

Ferumoxytol for Treating Iron Deficiency Anemia in CKD

Bruce S. Spinowitz,* Annamaria T. Kausz,^{†‡} Jovanna Baptista,[†] Sylvia D. Noble,[§] Renuka Sothinathan,^{||} Marializa V. Bernardo,[¶] Louis Brenner,^{†**} and Brian J. G. Pereira[†]

*Nephrology, New York Hospital Medical Center, Queens, New York; [†]AMAG Pharmaceuticals, Inc., Cambridge, Massachusetts; [‡]Nephrology, Tufts-New England Medical Center, Boston, Massachusetts; [§]Northwest Louisiana Nephrology, Shreveport, Louisiana; ^{||}Clinical Research and Consulting Center, Fairfax, Virginia; [¶]Southwest Houston Research, Houston, Texas; ^{**}Nephrology, Brigham and Women's Hospital, Boston, Massachusetts

ABSTRACT

Iron deficiency is an important cause of anemia in patients with chronic kidney disease (CKD), but intravenous iron is infrequently used among patients who are not on dialysis. Ferumoxytol is a novel intravenous iron product that can be administered as a rapid injection. This Phase III trial randomly assigned 304 patients with CKD in a 3:1 ratio to two 510-mg doses of intravenous ferumoxytol within 5 ± 3 d or 200 mg of elemental oral iron daily for 21 d. The increase in hemoglobin at day 35, the primary efficacy end point, was 0.82 ± 1.24 g/dl with ferumoxytol and 0.16 ± 1.02 g/dl with oral iron ($P < 0.0001$). Among patients who were not receiving erythropoiesis-stimulating agents, hemoglobin increased 0.62 ± 1.02 g/dl with ferumoxytol and 0.13 ± 0.93 g/dl with oral iron. Among patients who were receiving erythropoiesis-stimulating agents, hemoglobin increased 1.16 ± 1.49 g/dl with ferumoxytol and 0.19 ± 1.14 g/dl with oral iron. Treatment-related adverse events occurred in 10.6% of patients who were treated with ferumoxytol and 24.0% of those who were treated with oral iron; none was serious. In summary, a regimen of two doses of 510 mg of intravenous ferumoxytol administered rapidly within 5 ± 3 d was well tolerated and had the intended therapeutic effect. This regimen may offer a new, efficient option to treat iron deficiency anemia in patients with CKD.

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Anemia develops early during chronic kidney disease (CKD), affects virtually all individuals with stage 5 CKD (GFR < 15 ml/min per 1.73 m²),^{1–3} and is associated with increased cardiovascular morbidity and decreased quality of life.^{4,5} Iron deficiency is a common cause of anemia in CKD; the estimated prevalence ranges from 25 to 70%.^{2,6–9} The causes include decreased intake or absorption of iron; iron sequestration as a result of inflammation; blood loss; and increased iron use for red blood cell production in response to erythropoiesis stimulating agents (ESA).^{10–12} Inadequate production of erythropoietin by the kidney and/or insufficient response to erythropoietin as a result of inflammation contributes to anemia during later stages of CKD.^{13,14}

Appropriate management of anemia in CKD often requires both iron and ESA.^{15,16} Oral iron ther-

apy has limitations as a result of impaired absorption and gastrointestinal adverse effects that may affect patient compliance.^{17–19} Intravenous administration overcomes these limitations. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines recommend intravenous iron for patients who have CKD stage 5D and are on hemodialysis and either oral or intravenous iron for patients who are on peritoneal dialysis or

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Correspondence: Dr. Annamaria Kausz, 125 Cambridge Park Drive, 6th Floor, Cambridge, MA 02149. Phone: 617-498-3346; Fax: 617-498-3363; E-mail: akausz@amagpharma.com

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have CKD stages 1 to 5 and are not on dialysis.²⁰ The therapeutic course of intravenous iron typically used in clinical practice is 1 g.^{20–22}

The available intravenous iron formulations in the United States include iron dextran, iron sucrose, and sodium ferric gluconate.^{21–24} With iron dextran, up to 1 g can be administered at one time *via* a slow infusion, but life-threatening anaphylaxis can rarely occur.^{25–27} Iron sucrose and sodium ferric gluconate seem to have a lower incidence of anaphylaxis^{28–30} but can be safely given in small dosages (≤ 200 mg) (necessitating five to eight visits for the administration of 1 g) or as an infusion of larger dosages.^{21,22,31–33} This is impractical in the outpatient setting and may partly account for suboptimal iron replacement in patients who have stages 1 through 5 CKD or are on home dialysis.^{34–36}

Ferumoxytol is a superparamagnetic iron oxide nanoparticle with a polyglucose sorbitol carboxymethylether coating. Ferumoxytol is isotonic, and preliminary data suggest that it contains less free iron than other intravenous iron preparations.³⁷ These physicochemical properties may explain why ferumoxytol can be given rapidly at relatively high dosages.^{38,39} In addition, ferumoxytol appears quickly in circulating red blood cells, suggesting ready bioavailability for erythropoiesis.⁴⁰ This report describes a Phase III clinical trial of ferumoxytol for intravenous iron replacement in patients with CKD stages 1 to 5.

RESULTS

Between May 2004 and August 2006, 304 patients were randomly assigned, 228 to ferumoxytol and 76 to oral iron. The rate of study completion was 91% in the ferumoxytol group and 83% in the oral iron group. Demographic and baseline clinical characteristics of the study population were similar in the two groups (Table 1), as were hemoglobin and iron indices. The majority of patients had transferrin saturation (TSAT) $< 20\%$ (90.4% ferumoxytol, 94.7% oral iron), and the 75th percentile was 14% in the ferumoxytol group and 13% in the oral iron group. There were 23 protocol violations related to starting ESA or changing the dosage, 6.1% ferumoxytol and 11.8% oral iron.

Efficacy

Ferumoxytol significantly increased hemoglobin at days 21 and 35, compared with oral iron (Table 2). At day 35, the mean increase in hemoglobin was 0.82 ± 1.24 g/dl (8.2 ± 12.4 g/L) with ferumoxytol and 0.16 ± 1.02 g/dl (1.6 ± 10.2 g/L) with oral iron ($P < 0.0001$ for treatment difference), and 39.0% of the ferumoxytol group achieved a ≥ 1 g/dl (≥ 10 g/L) increase in hemoglobin (*versus* 18.4% with oral iron). The increases in ferritin, TSAT, and iron were also significantly greater with ferumoxytol compared with oral iron.

Among both patients on and not on ESA, ferumoxytol resulted in a significantly greater increase in hemoglobin com-

Table 1. Demographic and baseline clinical characteristics of the study population (intention-to-treat)^a

Characteristic	Ferumoxytol	Oral Iron
No. of patients	228	76
Age (yr; mean \pm SD)	65.1 \pm 14.3	63.7 \pm 11.1
Male (%)	41.2	31.6
Race (%)		
white	57.0	60.5
black/African American	34.2	36.8
Asian	6.1	1.3
other	2.7	1.4
Stage of CKD (%)		
1 (GFR ≥ 90)	0.4	1.3
2 (GFR 60 to 89)	1.3	1.3
3 (GFR 30 to 59)	36.0	39.5
4 (GFR 15 to 29)	46.9	47.4
5 (GFR < 15)	13.6	10.5
missing	1.8	0.0
Erythropoiesis stimulating agent use (%)	36.4	43.4
Hemoglobin (g/dl; mean \pm SD)	9.96 \pm 0.69	9.96 \pm 0.78
Ferritin (ng/ml; mean \pm SD)	146.1 \pm 173.6	143.5 \pm 144.9
TSAT (%; mean \pm SD)	11.3 \pm 6.1	10.1 \pm 5.5

^aTo convert to SI units, multiply hemoglobin by 10 to obtain g/dl and ferritin by 1 to obtain $\mu\text{g/L}$.

pared with oral iron (Figure 1). In the subgroup not on ESA, mean hemoglobin increase at day 35 was 0.62 ± 1.02 g/dl (6.2 ± 10.2 g/L) with ferumoxytol ($n = 145$) *versus* 0.13 ± 0.93 g/dl (1.3 ± 9.3 g/L) with oral iron ($n = 43$; $P = 0.0045$ for treatment difference). Among ESA-treated patients, hemoglobin increased by 1.16 ± 1.49 g/dl (11.6 ± 14.9 g/L) with ferumoxytol ($n = 83$) *versus* 0.19 ± 1.14 g/dl (1.9 ± 11.4 g/L) with oral iron ($n = 33$; $P = 0.0010$). In the ferumoxytol group, 29.7 and 55.4% of patients who were not on ESA and were on ESA, respectively, achieved a ≥ 1 g/dl (≥ 10 g/L) increase in hemoglobin at day 35 compared with 14.0 and 24.2% of oral iron-treated patients.

In the nonrandomized readmission phase of the study, 22 patients who had received ferumoxytol during the randomized phase received a second course of ferumoxytol, and 40 from the oral iron group received a first course of ferumoxytol. The readmission baseline mean hemoglobin was 9.91 and 9.95 g/dl (99.1 and 99.5 g/L) in the original ferumoxytol and oral iron treatment groups, respectively. At day 35, the mean increase in hemoglobin among all patients in the readmission phase was 0.64 ± 0.83 g/dl (6.4 ± 8.3 g/L). The increase was 0.55 ± 0.89 g/dl (5.5 ± 8.9 g/L) among patients previously treated with ferumoxytol and 0.69 ± 0.80 g/dl (6.9 ± 8.0 g/L) among patients previously treated with oral iron.

Safety

A total of 292 patients who received study drug (217 ferumoxytol and 75 oral iron) were included in the safety analysis. Ferumoxytol was generally well tolerated, with 35.5% of patients reporting adverse events, compared with 52.0% of oral iron

Table 2. Baseline and follow-up hemoglobin and indices of iron stores, intent-to-treat population^a

Parameter	Ferumoxytol (n = 228)	Oral Iron (n = 76)	p ^b
Hemoglobin (g/dl; mean ± SD)			
baseline ^c	9.96 ± 0.69	9.96 ± 0.78	
day 21	10.71 ± 1.03	10.21 ± 0.80	
day 35	10.88 ± 1.27	10.15 ± 1.07	
day 35 change from baseline ^d	0.82 ± 1.24	0.16 ± 1.02	<0.0001
Hemoglobin ≥1-g/dl increase from baseline (%)			
day 21	32.5	15.8	
day 35	39.0	18.4	0.0010
Ferritin (ng/ml; mean ± SD)			
baseline ^c	146.1 ± 173.6	143.5 ± 144.9	
day 21	703.1 ± 355.6	157.6 ± 154.5	
day 35	555.7 ± 320.0	160.8 ± 161.0	
day 35 change from baseline	381.7 ± 278.6	6.9 ± 60.1	<0.0001
Serum iron (μg/dl; mean ± SD)			
baseline ^c	45.0 ± 18.2	43.7 ± 18.6	
day 21	76.5 ± 35.8	52.7 ± 25.2	
day 35	68.0 ± 26.2	50.1 ± 19.1	
day 35 change from baseline ^d	22.7 ± 24.3	4.4 ± 19.2	<0.0001
TSAT (%; mean ± SD)			
baseline ^c	11.3 ± 6.1	10.1 ± 5.5	
day 21	24.1 ± 13.1	12.8 ± 8.1	
day 35	21.0 ± 10.1	11.8 ± 6.7	
day 35 change from baseline ^d	9.8 ± 9.2	1.3 ± 6.4	<0.0001

^aTo convert to SI units, multiply hemoglobin by 10 to obtain g/dl, ferritin by 1 to obtain μg/L, and iron by 0.179 to obtain μmol/L.

^bTwo-sample t test for evaluating a difference between the treatment groups in change from baseline.

^cBaseline value is the mean from the day -10 and day -5 values.

^dChange from baseline does not equal day 35 minus baseline because it includes imputed value of zero for change from baseline for patients who did not have a value obtained at day 35.

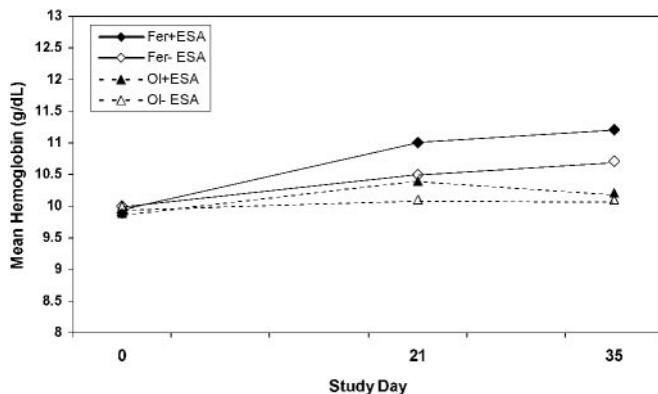


Figure 1. Hemoglobin response by treatment group and ESA use, from baseline to day 21 and day 35. Compared with patients who were randomly assigned to oral iron (OI), ferumoxytol (FER) resulted in a greater increase in hemoglobin during follow-up in patients who were on ESA as well as among patients who were not on ESA.

patients (Table 3). Most adverse events were mild to moderate in intensity. Adverse events considered treatment related by the investigator were reported in 10.6% of ferumoxytol-treated patients *versus* 24.0% of oral iron-treated patients. Serious adverse events occurred infrequently (4.6% ferumoxytol

and 9.3% oral iron), and none of the serious adverse events was considered treatment related.

Treatment related adverse events are listed in Table 4. Of the three most common treatment-related adverse events in the ferumoxytol group, only dizziness occurred more frequently with ferumoxytol. All other adverse events each occurred in only one or two patients. Hypersensitivity and hypotension were not observed. The greatest mean (median) change in systolic BP (SBP) was -4.4 (-2.0) mmHg at 10 min, and only 20% had a decrease in SBP of >10 mmHg at any time after dosing.

There were no clinically meaningful changes in laboratory tests. The mean changes from baseline to day 35 in parameters of interest for safety were minimal, including serum creatinine (change 0.01 mg/dl from baseline), glucose (-3.16 mg/dl), phosphorus (-0.03 mg/dl), aspartate and alanine aminotransferase (<3 μ/L), γ-glutamyl transferase (<8 μ/L), and platelet count (-28,000/mm³).

The incidence of adverse events in the nonrandomized re-admission phase was similar in the 22 patients who received a second course of ferumoxytol (40.9%) and the 40 patients who received ferumoxytol after previous oral iron therapy (37.5%) and was comparable to the rate in ferumoxytol-treated patients in the randomized phase. Only two (3.2%) patients, previously in the oral iron group, had treatment related adverse

Table 3. Summary of adverse events in the safety population^a

Parameter	Ferumoxytol (n = 217)		Oral Iron (n = 75)	
	Events (n)	Patients (n [%])	Events (n)	Patients (n [%])
Adverse events	158	77 (35.5)	102	39 (52.0)
Related adverse events	41	23 (10.6)	25	18 (24.0)
Serious adverse events	15	10 (4.6)	11	7 (9.3)
Related serious adverse events	0	0 (0.0)	0	0 (0.0)

^aPatients who received at least one dose of study drug.

Table 4. Treatment-related adverse events

Parameter	Ferumoxytol (n = 217)		Oral Iron (n = 75)	
	Events (n)	Patients (n [%])	Events (n)	Patients (n [%])
Any related adverse event	41	23 (10.6)	25	18 (24.0)
Nausea	4	4 (1.8)	3	3 (4.0)
Dizziness	4	4 (1.8)	0	0 (0.0)
Diarrhea	3	3 (1.4)	4	4 (5.3)
Chills	2	2 (0.9)	1	1 (1.3)
Rash	2	2 (0.9)	1	1 (1.3)
Dysgeusia	2	2 (0.9)	0	0 (0.0)
Injection-site swelling	2	2 (0.9)	0	0 (0.0)
Constipation	1	1 (0.5)	6	6 (8.0)
Abdominal pain upper	1	1 (0.5)	3	3 (4.0)
Vomiting	0	0 (0.0)	2	2 (2.7)

events (constipation and increased appetite). There were no treatment related serious adverse events.

DISCUSSION

Although one third of patients initiating dialysis in the United States have received ESA, many are anemic at initiation (mean hemoglobin 10.1 g/dl [101 g/L]).⁴¹ This suggests that current anemia management is suboptimal in patients with CKD stages 1 to 5. Iron deficiency is underrecognized,⁴² and undertreatment may be related to physicians' perception that oral iron is neither effective nor well tolerated and that available intravenous iron preparations are too cumbersome to be widely used in this population. This study demonstrates that a regimen of two 510-mg doses of ferumoxytol administered as an undiluted injection in the outpatient office was convenient and well tolerated and had the intended therapeutic effect.

Intravenous ferumoxytol, given as two doses of 510 mg within 1 wk, was more effective than oral iron in raising hemoglobin in patients with CKD stages 1 to 5. At day 35, the mean increase in hemoglobin from baseline was four times higher among patients who were randomly assigned to ferumoxytol compared with oral iron, and twice as many ferumoxytol-treated patients achieved a ≥ 1 -g/dl increase in hemoglobin (39.0 versus 18.4% oral iron). It was not surprising that more patients did not have a ≥ 1 -g/dl increase in hemoglobin given that fewer than half of the patients were on ESA therapy (36%

ferumoxytol, 43% oral iron). Among those on ESA, 55% of ferumoxytol-treated patients had a ≥ 1 -g/dl increase in hemoglobin at day 35 versus 24% with oral iron. Among patients initially treated with oral iron in the randomized phase, subsequent treatment with ferumoxytol during the readmission phase led to a mean increase in hemoglobin of 0.69 ± 0.80 g/dl (6.9 ± 8.0 g/L), confirming persistent iron deficiency despite oral iron therapy.

Previous studies of available intravenous iron preparations have not shown substantially greater efficacy when compared with ferrous sulfate 325 mg three times per day.^{32,33,43} Among 89 patients who were not receiving ESA, sodium ferric gluconate (250 mg/wk for 4 wk) was not much more effective than oral iron (hemoglobin increase 0.4 g/dl [4 g/L] with intravenous versus 0.2 g/dl [2 g/L] with oral iron).⁴³ In a study of intravenous iron plus ESA in 96 patients with CKD, five doses of 200 mg of iron sucrose led to an increase in hemoglobin of 1.0 versus 0.7 g/dl with oral iron plus ESA (NS).³² In another study with 40% of patients on ESA, patients who were treated with 1 g of intravenous iron sucrose had a 0.7-g/dl (7-g/L) mean increase in hemoglobin, and 44% had a ≥ 1 -g/dl increase in hemoglobin, compared with 0.4 g/dl (4 g/L) and 28%, respectively, with oral iron ($P = 0.03$ for both end points).³³ More rapid correction of iron deficiency with ferumoxytol (within 1 wk) may explain the highly significant difference between oral and intravenous iron in the ferumoxytol trials not previously seen with available intravenous iron therapies, but other factors such as improved bioavailability and study design may also contribute.

Appropriate therapy of anemia in patients with CKD requires identification and repletion of iron deficiency before initiating ESA. In this study, patients who were not on ESA and were treated with ferumoxytol had a greater increase in hemoglobin at day 35 (0.62 g/dl [6.2 g/L]) than patients who were on oral iron and ESA (0.19 g/dl [1.9 g/L]); by comparison, the increase was 1.16 g/dl (11.6 g/L) among patients who were on ESA and were treated with ferumoxytol. The possibility that some patients could be treated with intravenous iron alone or that appropriate intravenous iron replacement may delay initiation or reduce the dosage of ESA could improve care and reduce costs.^{44,45} Safety concerns with ESA raised by recent clinical trials,^{46–48} which led to a Food and Drug Administration warning in their package insert, further make the case for appropriate intravenous iron therapy.

Ferumoxytol, administered as an intravenous injection in two doses of 510 mg within 5 ± 3 d, was well tolerated, with no reported adverse events of hypotension or hypersensitivity. In fact, the proportion of patients with related adverse events was lower in the ferumoxytol group (10.6%) compared with oral iron (24.0%). There was no increase in the incidence of adverse events among patients who received a second course of intravenous ferumoxytol. In contrast, other intravenous iron preparations administered rapidly or at higher dosages (e.g., >200 mg/dose) have been associated with a higher rate of adverse events.^{33,43,49} In non-dialysis-dependent patients with CKD, infusions of 250 mg of sodium ferric gluconate over 1 h resulted in adverse events in 13 (29.5%) of 44 patients, including three serious adverse events (hypotension [4.6%] and anaphylaxis [2.2%]).⁴³ Iron sucrose as a 500-mg infusion over 3.5 to 4 h caused hypotension in two (6.7%) of 30 patients,³³ and in another study, 200 mg over 2 min was associated with anaphylactoid reactions in seven (1.1%) of 657 patients.⁴⁹

The convenience of providing 1 g of iron as ferumoxytol with two intravenous injections in the outpatient office, instead of with five to eight smaller doses or larger dosages *via* infusion, could improve the management of anemia in patients with CKD stages 1 to 5 by facilitating compliance. Because ferumoxytol could be administered during routine phlebotomy, it would require fewer venipunctures and intravenous catheter placements than currently available intravenous iron products, potentially preserving veins for future hemodialysis access.⁵⁰ The ability to administer ferumoxytol safely at high dosages without dilution or infusion may also save nursing time and the cost of disposables incurred with multiple infusions.⁵¹

The results of this study emphasize key anemia management principles in patients with CKD stages 1 to 5. First, intravenous iron therapy is more effective than oral iron for increasing hemoglobin levels. Second, for most patients, correction of iron deficiency with intravenous iron is an appropriate first step in anemia management, before initiating ESA therapy. Third, patients on ESA need monitoring for and correction of iron deficiency. Finally, the ability to administer ferumoxytol in dosages up to 510 mg as a rapid intravenous injection could

facilitate iron deficiency anemia management in the physician's office.

CONCISE METHODS

Ferumoxytol

Ferumoxytol is produced by AMAG Pharmaceuticals, Inc. (Cambridge, MA). It has a colloidal particle size of 30 nm and a molecular weight of 750 kD. Ferumoxytol injection is a sterile liquid with a neutral pH, formulated with mannitol for isotonicity; each milliliter contains 30 mg of iron and 44 mg of mannitol.³⁷

Study Design and Conduct

This was an open-label, randomized, controlled, multicenter Phase III trial (ClinicalTrials.gov NCT00255424).⁵² The protocol received institutional review board approval. All patients gave written informed consent.

Patients were prescreened for anemia up to 8 wk before study drug dosing. Screening visits were undertaken on day $-10 (\pm 4$ d) and day $-5 (\pm 3$ d) before study drug dosing. Eligible patients were randomly assigned in a 3:1 ratio to intravenous ferumoxytol or oral iron, using a telephone-based system (ClinPhone, East Windsor, NJ). Ferumoxytol treatment consisted of two 510-mg doses within 5 ± 3 d, administered intravenously at a rate of 1 ml/s (30 mg of iron) in the outpatient office. Oral iron treatment consisted of 200 mg of elemental iron daily for 21 d, as Ferro-Sequels (50 mg of ferrous fumarate plus docusate sodium; Inverness Medical Innovations, Inc., Waltham, MA), two tablets twice daily on an empty stomach. Compliance was monitored at weekly visits and with a formal pill count on day 21. Patients receiving ESA were to be on a stable dosage (and on $\leq 35,000$ U/wk erythropoietin or ≤ 120 μ g of darbepoetin every 2 wk), and patients who were not on ESA were precluded from starting ESA during the study.

Follow-up visits and tests were scheduled for day 21 (± 5 d) and day 35 (± 5 d) after the initial dose of study drug. Laboratory tests were performed at MedTox Laboratories, Inc. (St. Paul, MN).

Eligibility Criteria

Anemic adult patients (≥ 18 yr) who had CKD stages 1 to 5 and hemoglobin ≤ 11.0 g/dl (110 g/L), serum ferritin ≤ 600 ng/ml (600 μ g/L), and TSAT $\leq 30\%$ and were able to provide informed consent were eligible. Exclusion criteria were pregnancy or breastfeeding, causes of anemia other than iron deficiency, malignancy (except nonmelanoma skin cancer or disease-free for ≥ 2 yr after curative therapy), use of another investigational drug or device within 30 d, recent iron therapy, serum parathyroid hormone > 1500 pg/ml (ng/L), active or recent bleeding, recent (or anticipated) surgery other than vascular access surgery, recent (or anticipated) blood transfusion, active infection requiring therapy, allergy to intravenous iron, and allergy to two or more drugs.

Sample Size

Sample size was calculated for 3:1 randomization to ferumoxytol:oral iron, to maximize exposure to ferumoxytol for safety assessments.

Assuming a mean treatment difference in hemoglobin between ferumoxytol and oral iron of 0.6 g/dl (SD 1.2 g/dl), 90% power using a two-sample *t* test (with 5% type I error), and a 25% dropout rate, the final sample size estimate was 304 patients.

Efficacy Analysis

Efficacy was assessed on the basis of changes in hemoglobin and serum iron indices (iron, TSAT, and ferritin) from baseline (average of day -10 and day -5 values). The primary efficacy end point was the mean change in hemoglobin from baseline to day 35. Other efficacy end points included mean change in ferritin and proportion of patients achieving a ≥ 1 -g/dl (10-g/L) increase in hemoglobin. For missing laboratory parameters at day 21 or 35, the analysis assumed no change from baseline (value of zero imputed for the change from baseline). In addition, an analysis of patients with fully evaluable data yielded similar results (data not shown). The primary end point variable, hemoglobin at day 35, was missing for 10% of ferumoxytol and 13% of oral iron treated patients.

Statistical significance of the comparison between treatment groups was assessed using a two-sided, two-sample *t* test or χ^2 test, as appropriate. The principal efficacy analyses were conducted using Intention-to-Treat principles, and prespecified efficacy analyses were also stratified by ESA use.

Safety Analysis

Safety was monitored during and for 1 h after ferumoxytol administration and throughout the 35-d study follow-up, by evaluating vital signs, adverse events (by direct observation and interview), and changes in laboratory tests and physical examinations. Patients in the oral iron group had vital signs obtained on days 0, 7, 14, 21, and 35 and in the ferumoxytol group at preadministration and 5, 10, 20, 30, and 60 min after, and at days 21 and 35. Mean arterial pressure was calculated using the formula $[(2 \times \text{diastolic BP}) + \text{systolic BP}]/3$.

Patients were monitored for hypotension and hypersensitivity reactions (urticaria, rash, pruritus, facial or laryngeal/pharyngeal edema, asthma, or other allergic reactions) after ferumoxytol administration. Hypotension was defined as a decrease in systolic BP of >20 mmHg and to <90 mmHg or a decrease in diastolic BP of >15 mmHg and to <50 mmHg. Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 8.0. Relatedness of adverse events to treatment was assessed by site investigators.

Readmission Phase

After completion of the randomized study at day 35 and at the discretion of the site investigator, patients in either treatment group who continued to be anemic and met other study entry criteria were eligible to receive two doses of 510 mg of ferumoxytol in an open-label manner. This optional readmission phase was conducted to examine the safety and efficacy of administering two courses of two doses of 510 mg of ferumoxytol and the response to ferumoxytol in patients who remained anemic after oral iron therapy. Because the readmission phase was neither randomized nor powered to demonstrate efficacy, the efficacy end points were examined for exploratory purposes only.

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DISCLOSURES

A.T.K., J.B., L.B., and B.J.G.P. are employees of AMAG Pharmaceuticals, and B.S.S. is a member of the Clinical Studies Steering Committee of AMAG Pharmaceuticals, Inc.

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