

A Novel Intravenous Iron Formulation for Treatment of Anemia in Inflammatory Bowel Disease: The Ferric Carboxymaltose (FERINJECT®) Randomized Controlled Trial

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BACKGROUND: Anemia is a common complication of inflammatory bowel diseases (IBD)

AIMS: This multicenter study tested the noninferiority and safety of a new intravenous iron preparation, ferric carboxymaltose (FeCarb), in comparison with oral ferrous sulfate (FeSulf) in reducing iron deficiency anemia (IDA) in IBD.

METHODS: Two hundred patients were randomized in a 2:1 ratio (137 FeCarb:63 FeSulf) to receive FeCarb (maximum 1,000 mg iron per infusion) at 1-wk intervals until the patients' calculated total iron deficit was reached or FeSulf (100 mg b.i.d.) for 12 wk. The primary end point was change in hemoglobin (Hb) from baseline to week 12.

RESULTS: The median Hb improved from 8.7 to 12.3 g/dL in the FeCarb group and from 9.1 to 12.1 g/dL in the FeSulf group, demonstrating noninferiority ($P = 0.6967$). Response (defined as Hb increase of >2.0 g/dL) was higher for FeCarb at week 2 ($P = 0.0051$) and week 4 ($P = 0.0346$). Median ferritin increased from 5.0 to 323.5 $\mu\text{g/L}$ at week 2, followed by a continuous decrease in the FeCarb group (43.5 $\mu\text{g/L}$ at week 12). In the FeSulf group, a moderate increase from 6.5 to 28.5 $\mu\text{g/L}$ at week 12 was observed. Treatment-related adverse events (AEs) occurred in 28.5% of the FeCarb and 22.2% of the FeSulf groups, with discontinuation of study medication due to AEs in 1.5% and 7.9%, respectively.

CONCLUSIONS: FeCarb is effective and safe in IBD-associated anemia. It is noninferior to FeSulf in terms of Hb change over 12 wk, and provides a fast Hb increase and a sufficient refill of iron stores.

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INTRODUCTION

Inflammatory bowel diseases (IBD) are a group of chronic intestinal diseases, including Crohn's disease (CD) and ulcerative colitis (UC), which share a variety of symptoms, such as diarrhea, abdominal pain, fever, and extraintestinal manifestations mostly at joints, skin, and eyes. Anemia is a frequent complication of IBD. At any given point, about one in three patients has reduced hemoglobin (Hb) levels, and every second patient is iron deficient (1). The cause of iron deficiency (ID) has been attributed to chronic blood loss at the ulcer-

ated intestinal mucosa and to impairment of iron intake and uptake (2-4), resulting in a negative iron balance. Common symptoms of anemia and ID are nonspecific, and may include fatigue, headache, or dizziness and reduced cognitive function or ability to work. In severe cases, anemia is a known trigger for hospitalization and prolongation of hospital stays, and is associated with comorbidity (e.g., heart failure) and even mortality (5).

In recent years, oral iron replacement has been questioned in the setting of IBD. Iron absorption is a limited process that may not be able to balance continuous iron loss (6). In the setting of systemic inflammation, elevated hepcidin

levels may further inhibit enterocytic iron transport through internalization of ferroportin (7). On the other hand, non-absorbed iron in the intestinal lumen enhances mucosal inflammation in animal models of colitis (reviewed in (1)). In IBD patients, oral iron therapy was associated with systemic consumption of oxygen scavengers (8) and increase in clinical activity (8, 9). Besides these limitations, intolerance and discontinuation due to side effects are frequent (9, 10). In contrast, intravenous iron replacement, especially iron sucrose (Venofer[®], Vifor Int., St. Gallen, Switzerland), was found to be safe and effective (10–12). The only disadvantage of iron sucrose is the need for repeated infusions, as single doses should not exceed 500 mg/infusion/wk. High-molecular weight iron dextran has the disadvantage of potentially life-threatening dextran-associated anaphylactic reactions (13), and should not be used.

Recently, a novel intravenous iron preparation (ferric-carboxymaltose [FeCarb], FERINJECT[®], Vifor Int., St. Gallen, Switzerland) has been developed. FeCarb can be applied at single doses up to 1,000 mg iron per week, and infusion speed is much higher than for iron sucrose (15 min for 1,000 mg iron compared with 210 min for a 500-mg iron dose). FeCarb builds a stable iron complex; after administration, it is rapidly taken up by the reticuloendothelial system in the spleen, liver, and bone marrow. Single and repeated toxicity studies, pharmacology studies, and local tolerance studies have been performed in several animal models (14). Three phase I studies in a total of 54 human subjects showed that FeCarb is safe and effective for a dosing interval of 500 mg every 3–4 days or 1,000 mg once per week. Two phase II studies in 158 patients found no safety concerns, and found FeCarb to be effective (14). Three phase III studies in a total of 464 patients receiving FeCarb were performed (14), two in women postpartum and one in patients with chronic renal failure. Altogether, FeCarb was well tolerated, and there were no safety concerns.

This study was designed to evaluate the noninferiority and safety of intravenous FeCarb compared with oral ferrous sulfate (FeSulf) (Plastufer[®], ICN Pharmaceuticals GmbH, Fran Kfurt, Germany) in a large multicenter cohort of patients with iron deficiency anemia (IDA) and IBD.

METHODS

The study was conducted according to the Helsinki Declaration (revised version of Hong Kong Declaration) and adhered to Good Clinical Practice guidelines. This multicenter, open-label, randomized, controlled phase III study was globally conducted between June 2004 and May 2005 at 36 sites in eight countries. The ethics committee at each site approved the protocol. This study was run and monitored by PAREXEL International (Berlin, Germany).

Patients

Patients with either CD or UC and IDA (defined by Hb \leq 10 g/dL and transferrin saturation [TfS] $<$ 20%, or serum ferritin $<$ 100 μ g/L) were eligible. The mean Hb level from

two screening visits was used to justify inclusion. The baseline Hb level was drawn on the first day of treatment, and therefore baseline data may differ from inclusion criteria. Inclusion criteria also included signed informed consent, age between 18 and 80 yr, and negative pregnancy test. Due to low recruitment, the inclusion criteria were modified after 4 months (protocol amendment 3, October 2004) to an Hb value of \leq 11 g/dL. Exclusion criteria were: untreated vitamin B₁₂ or folate deficiency, other types of anemia, erythropoietin treatment within 8 wk prior to enrolment, iron replacement therapy, or blood transfusion within 30 days.

Study Medication

The investigational drug was a new formulation of intravenous iron developed by Vifor Int. (St. Gallen, Switzerland). The active ingredient is ferric carboxymaltose (FeCarb), *i.e.*, 50 mg ferric iron (III) per milliliter in water that was diluted in sodium chloride and administered at a maximum rate of 16.7 mL per minute. The iron requirement for patients was individually calculated, according to the formula of Ganzoni (15). A maximum dose of 1,000 mg, or for patients with body weight (BW) below 66 kg, 15 mg/kg BW, was diluted in 250 mL (for doses 500–1,000 mg) or 100 mL (for doses 200–400 mg) sodium chloride. The total dose administered was split across visits, so that a maximal weekly dose of 1,000 mg, or if BW was less than 66 kg, a maximal weekly dose of 15 mg/kg BW, was not exceeded. A maximum of three infusions was permitted (per treatment cycle). A second treatment cycle was applicable in patients in the FeCarb group, if their iron status parameters indicated that IDA recurred in between the end of the first cycle and week 9 of the study. A subsequent treatment cycle could only be initiated a minimum of 2 wk after the last dose of the previous cycle.

The reference therapy was FeSulf containing 100 mg ferrous iron (II). Patients received one capsule *b.i.d.* for 12 wk.

Study Design

The primary objective was to evaluate the noninferiority in efficacy in reducing IDA secondary to IBD. The secondary objectives were to assess the safety and quality of life (QoL). Eligible patients were stratified according to gender and country, and randomized in a 2:1 ratio (FeCarb:FeSulf) using a central randomization system. The randomization sequence was generated by PAREXEL International. The primary end point was defined as change in Hb from baseline to week 12. Secondary end points were change in Hb from baseline to weeks 2, 4, and 8, change in serum ferritin and TfS from baseline to weeks 2, 4, 8, and 12, and the maximum increases in Hb, serum ferritin, and TfS. Further secondary end points were the number and proportion of patients who achieved target levels of Hb (men 13.5–18 g/dL, women 12–16 g/dL), ferritin (100–800 μ g/L), and TfS (20–50%) at weeks 2, 4, 8, and 12, patients whose Hb level increased more than 2 g/dL, as well as patients who discontinued treatment due to lack of response. No *post hoc* analyses are reported.

Table 1. Demographic Data, Baseline Clinical Characteristics, and Concomitant Medications

	ITT		PP	
	FeCarb (N = 136)	FeSulf (N = 60)	FeCarb (N = 111)	FeSulf (N = 49)
Females, N (%)	81 (59.6)	36 (60.0)	68 (61.3)	30 (61.2)
Age, median (range)	40.0 (19–78)	45.0 (20–78)	40.0 (19–78)	47.0 (20–78)
Body mass index, median (range)	21.9 (16.1–35.5)	22.1 (16.2–34.6)	21.9 (16.2–35.5)	22.0 (16.2–30.9)
Smoking “Yes,” N (%)	12 (8.8)	5 (8.3)	9 (8.1)	4 (8.2)
Crohn’s disease, N (%)	40 (29.4)	16 (26.7)	31 (27.9)	13 (26.5)
Ulcerative colitis, N (%)	96 (70.6)	44 (73.3)	80 (72.1)	36 (73.5)
QoL (SF-36) total score, median (range)	93.5 (54–134)	91.2 (50–136)	93.1 (54–134)	91.2 (50–126)
Concomitant medications				
Prednisolone, N (%)	13 (9.5)	4 (6.7)	10 (9.0)	3 (6.1)
Sulfasalazine, N (%)	7 (5.1)	5 (8.3)	7 (6.3)	5 (10.2)
Mesalazine, N (%)	7 (5.1)*	11 (18.3)*	7 (6.3)	6 (12.2)
Azathioprine, N (%)	2 (1.5)	0	1 (0.9)	0

*P = 0.006.

CAI = Colitis Activity Index; CDAI = Crohn’s Disease Activity Index; FeCarb = ferric carboxymaltose; FeSulf = ferrous sulfate; ITT = intention-to-treat; PP = per protocol; QoL = quality of life; SF-36 = 36-item short form.

Follow-Up, Safety, and Efficacy Evaluations

Patients in both groups were evaluated at weeks 0, 2, 4, 8, and 12; patients in the FeCarb group were also evaluated at week 1 if they received a second iron infusion. At each visit, blood tests were performed, and adverse events (AEs) and concomitant medications were recorded. QoL score and disease activity were determined every 4 wk. QoL was assessed using the 36-item short-form (SF-36) (16). Disease activity was assessed using the CD Activity Index (CDAI) for CD and the Colitis Activity Index (CAI) for UC (17, 18). Safety stopping rules for premature discontinuation included: Hb, serum ferritin, or TfS levels above the normal range (Hb 18 g/dL [men] or 16 g/dL [women], serum ferritin >800 µg/L, and TfS >50%) and liver function tests above three times the upper limit of normal.

Statistical Analyses

Sample size calculations indicated that 114 patients were required in the per protocol (PP) set, based on the demonstration of noninferiority, with a margin for the primary efficacy end point of 0.5 g/dL and a standard deviation (SD) of 1.5 g/dL to give 90% power and a 0.025 1-sided significance level. Initially, it was planned to randomize 252 patients to allow for

dropouts from the PP population. However, an interim analysis performed after randomization of 170 patients indicated sufficient statistical power, and recruitment was stopped after 200 randomized patients.

All data were analyzed using descriptive statistics on observed values. For the change in Hb, analysis of covariance (ANCOVA) was used to calculate the 2-sided 95% confidence interval (CI) for the difference “FeCarb minus FeSulf” in Hb change, and noninferiority was concluded if the lower bound was ≥−0.5 g/dL. Treatment groups were compared by a 2-sided χ² test, and P values not exceeding the 5% level were considered as indicative of a treatment difference. Summaries of treatment-emergent AEs were based upon the number and percentage of patients reporting AEs, with Fisher’s exact test for treatment group differences in incidences of AEs by body system.

RESULTS

Patient Characteristics (Tables 1 and 2, Fig. 1)

Of 422 patients screened, 200 underwent randomization. The most common reasons for screening failure are summarized

Table 2. Baseline Laboratory Measures

	ITT		PP	
	FeCarb (N = 136)	FeSulf (N = 60)	FeCarb (N = 111)	FeSulf (N = 49)
Hemoglobin (g/dL)	8.7 (5.0–11.5)	9.1 (5.3–11.1)	8.7 (5.0–11.5)	8.9 (5.3–11.1)
Serum ferritin (µg/L)	5.0 (1–399)	6.5 (1–383)	5.0 (1–102)	5.0 (1–383)
Transferrin saturation (%)*	4.0 (1–32)	6.0 (1–64)	4.0 (1–32)	5.0 (1–64)
Reticulocytes (g/L)	42.5 (3–435)	48.5 (4–384)	44.0 (3–216)	50.0 (4–384)
Platelets (g/L)	382.0 (147–733)	321.5 (109–784)	383.0 (147–733)	327.0 (109–784)
MCV (fL)	72.0 (51–96)	76.0 (52–107)	72.0 (51–96)	74.0 (52–107)
MCHC (g/L)	301.5 (243–353)	304.5 (255–345)	301.0 (243–346)	303.0 (255–345)
White blood cells (g/L)	6.77 (2.9–18.1)	7.05 (2.1–21.2)	6.60 (2.88–18.08)	7.09 (2.1–21.2)
C-reactive protein (mg/L)	4.55 (0.0–71.4)	4.55 (0.0–65.3)	4.50 (0.0–71.4)	5.00 (0.0–65.3)

Data are median (range).

*Not all patients had TfS data at baseline. Data presented for all patients who provided data.

FeCarb = ferric carboxymaltose; FeSulf = ferrous sulfate; ITT = intention-to-treat; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PP = per protocol.

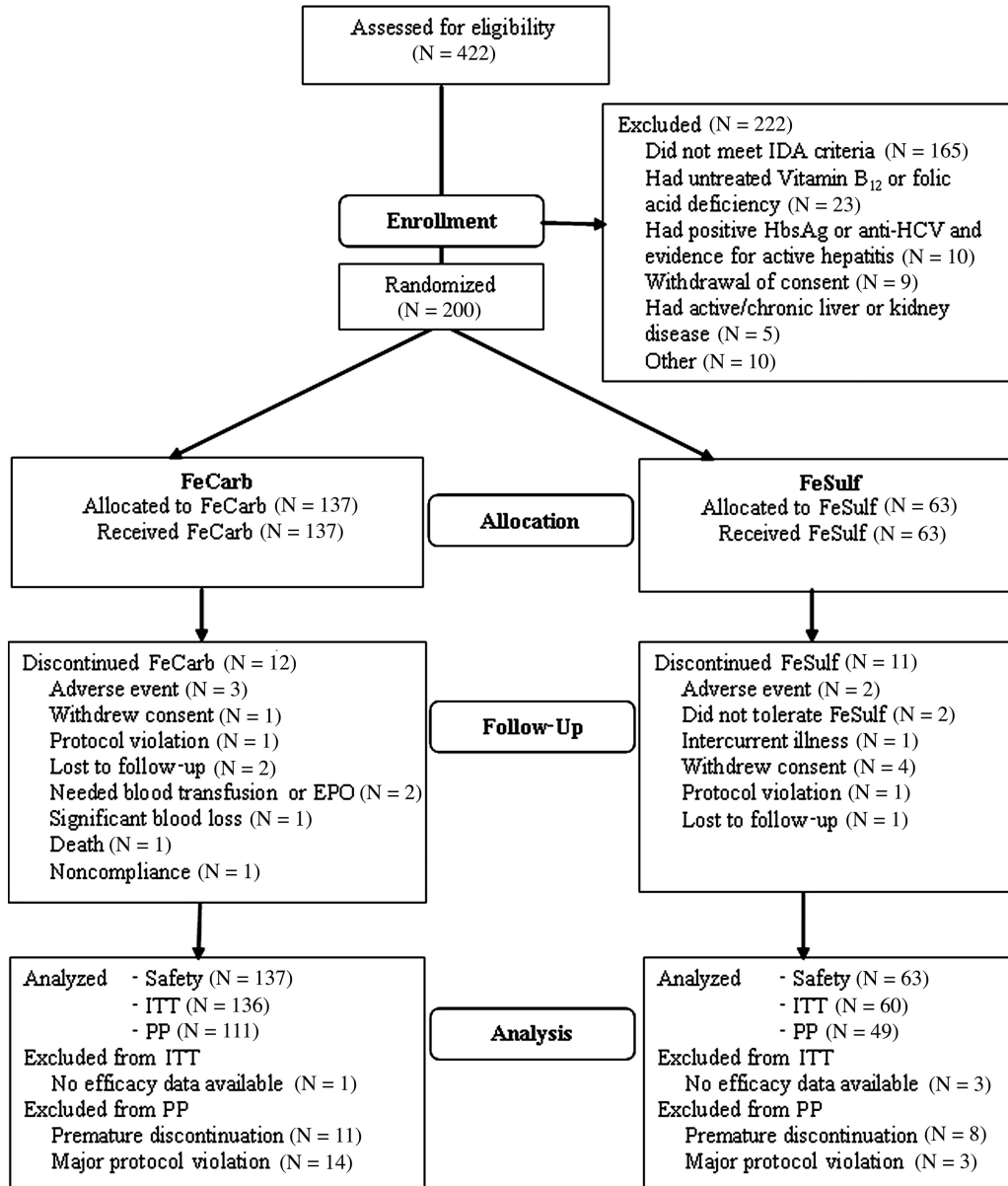


Figure 1. Study flowchart.

in Figure 1. Of the 200 patients randomized (all of whom received at least one dose of study medication), 137 received FeCarb and 63 received FeSulf. Overall, treatment was discontinued prematurely in 23 patients, 12 (8.8%) in the FeCarb group and 11 (17.5%) in the FeSulf group ($P = 0.094$). No patient was discontinued due to lack of treatment efficacy. Four patients withdrew before postbaseline efficacy data were recorded, and were therefore excluded from the intention-to-treat (ITT) set, another 19 did not complete the study because of several reasons (Fig. 1) and were excluded from the PP set. A further 17 patients were excluded from the PP set due to major protocol violations. These included violation of inclusion/exclusion criteria and visits outside allowed time windows. A total of 160 patients were included in the PP analysis. The ITT set has been used to present the efficacy re-

sults. The results for the PP set were similar unless otherwise described.

Generally, baseline characteristics (Table 1) and baseline laboratory measures (Table 2) were comparable in both groups. The median age was slightly higher in the FeSulf group, but was not considered clinically relevant. The most commonly reported concomitant medications during the study were prednisolone, sulfasalazine, and mesalazine; azathioprine was taken by only two patients in the FeCarb group. Infliximab was used at a stable dose in three patients. The proportion of patients taking mesalazine was significantly higher in the FeSulf group than that in the FeCarb group in the ITT set (18.3% vs 5.1%, $P = 0.006$). In the course of the study, in 20 patients, the dose of corticosteroids has been changed, in five patients treatment was discontinued, and in two it was

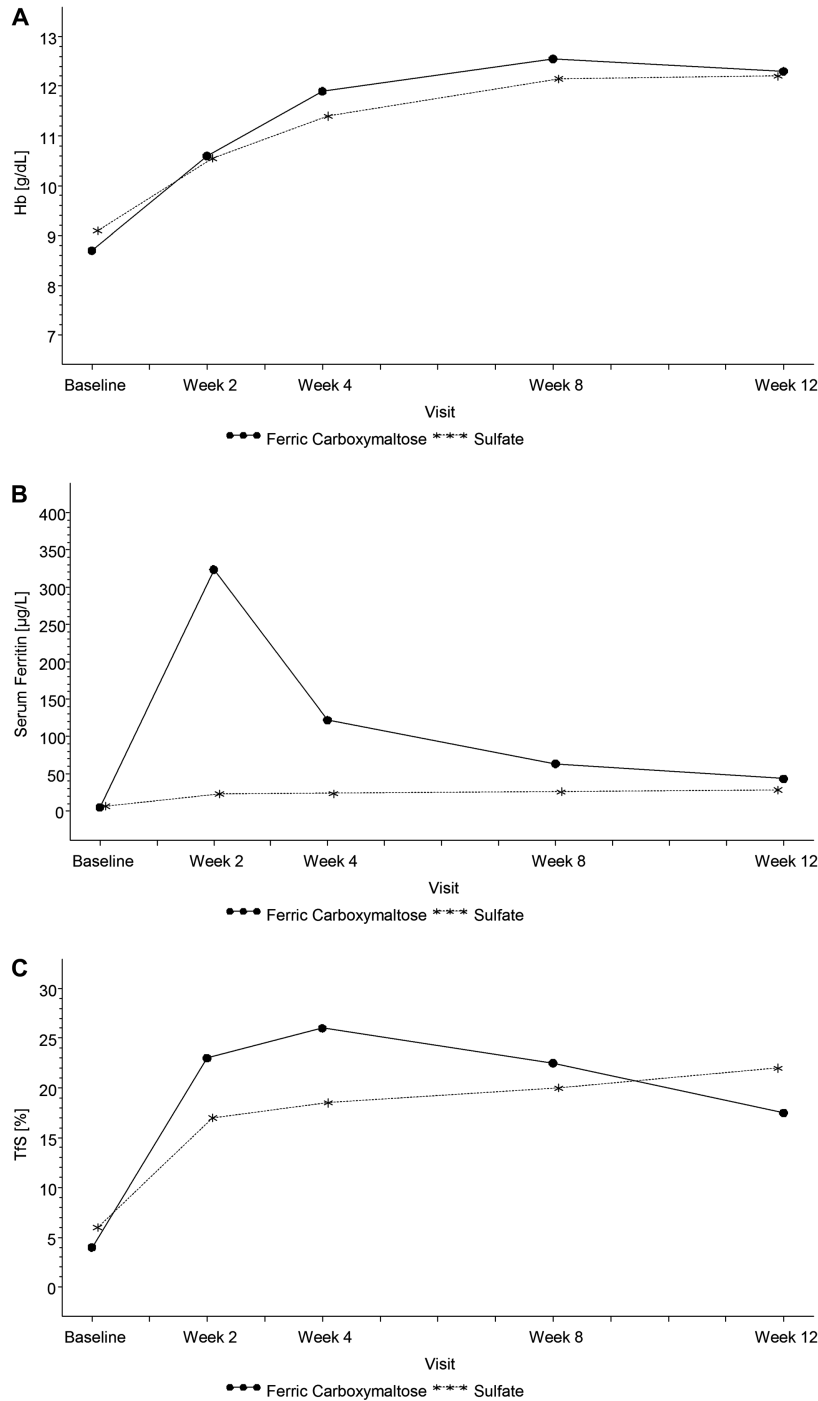


Figure 2. Hemoglobin, serum ferritin, and transferrin saturation over time—ITT set. (A) Median values of hemoglobin over time (g/dL). (B) Median values of serum ferritin over time ($\mu\text{g/L}$). (C) Median values of transferrin saturation over time (%).

started, as well as in one patient treatment with corticosteroids was started and again stopped. Treatment with azathioprine was initiated in one patient.

The median calculated iron deficit was 1,405.5 mg (range 937–2,102 mg) in the FeCarb group and 1,392.0 mg (range 982–1,927 mg) in the FeSulf group. Patients in the oral FeSulf group received 200 mg iron per day for 12 wk (total 16,800 mg), and mean treatment compliance was 99.2%. In the Fe-

Carb group, the majority of patients received two infusions (500–1,000 mg at first infusion). Six patients (two of whom were excluded from the PP set) received two infusions during a second FeCarb treatment cycle (see Methods).

Primary End Point (Figs. 2 and 3)

At baseline, the median (range) Hb value was 8.7 g/dL (5.0–11.5 g/dL) in the FeCarb group and 9.1 g/dL (5.3–11.1 g/dL)

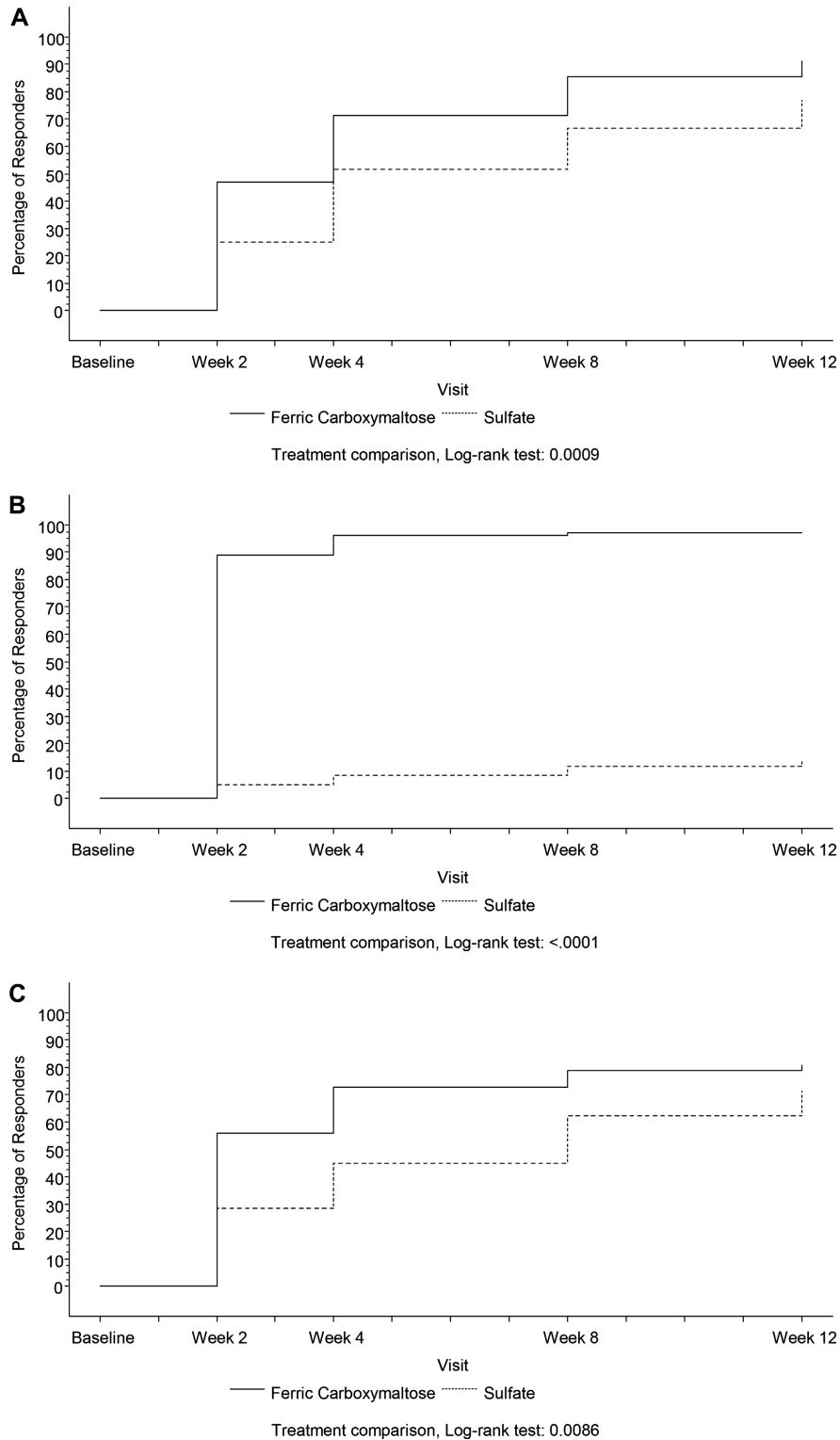


Figure 3. Kaplan-Meier analysis of responder rates for hemoglobin, serum ferritin, and transferrin saturation—ITT set. (A) Time to response with respect to hemoglobin (increase ≥ 2 g/dL). (B) Time to response with respect to serum ferritin (100–800 μ g/L). (C) Time to response with respect to transferrin saturation (20–50%).

in the FeSulf group. After 12 wk, Hb values increased to 12.3 g/dL (6.0–15.9 g/dL) and 12.1 g/dL (6.5–17.4 g/dL), respectively (Fig. 2A). The change from baseline to week 12 in Hb was similar in both treatment groups, with a me-

dian of 3.7 g/dL (–1.8–9.3 g/dL) in the FeCarb group and 2.8 g/dL (range –1.2–8.4 g/dL) in the FeSulf group. FeCarb was noninferior to FeSulf, as demonstrated by ANCOVA of Hb change from baseline to week 12, which showed a lower limit

Table 3. Secondary Efficacy End Points at Week 12

	ITT*		PP*	
	FeCarb (N = 136)	FeSulf (N = 60)	FeCarb (N = 111)	FeSulf (N = 49)
Serum ferritin (μg/L)	43.5 (2–586)	28.5 (2–255)	43.0 (2–586)	29.0 (7–255)
Transferrin saturation (%)	17.5 (2–98)	22.0 (4–112)	20.0 (2–98)	26.0 (5–112)
SF-36 total score	110.3 (48–143)	108.3 (45–137)	110.4 (48–143)	109.2 (45–135)
C-reactive protein (mg/L)	5.00 (0.0–123.0)	2.85 (0.0–59.2)	5.00 (0.0–123.0)	3.00 (0.1–59.2)
95% CI	11.65–19.71	6.33–14.10	10.77–19.62	6.49–15.16

Data are median (range).

*Not all patients provided data at week 12. Data presented for all patients who provided data.

CAI = Colitis Activity Index; CDAI = Crohn’s Disease Activity Index; CI = confidence interval; FeCarb = ferric carboxymaltose; FeSulf = ferrous sulfate; ITT = intention-to-treat; PP = per protocol; SF-36 = 36-item short form.

of the 95% CI of -0.44 g/dL for the ITT set ($P = 0.6967$). Superiority of FeCarb could not be concluded because the lower limit of the CI were below zero. The FeCarb group showed a faster response to treatment, and the percentage of responders (defined as the proportion of the patients with an Hb increase of >2.0 g/dL) was higher in the FeCarb group at week 2 ($P = 0.0051$) and week 4 ($P = 0.0346$). The proportion of responders was similar between treatment groups at week 8 and week 12 (76.5% in the FeCarb group and 68.3% in the FeSulf group at week 12). A Kaplan-Meier analysis of cumulative Hb responder rate over 12 wk demonstrated a statistically significant difference between the treatment groups ($P = 0.0009$, Fig. 3A).

Secondary End Points (Table 3)

At baseline, the median serum ferritin levels were 5 μg/L (range 1–399 μg/L) in the FeCarb and 6.5 μg/L (range 1–383 μg/L) in the FeSulf groups (Table 2). After 12 wk, the median serum ferritin values increased to 43.5 μg/L (range 2–586 μg/L) and 28.5 μg/L (range 2–255 μg/L), respectively (Table 3). Serum ferritin levels increased significantly during FeCarb treatment, and the median serum ferritin in the FeCarb group reached 323.5 μg/L (range 2–3,202 μg/L) at week 2, followed by a steady decrease thereafter (Fig. 2B). In the FeSulf group, there were only modest increases in serum ferritin, with a maximum median value of 28.5 μg/L. The number of responders (defined as the proportion of patients with serum ferritin target levels of 100–800 μg/L) was higher at all weeks in the FeCarb group ($P \leq 0.0002$ at all time points). The final percentage of responders at week 12 was 26.5% in the FeCarb group versus 3.3% in the FeSulf group (Kaplan-Meier analysis $P < 0.001$, Fig. 3B).

TfS increased in both groups from baseline median values of 4% and 6% to values of 23% and 17% at week 2,

respectively, and did not change greatly until the end of the study (Fig. 2C). The percentage of responders (defined as the proportion of patients with TfS 20–50%) was higher in the FeCarb group at week 2 ($P = 0.0006$) and week 4 ($P = 0.0130$), but was similar at week 12 (Kaplan-Meier analysis $P = 0.0086$, Fig. 3C).

SF-36 total scores increased during the study in both treatment groups, indicating improvement in QoL (Tables 1 and 3), with a slightly higher median change from baseline in the FeCarb group than that in the FeSulf group at all time points (+14.1 vs +8.6 at week 12). The clinical activity indices as measured by CDAI and CAI decreased during therapy (Table 4). To better judge the effect of iron replacement on disease activity, scores were also calculated without including Hb or hematocrit counts.

Safety (Table 5)

FeCarb was well tolerated, and the dosing schedule was not associated with any clinically relevant safety concerns. One patient in the FeCarb group died during the study. This patient died following a cardiac arrest 1 day after receiving his first FeCarb infusion. The patient had an ongoing history of aortic valve disease, and the event was considered unrelated to study medication but related to the underlying cardiac disease.

Overall, AEs were experienced by 56.9% (78 of 137) of patients in the FeCarb group and by 42.9% (27 of 63) of patients in the FeSulf group (safety set). Treatment-related AEs were experienced by 28.5% and 22.2% of patients in the FeCarb and FeSulf groups, respectively (Table 5, safety set). In the FeCarb group, AEs considered certainly related were erythematous rash (N = 2), urticaria (N = 2), and pruritus (N = 1). In the FeSulf group, diarrhea (N = 1) was

Table 4. CDAI and CAI: Regular and Adjusted to Hemoglobin/Hematocrit (ITT Set)

Median (Range)	W0		W12	
	FeCarb	FeSulf	FeCarb	FeSulf
CAI	8 (0–14)	7 (0–15)	2 (0–10)	2 (0–17)
CAI without hemoglobin	4 (0–11)	4 (0–11)	2 (0–9)	2 (0–13)
CDAI	217 (72–424)	238 (63–363)	150 (2–436)	143 (45–347)
CDAI without hematocrit	123 (30–316)	142 (0–295)	114 (0–274)	97 (9–269)

CAI = Colitis Activity Index; CDAI = Crohn’s Disease Activity Index; FeCarb = ferric carboxymaltose; FeSulf = ferrous sulfate.

Table 5. Tolerability

%(N)	FeCarb (N = 137)	FeSulf (N = 63)
At least one treatment-related AE*	28.5 (39)	22.2 (14)
At least one serious AE	6.6 (9)	0.0 (0)
At least one AE leading to study medication discontinuation	1.5 (2)	7.9 (5)
Premature study termination due to AE	2.2 (3)	3.2 (2)
Death	0.7 (1)	0.0 (0)
Most commonly reported treatment-related AE (>2% of patients overall)*		
Abdominal pain	2.9 (4)	3.2 (2)
Nausea	2.2 (3)	4.8 (3)
Headache	2.9 (4)	1.6 (1)
Diarrhea	0.7 (1)	6.3 (4)

*Includes all events considered at least possibly, probably, or certainly treatment related. AE = adverse event.

considered certainly related. AEs of hypersensitivity, erythematous rash, and urticaria were mostly experienced by patients in the FeCarb group rather than those in the FeSulf group (9 [6.6%] patients vs 1 [1.6%] patient, respectively); these events were all of mild or moderate intensity, and most occurred after the first dose of study medication. Generally, the lack of recurrence after rechallenge indicated that these events were not due to immunological reactions to FeCarb. There were no cases of anaphylactic shock/reaction. One patient in the FeCarb group experienced tachycardia at week 1 (considered possibly treatment related), but this event did not recur with rechallenge.

A higher proportion of patients in the FeSulf group discontinued study medication due to an AE (2 [1.5%] patients in the FeCarb group vs 5 [7.9%] patients in the FeSulf group, $P = 0.057$). AEs leading to discontinuation of study medication were erythematous rash and small intestinal hemorrhage (1 patient each) in the FeCarb group and flare of UC, diarrhea, asthma, vomiting, and gastrointestinal pain (1 patient each) in the FeSulf group. One further patient in the FeCarb group was withdrawn from the study 3 wk after completion of dosing due to tachycardia, flare of UC, and anemia. Serious AEs were experienced by nine (6.6%) patients in the FeCarb group, and by no patient in the FeSulf group. These were hospitalization due to intestinal bleeding ($N = 1$), small intestine hemorrhage ($N = 1$), flare of autoimmune hepatitis ($N = 1$), anemia ($N = 2$), electrolyte depletion ($N = 1$), rectal cancer ($N = 1$), cardiac arrest, as described above ($N = 1$), and hospitalization due to Port-a-Cath implantation ($N = 1$). All of these AEs were considered unrelated or unlikely to be related to study medication. There were no statistically significant differences between the two treatment groups in the overall AE profile ($P = 0.0693$, Fisher's exact test).

There were no clinically relevant changes in vital signs or physical examinations during the study. Transient elevations in liver enzymes were observed in a minority of patients in the FeCarb group. Dangerously high levels of serum ferritin and TfS, indicating iron intoxication, were not observed.

DISCUSSION

ID is the most common and widespread nutritional disorder in the world. Apart from affecting a large number of children and women in developing countries, it is the only nutrient deficiency that is also significantly prevalent in industrialized countries. Certain disorders, such as IBD, that are associated with chronic blood loss are prone to develop into IDA. This study was designed to evaluate intravenous FeCarb for treatment of IBD-associated IDA in a large multicenter setting. In contrast to most controlled trials, which test for superiority of a drug by using a placebo group, this trial tested for noninferiority because it is considered unethical to include a placebo in patients with severe ID. Noninferiority of FeCarb to FeSulf was statistically proven at week 12 in the ITT and the PP population. In fact, when secondary end points, such as response at earlier points in time or rate of Hb increase, were analyzed, FeCarb was superior to FeSulf. As the main outcome parameter is an objective measure, which is not subject to influence by patients or physicians, our findings are considered sound and reliable despite the nonblinded trial design. This might not be completely true for subjective parameters, such as QoL or disease activity measurements, that, as such, are influenced by patients' perception. The CDAI and CAI scores reflected mild-to-moderately active disease; however, as the anemia was accounting for most of the score, disease activity was generally mild and only a few patients received concomitant medications.

The therapeutic efficacy of FeCarb is further underlined by its excellent safety record. This trial did not reveal any unexpected allergic AEs, as observed with iron dextran. Not a single case of anaphylaxis was observed in the set of 137 patients treated with FeCarb. In a few patients, transient tachycardia, headache, rash, or urticaria was reported, but none of these were observed during re-exposure, and none of these events were considered as severe in intensity. Further unpublished safety data from FeCarb include administrations of up to 1,000 mg iron in over 2,000 patients with no evidence of any treatment-related serious AEs. Of course, the risk of iron overload exists with any parenteral iron compound. After

intravenous iron therapy, serum ferritin levels are known not to correlate with the body iron stores but rather overestimate those (19). Accordingly, serum ferritin levels increased immediately after the FeCarb, but normalized during the study period. In IBD, iron overload is not clinically relevant as patients lose excess iron through continuous intestinal bleeding within short periods of time.

When analyzing AEs that were considered potentially related to any of the study treatments, abdominal complaints were more frequently observed with FeSulf. In this trial, however, the number of patients who discontinued treatment due to AEs was unexpectedly low, as FeSulf intolerance is expected to occur in at least 25% of IBD patients (9, 20). As patients with a history of iron intolerance were excluded, selection bias for iron-tolerant patients may play an important role in such randomized trials (10). Nevertheless, much evidence from animal models and humans links oral iron therapy with an increase in oxidative stress (8) (through iron-induced generation of hydroxyl radicals), worsening of mucosal inflammation (9) and disease activity (21), and induction of colon carcinogenesis (reviewed in (1)). In some areas of the world, the oral iron dose (200 mg) may be considered low, as standard regimens up to 3×200 mg exist (e.g., in the United Kingdom). Recent guidelines on the diagnosis and treatment of anemia in IBD (22), however, suggest a low oral iron dosage, as it should result in fewer side effects without losing efficacy. On the other hand, the FeCarb dose, as calculated by Ganzoni's formula, did not fully refill iron stores, indicated by the fact that most ferritin levels were below 100 $\mu\text{g/L}$ at the end of the study. This should be taken into account when using Ganzoni's formula in the future.

Most data on intravenous iron therapy in IBD exist on iron sucrose. Studies mostly used 200 mg for single infusions once or twice a week (11, 12, 21, 23, 24). Recently, a single 500-mg infusion was safely administered in 31 CD patients (25), and in a randomized controlled trial in another 22 IBD patients followed by weekly infusions of 200 mg (10). Though guidelines in IBD do not exist, recommendations are currently based on data from patients with renal failure that consider weekly infusions of 300 mg as safe (5, 26). This compares with the 1,000 mg of FeCarb that has been safely administered during this trial. The advantage of FeCarb is a combination of both a sufficient single dose and a fast administration (15 min vs 60–210 min with iron sucrose, depending on the respective dose). Chemically, iron sucrose is considered a semilabile iron–sugar complex that allows some of the iron to bind to transferrin immediately after infusion, while FeCarb is a stable complex that needs to be taken up by macrophages before iron is released to transferrin and made available for erythropoiesis. In the setting of chronic inflammation, however, hepcidin is a factor that not

only inhibits iron absorption but also inhibits the iron release from macrophages (27, 28). This is a theoretical advantage of iron sucrose over FeCarb. When comparing the speed of Hb increase from this study with data from a large multicenter trial with iron sucrose (12), FeCarb, however, was superior, with a median Hb increase after 4 wk of 3 g/dL over 2.2 g/dL in the iron sucrose-treated group. The retrospective nature and differences in inclusion criteria, however, make such a comparison unreliable. A direct comparison of drug efficacy and drug economy of FeCarb and iron sucrose will solve this question.

In conclusion, FeCarb is a novel and safe iron–sugar complex that allows convenient administration of up to 1,000 mg iron within 15 min, and which is effective in the treatment of IBD-associated anemia. FeCarb provides a fast Hb increase and a refill of iron stores with few gastrointestinal side effects.

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STUDY HIGHLIGHTS

What Is Current Knowledge

- Iron deficiency anemia (IDA) is very common in inflammatory bowel disease (IBD).
- Anemia has a great impact on quality of life.
- Only a few data on the efficacy and safety of iron compounds are available, mostly from small, uncontrolled series.

What Is New Here

- We test the novel intravenous iron compound iron carboxymaltose for treatment of anemia in IBD.
- This is the largest study ever comparing two different iron preparations.
- We found iron carboxymaltose to be safe and effective in treating IDA in IBD.
- Up to 1,000 mg per infusion can be given with an infusion duration of 15 min.

APPENDIX

The following institutions and local principal investigators participated in this study:

Country	Principal Investigator	Institution	Recruitment
Argentina	Sambuelli, AM	Hospital de Gastroenterología "Dr Carlos Bonorino Udaondo," Capital Federal	2 (1.0%)
	German, JC	Centro Integral de Diagnóstico y Tratamiento en Gastroenterología, Córdoba	2 (1.0%)
Austria	Gasche, C	Medical University of Vienna, Vienna	12 (6.0%)
Belgium	D'Haens, G	Imeldaziekenhuis, Bonheiden	2 (1.0%)
	Van Assche, G	UZ Gashuisberg, Leuven	1 (0.5%)
Bulgaria	Zachary, K	Multi-Profile Hospital for Active Treatment "St. Ivan Rilski," Sofia	2 (1.0%)
	Akrabova, P	Multi-Profile Hospital for Active Treatment "St. Georgi," Plovdiv	2 (1.0%)
	Vassileva, G	Multi-Profile Hospital for Active Treatment—Russe, Russe	9 (4.5%)
	Kotsev, I	Multi-Profile Hospital for Active Treatment "St. Marina," Varna	6 (3.0%)
	Naidenov, N	Multi-Profile District Hospital for Active Treatment "Dr. Stefan Cherkezev," Veliko Tarnovo	5 (2.5%)
	Stoinov, S	Multi-Profile Hospital for Active Treatment "Queen Joanna," Sofia	15 (7.5%)
	Takov, D	Military Medical Academy, Sofia	4 (2.0%)
Mexico	Uscanga Dominguez, LF	Ins. Nacional de Ciencias Médicas y Nutrición, Tlalpan	1 (0.5%)
	Chaires Garcia, L	Hospital Central Dr. Ignacio Morones Prieto, Mexico City	2 (1.0%)
Poland	Malecka-Panas, E	Klinika Chorob Przewodu Pokarmowego, Łódź	4 (2.0%)
	Kleczkowski, D	Centrum Medyczne SOPMED, Sopot	3 (1.5%)
	Karnafel, W	Katedra i Klinika Gastroenterologii, Warsaw	10 (5.0%)
Russian Federation	Świtkowski, M	Wojewodzki Szpital, Bydgoszcz	7 (3.5%)
	Gutman, E	Regional Clinic Hospital, St. Petersburg	1 (0.5%)
	Grinevich, V	St. Elisabeth City Hospital, St. Petersburg	4 (2.0%)
	Baranovskiy, A	City Hospital N31, St. Petersburg	9 (4.5%)
	Khrustalev, O	Regional Hospital, Yaroslavl	1 (0.5%)
	Yakusevich, V	Solovyov Hospital, Yaroslavl	1 (0.5%)
	Yurkov, M	Municipal Hospital #24, Moscow	11 (5.5%)
	Alexeeva, O	City Clinical Hospital #33, Nizhny Novgorod	13 (6.5%)
Ukraine	Minushkin, O	Municipal Hospital #51, Moscow	1 (0.5%)
	Simanenkov, V	City Hospital N26, St. Petersburg	14 (7.0%)
	Pérez Ravier, RR	Hospital Italiano de Mendoza, Mendoza	2 (1.0%)
	Stepanov, YM	Medical Academy, Dnipropetrovsk	7 (3.5%)
	Svintsitsky, AS	National Medical University, Kiev	11 (5.5%)
	Dudar, L	Crimean Medical University, Simferopo	12 (6.0%)
	Pertseva, T	Medical Academy, Dnipropetrovsk	5 (2.5%)
	Levchenko, EM	Regional Clinic Hospital, Odessa	9 (4.5%)
	Fadeenko, G	Research Institute of Therapy, Kharkov	3 (1.5%)
	Kharchenko, NV	Kiev Medical Academy Postgraduate Education, Kiev	4 (2.0%)
Vdovichenko, VI	Medical University, Lviv	3 (1.5%)	

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CONFLICT OF INTEREST

Guarantor of the article: Christoph Gasche, M.D.
Specific author contributions: Stefanie Kulnigg contributed to the collection of data, performing the study, and drafting the manuscript. Christoph Gasche contributed to designing the study, collection of the data, performing the study, and editing the manuscript. Simeon Stoinov, Vladimir Simanenkov, Larisa V. Dudar, Waldemar Karnafel, Luis Chaires Garcia, Alicia M. Sambuelli, and Geert D'Haens contributed to the collection of data and performing the study. All authors approved the final version of the manuscript.
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