A Randomized Comparison of Ferumoxytol and Iron Sucrose for Treating Iron Deficiency Anemia in Patients with CKD

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Abstract

Background and objectives Few randomized controlled trials have compared intravenous iron products head to head in CKD patients with iron deficiency anemia. This study compared the efficacy and safety of two intravenous iron products (ferumoxytol [Feraheme injection] and iron sucrose [Venofer]) in patients with CKD and iron deficiency anemia.

Design, setting, participants, & measurements In this phase II, randomized, open-label, active-controlled, multicenter clinical trial, patients were randomized 1:1 to either 1.02 g ferumoxytol (2×510-mg injections) or 1.0 g iron sucrose administered as either a slow injection or infusion (10 doses for dialysis patients and 5 doses for nondialysis patients). Inclusion criteria included hemoglobin<11.0 g/dl, transferrin saturation<30%, and eGFR<60 ml/min per 1.73 m^2 or a diagnosis of underlying CKD (*e.g.*, nephropathy or nephritis). The primary end point was change in hemoglobin from baseline to week 5.

Results In total, 162 patients were randomized. Demographics were balanced between the treatment groups. Adverse event profiles of the two regimens were fairly similar: overall adverse events, 48% ferumoxytol versus 65% iron sucrose; related adverse events, 10% ferumoxytol versus 16% iron sucrose; and adverse events leading to study discontinuation, 1% ferumoxytol versus 5% iron sucrose. Rates of serious adverse events and related serious adverse events were similar between the ferumoxytol and iron sucrose groups: serious adverse events, 9% versus 7%, respectively and related serious adverse events, 1% versus 1%, respectively. Overall, increases in hemoglobin were similar between treatment groups. Based on an ANOVA model adjusted for baseline hemoglobin level and dialysis status, the least squares mean change from baseline to week 5 was 0.8±0.1 g/dl in the ferumoxytol-treated group and 0.7±0.1 g/dl in the iron sucrose group. The difference in the mean change from baseline between the two treatment groups was 0.1 g/dl (95% confidence interval, −0.2 to 0.4).

Conclusion In this randomized, controlled trial, ferumoxytol and iron sucrose showed comparable efficacy and adverse events rates.

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Introduction

Iron deficiency anemia (IDA) is common in CKD, affecting most patients with CKD stage 5 (1–4). Recently released Kidney Disease: Improving Global Outcomes guidelines recommend intravenous (IV) iron administration for hemodialysis patients and either oral or IV iron for patients in CKD stages 1–5 (5) who are anemic. For iron replacement therapy, the therapeutic course of IV iron typically is 1000 mg (6–8). Because of their safety profile, many of the approved IV iron products in the United States, including iron sucrose, require the administration of small doses (100–200 mg), with a full therapeutic course requiring 5–10 separate administrations (6,7,9,10). This requirement may impact patient adherence. Ferumoxytol is an IV iron product approved for the treatment of IDA in adults with CKD in the United States and Canada (Feraheme injection) as well as the European Union and Switzerland (Rienso). Unlike most other IV iron preparations, a full course of ferumoxytol (1.02 g) requires only two IV injections of 510 mg delivered at a rate of up to 1 ml/s (30 mg/ml) between 3 and 8 days apart.

Iron sucrose (Venofer) has been used as an iron replacement product for the last 20 years and is approved for the treatment of IDA in adults with CKD. It is administered intravenously by either slow injection or infusion (6). To date, few randomized controlled trials have compared IV iron products head to head in the treatment of IDA in CKD patients (11–14). Additional comparative clinical trial data are needed to better guide treatment choice among the various currently available IV iron preparations.

The purpose of the Ferumoxytol Compared with Iron Sucrose Trial was to evaluate the safety and efficacy of ferumoxytol compared with iron sucrose

for the treatment of IDA in adult patients with CKD either on or not on dialysis.

Materials and Methods

Study Design and Conduct

This study was a randomized, open-label, multicenter, international, phase II trial (ClinicalTrials.gov identifier NCT01052779) (15). The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by Institutional Review Boards or Ethics Committees of the participating sites. Eligible patients (who provided informed consent) were randomized 1:1 to receive either ferumoxytol or iron sucrose. Both hemodialysis and nondialysis patients assigned to ferumoxytol received two IV injections of 510 mg (17 ml; no faster than over 17 seconds) within 5±3 days for a cumulative dose of 1.02 g. Hemodialysis patients assigned to iron sucrose received a cumulative dose of 1.0 g as 100-mg doses at 10 consecutive dialysis sessions within 3 weeks; nondialysis patients received a cumulative dose of 1.0 g as 200-mg doses at five visits within approximately 14 days. For consistency across the various countries, all patients receiving a first exposure to iron sucrose were administered a test dose before their first dose. Total subject participation was 7 weeks, which included a 2-week screening period and a 5-week treatment period. The primary efficacy end point was assessed at week 5.

Eligibility Criteria

This study enrolled adult patients with CKD and IDA on or not on hemodialysis. Key inclusion criteria included age≥18 years, eGFR<60 ml/min per 1.73 m^2 or a diagnosis of CKD (*e.g.*, nephropathy or nephritis), hemoglobin (Hgb)<11.0 and ≥7 g/dl, and a transferrin saturation (TSAT)<30%. Key exclusion criteria included a history of allergy to IV iron or two or more classes of drugs.

Safety Analyses

The primary end point of the study was the descriptive review of adverse effects. Safety analyses were performed on all randomized patients who had any exposure to study drug (safety population). During the study, safety was monitored for 60 minutes after each administration of study medication and through the 35-day study period by evaluating adverse events (AEs; by direct observation and interview), vital signs, and changes in laboratory tests and physical examinations. Vital signs were captured at 5, 10, 15, 30, 45, and 60 minutes postdose on dosing days in treatment groups and baseline (predose) as well as weeks 2–5. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA 13.0) and summarized by incidence, severity, and relationship to study drug. The site investigator assessed the intensity and relatedness of AEs to treatment. An AE was considered serious if, according to the investigator or sponsor, it resulted in death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or an important medical event.

Efficacy Analyses

Analyses were performed on the intent-to-treat (ITT) population, which included all patients who received any exposure to study medication. Efficacy analyses included mean change in Hgb from baseline to week 5 adjusted for the covariates of baseline Hgb and dialysis status (primary efficacy end point), proportion of patients with an increase in Hgb≥1 g/dl during the period from baseline to week 5, and time to 1-g/dl increase from baseline or Hgb≥12 g/dl. Hgb, TSAT, and ferritin were measured at baseline as well as weeks 2–5. Other efficacy parameters included the proportion of patients who initiated, ceased, or increased/decreased erythropoiesis-stimulating agent (ESA) use by ≥20% over the course of the study. For the primary end point, the *P* value and two-sided 95% confidence interval (95% CI) for the treatment difference from baseline to week 5 were generated based on an ANOVA model adjusted for baseline Hgb level and dialysis status. For the analysis of the ITT population, missing postbaseline values for efficacy parameters were imputed using the last observation carried forward method. Sensitivity analyses for the efficacy parameters were used to assess the impact of imputation of missing data with no imputation using the Markov chain Monte Carlo method. Subjects lost to follow-up before week 5 without any recorded response were treated as nonresponders. For the intervention binary end points (transfusion and/or ESA use), patients who discontinued the study before week 5 without an observed intervention were treated as having no intervention. This study was designed as a noninferiority study, with noninferiority concluded if the lower bound of the 95% CI was ≥−0.5 g/dl. A sample size of 75 subjects per treatment group would provide 81% power assuming an α of 0.05 and a noninferiority margin of 0.5 g/dl, with a common SD of 1.2 g/dl for the difference between treatment groups in change in Hgb from baseline to week 5. Descriptive statistics for Hgb change from baseline and the change in other markers of iron storage by visit were also performed.

Results

In total, 162 patients (of 306 patients screened; 52.9%) were randomized (80 patients to ferumoxytol and 82 patients to iron sucrose) in the period between March of 2010 and June of 2011.

Demographics and Baseline Characteristics

Demographics and baseline characteristics were well balanced between treatment groups (Table 1). Nearly all enrolled patients were CKD stage 3 or greater (94% ferumoxytol and 100% iron sucrose). Across treatment groups, approximately 43% of patients were on hemodialysis, and most (87%) had baseline Hgb between 9 and 11 g/dl.

All 162 patients were exposed to study medication and therefore, included in both the ITT population and safety population. Overall, 96% of ferumoxytol-treated patients completed both doses of study medication; 90% of iron sucrose–treated patients completed all doses of study medication. The mean administration time per dose for patients treated with ferumoxytol was 50 seconds, whereas for patients treated with iron sucrose, it was 7.9 minutes (474 seconds).

Table 1. Clinical and demographic characteristics by treatment arm (safety population)

Characteristic	Ferumoxytol	Iron Sucrose
Patients (*N*)	80	82
Age (yr), mean±SD	62±15	63±15
Sex, *n* (%)		
Women	41 (51)	39 (47)
Race, *n* (%)		
White	52 (65)	62 (76)
Black/African American	21 (26)	14 (17)
Asian	4 (5)	1 (1)
Native Hawaiian or other Pacific Islander	2 (3)	1 (1)
Other	1 (1)	3 (4)
Dialysis status, *n* (%)		
Hemodialysis	34 (43)	36 (44)
Baseline hemoglobin level (g/dl), *n* (%)		
>7 to ≤9	10 (13)	11 (13)
>9 to <11	70 (87)	71 (87)
CKD stage, *n* (%)		
2 (GFR=60 to <90 ml/min per 1.73 m^2)	5 (6)	0
3 (GFR=30 to <60 ml/min per 1.73 m^2)	15 (19)	19 (23)
4 (GFR=15 to <30 ml/min per 1.73 m^2)	22 (27)	20 (24)
5 (GFR<15 ml/min per 1.73 m^2)	38 (48)	42 (51)
Unknown	0	1 (1)
Erythropoiesis-stimulating agent therapy, *n* (%)		
Yes	44 (55)	40 (49)

AEs

AE profiles of the two regimens were fairly similar (Table 2). Serious AEs (SAEs) were reported in 9% with ferumoxytol compared with 7% with iron sucrose; the rate of related SAEs (1%) was the same in both treatment groups. Overall, 1% of ferumoxytol-treated patients discontinued therapy because of an AE compared with 5% of iron sucrose–treated patients. No deaths were reported during the study.

The analysis of AEs is descriptive; because of the size of the study, no statistical comparisons between groups are appropriate. In total, 247 AEs were reported (48% in ferumoxytol-treated patients and 65% iron sucrose–treated patients). Related AEs were reported in 10% with ferumoxytol and 16% with iron sucrose; the rate of related AEs with iron sucrose was primarily driven by the greater rates of hypotension and parosmia. The most frequently occurring AEs (three or more patients) with ferumoxytol included (Table 3) nausea (7.5%), muscle spasms (5%), nasopharyngitis (3.8%), headache (3.8%), cough (3.8%), hyperkalemia (3.8%), and urinary tract infection (3.8%). The most frequently occurring AEs with iron sucrose included hypotension (9.8%), peripheral edema (7.3%), urinary tract infection (7.3%), muscle spasms (7.3%), parosmia (4.9%), constipation (3.7%), nausea (3.7%), gout (3.7%), and hypoglycemia (3.7%). No related AE occurred in more than one (1.3%) ferumoxytol-treated patient (Table 3). The most commonly reported AEs considered related to iron sucrose treatment were hypotension (3.7%), parosmia (3.7%), and injection site pain (2.4%). Severe AEs were reported in 3.8% of ferumoxytol-treated patients and 1.2% of iron sucrose–treated patients. None of the severe AEs in either group were considered related to study drug by the investigator.

Acute hypotension and hypersensitivity reactions were reported in both treatment groups. They were considered AEs of special interest (AESIs) and included moderate or severe hypotension requiring medical intervention or hospitalization, acute decreases in systolic BP from baseline of ≥30% during the 60-minute postdose observation period, hypotension associated with symptoms, systemic allergic reactions (anaphylaxis/anaphylactoid reactions), and milder symptoms of hypersensitivity. Overall, AESIs occurred in 1.3% of ferumoxytol-treated patients and 6.1% of iron sucrose–treated patients. In the ferumoxytol treatment group, the AESI was an anaphylactic-type reaction in one (1.3%) patient that resolved on the day of dosing. In the iron sucrose group, five (6.1%) patients experienced AESIs, including six AEs of hypotension and one AE of unresponsive to stimuli.

In the ferumoxytol group, the incidence of SAEs was highest in the gastrointestinal disorders category (2.5%; two patients); otherwise, the remainder of SAEs occurred in individual patients. In the iron sucrose group, the incidence of SAEs was highest in the infections and infestations category (3.7%; three patients) and the injury, poisoning, and procedural complications category (2.4%; two patients); the remainder of SAEs occurred in individual patients. Two of the SAEs were considered related to treatment. One ferumoxytol-treated patient experienced an anaphylactoid reaction after receiving the first dose that was moderate in intensity and later resolved after treatment with epinephrine, hydrocortisone, and diphenhydramine. The patient was discontinued from the study. One iron sucrose-treated patient experienced hypotension that was moderate in intensity after receiving the first dose of study drug and was treated with volume resuscitation and Trendelenburg positioning; subsequently, it was resolved. This patient again experienced hypotension with administration of the second dose of iron sucrose and was discontinued from the study. Neither patient was hospitalized.

Vital Signs and Laboratory Findings

The mean changes in systolic and diastolic BPs after either treatment were small (<2 mmHg change from predose). Overall, there were no clinically meaningful differences between the two treatment groups in mean BP changes over 60 minutes after dosing. In addition, there were no clinically meaningful changes in nonanemia-related laboratory tests over the entire study period in either treatment group.

Efficacy: Hgb and Iron Parameters

The primary efficacy end point of the study was the mean change in Hgb from baseline to week 5. This change, adjusted for baseline Hgb and dialysis status, was 0.8±0.1 g/dl for ferumoxytol-treated patients and 0.7±0.1 g/dl for iron sucrose–treated patients. The difference between the two treatment groups was 0.1 g/dl (95% CI, −0.21 to 0.41) based on an ANOVA adjusted for baseline Hgb level and dialysis status. Ferumoxytol was, therefore, shown to be noninferior to iron sucrose, with the lower bound of the

Table 2. Summary of adverse events (safety population)

AE Category	Ferumoxytol (*n*=80)		Iron Sucrose (*n*=82)	
	Events	Patients *N* (%)	Events	Patients *N* (%)
All AEs	86	38 (48)	161	53 (65)
Related AEs	8	8 (10)	46	13 (16)
SAEs	8	7 (9)	11	6 (7)
Related SAEs	1	1 (1)	1	1 (1)
AEs of special interest	1	1 (1.3)	7	5 (6.1)
AEs leading to drug discontinuation	1	1 (1)	7	4 (5)
Deaths	0	0	0	0

AE, adverse events; SAE, serious adverse events.

Table 3. AEs and related AEs by frequency (safety population)

AE Preferred Term	Ferumoxytol (*n*=80)		Iron Sucrose (*n*=82)	
	Events	Patients *n* (%)	Events	Patients *n* (%)
Overall AEs in patients (AEs occurring in >2% of patients)	86	38 (47.5)	161	53 (64.6)
Nasopharyngitis	3	3 (3.8)	2	2 (2.4)
Urinary tract infection	4	3 (3.8)	7	6 (7.3)
Muscle spasms	4	4 (5.0)	12	6 (7.3)
Myalgia	0	0	2	2 (2.4)
Pain in extremity	1	1 (1.3)	2	2 (2.4)
Injection site pain	1	1 (1.3)	2	2 (2.4)
Edema peripheral	2	2 (2.5)	6	6 (7.3)
Constipation	2	2 (2.5)	3	3 (3.7)
Diarrhea	2	2 (2.5)	2	1 (1.2)
Nausea	6	6 (7.5)	3	3 (3.7)
Headache	3	3 (3.8)	2	2 (2.4)
Parosmia	0	0	31	4 (4.9)
Hypotension	3	2 (2.5)	18	8 (9.8)
Hyperkalemia	3	3 (3.8)	1	1 (1.2)
Hypoglycemia	2	2 (2.5)	4	3 (3.7)
Cough	3	3 (3.8)	0	0
Anemia	2	2 (2.5)	1	1 (1.2)
Overall related AEs	8	8 (10.0)	46	13 (15.9)
Anaphylactic reaction	1	1 (1.3)	0	0
Dysgeusia	1	1 (1.3)	0	0
Feeling hot	1	1 (1.3)	1	1 (1.2)
Flushing	1	1 (1.3)	0	0
Headache	1	1 (1.3)	0	0
Injection site hematoma	1	1 (1.3)	0	0
Injection site pain	1	1 (1.3)	2	2 (2.4)
Nausea	1	1 (1.3)	0	0
Cold sweat	0	0	1	1 (1.2)
Constipation	0	0	1	1 (1.2)
Diarrhea	0	0	2	1 (1.2)
Hypotension	0	0	6	3 (3.7)
Injection site hemorrhage	0	0	1	1 (1.2)
Myalgia	0	0	1	1 (1.2)
Parosmia	0	0	30	3 (3.7)
Unresponsive to stimuli	0	0	1	1 (1.2)

95% CI within the predefined 0.5-g/dl noninferiority margin (Table 4). Sensitivity analyses conducted on the ITT population without imputation of missing values and using the Markov chain Monte Carlo method confirmed the results of primary analysis of the last observation carried forward method on the ITT population.

Ferumoxytol-treated patients were shown to have an earlier increase in mean Hgb compared with patients treated with iron

sucrose, with higher Hgb values in the ferumoxytol-treated patients observed at every postdose time point (Table 4); this difference between treatment groups (+0.3 g/dl) was statistically significant beginning at week 2 (P=0.01). The larger increase in Hgb with ferumoxytol compared with iron sucrose persisted through week 3 (+0.3 g/dl; $P<0.05$) (Figure 1).

An analysis of the change in Hgb from baseline to week 5 was also examined by dialysis status. For patients on hemodialysis, the mean change from baseline for ferumoxytol was 1.0 g/dl compared with 0.5 g/dl for iron sucrose (P=0.08). For patients not on dialysis, the mean change from baseline for ferumoxytol was 0.7 g/dl compared with 0.9 g/dl for iron sucrose (P=0.37). Another subgroup analysis examined the mean change in Hgb from baseline to week 5 by Hgb level at baseline (>7.0 to ≤9.0 g/dl or 9.0 to <11.0 g/dl). Results from this analysis showed that the mean change in Hgb for ferumoxytol-treated patients was greater (1.4 g/dl compared with 0.6 g/dl for iron sucrose–treated patients; P=0.09) in more anemic patients (>7.0 to ≤9.0 g/dl at baseline), but this difference did not reach statistical significance. In patients with a higher Hgb level at baseline (9.0 to <11.0 g/dl), the mean change in Hgb was comparable (ferumoxytol, 0.6 g/dl; iron sucrose, 0.6 g/dl; P=0.93).

Approximately 50% of ferumoxytol-treated patients achieved a ≥1-g/dl increase compared with 42% of iron sucrose–treated patients (P=0.29). An exploratory analysis of the time (in days) to an Hgb response (defined as either a ≥1-g/dl increase from baseline or an achieved Hgb≥12 g/dl) found no significant difference between treatment groups (28.8 days for ferumoxytol-treated patients versus 33.4 days for iron sucrose–treated patients).

All iron indices examined (Table 4), regardless of treatment group, increased initially after treatment and fell through the remainder the study. Both ferumoxytol- and iron sucrose–treated patients had a peak in TSAT (Figure 2) and serum iron at week 2, whereas ferritin peaked at

Table 4. Baseline and postdose measurements of hemoglobin and iron indices (intent-to-treat population)

Parameter[a]	Ferumoxytol (n=80)	Iron Sucrose (n=82)	P Value[b]
Hemoglobin, g/dl (mean±SD)			
Baseline	10.1±0.9	10.0±1.0	
Week 2	10.6±1.0	10.2±0.9	
Change from baseline to week 2[c]	0.6±0.1	0.3±0.1	0.01
Week 3	10.7±1.0	10.4±0.9	
Change from baseline to week 3[c]	0.7±0.1	0.4±0.1	<0.05
Week 4	10.8±1.0	10.6±1.0	
Change from baseline to week 4[c]	0.8±0.1	0.7±0.1	0.40
Week 5	10.8±1.0	10.7±1.0	
Change from baseline to week 5[c]	0.8±0.1	0.7±0.1	0.52
Hemoglobin≥1-g/dl increase from baseline (%)			
Week 2	25.0	13.4	
Week 3	40.0	24.4	
Week 4	46.3	37.8	
Week 5[d]	50.0	41.5	0.29
Transferrin saturation, % (mean±SD)			
Baseline	21.5±18.1	18.9±11.8	
Week 2	33.0±13.1	26.0±17.2	
Week 3	30.3±11.5	23.5±7.4	
Week 4	30.0±11.6	26.0±11.0	
Week 5	27.5±8.0	25.5±12.7	
Ferritin, ng/ml (median [quartile 1, quartile 3])			
Baseline	164 (72, 381)	150 (51, 417)	
Week 2	854 (593, 1143)	509 (341, 752)	
Week 3	788 (467, 1096)	546 (363, 817)	
Week 4	647 (348, 1016)	509 (304, 747)	
Week 5	631 (361, 881)	456 (258, 671)	
Serum iron, μg/dl (mean±SD)			
Baseline	57.7±46.0	52.5±31.7	
Week 2	80.0±32.7	66.8±42.6	
Week 3	72.0±28.2	60.1±20.7	
Week 4	70.4±32.2	66.3±25.9	
Week 5	64.2±20.8	64.2±26.9	

[a]Means associated with P values for change in hemoglobin from baseline are least square means adjusted for covariates (reported as least square means±SEMs). Other means are arithmetic means (reported as means±SDs).
[b]All P values refer to comparisons between treatment groups.
[c]For analysis of the change from baseline, P values were calculated using ANOVA adjusted for baseline hemoglobin level and hemodialysis status.
[d]P value for percent with ≥1-g/dl increase in hemoglobin is from the Cochran–Mantel–Haenszel test adjusted for baseline hemoglobin level and hemodialysis status.

week 2 for ferumoxytol-treated patients and week 3 for iron sucrose–treated patients (Figure 3).

Efficacy: Changes in ESA Dosing and Administration of Blood Transfusions

Per protocol, ESA doses were not to be modified over the 5-week treatment period of the study unless required for patient safety. Over the course of the study, the administration of other therapies (ESAs and blood transfusions) to treat anemia was similar between the two treatment groups. At the start of the study, a slight majority of patients was on ESA therapy (51%), and these patients were fairly evenly distributed across treatment groups (54% ferumoxytol; 48% iron sucrose). Regardless of treatment,

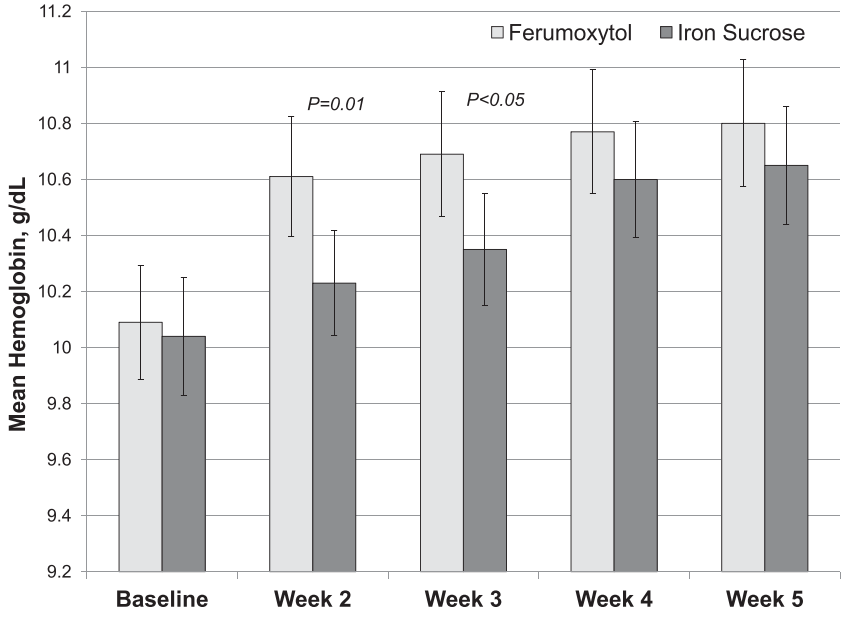

Figure 1. | **Comparable hemoglobin change over time by treatment group (intent-to-treat [ITT] population)**. For missing hemoglobin values, the last observed value was carried forward for imputation. *P* values were calculated using ANOVA adjusted for baseline hemoglobin level and hemodialysis status. Bars represent 95% confidence intervals. Ferumoxytol, *n*=80; iron sucrose, *n*=82.

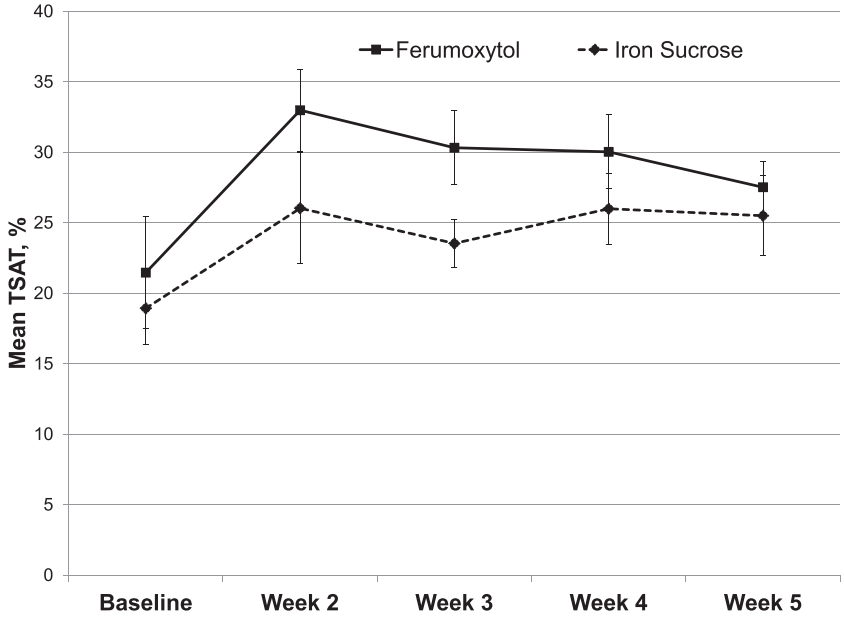

Figure 2. | **Transferrin saturation (TSAT) over time by treatment group (ITT population).** Error bars represent 95% confidence intervals. Ferumoxytol, *n*=80; iron sucrose, *n*=82.

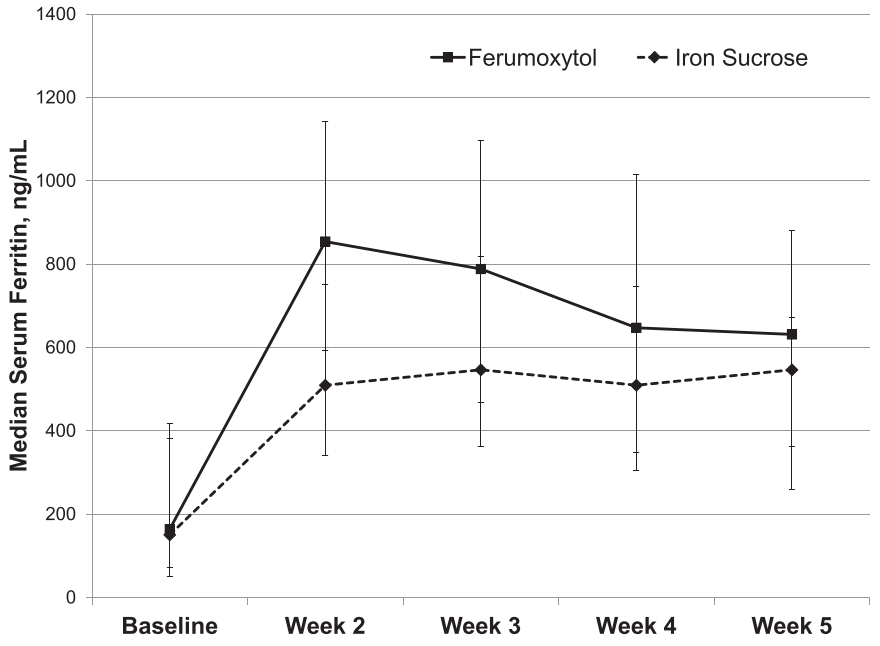

Figure 3. | **Serum ferritin over time by treatment group (ITT population).** Error bars represent interquartile ranges. Ferumoxytol, *n*=80; iron sucrose, *n*=82.

the vast majority of patients had no change (≥20% from baseline) in their ESA therapy (91%).

Discussion

IV iron is the recommended route of administration for the treatment of IDA in CKD patients on hemodialysis and nondialysis CKD patients who have failed a course of oral iron to allow an adequate iron supply to support erythropoiesis (4,5). Although most publications regarding IV iron products discuss the immediate hypersensitivity/vasoactive reactions, few studies have assessed the comparative frequency and nature of these reactions or the other AEs associated with the administration of IV iron compounds. The few head-to-head, randomized, controlled trials of different IV iron products have mainly focused on comparative efficacy in terms of Hgb response, with less emphasis on AEs and immediate adverse reactions. This study examined the efficacy and safety of two approved IV irons (ferumoxytol and iron sucrose) in the treatment of IDA in patients with CKD either on or not on hemodialysis in a randomized, open-label, multicenter, international trial.

Overall, the results showed that ferumoxytol at 1.02 g (delivered as two injections of 510 mg within 5±3 days) had generally similar occurrences of AEs and comparable efficacy to 1.0 g iron sucrose (dosed as 100 or 200 mg over 5–10 administrations over a 5-week period). The rates of AEs overall (48% versus 65%), AEs considered to be related to study drug (10% versus 16%), study drug discontinuations because of an AE (1% versus 5%), and SAEs and related SAEs (SAEs, 9% versus 7%; related SAEs, 1% versus 1%, all ferumoxytol- and iron sucrose–treated patients, respectively) were similar between the two treatment groups. No individual SAE was reported in more than one patient. Acute hypotension or hypersensitivity reactions, known to be associated with all IV iron products, were observed in both treatment groups. However, it is worth noting that, given the *N* of 162, any examination of the frequency of AEs is purely descriptive, and no statistical analysis is appropriate.

One of the possible reasons for numerically lower AE and related AE rates noted with ferumoxytol-treated patients may be the number of doses (*i.e.*, unique IV administrations or exposures) required to administer the full therapeutic dose of IV iron (1 g) for each product. Because each administration carries the risk of an AE, the additional three (nondialysis patients) or eight injections (hemodialysis patients) required to administer a complete therapeutic course with iron sucrose increase the chance of related AEs. A *post hoc* analysis showed that the rate of AEs and related AEs in patients treated with either iron product did not diminish with successive doses. These data suggest that there is a relative risk associated with each administration of IV iron, which could contribute to the higher overall rates of AEs and related AEs for iron sucrose relative to ferumoxytol.

The rates of the various AE categories for ferumoxytol-treated patients observed in this study were similar to the rates previously reported in three randomized phase III CKD studies (NCT00233597, NCT00255437, and NCT00255424; *n*=605 CKD patients) (16–18). In those pivotal trials, the rate for ferumoxytol was 44% for AEs (versus 48% in this trial), 14% for related AEs (versus 10% in this trial), 10% for SAEs (versus 9% in this trial), and 2% for AEs leading to study drug discontinuation (versus 1% in this trial). This observed consistency in the safety profile of ferumoxytol across these studies supports the reliability of the safety data observed in this trial.

The efficacy results show that ferumoxytol was noninferior to iron sucrose. At week 5 after treatment, the

difference in the mean change in Hgb from baseline between ferumoxytol and iron sucrose treatments was +0.10 g/dl, with the lower bound of the 95% CI being greater than the predefined noninferiority margin. In addition, ferumoxytol produced an earlier increase in Hgb compared with iron sucrose. Furthermore, ferumoxytol-treated patients consistently had higher Hgb at every post-dose time point.

Results from this trial contribute to clinicians' understanding of the relative safety and efficacy profiles of both ferumoxytol and iron sucrose used for the treatment of IDA in patients with CKD. Data from this study show that both ferumoxytol and iron sucrose are safe and effective in this patient population and that no major differences were observed. Trends, which need to be confirmed with trials in larger patient populations, suggest that there may be fewer AEs and related AEs with ferumoxytol compared with iron sucrose, possibly related to the reduced number of injections required to administer the target 1-g dose of ferumoxytol. The two-dose paradigm for ferumoxytol could have potential advantages for both patients and health care professionals. It is, of course, up to each practitioner to weigh the relative AE profiles and other properties for choice of an agent for his or her patients.

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Disclosures

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