrate 6 g per day for eight weeks. Patients were withdrawn from the study at follow-up visits if they had two consecutive serum phosphorus levels of 9 mg/dL or greater or TSAT values of 55% or greater. The primary efficacy endpoint was the change in serum phosphorous at week 8. Secondary endpoints were the changes in serum phosphorous at week 4 and the calcium-phosphorous product at weeks 4 and 8. Safety was evaluated by monitoring for AEs, including severe AEs as well as new-onset or worsened abnormal biochemical and laboratory parameters, vital-sign changes, and ECG abnormalities.

The results of the study included data from 166 subjects in the efficacy population (defined as patients who had a pre-dose and at least one serum phosphorous measurement at day 14 or later) and 183 subjects in the safety evaluation. Of the 41 patients who terminated the study early,

24 (66.7%) were in the placebo group, nine (12.0%) were in the ferric citrate 4-g per day group, and 18 (25.0%) were in the ferric citrate 6-g per day group. Baseline characteristics were well matched among groups. As for the primary endpoint, the changes in serum phosphorous levels (mg/dL, mean ± standard deviation) at week 8 in the placebo, ferric citrate 4-g per day, and ferric citrate 6-g per day groups were 0.08 ± 1.51, -1.60 ± 1.38, and -2.27 ± 1.29, respectively. The difference among groups relating to the primary endpoint was statistically significant (*P* < 0.001). The proportion of patients reaching the target serum phosphorous range (5.5 mg/dL or less) was 16.7%, 57.6%, and 74.1% in the three groups, respectively.

Only one of the prespecified secondary endpoints significantly favored ferric citrate over placebo. While the study drug was not shown to significantly increase TSAT, the changes in serum ferritin levels at eight weeks in patients taking placebo, ferric citrate 4 g per day, and ferric citrate 6 g per day were -41.75 (interquartile range [IQR], -131.15 to 13.60), 73.90 (IQR, 3.00 to 129.60), and 103.40 (IQR, 14.00 to 157.80), respectively. Serum hemoglobin and serum bicarbonate levels did not differ significantly among the groups. Of the 183 patients in the safety population, four experienced a severe AE, none of which was attributed to the use of the study drug. The most common AEs occurred in the ferric citrate groups and were related to GI function. The most frequently reported AEs included discolored feces, diarrhea, abdominal distension, constipation, and abdominal pain.

The authors concluded that oral ferric citrate was a safe and effective option for lowering serum phosphorous in CKD patients on hemodialysis. They concluded that the drug's effects on iron parameters showed either statistically sig-

nificant improvement or a trend toward significant improvement. In addition, they stated that the drug was well tolerated despite a preponderance of GI AEs associated with its use, a reference to the low incidence of severe AEs experienced by the study population.

SAFETY AND TOLERABILITY

In clinical trials, ferric citrate has been relatively well tolerated. In the active-controlled trials by Lewis et al.^{19,20} and Yokoyama et al.²¹ (May 2014), the incidence of AEs, serious or nonserious, was shown to be similar among ferric citrate, sevelamer carbonate or hydrochloride, and calcium acetate. GI discomfort is a well-known AE of iron formulations, so it is not surprising that studies have shown GI AEs to be the most common ones with the use of ferric citrate (Table 5). Patients should be counseled that any of the following AEs may occur with ferric citrate: fecal discoloration, bloating, diarrhea, constipation, nausea, and vomiting. Patients should also be counseled to seek the advice of their physicians if they cannot tolerate the untoward effects of the drug, as they may be able to tolerate an alternative phosphate binder. It should be noted, however, that the incidence of GI AEs was shown to be similar between ferric citrate and sevelamer or calcium acetate.

The major AE of concern is the potential for ferric citrate to cause clinically evident iron overload. The manufacturer has included multiple warnings in the product labeling relating to the potential of ferric citrate to cause iron overload and accidental iron overdose.¹⁶ The evidence cited by the product's labeling related to iron overload is derived from the trial by Lewis et al. in which 19% of patients in the ferric citrate group had a ferritin level higher than 1,500 ng/mL on one or more occasions throughout the study, while only 9% of subjects in the active control group reached the same cutoff.^{19,20} Despite these findings, Lewis et al. postulated that iron overload from orally administered iron is unlikely due to the propensity of the GI tract to tightly regulate iron absorption, so it was most likely the combination of IV iron dosing and ferric citrate that caused the difference between the two groups.^{19,20} Even so, the manufacturer recommends that all patients have their iron parameters assessed prior to initiating ferric citrate

**Table 5 Lewis et al. (July 2014):¹⁹
Ferric Citrate Adverse Events
(Incidence Greater Than 5%)**

Adverse Event	Incidence
Diarrhea	21%
Nausea	11%
Constipation	8%
Vomiting	7%
Cough	6%

Table 6 Cost Comparison of Available Phosphate Binders³⁰

Product	Pharmacological Class	Starting Dose and Dosage Forms	Cost Per Month*
Aluminum hydroxide	Ionic, noncalcium, metal-based dietary phosphate binder	320 mg/5 mL gel/suspension by mouth three times daily with meals	\$6 (OTC)
Calcium carbonate	Ionic, calcium-based, nonmetal dietary phosphate binder	500-mg tablet by mouth three times daily with meals	\$2 (OTC)
Calcium acetate (PhosLo, Fresenius Medical Care; Phoslyra, Fresenius Medical Care; Eliphos, Cypress Pharmaceuticals)	Ionic, calcium-based, nonmetal dietary phosphate binder	667-mg capsule (PhosLo) or tablet (Eliphos) or 667-mg/5-mL solution (Phoslyra), each by mouth three times daily with meals	PhosLo: \$76 (generic, \$47) Eliphos: \$56 Phoslyra: \$100
Ferric citrate (Auryxia, Keryx Biopharmaceuticals)	Ionic, noncalcium, metal-based dietary phosphate binder	1-g tablets; take two by mouth three times daily with meals	\$909
Lanthanum carbonate (Fosrenol, Shire)	Ionic, noncalcium, nonmetal-based dietary phosphate binder	500-mg tablet by mouth three times daily with meals	\$1,009
Sevelamer carbonate (Renvela, Genzyme)	Ion-exchange resin, noncalcium, nonmetal dietary phosphate binder	800-mg packet or tablet by mouth three times daily with meals	Packet: \$1,252 Tablet: \$504 (generic, \$371)
Sucroferric oxyhydroxide (Velphoro, Vifor Pharma)	Ligand-exchange, noncalcium, metal-based dietary phosphate binder	500-mg tablet by mouth three times daily with meals	\$1,026

* Cost is based on the average wholesale price for a 30-day supply of a starting dose, assuming one dose by mouth three times daily with meals; prices are rounded to the nearest dollar. Drug prices as of April 9, 2015.

and periodically throughout treatment. In addition, physicians administering ferric citrate in combination with IV iron should consider reducing the dose of IV iron.¹⁵

As mentioned by Yokoyama et al.,²² there is a theoretical risk of aluminum toxicity secondary to increased absorption of aluminum in the gut mediated by the citrate moiety of ferric citrate. Although the authors of this study concluded that use of ferric citrate was not associated with elevations in plasma aluminum concentrations (Table 4), there is published evidence to support the existence of a theoretical risk of aluminum toxicity using animal models. One commentary found that the use of ferric citrate hydrate (Riona, approved in Japan) was associated with increased aluminum deposition in the brains and bones of healthy animals drinking tap water by about twofold and 20-fold, respectively. Although these findings support further investigation, this evidence was derived from an animal study analyzing a different therapeutic agent, and as such cannot be directly associated with the use of ferric citrate.²⁸

Contraindications and Precautions

The use of ferric citrate is contraindicated in patients with iron overload syndromes because it has been shown to increase serum iron and ferritin concentrations as well as TSAT levels. Iron parameters should be assessed prior to

initiating therapy with ferric citrate and periodically throughout the course of treatment. Because of the risk of iron overload, IV iron use may need to be reduced or discontinued entirely. In addition, the drug carries the potential for accidental iron overdose and toxicity in children. Accidental iron overdose is a leading cause of fatal poisoning in children younger than 6 years of age, so ferric citrate should be kept in a household location that is inaccessible to children. Lastly, ferric citrate was not studied in patients with inflammatory bowel disease or symptomatic GI bleeding, so its use in these populations is discouraged. Oral iron preparations have the potential for troublesome GI AEs, which may make ferric citrate an undesirable choice in patients with active GI disorders.¹⁶

DOSAGE AND ADMINISTRATION

The manufacturer recommends a starting dose of two tablets by mouth administered three times daily with meals. Serum phosphorus levels must be monitored and the dose of ferric citrate should be titrated in decrements or increments of one to two tablets per day to maintain serum phosphorus levels within a desirable range; titration should occur no more frequently than once a week. The maximum daily dose of ferric citrate is 12 tablets.¹⁶

DRUG INTERACTIONS

Data are limited regarding the interaction between ferric citrate and other medications. However, it is useful to consider common interactions historically known to occur with iron salts. Divalent and trivalent cations, including ferric iron, have been implicated in drug interactions that involve the binding and reduced absorption of several oral therapeutic agents when coadministered. These include but are not limited to: bisphosphonates, fluoroquinolone antibiotics, tetracycline antibiotics, levothyroxine, levodopa, and methyl dopa.²⁹ These medications should be administered two to three hours apart from ferric citrate if they are taken orally. Ferric citrate may, however, be safely coadministered with several common medications based on the recommendation of the manufacturer. These medications include: amlodipine, aspirin, atorvastatin, calcitriol, clopidogrel, digoxin, doxercalciferol, enalapril, fluvastatin, levofloxacin, metoprolol, pravastatin, propranolol, sitagliptin, and warfarin. Although the fluoroquinolone levofloxacin is on this list, it should be noted that it is an exception among quinolone antibiotics. The tetracycline antibiotic doxycycline is not recommended for coadministration with ferric citrate; the manufacturer specifically recommends in the package insert that administration of doxycycline be separated by one hour from that of ferric citrate.¹⁶

COST AND ECONOMIC IMPACT

Available price data indicate ferric citrate has a monthly cost comparable with the other non-calcium-based phosphate binders, lanthanum carbonate, sevelamer carbonate, and sucroferric oxyhydroxide (Table 6). Ferric citrate may offer some financial advantage with its study-proven reduction of ESA and IV iron dosing. To this end, a small study was conducted of the financial impact of ferric citrate use versus the standard of care.³¹ The study utilized data derived from the Lewis et al. trial and the U.S. Renal Data System to determine a projected cost savings of \$2,101 per patient per year, with approximately \$1,585 of those savings coming from reduction in ESA dosage and the remainder from reduced iron usage.^{19,31} Since CKD is a chronic disease requiring lifetime therapy with ESAs and IV iron, the authors noted that these cost savings can be projected to continue indefinitely.

Another study analyzing the economic benefit of using ferric citrate relied on data derived from Red Book and the Centers for Medicare and Medicaid Services to determine potential cost-savings associated with reduced ESA and IV iron requirements.³² The study utilized data from 2011 to estimate annual costs in U.S. health care dollars of ESA and IV iron requirements, and used dose reduction findings from unpublished phase 3 trial data to propose potential cost-savings associated with the use of ferric citrate. The authors assumed reductions of 20% and 40% for ESA and IV iron requirements, respectively, and determined that the use of ferric citrate could potentially reduce costs of CKD therapy in the U.S. by 21.2%. This equates to a cost reduction from \$5.127 billion to \$4.038 billion, based on actual utilization of ESA and IV iron in 2011.

CONCLUSION

Ferric citrate is an oral, insoluble, aluminum-free, calcium-free, ferric iron-based dietary phosphate binder that represents an alternative to calcium- and nonionic binders previously available for use in the treatment of hyperphosphatemia in patients with CKD on dialysis. For P&T committees reviewing this agent for formulary inclusion, ferric citrate's favorable safety and efficacy profile coupled with its reduction of the need for IV iron and ESA products in patients with comorbid iron deficiency may make it a desir-

able addition to the formulary. Results of ongoing clinical trials evaluating the use of this agent in the treatment of iron-deficiency anemia in patients with non-dialysis-dependent CKD are pending.

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