A multicenter, randomized, active-controlled study to investigate the efficacy and safety of intravenous ferric carboxymaltose in patients with iron deficiency anemia

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BACKGROUND: Many patients receiving oral iron for iron deficiency anemia (IDA) cannot tolerate or fail to respond to therapy, and existing intravenous (IV) iron formulations often require repeated administrations. Ferric carboxymaltose (FCM), a nondextran IV formulation, permits larger single doses.

STUDY DESIGN AND METHODS: We evaluated FCM versus oral iron in IDA patients. After 14 days of oral iron, 507 participants responding inadequately to oral iron (hemoglobin [Hb] increase <1 g/dL; Cohort 1) were assigned to Group A (two doses of FCM, 750 mg, 1 week apart) or Group B (oral iron, 325 mg, 3 × day for 14 additional days). Also, 504 subjects not appropriate for oral iron (Cohort 2) were assigned to Group C (FCM as above) or Group D (standard-of-care IV iron). The primary efficacy endpoint was change to highest observed Hb from baseline to Day 35. The composite safety endpoint included all-cause mortality, nonfatal myocardial infarction, nonfatal stroke, unstable angina, heart failure, arrhythmias, and hyper- or hypotensive events.

RESULTS: Mean (± standard deviation [SD]) Hb increase was significantly greater in Group A–FCM than Group B–oral iron: 1.57 (±1.19) g/dL versus 0.80 (±0.80) g/dL ($p = 0.001$). Post hoc comparison of Group C–FCM and Group D–IV standard of care also demonstrated significant mean (±SD) increase in Hb from baseline to highest value by Day 35 in Group C versus Group D: 2.90 (±1.64) g/dL versus 2.16 (±1.25) g/dL ($p = 0.001$). Safety endpoints occurred in 17 of 499 (3.4%) participants receiving FCM versus 16 of 498 (3.2%) in comparator groups.

CONCLUSION: Two 750-mg FCM infusions are safe and superior to oral iron in increasing Hb levels in IDA patients with inadequate oral iron response.

Iron deficiency is the most common cause of anemia[1] and typically results from impaired absorption of dietary iron, increased iron losses (e.g., menstruation, gastrointestinal bleeding), and increased utilization (e.g., treatment with erythropoiesis-stimulating agents). Therapy for iron deficiency anemia (IDA) includes repletion of iron stores and, where appropriate, correction of the underlying cause of iron loss.

Oral iron therapy for IDA is relatively safe, effective, and inexpensive. However, up to 40% of patients

ABBREVIATIONS: CKD = chronic kidney disease; FCM = ferric carboxymaltose; HUB = heavy uterine bleeding; IDA = iron deficiency anemia; IVSC = intravenous standard of care; mITT = modified intent to treat; PCS = potentially clinically significant; TSAT = transferrin saturation.

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experience side effects that include nausea, constipation, and abdominal pain.[2] Some patients may be unable to absorb oral iron adequately due to impaired intestinal absorption resulting from gastrointestinal disease or clinical conditions such as chronic inflammation, which may in turn lead to elevated levels of hepcidin, a hormone that down regulates the iron transport protein ferroportin.[3,4] In other instances, the rate of absorption of even high-dose oral iron is insufficient to correct the anemia and blood transfusion may be indicated.[3] Intravenous (IV) iron is the preferred therapy for such patients; however, earlier-generation parenteral therapies have been associated with bioactive iron reactions characterized by hypotension, chest and abdominal pain, vomiting, and diarrhea (e.g., sodium ferric gluconate; iron sucrose) that limit the amount of iron that can be administered in a single dose to 100 to 200 mg. A typical therapeutic course of such agents requires 5 to 10 injections and multiple clinic visits.

Two newer iron formulations permit much higher single doses of IV iron to be administered over shorter periods of time. Ferumoxytol, an iron oxide with a carbohydrate coating, has demonstrated superiority over oral iron supplementation in patients with chronic kidney disease (CKD)[5] and was approved by the Food and Drug Administration for use in CKD in 2009. The recommended dose is two 510-mg injections, 3 to 8 days apart.

Ferric carboxymaltose (FCM) (Injectafer, Luitpold Pharmaceuticals, Shirley, NY) is a stable, nondextran IV iron preparation whose properties permit administration of single doses of 750 to 1000 mg over short intervals.[6] Phase II and III trials have demonstrated the efficacy and safety of FCM in patients with heavy uterine bleeding (HUB) or postpartum IDA,[7-10] as well as in the settings of heart failure,[11] inflammatory bowel disease,[12] and CKD.[13] The primary objective of this study was to assess the efficacy and safety of IV FCM compared with oral iron in subjects with IDA who experienced an unsatisfactory response to oral iron.

MATERIALS AND METHODS

Study overview

Our study (NCT00982007) was a randomized, multicenter, open-label, active-controlled trial evaluating the efficacy and safety of IV FCM in patients with IDA compared with oral iron (Cohort 1) and IV standard-of-care iron (IVSC; Cohort 2). The study was conducted from September 2009 to March 2011 at 84 US centers and in accordance with US federal regulations, institutional review board requirements, and the Declaration of Helsinki. All study participants provided written informed consent. Participant safety and study integrity were overseen by an independent data and safety monitoring board.

Eligibility criteria, randomization, and study medication

Consenting patients at least 18 years of age who had a screening hemoglobin (Hb) value of not more than 11 g/dL with a ferritin level of not more than 100 or not more than 300 ng/mL when transferrin saturation (TSAT) was not more than 30% and who met all other eligibility criteria (Appendix Table S1, available as supporting information in the online version of this paper) were given a 14-day run-in of oral ferrous sulfate, 325 mg three times daily. All participants returned on Day 7 of the run-in phase to assess compliance (via pill counts) and tolerance of oral iron. Participants who experienced severe diarrhea, constipation, vomiting, or abdominal pain with oral iron were withdrawn from the run-in. Those who experienced other side effects were instructed to decrease the oral iron dose to 325 mg once daily for the balance of the run-in.

Study participants who responded adequately to oral iron during run-in (Hb increase ≥1 g/dL) were not randomized. Participants who had a Hb level measurement of less than 12 g/dL after run-in and either an inadequate response to oral iron (i.e., Hb level increase <1 g/dL/14 days, Cohort 1) or an inability to tolerate oral iron (Cohort 2) were randomly allocated by an interactive voice response system to Group A or B (Cohort 1) or Group C or D (Cohort 2) as described below. Randomly assigned subjects returned for efficacy and safety evaluations on Days 7, 14, and 35. Adverse event information was also collected on Days 90 and 120.

Cohort 1

Subjects who 1) exhibited unsatisfactory response to a 14-day run-in of oral iron (i.e., Hb increase <1 g/dL from baseline despite ≥67% compliance based on pill count), 2) had ferritin and TSAT values within inclusion criteria ranges, and 3) met none of the exclusion criteria were randomly assigned in a 1:1 ratio either to receive IV FCM (15 mg iron/kg) for a maximum dose of 750 mg on Days 0 and 7 (Group A) or to continue oral iron 325 mg three times a day for an additional 14 days (Group B). Subjects were stratified according to underlying etiology of IDA (HUB, gastrointestinal disorders, or other), baseline Hb (≤9, 9.1-10.0, ≥10.1 g/dL), and baseline cardiovascular risk (Category 0-1 or 2-3 per Framingham model).[14]

Cohort 2

Participants who tolerated oral iron poorly or for whom oral iron was deemed inappropriate, but who otherwise satisfied the entry criteria, were randomly assigned in a 1:1 ratio to receive either IV FCM according to criteria described above (Group C) or other IVSC preparation (Group D; Appendix Table S2, available as supporting information in the online version of this paper). Subjects

inappropriate for oral iron were defined in this study as those who either were intolerant of oral iron based on documented occurrence of adverse reactions during the oral run-in phase or in whom the baseline Hb measurement was sufficiently low as to require rapid repletion of iron stores to minimize the risk of eventual blood transfusion. IVSC was defined at the individual's investigator's discretion; all available IV iron product information sheets were provided with the full study protocol.

Study outcome measures

The primary efficacy endpoint was mean change from baseline to highest observed Hb value at any time between baseline and Day 35 or time of intervention for subjects in Cohort 1 (Groups A and B). A secondary efficacy endpoint was mean change from baseline to highest observed Hb any time between baseline and Day 35 or time of intervention for subjects in Cohort 2 (Groups C and D).

Other secondary efficacy endpoints in both cohorts included: 1) proportion of participants achieving a Hb level of more than 12 g/dL any time between baseline and Day 35; 2) mean change from baseline to highest ferritin measurement any time between baseline and Day 35; 3) proportion of participants achieving a Hb level of more than 12 g/dL and an increase in ferritin of at least 160 ng/mL any time between baseline and Day 35; 4) proportion of participants achieving an increase in Hb level of at least 2 g/dL any time between baseline and Day 35; and 5) mean change from baseline to each scheduled visit for Hb, ferritin, and TSAT levels.

Safety endpoints included 1) the proportion of study participants reporting treatment-emergent adverse events (overall and related to study drug); 2) treatment-emergent serious adverse events (overall and related to study drug); 3) events as components of a composite safety endpoint that included all-cause mortality, nonfatal myocardial infarction, nonfatal stroke, unstable angina requiring hospitalization, congestive heart failure, arrhythmias, and protocol-defined hypotension or hypertension; and 4) incidence of treatment-emergent potentially clinically significant (PCS) laboratory values. Composite safety events were adjudicated in blinded fashion by an independent clinical events classification committee at the Duke Clinical Research Institute (Durham, NC). Details regarding adjudicated endpoints are available in the Appendix (available as supporting information in the online version of this paper).

Statistical analysis

The safety analysis population included all study participants who received a dose of randomized treatment. The primary population for evaluating efficacy was the modified intent-to-treat (mITT) population, defined as participants from the safety population who received at least one dose of randomized treatment and had at least one postbaseline Hb assessment. All statistical tests were at the 0.05 alpha level, two-tailed, unless stated otherwise. The primary efficacy comparison was Group A (FCM) versus Group B (oral iron) in Cohort 1. All other comparisons were descriptive in nature. The superiority of Group A over Group B for change from baseline to highest observed Hb measurement any time between baseline and Day 35 was assessed by analysis of covariance, with treatment and etiology of IDA (HUB, gastrointestinal disorders, or other) as fixed factors and baseline Hb as a continuous covariate. Differences between Group A and Group B for proportions were assessed with the Cochran-Mantel-Haenszel test, with strata defined by etiology of IDA.

Sample size determination

A sample size of 250 study participants in each of Groups A (FCM) and B (oral iron) provided more than 90% power to detect a treatment difference of 0.47 g/dL (SD, $\pm$1.6 g/dL) for the assessment of superiority of Group A versus Group B with respect to mean increase from baseline to highest observed Hb level at any time between baseline and Day 35. Estimates were based on previous studies comparing FCM and oral iron in patients with HUB and in patients with chronic inflammatory bowel disease (data on file, Luitpold Pharmaceuticals).

RESULTS

Patient characteristics

A total of 1497 consenting patients entered run-in and received oral iron. Of these, 1011 participants who continued to meet eligibility criteria at the end of run-in were assigned to one of two cohorts, each comprising two randomized treatment groups: Cohort 1 (Group A [FCM], n = 250; Group B [oral iron], n = 257) and Cohort 2 (Group C [FCM], n = 253; Group D [IVSC], n = 251). Fourteen participants were discontinued before dosing, leaving 246 participants treated in Group A, 253 in Group B, 253 in Group C, and 245 in Group D. Study flow is summarized in Figure 1; baseline characteristics of study participants are detailed in Table 1. Group C exhibited lower mean values for weight and body mass index than Group D. The most common race represented in Groups A and B was black; the most common race in Groups C and D was white. These differences were felt to be insufficient to cause confounding.

Iron exposure

During oral iron treatment, levels of iron exposure were similar between groups within cohorts, both before and after randomization (Table 2). The majority of subjects

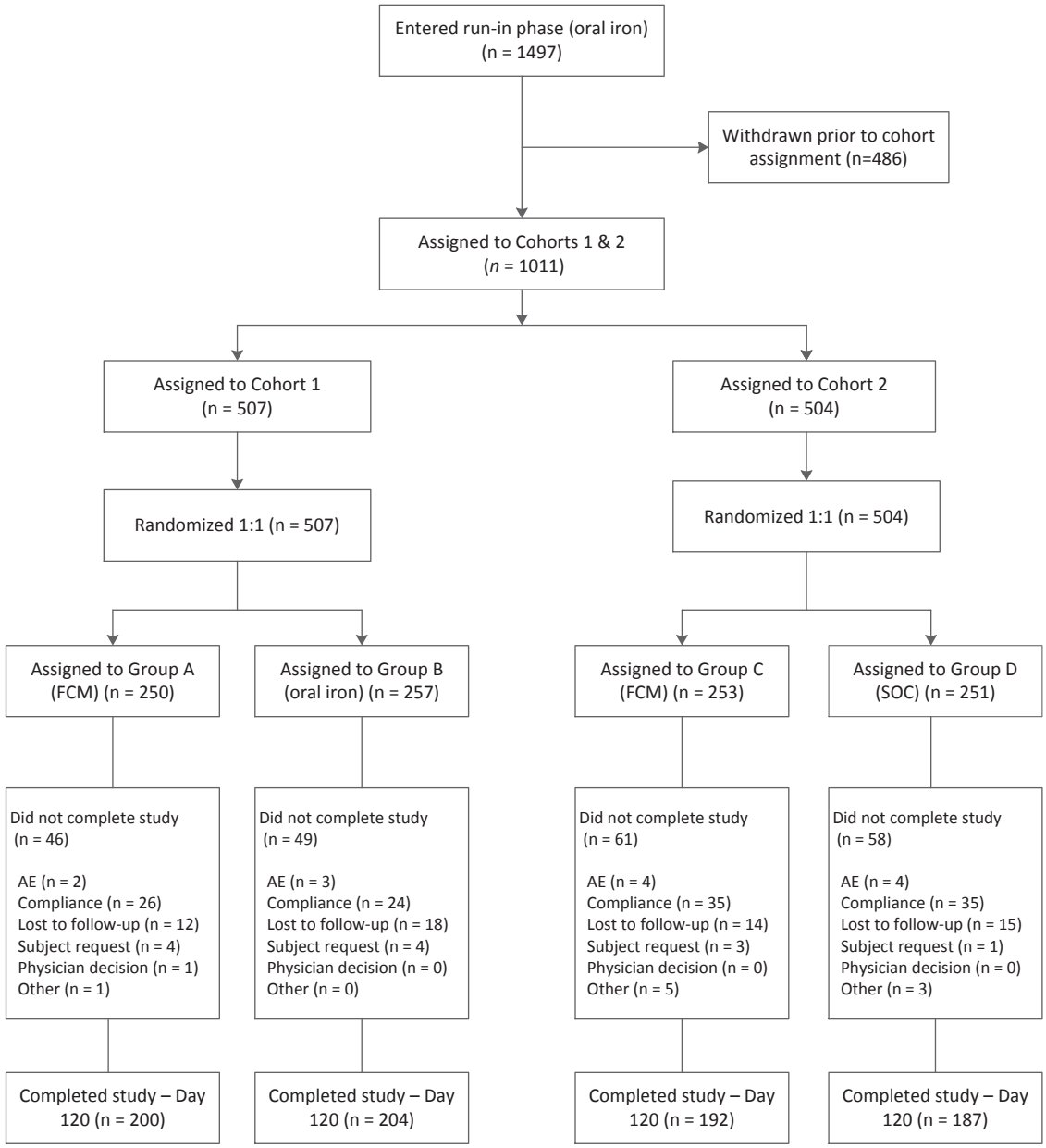

Fig. 1. Study flow. Consenting patients meeting eligibility criteria entered the trial if they had Hb levels of not more than 11 g/dL with IDA of any etiology. After the 14-day run-in with oral iron, subjects with an increase in Hb of less than 1 g/dL entered Cohort 1 and were randomly assigned to FCM or oral iron. Subjects entered Cohort 2 if they had poor tolerance or were not appropriate for oral iron. Study treatment was as follows: Group A—IV FCM 15 mg iron/kg, administered as 100 mg/min push for maximum dose of 750 mg, Days 0 and 7; Group B—oral ferrous sulfate, 325 mg (65 mg elemental Fe) tablets three times daily for 14 days; Group C—IV FCM 15 mg iron/kg, administered as 100 mg/min push for maximum dose of 750 mg, Days 0 and 7; Group D—IVSC iron as selected by site physician. All participants receiving IV iron had sitting pulse and blood pressure assessed before infusion, immediately after infusion, and 30-minutes after infusion and were monitored for serious acute reactions including hypotension, loss of consciousness, bronchospasm, shortness of breath, and seizures during and after infusions. AE = adverse event.

allocated to FCM (95.1% in Group A and 92.9% in Group C) received two infusions. Subjects in Group D (IVSC) received one to 14 infusions; the most common number of infusions was three, and iron sucrose was the most common form of IV iron administered (89.8%).

Primary efficacy endpoint: changes in Hb and iron indices

For the protocol-specified primary treatment group comparison, mean (±SD) increase in Hb from baseline to

TABLE 1. Demographic characteristics*

Characteristic	Cohort 1		Cohort 2	
	Group A: FCM (n = 246)	Group B: oral iron (n = 253)	Group C: FCM (n = 253)	Group D: IVSC (n = 245)
Age (years)	43.1 (±17.2)	43.5 (±17.7)	43.6 (±16.9)	42.6 (±15.5)
Female	233 (94.7)	238 (94.1)	239 (94.5)	231 (94.3)
Race				
Black	95 (38.6)	98 (38.7)	63 (24.9)	62 (25.3)
Asian	2 (0.8)	1 (0.4)	0	3 (1.2)
White	67 (27.2)	79 (31.2)	135 (53.4)	136 (55.5)
Hispanic	79 (32.1)	69 (27.3)	51 (20.2)	41 (16.7)
Other	3 (1.2)	6 (2.4)	4 (1.6)	3 (1.2)
Weight (kg)†	(n = 246)	(n = 253)	(n = 252)	(n = 245)
	82.8 (±22.5)	84.2 (±24.8)	79.5 (±20.4)	84.7 (±25.9)
Height (cm)	(n = 246)	(n = 253)	(n = 252)	(n = 245)
	162.8 (±8.2)	162.9 (±7.6)	163.6 (±7.8)	164.2 (±7.6)
BMI (kg/m^2)†	(n = 246)	(n = 253)	(n = 252)	(n = 245)
	31.2 (±8.4)	31.6 (±8.5)	29.7 (±7.6)	31.3 (±8.9)
History of iron intolerance	5 (2.0)	5 (2.0)	70 (27.7)	70 (28.6)
Previous iron therapy	129 (52.4)	140 (55.3)	186 (73.5)	183 (74.7)
History of drug allergy	59 (24.0)	62 (24.5)	79 (31.2)	84 (34.3)
Days since last dose of iron‡				
≤7	1 (0.8)	0	40 (21.5)	41 (22.4)
8-14	2 (1.6)	0	27 (14.5)	34 (18.6)
15-30	54 (41.9)	66 (47.1)	34 (18.3)	31 (16.9)
31-90	19 (14.7)	18 (12.9)	22 (11.8)	21 (11.5)
91-180	13 (10.1)	9 (6.4)	15 (8.1)	14 (7.7)
181-365	14 (10.9)	17 (12.1)	14 (7.5)	10 (5.5)
>365	25 (19.4)	28 (20.0)	31 (16.7)	28 (15.3)
Missing	1 (0.8)	2 (1.4)	3 (1.6)	4 (2.2)
Baseline Hb (g/dL)§	10.6 (±1.0)	10.6 (±1.1)	9.1 (±1.6)	9.0 (±1.5)
Hb category (g/dL)				
≤9.0	23 (9.3)	24 (9.5)	122 (48.2)	120 (49.0)
9.1-10.0	48 (19.5)	48 (19.0)	60 (23.7)	60 (24.5)
≥10.1	175 (71.1)	181 (71.5)	71 (28.1)	65 (26.5)
CV risk factors				
Any risk factor	100 (40.7)	107 (42.3)	103 (40.7)	104 (42.4)
Age > 75 years	16 (6.5)	19 (7.5)	14 (5.5)	12 (4.9)
History of CVD	13 (5.3)	17 (6.7)	24 (9.5)	18 (7.3)
Current smoker	14 (5.7)	17 (6.7)	25 (9.9)	21 (8.6)
Hypertension‖	72 (29.3)	77 (30.4)	65 (25.7)	70 (28.6)
Hyperlipidemia¶	35 (14.2)	43 (17.0)	36 (14.2)	38 (15.5)
Diabetes	34 (13.8)	48 (19.0)	25 (9.9)	28 (11.4)
CV risk category				
0-1	191 (77.6)	185 (73.1)	200 (79.1)	188 (76.7)
2-3	55 (22.4)	68 (26.9)	53 (20.9)	57 (23.3)
Etiology of IDA				
HUB	126 (51.2)	124 (49.0)	111 (43.9)	109 (44.5)
GI disorders	26 (10.6)	27 (10.7)	59 (23.3)	56 (22.9)
Postpartum	3 (1.2)	10 (4.0)	35 (13.8)	42 (17.1)
Nutritional or dietary deficiency	10 (4.1)	14 (5.5)	4 (1.6)	2 (0.8)
Other	81 (32.9)	78 (30.8)	44 (17.4)	36 (14.7)
Baseline TSAT (%)§	22.1 (14.8)	22.4 (15.1)	11.5 (12.2)	10.3 (9.7)
Baseline ferritin (ng/mL)§	31.3 (67.7)	28.2 (39.2)	25.9 (63.8)	14.9 (29.3)
ESA use	0	0	5 (2.0)	5 (2.0)

* Data are reported as mean (±SD) or number (%).
† Significant difference between Group C and Group D.
‡ For subjects with previous iron therapy.
§ Average of last two central laboratory values before first dose of study drug or single value if only one was available.
‖ Includes patients taking medication for control of hypertension.
¶ Includes patients taking lipid-lowering agents.
BMI = body mass index; CV = cardiovascular; CVD = cardiovascular disease; ESA = erythropoiesis-stimulating agents; GI = gastrointestinal.

TABLE 2. Iron exposure, before and after randomization

	Cohort 1		Cohort 2	
Mean (±SD) iron dosage	Group A	Group B	Group C	Group D
Oral iron exposure, before randomization (mg)	2804.8 (±260.7)	2846.9 (±298.1)	1332.2 (±746.9)	1407.6 (±809.8)
Total iron dose, after randomization (mg)	1437.9 (±215.7)	2608.2 (±435.0)	1432.3 (±214.5)	812.9 (±414.5)

TABLE 3. Summary of mean change in Hb from baseline to highest value between baseline and Day 35 or time of intervention (mITT population)*

	Cohort 1			Cohort 2		
Hemoglobin measurement	Group A: FCM (n = 244)	Group B: oral iron (n = 251)	p value	Group C: FCM (n = 245)	Group D: IVSC* (n = 237)	p value
Baseline (g/dL)	10.59 (±1.008)	10.62 (±1.033)		9.12 (±1.598)	9.02 (±1.465)	
Highest value (g/dL)	12.16 (±1.112)	11.42 (±1.181)		12.02 (±1.222)	11.17 (±1.256)	
Δ to highest value (g/dL)	1.57 (±1.194)	0.80 (±0.799)	0.001	2.90 (±1.640)	2.16 (±1.252)	0.001†
Adjusted mean (±SE)‡	1.44 (±0.088)	0.68 (±0.082)		2.81 (±0.107)	1.97 (±0.110)	

* Values are presented as mean (±SD) unless otherwise noted.
† Post hoc comparison.
‡ Group A versus Group B and Group C versus Group D from analysis of covariance with treatment and etiology of IDA as fixed factors and baseline Hb as a continuous covariate.

TABLE 4. Proportion of participants with Hb level of more than 12.0 g/dL any time between baseline and Day 35 or time of intervention (mITT population)*

	Cohort 1			Cohort 2		
Characteristic	Group A: FCM (N = 244)	Group B: oral iron (N = 251)	p^{diff}	Group C: FCM (N = 245)	Group D: IVSC (N = 237)	p^{diff}
Overall	139/244 (57.0)	73/251 (29.1)	0.001	124/245 (50.6)	58/237 (24.5)	0.001
Baseline Hb (g/dL)						
≤9.0	9/23 (39.1)	2/23 (8.7)		49/117 (41.9)	12/116 (10.3)	
9.1-10.0	21/48 (43.8)	5/48 (10.4)		31/58 (53.4)	16/58 (27.6)	
≥10.1	109/173 (63.0)	66/180 (36.7)		44/70 (62.9)	30/63 (47.6)	
Etiology of IDA						
HUB	79/125 (63.2)	36/123 (29.3)		64/108 (59.3)	24/106 (22.6)	
GI	12/26 (46.2)	4/27 (14.8)		29/57 (50.9)	13/53 (24.5)	
Postpartum	1/3 (33.3)	5/10 (50.0)		22/33 (66.7)	12/41 (29.3)	
Nutritional or dietary	6/10 (60.0)	4/14 (28.6)		0/4	0/2	
Other	41/80 (51.3)	24/77 (31.2)		9/43 (20.9)	9/35 (25.7)	

* Data are reported as n/N (%). Numerator = number of subjects with response; denominator = number of subjects with baseline and post-baseline Hb values.
GI = gastrointestinal.

highest value by Day 35 was significantly greater in Group A (FCM) than Group B (oral iron): 1.57 (±1.19) g/dL versus 0.80 (±0.80) g/dL (p = 0.001). Interestingly, a post hoc comparison of Groups C (FCM) and D (IVSC) also demonstrated a significant increase in Hb from baseline to highest value by Day 35 in the FCM group: 2.90 (±1.64) g/dL versus 2.16 (±1.25) g/dL (p = 0.001; Table 3). Subgroup analysis showed that mean changes in Hb levels from baseline to Day 35 were greater among FCM recipients (Group A vs. Group B and Group C vs. Group D) regardless of baseline Hb value or etiology of IDA (Table 4).

For each cohort, the proportion of study participants achieving a Hb value of more than 12.0 g/dL, a Hb value of at least 12.0 g/dL with a ferritin increase of at least 160 ng/mL, and a clinically meaningful increase in Hb any time between baseline and Day 35 was significantly greater in the FCM groups (Groups A and C) than in the comparison groups (Groups B and D). Clinically meaningful increases in Hb were defined as at least 1 g/dL for CKD, at least 2 g/dL for HUB or gastrointestinal disorder, at least 3 g/dL for postpartum participants, and at least 2 g/dL for others. Similar significant mean changes in Hb, ferritin, TSAT, serum iron, and total iron binding capacity from baseline to Day 35 were observed in the FCM groups (Groups A and C) versus their respective comparison groups (Groups B and D; Table 5).

TABLE 5. Mean change in Hb and other iron indices from baseline to Day 35 or time of intervention (mITT population)*

	Cohort 1					Cohort 2				
	Group A (FCM) N = 244		Group B (oral iron) N = 251			Group C (FCM) N = 245		Group D (IVSC) N = 237		
Iron index	Baseline	Change to Day 35	Baseline	Change to Day 35	p value	Baseline	Change to Day 35	Baseline	Change to Day 35	p value
Hb (g/dL)	n = 199		n = 204		0.001	n = 220		n = 202		0.001
	10.62 (±1.04)	1.58 (±1.21)	10.70 (±0.97)	0.58 (±0.83)		9.12 (±1.60)	2.87 (±1.70)	9.03 (±1.48)	2.13 (±1.31)	
Ferritin (ng/mL)	n = 200		n = 207		0.001	n = 223		n = 204		0.001
	32.89 (±73.07)	264.21 (±224.25)	27.45 (±34.36)	−3.83 (±26.71)		26.56 (±65.96)	218.15 (±211.43)	14.45 (±29.70)	74.65 (±115.69)	
TSAT (%)	n = 199		n = 204		0.001	n = 221		n = 205		0.001
	21.42 (±13.84)	12.99 (±16.29)	23.34 (±15.67)	−5.70 (±15.86)		11.69 (±12.62)	20.18 (±15.47)	10.30 (±9.75)	8.77 (±12.73)	
Serum iron (µg/dL)	n = 199		n = 204		0.001	n = 221		n = 205		0.001
	72.44 (±56.64)	10.49 (±57.21)	76.82 (±57.56)	−22.05 (±57.79)		42.34 (±63.16)	35.51 (±66.47)	35.97 (±34.26)	19.54 (±41.08)	
TIBC (µg/dL)	n = 199		n = 204		0.001	n = 221		n = 205		0.001
	327.12 (±60.72)	−81.40 (±46.50)	325.13 (±54.96)	−0.66 (±39.87)		359.19 (±80.82)	−108.62 (±66.18)	368.61 (±67.66)	−60.92 (±51.81)	
Unsaturated IBC (µg/dL)	n = 199		n = 203		0.001	n = 221		n = 205		0.001
	254.69 (±71.11)	−91.89 (±63.18)	248.87 (±73.02)	19.16 (±62.72)		316.85 (±91.82)	−144.13 (±82.37)	332.65 (±78.87)	−80.48 (±68.29)	

* Data are reported as mean (±SD).
IBC = iron-binding capacity; TIBC = total iron -binding capacity.

Primary composite safety endpoint

Seven participants (2.85%) in Group A (FCM), four (1.58%) in Group B (oral iron), 10 (3.95%) in Group C (FCM), and 12 (4.90%) in Group D (IVSC) met the primary composite safety endpoint (Table 6). The most common components of the composite endpoint were death due to any cause (two participants [8%] in Group B [oral iron]) and protocol-defined hypertension (four participants [1.6%] in Group A [FCM], seven [2.8%] in Group C [FCM], and six [2.5%] in Group D [IVSC]). Comparing IV therapies, the proportion of participants meeting the composite safety endpoint was 17 of 499 (3.4%) in the two groups receiving FCM and 12 of 245 (4.9%) in the IVSC group.

Mortality

Four participants died during the study period: two in Group B (oral iron), one in Group C (FCM), and one in Group D (IVSC). One of the deaths in Group B was due to sepsis; the other was reported only as "death." The death in Group C was due to lung cancer with metastases to the brain, and the death in Group D due to an accidental overdose of nonstudy drugs. None of the deaths was considered related to study drug.

Treatment-emergent adverse events

At least one treatment-emergent adverse event was experienced by 28.1% of study participants during the oral run-in phase. The most common (≥5.0%) events reported were constipation (9.6%) and nausea (7.5%). Drug-related treatment-emergent adverse events occurred in 19.0% of participants during the run-in period; events experienced by two or more participants included constipation, nausea, abdominal pain, and diarrhea. The majority of treatment-emergent adverse events were classified as Grade 1 or Grade 2 in severity. Eight (0.5%) participants experienced serious adverse events during the oral run-in phase, none of which was considered related to study drug.

During the treatment phase, at least one drug-related treatment-emergent adverse event was experienced by 22.8% of participants in Group A (FCM), 6.3% in Group B (oral iron), 25.3% in Group C (FCM), and 26.5% in Group D (IVSC). Drug-related events occurring in at least two participants are shown in Appendix Table S3 (available as supporting information in the online version of this paper). The most common events were hypophosphatemia (Group C, 5.5%; Group A, 3.7%), nausea (Group A, 4.1%; Group D, 3.3%), protocol-defined hypotension (Group D, 3.7%), and constipation (Group B, 3.2%). The majority of treatment-emergent adverse events were classified as Grade 1 or 2 in severity.

Serious adverse events were described in eight (3.3%) participants in Group A, 10 (4.0%) in Group B, 17 (6.7%) in Group C, and 16 (6.5%) in Group D during the treatment

TABLE 6. Summary of primary composite safety endpoint (safety population)*

	Cohort 1		Cohort 2	
	Group A: FCM (N = 246)	Group B: oral iron (N = 253)	Group C: FCM (N = 253)	Group D: IVSC (N = 245)
All subjects	7/246 (2.9)	4/253 (1.6)	10/253 (4.0)	12/245 (4.9)
Baseline Hb (g/dL)				
≤9.0	2/23 (8.7)	0/24	4/122 (3.3)	6/120 (5.0)
9.1-10.0	1/48 (2.1)	3/48 (6.3)	3/60 (5.0)	6/60 (10.0)
≥10.1	4/175 (2.3)	1/181 (0.6)	3/71 (4.2)	0/65
Baseline CV risk category				
0-1	5/191 (2.6)	0/185	5/200 (2.5)	6/188 (3.2)
2-3	2/55 (3.6)	4/68 (5.9)	5/53 (9.4)	6/57 (10.5)
Etiology of IDA				
HUB	4/126 (3.2)	0/124	3/111 (2.7)	3/109 (2.8)
GI disorders	0/26	1/27 (3.7)	2/59 (3.4)	5/56 (8.9)
Postpartum	0/3	0/10	0/35	2/42 (4.8)
Nutrition	0/10	0/14	1/4 (25.0)	0/2
Other	3/81 (3.7)	3/78 (3.9)	4/44 (9.1)	2/36 (5.6)

* Data are reported as n/N (%). One Group B (oral iron) subject (310132) had a hypotension event during the oral iron run-in phase that is not reflected in this table.
CV = cardiovascular; GI = gastrointestinal.
Correction added after online publication 17-Jun-2013: Other, Group A: FCM data has been updated.

phase; the majority were Grade 3 or 4. Fourteen participants (two in Group A, three in Group B, five in Group C, and four in Group D) experienced an adverse event that resulted in study discontinuation. The majority of events were considered unrelated to study drug. Hypersensitivity events were reported in 11 participants: three (0.8%) were in Group A (FCM), two (0.8%) were in Group C (FCM), and six (2.4%) in Group D (IVSC). Three of the events were considered serious; all occurred in the IVSC group. No subjects in Group B (oral iron) experienced hypersensitivity.

PCS changes in laboratory values

No clinically important differences were observed among the four groups with respect to the proportions of participants with treatment-emergent PCS hematology values. The proportion of subjects with PCS low phosphorus was greater in the FCM groups (Group A, 53.1%; and Group C, 40.7%) compared with the oral iron group (Group B, 0.4%) and the IVSC group (Group D, 0.9%).

DISCUSSION

In a population of patients with IDA who had an inadequate Hb response to a 14-day run-in of oral iron, or who could not tolerate or were deemed unsuitable for oral iron, therapy with IV FCM was associated with significantly greater increases in Hb levels compared with oral iron therapy. These findings were also observed regardless of baseline Hb measurements or underlying etiology of IDA. In addition, the safety profile of FCM was comparable to that of oral iron, both for the adjudicated primary composite safety endpoint and for the outcomes of death and major cardiovascular events.

In clinical practice, available IV iron preparations are distinguished primarily by the rate at which a maximum single dose can be administered safely and by the associated adverse event profile. Nondextran formulations such as iron gluconate and iron sucrose have dosing limitations that necessitate repeated treatment visits, and bioactive reactions have been reported. FCM, the first third-generation IV iron therapy, is a stable polynuclear iron-hydroxide carbohydrate complex developed as a treatment for iron deficiency. No ionic iron is available to react with proteins, and animal studies have shown an acute toxicity one-fifth that of iron sucrose (data on file, Luitpold Pharmaceuticals). Although the primary outcome in this study was a comparison of FCM with oral iron therapy, the design permitted a post hoc analysis that also demonstrated a significant increase in Hb for FCM compared with IVSC iron replacement.

The safety profile of FCM was generally comparable to that of oral iron, both for the adjudicated primary composite safety endpoint and for the outcomes of death and major cardiovascular events. The only component of the composite that was appreciably higher in the pooled FCM group than the pooled comparators group was protocol-defined hypertensive events, experienced by 11 participants in the pooled FCM group and six in the pooled comparators group. As noted above, when protocol-defined hypertensive and hypotensive events were excluded, only two participants in the FCM groups (0.4%) and five subjects in the comparison groups (1.0%) met the primary composite endpoint.

A higher proportion of participants receiving FCM experienced hypophosphatemia than did those in the oral iron and IVSC groups. A decrease in phosphorus has been observed in other FCM trials, but no adverse events due to symptoms or discontinuations of treatment due to

hypophosphatemia have been reported. Similar decreases in phosphate levels have been observed in trials of FCM in other long-term conditions such as inflammatory bowel disease.[12] FCM transiently increases the levels of the uncleaved, full-length form of fibroblast growth factor 23, a hormone that reduces renal tubular reabsorption of phosphate, leading to temporary reductions in plasma phosphate levels.[15]

The relatively low frequency of drug-related treatment-emergent adverse events in Group B (oral iron, 6.3%) with respect to Group A (FCM, 22.8%) may be explained in part by the trial design: participants in Cohort 1 were preselected for lack of severe reaction to oral iron. In addition, events related to oral iron for participants in Group B that began during run-in would not have been counted as adverse events during treatment phase because the study drug was the same, whereas all drug-related treatment-emergent adverse events in Group A after randomization to FCM were considered new events. When comparing treatment-emergent adverse events in Group C (FCM) with Group D (IVSC), both groups having received IV iron, the overall rates were similar (0.8 and 0%, respectively). This was particularly remarkable because the mean dose of iron administered to Group C (FCM, 1432 mg) was nearly twice that given to Group D (IVSC, 813 mg). Thus, nearly 76% more iron in the form of FCM can be administered in fewer infusions while maintaining a safety profile comparable to that of other IVSC preparations.

One potential limitation arising from the design of our study is the lack of longer-term data on Hb values or patient-reported outcomes that would have been helpful in evaluating the clinical significance of our findings. It is plausible that oral iron may achieve an equivalent increase in Hb at a later date. However, our finding of a nearly flat slope in the graph of the change in Hb from Day 7 to Day 35 in the oral iron group (Fig. 2), as well as the fact that the oral iron group received nearly twice as much iron as the FCM group after randomization raises the question of how long would be considered practicable to wait for a commensurate response to oral iron.

The design of our study permitted an efficacy and safety comparison of switching from oral to IV iron versus continuing oral iron in a scenario that was felt to reflect actual use of parenteral iron in clinical practice for patients who did not respond well to a 2-week trial of oral iron. Thus, the changes in Hb in the oral iron group at Day 35 actually represent the response to 28 to 29 days of oral iron therapy. Furthermore, it has been shown that subjects in this trial who did not respond well to the 2-week run-in of oral iron had significantly higher hepcidin levels than those who did respond well to oral iron.[16] Because hepcidin is known to down regulate levels of the iron transporter ferroportin,[3,4] this suggests that subjects randomized to oral iron would likely exhibit a chronically compromised ability to absorb oral iron from the gastrointestinal tract.

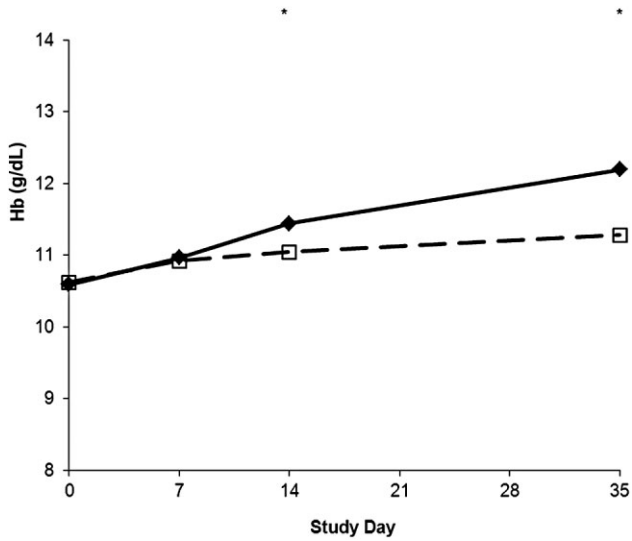

Fig. 2. Change in Hb from Day 7 to Day 35. (—◆—) FCM; (—□ –) oral iron.

Additionally, this study was not designed to make a formal cost comparison among the various therapies. Although oral iron would be expected to be a less expensive alternative to parenteral treatments, factors that would need to be taken into consideration include the relative effectiveness of the therapeutic strategies; the cost of the drugs; and the cost of infusions, potential toxicities, speed of response, and tolerability of the therapies.

Finally, due to the open-label study design, we cannot rule out the possibility of bias. The safety outcomes reported here should thus be interpreted with these limitations in mind, although the composite safety endpoints were assessed by an independent adjudication committee who were blinded to treatment. In conclusion, in this head-to-head trial, FCM administered as two infusions of 750 mg given 1 week apart was safe and effective and should be considered a treatment option for IDA in subjects who have an unsatisfactory response to oral iron, as well as for those who are intolerant of or unsuitable for oral iron replacement.

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CONFLICT OF INTEREST

JEO reports serving as a site principal investigator for trials with Abbott Laboratories, Bristol-Myers Squibb, Centocor, Inc. (Johnson & Johnson), GlaxoSmithKline, and Pfizer, Inc.; as a consultant and steering committee member for the current study

with Luitpold Pharmaceuticals, Inc. (Daiichi Sankyo); as a former Advisory Board member for Marathon Pharmaceuticals; as a data and safety monitoring board member for Bristol-Myers Squibb; and as a stockholder for Schering-Plough Corp. (Merck & Co.). DBB, AB, and TAK are employees of Luitpold Pharmaceuticals, Inc. LTG and DM are consultants to Luitpold Pharmaceuticals, Inc. Complete listings of disclosure information for RAH are available at: https://dcri.org/about-us/conflict-of-interest and at: http://med.stanford.edu/profiles/medicine/frdActionServlet?choiceId=showCOIs&&fid=34240.

None of the other authors reports any conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Study eligibility criteria
Table S2. Administration of 1500 mg of IV iron with currently available iron preparations and FCM
Table S3. Drug-related treatment-emergent adverse events experienced by >2 subjects during treatment phase (safety population)