Ferric Citrate Reduces Intravenous Iron and Erythropoiesis-Stimulating Agent Use in ESRD

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ABSTRACT

Ferric citrate (FC) is a phosphate binder with shown efficacy and additional effects on iron stores and use of intravenous (iv) iron and erythropoiesis-stimulating agents (ESAs). We provide detailed analyses of changes in iron/hematologic parameters and iv iron/ESA use at time points throughout the active control period of a phase 3 international randomized clinical trial. In all, 441 subjects were randomized (292 to FC and 149 to sevelamer carbonate and/or calcium acetate [active control (AC)]) and followed for 52 weeks. Subjects on FC had increased ferritin and transferrin saturation (TSAT) levels compared with subjects on AC by week 12 (change in ferritin, 114.1±29.35 ng/ml; P=0.001; change in TSAT, 8.62%±1.57%; P=0.001). Change in TSAT plateaued at this point, whereas change in ferritin increased through week 24, remaining relatively stable thereafter. Subjects on FC needed less iv iron compared with subjects on AC over 52 weeks (median [interquartile range] dose=12.9 [1.0–28.9] versus 26.8 [13.4–47.6] mg/wk; P<0.001), and the percentage of subjects not requiring iv iron was higher with FC (P<0.001). Cumulative ESA over 52 weeks was lower with FC than AC (median [interquartile range] dose=5303 [2023–9695] versus 6954 [2664–12,375] units/wk; P=0.04). Overall, 90.3% of subjects on FC and 89.3% of subjects on AC experienced adverse events. In conclusion, treatment with FC as a phosphate binder results in increased iron parameters apparent after 12 weeks and reduces iv iron and ESA use while maintaining hemoglobin over 52 weeks, with a safety profile similar to that of available binders.


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CKD–associated mineral and bone disorders (CKD-MBDs) and anemia complicate the management of almost all patients with ESRD.1 Complex mechanisms initiated by reduction in kidney function regulate the pathogenesis of these disorders. Phosphate-binding agents provide the mainstay of therapy for CKD-MBD.2,3 The treatment of anemia in ESRD is centered on the use of erythropoiesis-stimulating agents (ESAs) and the maintenance of adequate iron stores, typically requiring intravenous (iv) iron administration.4,5 There are several currently available oral phosphate-binding medications, but...
none have been shown to provide benefits across the domains of both CKD-MBD and anemia.

Ferric compounds were noted to cause hypophosphatemia when used to treat anemia in the 1940s. Later, these compounds were used in small studies to treat the hyperphosphatemia of CKD.6–8 Ferric citrate (FC) was developed as a phosphate binder, and its clinical development is discussed in detail elsewhere.8–10 We recently reported a phase 3 sequential randomized clinical trial consisting of two randomized periods (a 52-week active control (AC) period followed by a 4-week placebo control period) to evaluate the safety and efficacy of FC as a phosphate binder.11 FC showed efficacy and safety as a phosphate binder. FC also increased iron stores and reduced iv iron and ESA use while maintaining hemoglobin levels compared with AC.11 Here, we provide detailed analyses of the course of changes in serum iron parameters and hemoglobin at additional time points, describe and analyze monthly changes in iv iron and ESA usage, and present detailed safety data of multiple organ systems over the 52-week AC period of the trial of FC as a phosphate binder.

RESULTS

In total, 441 subjects were randomized into the 52-week AC period: 292 subjects were assigned to FC, and 149 subjects were assigned to AC. Three subjects assigned FC never received the study drug. Thus, 289 subjects comprise the safety population for FC. The demographics and clinical characteristics for both groups are shown in Table 1 and were well balanced. Baseline serum ferritin (594±292 mg/dl for FC versus 595±306 mg/dl for AC) and transferrin saturation (TSAT; 30.9%±11.3% for FC versus 30.8%±12.1% for AC) values were similar in both groups. Approximately 82% of subjects were on ESA therapy at baseline in both groups. Also, similar proportions of subjects were receiving iv iron at entry into the study (Table 1).

Figure 1 displays box plots of iron parameters at each time point over the 52-week AC period of the trial. The FC group exhibited increased ferritin and TSAT levels compared with the AC group by week 12 (mean differences of 114.1±35 ng/ml [P<0.001] for ferritin and 8.62%±1.57% [P<0.001] for TSAT). These differences persisted or increased throughout the follow-up period, with mean differences of 281.8±42.9 ng/ml (P<0.001) and 9.55%±1.58% (P<0.001) for ferritin and TSAT, respectively, at week 52. Similarly, mean serum iron increased in the FC group compared with controls by 15.82±3.85 μg/dl (P<0.001) by week 12. This difference persisted throughout follow-up and was 17.91±4.05 μg/dl (P<0.001) at week 52. A reduction in total iron-binding capacity (TIBC) was noted in the FC group compared with controls at week 12 (mean difference=14.2±2.6 μg/dl; P<0.001) and sustained at weeks 24, 36, 48, and 52 (P<0.001 for each analysis). Slopes were compared between the FC and AC groups to characterize treatment difference in the longitudinal changes in serum ferritin and TSAT. The difference between treatment groups in mean TSAT seemed to reach a plateau by week 12. (The difference in mean slope of TSAT between the FC and AC groups after week 12 was 0.036%±0.044% per week; P=0.42.) Relative to the AC group, ferritin increased in the FC group by 8.93±1.37 ng/ml (P<0.001) per week from baseline to week 24 and then continued to increase at a slower rate thereafter, with a subsequent difference in mean slope of 3.06±1.49 ng/ml (P=0.04) per week. The mean slope within the FC group did not differ significantly from 0 after week 24 (mean slope of 1.59±0.90 ng/ml; P=0.08).

Subjects assigned to the FC group required less cumulative elemental iv iron (milligrams per week) than subjects in the AC group over the entire 52-week AC period (median [interquartile range] dose of 12.9 [10.0–28.9] versus 26.8 [13.4–47.6]; P<0.001, Wilcoxon rank-sum test). The proportion of subjects who needed no iv iron was numerically larger in the FC group than in the AC group at all time points over the 52-week period (Figure 2), with 85.4% and 69.0% of subjects requiring no iv iron at week 52 in the FC and AC groups, respectively (P<0.001). Similarly, in the defined categories of iv iron dosing, fewer subjects required the largest doses of iv iron (>70 mg/wk) in the FC group compared with the AC group over all time points (3.9% and 14.1%, respectively, of subjects on iv iron at week 52 in the FC and AC groups, respectively [P<0.001]). In general, the defined categories of iv iron dosing were statistically significantly lower in the FC group compared with the AC group over all time points (P<0.001).

Table 1. Baseline characteristics of subjects as they entered the 52-week AC period of the trial

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FC (n=292)</th>
<th>AC (n=149)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr), mean±SD</td>
<td>54.9±13.4</td>
<td>53.7±13.0</td>
<td>0.35</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>183 (62.7)</td>
<td>87 (58.4)</td>
<td>0.38</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>1.58%</td>
<td>1.57%</td>
<td>0.98</td>
</tr>
<tr>
<td>Black or African American</td>
<td>154 (52.7)</td>
<td>78 (52.4)</td>
<td>0.50</td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>124 (42.5)</td>
<td>62 (41.6)</td>
<td>0.50</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td>0.30</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>43 (14.8)</td>
<td>23 (15.4)</td>
<td>0.86</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>120 (41.1)</td>
<td>65 (43.6)</td>
<td></td>
</tr>
<tr>
<td>Hypertensive nephrosclerosis</td>
<td>89 (30.5)</td>
<td>45 (30.2)</td>
<td>0.93</td>
</tr>
<tr>
<td>Hemoglobin* (g/dl), mean±SD</td>
<td>292 ±292</td>
<td>595±306</td>
<td></td>
</tr>
<tr>
<td>TSAT* (%), mean±SD</td>
<td>30.9±11.3</td>
<td>30.8±12.1</td>
<td>0.31</td>
</tr>
<tr>
<td>ESA use at entry, n (%)</td>
<td>238 (81.5)</td>
<td>123 (82.6)</td>
<td>0.79</td>
</tr>
<tr>
<td>iv Iron use at entry, n (%)</td>
<td>177 (60.6)</td>
<td>90 (60.4)</td>
<td>0.97</td>
</tr>
</tbody>
</table>

*For ferritin and TSAT, baseline values are computed on n=440 subjects who had data available; for hemoglobin, it is on the basis of n=427 subjects who had data available.
Table 2 characterizes the changes in hematologic parameters over 52 weeks. Red blood cell (RBC) mean corpuscular volume (MCV) increased in the FC group throughout the 52 weeks compared with in the AC group (FC, 98.18 ± 7.27 fl versus AC, 96.07 ± 6.55 fl; *P* < 0.001). Likewise, mean cell hemoglobin (MCH) increased in the FC group compared to the AC group. There was no significant change in other red cell indices or platelet counts. Hemoglobin levels were similar at baseline for both groups and remained relatively stable throughout the 52-week AC period in both groups, but they were significantly and numerically slightly higher in the FC group at week 52 (11.42 ± 0.10 g/dl in FC versus 11.14 ± 0.12 g/dl in AC; *P* = 0.02) (Figure 4). As previously reported, aluminum levels were not different between the two groups.

FC was noted to have a similar safety profile to AC, because the proportions of subjects experiencing any adverse event (sum of serious adverse events [SAEs] and non-SAEs) were similar between the two groups (FC, 90.3%; AC, 89.3%). Subjects experiencing infection-related SAEs were fewer in the FC group (FC, 12.5%; AC, 18.1%). Similarly, there were fewer subjects who experienced cardiovascular SAEs in the FC group (7.3%) versus the AC group (12.1%). Likewise, fewer subjects on FC experienced gastrointestinal (GI) system and hepatobiliary SAEs compared with subjects on AC (GI: FC, 6.9% versus AC, 12.8%; hepatobiliary: FC, 0.7% versus AC, 1.3%). At least one serum ferritin measurement of >1500 ng/ml occurred in 57 of 288 (19.8%) subjects on FC and 14 of 148 (9.5%) subjects on AC. In total, 39 of 57 patients in the FC group with elevated serum ferritin during follow-up had resolution of the elevation at 52 weeks, and 10 of 14 patients in the AC group with elevated serum ferritin during follow-up had resolution of the elevation at 52 weeks. As shown in Table 3, the majority of the patients with ferritin >1500 ng/ml was adjudicated to be a result of iv iron administration, an SAE, or both. A total of three subjects had FC discontinued because of elevated serum ferritin. Of seven subjects listed in Table 3 adjudicated to have an unknown cause of at least a single value of ferritin >1500 ng/ml, all but one subject had resolution while remaining on FC. The remaining subject was not reviewed for a ferritin >1500 ng/ml, but because the subject underwent a liver biopsy for evaluation of abnormal
hepatic imaging in the presence normal liver function tests after an episode of hematemesis caused by reflux esophagitis and was noted to have increased iron staining in the liver. The serum ferritin was 799 ng/ml at the time of the liver biopsy. The site elected not to perform genetic testing for hereditary hemochromatosis, but FC was discontinued because of the liver biopsy findings, and the use of iv iron was left at the discretion of the treating physicians. The increased iron staining was felt to be unrelated to solely FC according to the site investigator, data safety monitoring board, and study chair.

**DISCUSSION**

FC has been shown to be an efficacious phosphate binder that increases iron stores and reduces iv iron and ESA use while sustaining hemoglobin levels. Iron supplementation and ESA use have been mainstays in treating the anemia that develops in patients on dialysis. Patients on dialysis require sufficient iron stores to appropriately respond to ESA therapy. Historically, oral iron supplementation given in the fasting state to treat functional and absolute iron deficiency in patients with ESRD was unable to maintain adequate iron stores. Multiple studies using different oral iron formulations (ferrous sulfate and ferrous fumarate) in doses of up to 200 mg/d of elemental iron were unable to show achievement or maintenance of adequate iron stores in patients with ESRD. Similarly, a recently approved iron–based phosphate binder, sucroferric oxyhydroxide, has not been shown to increase iron stores, presumably because its chemical composition does not release ferric iron for absorption. Currently, there is widespread use of iv iron in patients with ESRD. The Dialysis Outcomes and Practice Patterns Study Practice Monitor reported that >70% of patients on dialysis received iv iron at some time in 2011, the time during which the trial was conducted. There has been increasing concern over the use of iv iron, because it bypasses many of the physiologic controls in place to regulate iron absorption and total iron stores and may associate with infection risks. FC was used as a phosphate binder in this randomized trial over 52 weeks compared with an AC consisting of calcium acetate and/or sevelamer carbonate. Over the 52-week AC period, sustained and statistically significant increases were seen in the

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**Figure 2.** Ferric citrate reduces IV iron use. Relative proportions of iv iron use during each month of the trial for specific dose categories of iv iron; iv iron use is expressed as milligrams per week.
commonly measured indicators of total body iron stores, namely serum iron, TSAT, and serum ferritin, with corresponding and expected reductions in TIBC, consistent with improved iron stores in subjects treated with FC. As illustrated in Figures 2 and 3, there was a sustained and consistent reduction in the use of iv iron and ESA therapy with maintenance of stable hemoglobin levels (Figure 4). Significantly more elemental iron through the iv route was administered over the course of the trial to subjects on AC. These data strongly suggest that the use of FC as a phosphate binder is associated with some GI absorption of iron. The TSAT plateau and the decrease in the rate of rise of serum ferritin levels further suggest that the absorption of iron is regulated and saturable. The increase in MCV and MCH in the FC group compared with the AC group also suggests iron uptake into the RBCs. Stable hemoglobin levels, despite reductions in the use of iv iron and ESA, suggest that hematopoiesis remained well supported during treatment with FC. These data suggest that the continued use of FC would provide a source of maintenance iron, reducing or eliminating the need for iv iron.

The absorption of soluble inorganic iron is tightly regulated in the intestine. Ferric (Fe$^{3+}$) iron must first be reduced to the ferrous form (Fe$^{2+}$) by ferric reductase (duodenal cytochrome b) before being absorbed, because only ferrous iron can be absorbed by the enterocyte. Additionally, there are both intracellular and extracellular regulation provided by iron regulatory proteins and hepcidin.$^{23,26}$ This tight duodenal-based regulation protects the body against iron overload in the absence of hemochromatosis. Our data support the concept that the rise in iron stores associated with FC treatment occurred through intact regulatory pathways for GI iron absorption. The plateau of TSAT at 12 weeks and the reduced rate of rise of ferritin at 24 weeks provides additional evidence to suggest that the body absorbed iron in a physiologic manner, allowing for any excess to be eliminated in the stool in the usual manner. In contrast, iv iron administration bypasses the body’s physiologic control mechanisms. Studies, such as dialysis patients response to IV iron with elevated ferritin (DRIVE),$^{27,28}$ have shown that iv iron use improves hemoglobin levels and ESA dose-response over short time periods, but long-term safety data are lacking for this approach to iron supplementation. In fact, a recent retrospective study suggested that a maintenance iv iron dosing approach may result in fewer infectious complications relative to a bolus iv iron dosing regimen.

Figure 3. Ferric citrate reduces ESA use. Relative proportions of ESA use during each month of the trial for specific dose categories of ESA; ESA use is expressed in units per week.
Our trial extends the length of follow-up from 12 weeks in DRIVE and DRIVE-II using iv iron to 52 weeks using oral iron. There is potential inherent benefit to stabilizing total body iron stores by using a more physiologic approach to iron delivery. Lastly, from a payer and health economics perspective, reductions in iv iron and ESA use have the potential to provide a significant cost savings.29

A hypothetical potential harm of long-term oral FC administration is increased iron accumulation. However, because the duodenal iron absorption from FC is limited by the physiologic feedback response to increased iron mediated by hepcidin and iron regulatory proteins, one could hypothesize that oral FC is safer than iv iron, which is not subject to this feedback regulation and used extensively in patients on hemodialysis currently; iv iron is also more likely than oral FC to increase the plasma nontransferrin-bound iron, which is more readily accumulated in the liver, heart, and endocrine organs. The exception to the hepcidin feedback control of iron absorption is the #1% of patients who may have mutant human hemochromatosis protein (HFE). HFE is part of the bone-morphogenetic protein receptor complex that regulates hepcidin transcription and in turn, the absorption of oral iron by the duodenum. In our study, we had two patients in the FC group who had progressive increases in serum ferritin that were not explained by concomitant iv iron administration or chronic inflammation, another cause of increased serum ferritin. We stopped the FC in these two patients and suggested that they be tested for HFE mutations.

The safety of oral FC has been shown over 52 weeks,11 and this report details the safety of organ systems (cardiovascular, GI/hepatobiliary, or infection) that are traditionally considered vulnerable to iron overload.22,23 Organ biopsies were not done in this study to assess the deposition of iron. However, iron deposition in an organ can reflect iron stores but not necessarily be associated with organ dysfunction caused by iron accumulation. No safety concerns were identified in these areas. Of note, across all of these organ systems, fewer subjects on FC versus AC experienced SAEs, suggesting no organ dysfunction related to the accumulation or deposition of iron. We hypothesize that the reductions in SAEs may reflect a benefit of supplying iron orally. Subjects on FC received their iron predominantly through the oral versus iv route, whereas subjects on AC received iron solely through the iv route. We hypothesize that it may be that fewer iv infusions accrue less infection risk, or it may be that there is an inherent inflammatory risk of iron delivered through the iv versus oral route. In this 52-week trial, we found no evidence of iron overload as a result of FC administration. However, as with all iron therapies, physicians must regularly monitor for laboratory or clinical evidence of iron overload when prescribing FC.

In our study, we restricted the administration of iv iron in study subjects if their central laboratory monthly serum ferritin was >1000 ng/dl or their TSAT was >50%. We chose a serum ferritin ≥1500 mg/dl as an arbitrary cutoff to adjudicate subjects for the etiology of the value and follow the subjects until

<table>
<thead>
<tr>
<th>Time Point</th>
<th>FC Mean (SD)</th>
<th>AC Mean (SD)</th>
<th>P Value</th>
<th>FC Mean (SD)</th>
<th>AC Mean (SD)</th>
<th>P Value</th>
<th>FC Mean (SD)</th>
<th>AC Mean (SD)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>95.79 (6.47)</td>
<td>95.58 (6.49)</td>
<td>0.05</td>
<td>95.58 (6.49)</td>
<td>95.58 (6.49)</td>
<td>0.001</td>
<td>95.58 (6.49)</td>
<td>95.58 (6.49)</td>
<td>0.001</td>
</tr>
<tr>
<td>Week 12</td>
<td>94.37 (6.46)</td>
<td>94.37 (6.49)</td>
<td>0.02</td>
<td>94.37 (6.46)</td>
<td>94.37 (6.49)</td>
<td>0.001</td>
<td>94.37 (6.46)</td>
<td>94.37 (6.49)</td>
<td>0.001</td>
</tr>
<tr>
<td>Week 24</td>
<td>97.34 (6.49)</td>
<td>97.34 (6.49)</td>
<td>0.001</td>
<td>97.34 (6.49)</td>
<td>97.34 (6.49)</td>
<td>0.001</td>
<td>97.34 (6.49)</td>
<td>97.34 (6.49)</td>
<td>0.001</td>
</tr>
<tr>
<td>Week 36</td>
<td>98.19 (6.72)</td>
<td>98.19 (6.72)</td>
<td>0.001</td>
<td>98.19 (6.72)</td>
<td>98.19 (6.72)</td>
<td>0.001</td>
<td>98.19 (6.72)</td>
<td>98.19 (6.72)</td>
<td>0.001</td>
</tr>
<tr>
<td>Week 48</td>
<td>98.19 (6.72)</td>
<td>98.19 (6.72)</td>
<td>0.001</td>
<td>98.19 (6.72)</td>
<td>98.19 (6.72)</td>
<td>0.001</td>
<td>98.19 (6.72)</td>
<td>98.19 (6.72)</td>
<td>0.001</td>
</tr>
<tr>
<td>Week 52</td>
<td>98.19 (6.72)</td>
<td>98.19 (6.72)</td>
<td>0.001</td>
<td>98.19 (6.72)</td>
<td>98.19 (6.72)</td>
<td>0.001</td>
<td>98.19 (6.72)</td>
<td>98.19 (6.72)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

P values are for comparison of FC with AC at each time point.
Figure 4. Treatment with FC maintains hemoglobin throughout the 52-week AC period. Week 52 median hemoglobin was 11.2 g/dl in subjects treated with FC versus 11.0 g/dl in subjects treated with AC (P=0.02).

Table 3. Results of the committee’s adjudications for subjects with ferritin >1500 ng/ml as well as one subject who underwent a liver biopsy

<table>
<thead>
<tr>
<th></th>
<th>FC (n=288), n (%)</th>
<th>AC (n=148), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>57 (19.8)</td>
<td>14 (9.5)</td>
</tr>
<tr>
<td>Resolved</td>
<td>39* (68.4)</td>
<td>10 (71.4)</td>
</tr>
<tr>
<td>Adjudication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caused by iv iron administration</td>
<td>23 (40.4)</td>
<td>7 (50.0)</td>
</tr>
<tr>
<td>Caused by SAE</td>
<td>12 (21.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Caused by iv iron+SAE</td>
<td>15 (26.3)</td>
<td>7 (50.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>7* (12.3)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*One subject had a liver biopsy for abnormal liver imaging but did not have ferritin >1500 ng/ml.

There was a difference in the proportion of subjects treated with FC (19.8%) who achieved an elevated ferritin compared with subjects treated with AC (9.5%).

There are several limitations to our study. First, entry into the trial was limited by the inclusion/exclusion criteria, thus potentially limiting the generalizability of the results to those patients who meet these criteria. Second, we did not perform radionuclide-tagged balance studies, and as such, improvements in iron stores, reductions in iv iron and ESA use, increased MCV and MCH, and stabilization of hemoglobin levels, while highly suggestive of ferric iron absorption and incorporation into the RBCs, cannot prove it conclusively. Hepcidin levels were not measured during the course of the study, although the precise interpretation of these levels is controversial. Third, safety analyses are limited to the 52-week length of this trial, and therefore, our conclusions are limited to this time frame. However, a long-term open-label extension study (NCT01554982) has recently concluded and will provide additional data, with results expected in early 2015. Fourth, we did not routinely perform organ biopsies to examine them for iron accumulation nor did the developers of the iv iron preparations currently in use. Nonetheless, from a practical standpoint, the subjects in this trial were similar to United States patients on dialysis, and these changes in measured parameters have the potential to benefit them for the reasons outlined above. Although the analyses presented here are secondary outcomes, they were prespecified on the basis of prospective, randomized comparisons, with study-wise error rates limited by the sequential gatekeeping strategy in the study design.

This report shows that the use of FC as a phosphate binder results in improved iron parameters reflective of total body iron stores, and this change is apparent after only 12 weeks of use. FC reduces iv iron and ESA use while maintaining hemoglobin levels...
over 52 weeks of use, with a significant portion of subjects requiring no iv iron. The use of FC is associated with fewer SAEs in those organ systems typically considered vulnerable to iron overload, thus suggesting that there was no clinical evidence of clinically significant iron overload associated with the use of FC in this study. The use of FC was well tolerated, and its favorable effects on systemic iron parameters and the reduced use of iv iron and ESA warrant its consideration as a phosphate binder in clinical practice.

CONCISE METHODS

This was a phase 3, randomized, open-label trial conducted at 60 sites across the United States and Israel. The rationale, study design, and principal results of this trial have been published previously.13,33 This manuscript focuses on change in ferritin and TSAT from baseline to week 52 and the cumulative use of iv iron and ESA over 52 weeks. All of these endpoints were among five key prespecified outcomes that were designated in a five-step gatekeeping strategy to protect the study-wise α-level.

Participants

Eligible subjects were adult patients with ESRD maintained on either three times per week hemodialysis or peritoneal dialysis for at least 3 months before enrollment. They were required to have a screening ferritin <1000 ng/ml and TSAT <50%. Key exclusion criteria for the trial relevant to these analyses included actively symptomatic GI tract bleeding, inflammatory bowel disease, or an absolute requirement for oral iron therapy, vitamin C, or calcium-, magnesium-, or aluminum-containing drugs with meals.

Design

After a washout period, subjects were randomized 2:1 to FC or AC consisting of study-supplied calcium acetate and/or sevelamer carbonate. FC was dosed based on a study-supplied titration schedule and provided as 1-g tablets containing 210 mg ferric iron. Investigators were instructed to prescribe AC guided by their package inserts.33-35 Both FC and AC were titrated on the basis of centrally measured serum phosphorus levels to achieve prespecified target levels. FC and AC were administered for 52 weeks during the 52-week AC period. ESA dosing was at the discretion of the local investigator; iv iron use was at the discretion of the site as long as the serum ferritin was ≤1000 ng/ml and the TSAT was ≤30%. All oral iron and vitamin C supplements were prohibited.

Outcome Measurements

Changes over 52 weeks in ferritin and TSAT were used to characterize the effect of FC on iron stores. Cumulative doses of iv iron and ESA were used to determine the effect of FC on iv iron and ESA usage.

Hemoglobin levels were collected every 12 weeks, and serum iron level, serum ferritin, and TIBC were collected every 4 weeks. Serum TSAT was calculated as serum iron/TIBC×100; iv iron and ESA usage were recorded monthly. Adverse events were collected at every study visit. SAEs were reviewed by the Collaborative Study Group (CSG) Medical Monitoring Committee (M.J.K. and J.P.D.) within 24 hours of receipt at the Clinical Coordinating Center. Additionally, all subjects with a ferritin ≥1500 ng/ml at any time point were reviewed by three members of the CSG (M.J.K., J.B.L., and J.P.D.) for adjudication as to the apparent cause of elevated serum ferritin, and recommendations on continued use of the study drug were made. Subjects were followed to resolution or the end of the study.

All subjects gave written informed consent before any investigational procedures, and the trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

This trial is registered with ClinicalTrials.gov (NCT01191255). All laboratory measurements reported here were performed at the central laboratory. All authors contributed to the final manuscript. This trial was conducted under a Special Protocol Assessment agreement with the US Food and Drug Administration. The study was sponsored by Keryx Biopharmaceuticals, Inc.

Statistical Analyses

The study’s analysis plan used a sequential gatekeeping strategy36 with two-sided α = 0.05 at each step to protect the study-wise α-level for the treatment comparisons of the primary and four prespecified secondary outcomes in the following sequence: (1) change in serum phosphorus during the final 4-week placebo-control period, changes in (2) ferritin and (3) TSAT from baseline to week 52 in the 52-week period, and finally, cumulative use of (4) iv iron and (5) ESA over the 52-week period. Because each of these five comparisons attained the designated α-level of 0.05, we report comparisons of ferritin, TSAT, iv iron, and ESA between the treatment groups using a two-sided α = 0.05 in accordance with the prespecified gatekeeping rule. Additional hypothesis tests were performed at the two-sided α = 0.05 level without formal adjustment for multiple comparisons.

Continuous data were summarized using descriptive statistics (number of observations [n], mean, SD, median, minimum, and maximum). Frequencies and percentages were used to summarize categorical (discrete) data. Separate analysis of covariance (ANCOVA) models were used to analyze the mean change in each laboratory parameter, including iron panel values, from baseline to each follow-up assessment after controlling for the baseline value. After first defining outcome measurements after study drug discontinuation as missing, all missing values were imputed using a last follow-up value carried forward algorithm. The analyses of laboratory parameters using last follow-up value carried forward were confirmed using corresponding ANCOVAs on the basis of longitudinal mixed effect models with unstructured covariance matrices to account for repeated measurements.

Mixed effect analyses using two-slope linear splines with post hoc selection of knot points were used to compare the relative rates of increase in TSAT and ferritin during the early and later portions of follow-up, with separate mean slopes estimated for TSAT before and after 12 weeks and separate mean slopes estimated for ferritin before and after 24 weeks. ESA dose was converted to epoetin alfa equivalent units, and the dose per week was computed. Wilcoxon rank-sum tests were used to compare the cumulative iv iron use and ESA dose throughout the follow-up period between the treatment groups. The cumulative levels were computed without imputation of missing values, because almost all missing values were determined to be caused by no drug administered rather than...
missingness of data. Wilcoxon rank-sum tests were also used to confirm the ANCOVA results for serum ferritin and TSAT, because these outcomes exhibited moderate departures from normality.

Statistical analyses were performed using SAS, versions 9.3 and 9.4 (SAS Institute Inc., Cary, NC). The independent CSG statistician (T.G.) had full access to the locked clinical trial database to prepare this manuscript.

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DISCLOSURES


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