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Safety and tolerability of intravenous ferric carboxymaltose in patients with iron deficiency anemia

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Abstract

There is limited safety information about ferric carboxymaltose (FCM), a new intravenous iron preparation. This randomized, crossover study compared the safety and tolerability of double-blinded intravenous doses of FCM or placebo in patients with iron deficiency anemia. Subjects (559) with iron deficiency anemia received a dose of either FCM (15 mg/kg, maximum 1000 mg) over 15 minutes or placebo on day 0. On day 7, subjects received the other agent. Safety evaluations were performed on days 7 and 14. The primary endpoint was the incidence of treatment-emergent adverse events during each 7-day study period. During the first 24 hours and during the 7-day treatment period, at least one treatment-emergent adverse event was experienced by 15.0% and 29.3% of subjects after FCM and 11.4% and 19.7% after placebo, respectively. Most were classified as Grade 1 or 2. Six subjects had Grade 3 treatment-emergent adverse events after FCM and 9 subjects after placebo. One subject had a Grade 4, and 1 subject had a Grade 5 treatment-emergent adverse event, but neither was considered study drug-related. During the first 24 hours of the treatment period, drug-related adverse events were reported in 9.3% of subjects receiving FCM and 4.8% receiving placebo. Of drug-related Grade 3 events, 4 subjects received FCM and 5 subjects received placebo. Administration of FCM (15 mg/kg, maximum of 1000 mg) over 15 minutes was well tolerated and associated with minimal risk of adverse reactions in patients with iron deficiency anemia.

Key words: Ferric carboxymaltose, intravenous iron, iron deficiency anemia, safety

INTRODUCTION

Iron deficiency is the most common cause of anemia.[1] Some patient groups are particularly at risk due to malabsorption of dietary iron (e.g., inflammatory bowel disease, gastrointestinal surgery), increased utilization of iron (e.g., pregnancy, lactation, or concurrent use of erythropoiesis-stimulating agents [ESAs]), or blood loss from the body (e.g., menstruation, surgery, hemodialysis, or trauma). Therapy consists of replenishing iron stores and treatment of the underlying disease.[2] The aim of treatment is to increase hemoglobin values, to restore iron stores to normal levels, and to improve quality of life.[3]

Oral iron therapy is usually the first choice for iron repletion. However, parenteral iron supplementation may be indicated in certain clinical situations such as iron malabsorption, blood transfusion avoidance, iron loss, and/or utilization exceeding the rate of replacement with oral treatment, concurrent ESA use (when oral iron is inadequate to support erythropoiesis), when there is a need for rapid delivery of iron (e.g., pregnancy, preoperatively in patients scheduled for autologous blood donation), and in patients intolerant to or noncompliant with oral iron therapy.[4,5]

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Iron dextran, the first parenteral iron product available in the United States, is associated with the development of anaphylaxis and reactions described as allergic and anaphylactoid (e.g., dyspnea, wheezing, hypotension, urticaria, and angioedema). The incidence of these reactions may be as high as 1.7%,[6,7] and over 30 deaths have been attributed to the use of intravenous (IV) iron dextran over the last 20 years despite its decreased clinical use.[6] These reactions are believed to be caused by the formation of antibodies to the dextran moiety. The newer parenteral iron products (iron sucrose and ferric gluconate) do not contain the dextran moiety, and the incidence of allergic reactions with these products is markedly lower.[6] The physicochemical characteristics of iron sucrose and ferric gluconate are different from iron dextran, in that they are less robust and the iron dissociates from the complex at a faster rate. These characteristics tend to limit the dose of iron sucrose and ferric gluconate that can be administered in one injection, and also limit the rate of administration.

Ferric carboxymaltose (FCM) is a type I polynuclear iron (III)–hydroxide carbohydrate complex currently being investigated as a parenteral iron replacement therapy for the treatment of iron deficiency anemia (IDA). Ferric carboxymaltose offers several potential advantages over other currently available parenteral iron preparations. It does not contain dextran or modified dextran and does not react with dextran antibodies, thereby minimizing the risk of allergic reactions (data on file, Luitpold Pharmaceuticals Inc., Norristown, PA, USA). It has a nearly neutral pH (5.0–7.0) and physiological osmolarity and is generally less bioreactive than iron sucrose and ferric gluconate, producing a slow and competitive delivery of the complexed iron to endogenous iron-binding sites (data on file, Luitpold Pharmaceuticals Inc.). The physicochemical characteristics of FCM make it possible to administer much higher single doses over shorter periods of time than iron sucrose or ferric gluconate, resulting in the need for fewer injections to replete iron stores and correct IDA, and consequently may make it better suited for outpatient use.

The purpose of this study was to evaluate the short-term safety and tolerability of a single dose of FCM (15 mg/kg; maximum of 1000 mg) over 15 minutes vs. placebo in a variety of populations with IDA.

METHODS

Study design

This was a phase 3, multicenter, randomized, double-blinded, placebo-controlled, noninferiority, crossover study conducted at 62 sites in the United States. The sites were primarily clinics, and subjects recruited at each site ranged from 1 to 69 patients. This study was performed in accordance with the United States Code of Federal Regulations (CFR) on Protection of Human Subjects (21 CFR 50), Institutional Review Board regulations (21 CFR 56), the 2000 Edinburgh, Scotland Revision of the Declaration of Helsinki, all applicable local and state regulations, 21 CFR Part 312, and applicable International Conference on Harmonization (ICH) guidelines.

All patients with IDA who gave consent and who attended the clinics were screened. All outpatient male or female subjects ≥ 18 years old who met the following criteria were eligible for enrollment: anemia (defined as historical local laboratory hemoglobin ≤ 12 g/dL within the 3 months before the screening visit and screening visit hemoglobin ≤ 12 g/dL) and screening iron indices indicative of iron deficiency. Patients were assigned to 1 of 3 cohorts. Subjects with IDA secondary to anemia of chronic kidney disease (CKD) (including nondialysis-dependent [NDD-CKD], hemodialysis-dependent [HDD-CKD], or peritoneal dialysis-dependent [PDD-CKD]) were assigned to Cohort I. Subjects with IDA secondary to inflammatory bowel disease (IBD) were assigned to Cohort II. Iron deficiency anemia in both Cohorts I and II was defined as a transferrin saturation (TSAT) $\leq 25\%$ and a serum ferritin value < 300 ng/mL. Patients with IDA secondary to other conditions were assigned to Cohort III, where IDA was defined as TSAT $\leq 25\%$ and serum ferritin ≤ 100 ng/mL. Subjects were excluded if they had: previously received FCM or had received parenteral iron in the 4 weeks before screening; had a chronic or serious active infection; malignancy; active inflammatory arthritis; concomitant severe diseases of the liver or cardiovascular system; severe psychiatric disorders; or other conditions, which, in the opinion of the investigator, made participation unacceptable; aspartate aminotransferase or alanine aminotransferase greater than the upper limit of normal; known positive hepatitis B antigen or hepatitis C viral antibody with evidence of active hepatitis; positive human immunodeficiency virus (HIV)-1/HIV-2 antibodies (anti-HIV); current medications for the treatment of bronchospasm; anticipated need for surgery or initiation of dialysis during the study; chronic alcohol or drug abuse within the past 12 months; and hemochromatosis or hemosiderosis. Subjects who were pregnant or sexually active and of childbearing age and were not using hormonal or barrier methods of birth control were excluded. Subjects with hypersensitivity reactions to other iron preparations were permitted to enroll.

Eligible subjects were stratified and randomized in a 1:1 ratio (first dose FCM to first dose placebo). Subjects received a blinded dose of either FCM (American Regent Inc., Shirley, NY, USA) or placebo on day 0. On day 7, subjects were crossed over to receive either placebo or FCM utilizing the same dosing as on day 0. Ferric carboxymaltose was dosed at 15 mg/kg total body weight obtained at the screening visit, with a maximal dose of 1000 mg. Doses of 201 to 500 mg were administered IV in 100 mL normal saline over 15 minutes; doses of 501 to 1000 mg were administered in 250 mL normal saline over 15 minutes. Normal saline was used for placebo (250 mL for weight >33 kg, and 100 mL for <33 kg) administered over 15 minutes IV. All subjects, investigators, and study personnel were blinded to the content of the study drug, except for those responsible for preparing, concealing, and administering the doses. Ferric carboxymaltose is reddish-brown and slightly viscous, and the IV bag and tubing were concealed during administration. Blinded personnel were not present during study drug administration. Other standard therapies, including ESAs, were permitted.

The *completer* population was defined as all subjects in whom doses of both FCM and placebo were attempted. The *safety* population was defined as all subjects who received at least 1 dose of FCM or placebo.

The primary endpoint was the incidence of treatment-emergent adverse events during each 7-day study period. The 7-day study period for Study Period 1 started on day 0 and ended with the initiation of dosing for Study Period 2 (day 7). The 7-day study period for Study Period 2 started on day 7 and ended with the completion of day 14 procedures. Adverse events with missing onset times on days 7 and 14 were assigned to Study Period 2.

The secondary endpoint of the study was the incidence of treatment-emergent adverse events during the 24 hours following each dose.

All adverse events, including allergic reactions, were classified by grade according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.[8] Adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA) Terminology using the stratification of MedDRA System Organ Class, then Preferred Term. If a CTCAE criterion did not exist, individual investigators used the following grade or adjectives:

- Grade 1 or Mild (did not interfere with the subject's usual function).
- Grade 2 or Moderate (interfered to some extent with the subject's usual function).
- Grade 3 or Severe (interfered significantly with the subject's usual function).
- Grade 4 or Life-threatening (resulted in a threat to life or in an incapacitating disability).
- Grade 5 or Death.

Adverse events were classified as serious if they resulted in death, hospitalization, disability, or other medically important events that may have jeopardized the subject or may have required intervention to prevent one of the other outcomes listed above.

Treatment-emergent events were defined as events that started during or after administration of study drug that were not present when the study period began and also included events that were present when the study period began but increased in severity after the study drug was administered.

For drug-related adverse effects, the relationships between drug administration and the adverse events were classified as follows:

- None (no evidence of any causal relationship).
- Unlikely (little evidence to suggest there was a causal relationship).
- Possible (some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event).
- Probable (evidence to suggest a causal relationship, and the influence of other factors was unlikely).

Blinded investigators were responsible for all adverse event assessments. All nonserious adverse events were reported through the completion of the study (day 14) or 7 days after the last treatment. All serious adverse events were reported up to 30 days after the last administration of either study drug or placebo. All drug-related adverse events were followed until the subject had taken a confounding medication or returned to baseline grade. Adverse experiences were elicited by nonspecific questions (e.g., "Have you noticed any problems?"). Any adverse experience spontaneously reported by or elicited from the subject or observed by the investigator or study staff was recorded; the report included severity, the relationship with the study drug, and outcome. Investigators made a judgment as to the clinical significance of any laboratory abnormality. If the laboratory value was felt to represent a clinically significant worsening from the baseline value, it was to be considered an adverse event. For the purposes of this study, anemia (hemoglobin or hematocrit below the normal range or worsened from baseline) and iron deficiency (iron indices below the normal range or worsened from baseline) were not considered adverse events.

Statistics

Descriptive summaries were constructed for primary and secondary endpoints for both safety and completer populations. The primary and secondary endpoints were also summarized for each of the three subject cohorts and were further summarized for each subgroup that included at least 30 subjects (e.g., HDD-CKD, PDD-CKD, NDD-CKD, postpartum anemia, and IBD). A subgroup with fewer than 30 subjects may have been combined with another subgroup if clinically appropriate.

Statistical testing was performed in the completer population. The McNemar test was used to assess differences in the incidence of treatment-emergent adverse events between IV iron and placebo. The presence of period or carry-over effects was assessed descriptively. Clinical laboratory variables were presented in two ways. First, results were summarized for each study drug at the end of the relevant study period (day 7 or 14). Study drug differences in the completer population were assessed by analysis of variance having factors for study drug, sequence, and study period. A descriptive summary was provided for the safety population. Second, the number and proportion of subjects with treatment-emergent abnormal laboratory values were tabulated for each study drug at the end of the relevant study period (day 7 or day 14). The McNemar test was used to assess study drug differences in the incidence of treatment-emergent abnormal laboratory values. All statistical tests were 2-tailed with $\alpha = 0.05$. P values were rounded to 3 decimal places before assessment of statistical significance.

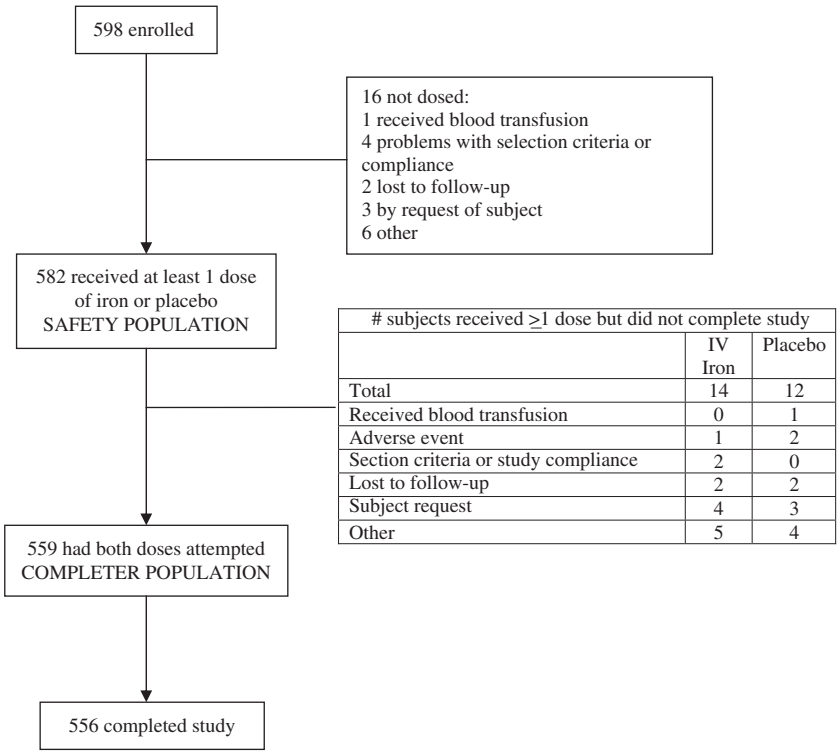
RESULTS

Subject disposition

A total of 598 subjects were enrolled at 62 centers (Figure 1). A total of 582 subjects received at least 1 dose of FCM or placebo and comprised the safety population. A total of 559 subjects had both doses attempted, and comprised the completer population.

Demographic and baseline characteristics

Patient characteristics are shown in Table 1. The majority of subjects in both the completer and the safety populations were female and Caucasian, had no drug allergies, and were included in Cohort III. The mean age, weight, hemoglobin, TSAT, and ferritin values at



# subjects received ≥1 dose but did not complete study		
	IV Iron	Placebo
Total	14	12
Received blood transfusion	0	1
Adverse event	1	2
Section criteria or study compliance	2	0
Lost to follow-up	2	2
Subject request	4	3
Other	5	4

Figure 1 Subject disposition (all randomized subjects).

Table 1 Baseline demographic characteristics of the safety and completer populations

Characteristics	Safety (N=594)	Completer (N=559)
Age (years)		
Mean (SD)	41.9 (16.7)	42.4 (16.8)
Median	39	40
Race		
Caucasian	368 (62.0%)	350 (62.6%)
African American	110 (18.5%)	100 (17.9%)
Hispanic	101 (17.0%)	95 (17.0%)
Other	11 (1.9%)	10 (1.8%)
Asian	4 (0.7%)	4 (0.7%)
Sex		
Female	524 (88.2%)	489 (87.5%)
Male	70 (11.8%)	70 (12.5%)
Cohort/subgroup		
Cohort I/CKD	70 (11.8%)	70 (12.5%)
Cohort II/IBD	64 (10.8%)	63 (11.3%)
Cohort III/	161 (27.1%)	140 (25.0%)
Postpartum		
Cohort III/HUB	122 (20.5%)	119 (21.3%)
Cohort III/other	177 (29.8%)	167 (29.9%)
Drug allergy		
No	384 (64.6%)	363 (64.9%)
Yes	210 (35.4%)	196 (35.1%)
Weight (kg)		
Mean (SD)	80.6 (20.7)	80.7 (21.0)
Median	78.0	78.0
Baseline hemoglobin (g/dL)	(N=593)	(N=558)
Mean (SD)	10.4 (1.2)	10.4 (1.2)
Median	10.6	10.6
Baseline TSAT (%)		
Mean (SD)	9.46 (5.9)	9.49 (6.0)
Median	7.7	7.7
Baseline ferritin (ng/mL)	(N=583)	(N=549)
Mean (SD)	32.9 (50.2)	33.5 (51.3)
Median	13.7	13.6
Iron intolerance		
No	501 (84.3%)	469 (83.9%)
Yes	93 (15.7%)	90 (16.1%)
Previous iron therapy		
No	136 (22.9%)	126 (22.5%)
Yes	458 (77.1%)	433 (77.5%)

CKD=chronic kidney disease; HUB=heavy uterine bleeding; IBD=inflammatory bowel disease; SD=standard deviation; TSAT=transferrin saturation.

baseline were similar in both populations. Most of the subjects in both populations had received previous IV iron therapy and similar numbers had a prior history of iron intolerance.

Extent of exposure

The mean dose of FCM was 962.0 (± 88.2) mg in the completer population and 944.8 (± 154.8) mg in the safety population.

Adverse events

Completer population

During the first 24 hours of the treatment period in the completer population, at least one treatment-emergent adverse event was experienced by 15.0% (84 of 559) of subjects after receiving FCM and 11.4% (64 of 559) after receiving placebo (P=0.066) (Table 2). The percentage of treatment-emergent adverse events was similar in both groups. The most common treatment-emergent adverse events (experienced by ≥1% of subjects) after receiving FCM were nausea (3.0%), headache (3.6%), and dizziness (1.3%). The most common treatment-emergent adverse events experienced by ≥1% of subjects after receiving placebo were diarrhea (1.1%), nausea (1.4%), and headache (2.9%).

During the 7-day treatment period in the completer population, at least 1 treatment-emergent adverse event was experienced by 29.3% (164 of 559) of the subjects after receiving FCM and 19.7% (110 of 559) of the subjects after receiving placebo (P<0.001) (Table 2). The most common (≥1%) treatment-emergent adverse events after receiving FCM were diarrhea (1.3%), nausea (3.8%), pyrexia (1.3%), fatigue (1.3%), ALT increase (1.6%), AST increase (1.6%), headache (5.4%), dizziness (1.8%), and rash (1.1%). The most common (≥1%) treatment-emergent adverse events after receiving placebo were diarrhea (1.6%), nausea (1.8%), and headache (3.4%).

Table 3 shows the incidence of drug-related adverse events in the completer population. During the first 24 hours of the treatment period, at least 1 drug-related adverse event was reported by 9.3% of subjects after receiving FCM and 4.8% of subjects after receiving placebo (P=0.003). The most common (≥1%) drug-related adverse events in subjects receiving FCM were nausea (2.1%), headache (2.0%), and dizziness (1.3%). The most common drug-related adverse events in patients receiving placebo were nausea (1.1%) and headache (1.3%). During the 7-day treatment period, at least 1 treatment-emergent drug-related adverse event was experienced by 13.4% of the subjects receiving FCM and 6.6% of the subjects after receiving placebo (P<0.001). The most common drug-related adverse events in the FCM subjects were nausea (2.5%), ALT increase (1.3%), AST increase (1.3%), headache (2.9%), dizziness (1.6%), and rash (1.1%). The most

Table 2 Treatment-emergent adverse events experienced by ≥1% of subjects in either treatment phase during the first 24 h and 7-d treatment periods (completer population)

	1st 24 h			7 d		
Adverse event[a]	Ferric carboxymaltose (N=559)	Placebo (N=559)	P value	Ferric carboxymaltose (N=559)	Placebo (N=559)	P value
At least 1 treatment-emergent adverse event	84 (15%)	64 (11.4%)	0.066	**164 (29.3%)**	**110 (19.7%)**	**<0.001**
Gastrointestinal disorders	30 (5.4%)	19 (3.4%)	0.101	46 (8.2%)	32 (5.7%)	0.090
Diarrhea	3 (0.5%)	6 (1.1%)	0.317	7 (1.3%)	9 (1.6%)	0.617
Nausea	17 (3.0%)	8 (1.4%)	0.072	**21 (3.8%)**	**10 (1.8%)**	**0.048**
General disorders and administration site conditions	**20 (3.6%)**	**7 (1.3)**	**0.009**	**32 (5.7%)**	**11 (2.0%)**	**0.001**
Pyrexia	2 (0.4%)	**0**	0.157	**7 (1.3%)**	**1 (0.2%)**	**0.034**
Fatigue	**5 (0.9%)**	0	**0.025**	**7 (1.3%)**	**0 (0.0%)**	**0.008**
Infections and infestations	2 (0.4%)	5 (0.9%)	0.257	27 (4.8%)	22 (3.9%)	0.446
Investigations	2 (0.4%)	5 (0.9%)	0.257	17 (3.0%)	10 (1.8%)	0.178
ALT increased	0 (0.0%)	0 (0.0)	0	**9 (1.6%)**	**2 (0.4%)**	**0.035**
AST increased	2 (0.4%)	0 (0.0)	0.317	**9 (1.6%)**	**1 (0.2%)**	**0.011**
Musculoskeletal and connective tissue disorders	8 (1.4%)	4 (0.7%)	0.248	17 (3.0%)	8 (1.4%)	0.072
Nervous system disorders	27 (4.8%)	26 (4.7%)	0.891	45 (8.1%)	30 (5.4%)	0.083
Headache	20 (3.6%)	16 (2.9%)	0.505	30 (5.4%)	19 (3.4%)	0.116
Dizziness	7 (1.3%)	3 (0.5%)	0.206	10 (1.8%)	3 (0.5%)	0.052
Respiratory, thoracic and mediastinal disorders	4 (0.7%)	3 (0.5%)	0.705	7 (1.3%)	4 (0.7%)	0.366
Skin and subcutaneous tissue disorders	**12 (2.1%)**	**4 (0.7%)**	**0.046**	15 (2.7%)	10 (1.8%)	0.317
Rash	5 (0.9%)	1 (0.2%)	0.102	6 (1.1%)	2 (0.4%)	0.157

[a]Adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA) Terminology using the stratification of MedDRA System Organ Class, then Preferred Term.
ALT=alanine aminotransferase; AST=aspartate aminotransferase; NEC=not elsewhere classified.
Bold values indicate statistical significance at $P<0.05$.

common drug-related adverse events in patients receiving placebo were nausea (1.1%) and headache (1.4%).

Safety population

During the 7-day treatment period in the safety population, the majority of the treatment-emergent adverse events experienced were classified by investigators as Grade 1 or 2. Grade 3 treatment-emergent adverse events were experienced by 6 subjects (1.0%) after receiving FCM (arthralgia, migraine, blood phosphorous decreased [N=3], and headache) and 9 subjects (1.6%) after receiving placebo (upper gastrointestinal hemorrhage, endometritis, fall, dehydration, worsening diabetes mellitus, generalized pruritus, hypertension, blood creatinine increased, blood phosphorous decreased [N=3], and rash). The majority of these subjects experienced the Grade 3 treatment-emergent adverse events after the first 24 hours of the treatment period (5 of 6 subjects after receiving FCM and 7 of 9 subjects after receiving placebo). Of those Grade 3 events considered by the investigator to be study drug-related, 4 subjects had received FCM (blood phosphorous decreased [N=3] and headache) and 5 subjects had received placebo (blood creatinine increased, blood phosphorous decreased [N=3], and rash). These results may underestimate the difference from placebo, because the nadir phosphate for subjects in the FCM/placebo treatment sequence sometimes occurred following placebo treatment. One subject was reported as having a Grade 4 treatment-emergent adverse event of intestinal obstruction after receiving FCM, which led to premature discontinuation. One subject was reported as having a Grade 5 treatment-emergent adverse event of Aeromonas pneumonia and died 27 days after receiving FCM. Neither of these Grade 4 or 5 events was considered by the investigator to be study drug-related.

Table 3 Drug-related adverse events experienced by ≥ 1% of subjects in either treatment during the first 24 h or 7 d treatment period (completer population)

	1st 24 h			7 d		
Adverse event[a]	Iron carboxymaltose (N = 559)	Placebo (N = 559)	P value	Iron carboxymaltose (N = 559)	Placebo (N = 559)	P value
At least 1 treatment-emergent adverse event	**52 (9.3%)**	**27 (4.8%)**	**0.003**	**75 (13.4%)**	**37 (6.6%)**	**<0.001**
Gastrointestinal disorders	17 (3.0%)	10 (1.8%)	0.178	21 (3.8%)	12 (2.1%)	0.106
Nausea	12 (2.1%)	6 (1.1%)	0.157	14 (2.5%)	6 (1.1%)	0.074
General disorders and administration site conditions	**12 (2.1%)**	**3 (0.5%)**	**0.020**	**19 (3.4%)**	**3 (0.5%)**	**0.001**
Investigations	2 (0.4%)	5 (0.9%)	0.257	14 (2.5%)	9 (1.6%)	0.297
ALT increased	0 (0.0%)	0 (0.0%)	0	**7 (1.3%)**	**1(0.2%)**	**0.034**
AST increased	1 (0.2%)	0 (0.0%)	0.317	**7 (1.3%)**	**0 (0.0%)**	**0.008**
Musculoskeletal and connective tissue disorders	3 (0.5%)	2 (0.4%)	0.655	6 (1.1%)	3 (0.5%)	0.317
Nervous system disorders	18 (3.2%)	11 (2.0%)	0.194	**26 (4.7%)**	**12 (2.1%)**	**0.023**
Headache	11 (2.0%)	7 (1.3%)	0.346	16 (2.9%)	8 (1.4%)	0.102
Dizziness	**7 (1.3%)**	**1 (0.2%)**	**0.034**	**9 (1.6%)**	**1 (0.2%)**	**0.011**
Skin and subcutaneous tissue disorders	**9 (1.6%)**	**1 (0.2%)**	**0.011**	9 (1.6%)	3 (0.5%)	0.083
Rash	**5 (0.9%)**	**0 (0.0%)**	**0.025**	6 (1.1%)	1 (0.2%)	0.059

[a]Adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA) Terminology using the stratification of MedDRA System Organ Class, then Preferred Term.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; NEC = not elsewhere classified.
Bold values indicate statistical significance at $P < 0.05$.

When treatment-emergent adverse events were summarized by subgroups (IDA etiology, males and females, Caucasian and non-Caucasian, ≤ median weight and > median weight) during the 7-day treatment period, no clinically important differences were observed among subgroups.

During the study, 2 (0.3%) subjects, including the 1 subject who died, experienced at least 1 serious adverse event after receiving FCM and 4 (0.7%) subjects experienced at least 1 serious adverse event after receiving placebo. Only one of these subjects (FCM) reported a serious adverse event (obstruction of the ileum due to Crohn's disease, confirmed by the investigator) during the first 24 hours of the treatment period. None of the subjects in either treatment group reported serious adverse events during the study that were considered by the investigator to be related to the study drug. Of subjects in either treatment group who prematurely discontinued the study drug due to adverse events (1 FCM subject, 2 placebo subjects), none of the adverse events were considered by investigators to be related to the study drug. The three subjects who prematurely discontinued the study drug due to the occurrence of adverse events were also excluded from the study.

No subjects were reported to have treatment-emergent abnormal hematology results.

The proportion of subjects with abnormally low phosphate values was greater after receiving FCM (16.0%) than after receiving placebo (9.9%). These results may underestimate the difference from placebo, because the nadir phosphate for subjects in the FCM/placebo treatment sequence sometimes occurred following placebo treatment. When follow-up phosphate measurements were obtained after abnormally low values, the mean values returned toward baseline levels.

Evaluations of vital signs and physical examinations showed no clinically important differences between subjects treated with FCM and placebo.

DISCUSSION

Historically, with available IV iron products, most adverse events of significance have been dose related and rate related. Therefore, it is important to assess the safety and tolerability of the largest possible single dose that may be available post approval of FCM. For this reason, this

short-term safety study utilizing FCM 15 mg/kg (up to 1000 mg per administration) was conducted.

Studies of IV iron dextran, iron sucrose, and sodium ferric gluconate have reported that these products are commonly associated with injection-site reactions, nausea, and diarrhea. The adverse events of most concern with IV iron products, however, are those associated with anaphylactic or hypersensitivity reactions. These reactions generally involve rash, urticaria, hypotension, dyspnea, and, in the most severe cases, have resulted in shock and/or death. Iron dextran is the product most implicated in this regard, with an estimated risk of immediate, severe anaphylactic reactions of 1.7%. Iron sucrose and sodium ferric gluconate are considered to have a significantly lower risk of severe reactions.[6]

A recent study has provided some insight into the adverse effect profile of ferumoxytol (Advanced Magnetics, Cambridge, MA, USA), a new investigational IV iron product that contains a reduced dextran molecule.[9] One patient in the series of over 700 who received ferumoxytol developed an anaphylactoid reaction (hot flashes and itching). This was an 85-year-old man with severe cardiovascular disease and with multiple drug allergies, and who recovered promptly after administration of epinephrine.

In this study of FCM, no cases of hypersensitivity reactions were observed. The incidence of serious adverse events and premature discontinuations due to adverse events was low and similar between the groups receiving FCM and placebo. In addition, FCM was shown to be well tolerated even though the study included 93 patients (15.7%) who had reported a previous intolerance to iron. Previous studies also support the safety profile of FCM. In 12 clinical studies conducted in over 3500 patients worldwide, there was a numerical imbalance (10 to 1) in mortality between patients receiving FCM (N = 2300) vs. comparators (N = 1200). However, none of the deaths were judged to be related to FCM administration by either the investigators or an independent panel of outside experts.[10] There is strong interest in administration of large single doses of iron products, especially for patients in whom it is impractical to administer the standard low-dose maintenance therapy (100–125 mg) used in hemodialysis patients. The FDA-approved maximum dose for iron sucrose by IV push is 200 mg over 2 to 5 minutes in NDD-CKD patients. For ferric gluconate, the maximum approved IV push dose is 125 mg administered over 10 minutes. Compared with the other IV iron agents, FCM offers the advantage that it can be administered in a much higher maximum dose and rate of infusion.

CONCLUSION

Rapid administration of a single dose of FCM of 15 mg/kg (to a maximum of 1000 mg) over 15 minutes is well tolerated and associated with minimal risk of hypersensitivity or other adverse drug reactions in a wide range of patients with IDA.

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