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Ferric Maltol Is Effective in Correcting Iron Deficiency Anemia in Patients with Inflammatory Bowel Disease: Results from a Phase-3 Clinical Trial Program

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Background: Iron deficiency anemia (IDA) is frequently seen in inflammatory bowel disease. Traditionally, oral iron supplementation is linked to extensive gastrointestinal side effects and possible disease exacerbation. This multicenter phase-3 study tested the efficacy and safety of ferric maltol, a complex of ferric (Fe³⁺) iron with maltol (3-hydroxy-2-methyl-4-pyrone), as a novel oral iron therapy for IDA.

Methods: Adult patients with quiescent or mild-to-moderate ulcerative colitis or Crohn's disease, mild-to-moderate IDA (9.5–12.0 g/dL and 9.5–13.0 g/dL in females and males, respectively), and documented failure on previous oral ferrous products received oral ferric maltol capsules (30 mg twice a day) or identical placebo for 12 weeks according to a randomized, double-blind, placebo-controlled study design. The primary efficacy endpoint was change in hemoglobin (Hb) from baseline to week 12. Safety and tolerability were assessed.

Results: Of 329 patients screened, 128 received randomized therapy (64 ferric maltol-treated and 64 placebo-treated patients) and comprised the intent-to-treat efficacy analysis: 55 ferric maltol patients (86%) and 53 placebo patients (83%) completed the trial. Significant improvements in Hb were observed with ferric maltol versus placebo at weeks 4, 8, and 12: mean (SE) 1.04 (0.11) g/dL, 1.76 (0.15) g/dL, and 2.25 (0.19) g/dL, respectively ($P < 0.0001$ at all time-points; analysis of covariance). Hb was normalized in two-thirds of patients by week 12. The safety profile of ferric maltol was comparable with placebo, with no impact on inflammatory bowel disease severity.

Conclusions: Ferric maltol provided rapid clinically meaningful improvements in Hb and showed a favorable safety profile, suggesting its possible use as an alternative to intravenous iron in IDA inflammatory bowel disease.

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Key Words: iron deficiency anemia, inflammatory bowel disease, ulcerative colitis, Crohn's disease, ferric maltol

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Anemia is a frequent complication of inflammatory bowel disease (IBD) estimated to occur in more than 70% of patients with Crohn's disease (CD) or ulcerative colitis (UC).¹⁻³ Iron deficiency is the most common cause of anemia in IBD and arises due to insufficient dietary intake, malabsorption, chronic inflammation, and/or intestinal bleeding.⁴⁻⁶ Iron deficiency anemia (IDA) in IBD has been shown to have important detrimental effects on patient's day-to-day functioning, with a wide range of clinical symptoms and psychosocial impairments including fatigue, headache, dizziness, shortness of breath, tachycardia, reduced cognitive function, depression, and decreased ability to work.^{4,5,7} Alone or in combination, these symptoms substantially impair quality of life (QoL) and, in severe cases, can lead to hospitalization and serious comorbidities.^{1,8-10}

Oral ferrous (Fe^{2+}) iron preparations such as ferrous sulfate, ferrous gluconate, and ferrous fumarate have traditionally been used to treat IDA-associated with IBD and a range of other conditions including nutritional deficiency, chronic kidney disease, and obstetric and gynecological conditions.^{6,11} However, a major difficulty with oral ferrous iron salts is that a large proportion of the administered iron is not absorbed and subsequently undergoes oxidation in the gut lumen and/or mucosa. This leads to the generation of reactive oxygen species, which can damage the intestine and cause a range of adverse gastrointestinal effects such as abdominal pain, nausea, diarrhea, and constipation.^{7,12-14} Poor gastrointestinal tolerance and the potential risk of an IBD flare after oral iron supplementation can reduce patient compliance with oral ferrous iron-based therapy.^{2,15,16}

The intestinal mucosa in patients with IBD is particularly sensitive to iron ingestion.^{2,17-19} Experimental and clinical data suggest that reactive oxygen species derived from oral ferrous iron might lead to re-activation or worsening of IBD, although clinical trial findings are not consistent in this respect.^{17,20-24} Nevertheless, based on accumulated knowledge, the labeling for a number of branded ferrous sulfate- and ferrous fumarate-based formulations in a number of countries now carries contraindications or special warnings regarding their use in patients with IBD.

For all patients with IDA, and for patients with IBD in particular, there is an ongoing need for well-tolerated oral iron therapies that rapidly normalize hemoglobin (Hb) without adversely affecting IBD activity.^{4,5} Current guidelines for treating IDA in patients with clinically active IBD address well-known drawbacks of oral therapy with ferrous iron salts, including poor gastrointestinal tolerability, slow treatment effects, and a potential for disease worsening.⁶ In Europe, intravenous iron is recommended for the treatment of patients with IBD with previous intolerance to oral iron and those with severe anemia ($\text{Hb} < 10 \text{ g/dL}$).^{6,25} Although intravenous iron is undoubtedly effective in correcting anemia, it is associated with higher health care costs and the inconvenience of intravenous infusion,^{1,6,26} with a small risk of anaphylactic reactions.²⁷⁻²⁹

Ferric maltol is a novel oral iron therapy based on a stable complex of ferric (Fe^{3+}) iron with maltol (3-hydroxy-2-methyl-4-pyrone), a naturally occurring sugar derivative that has been used for many years as a food additive.³⁰ After oral ingestion of ferric

maltol, ferric iron reaches the intestinal mucosa in complex form, which is believed to allow more efficient uptake of elemental ferric iron into enterocytes compared with ferrous iron salts.³¹⁻³³ In addition, iron uptake can be achieved at a relatively low daily oral iron dose.³⁴⁻³⁶ Early, experimental data indicate a clear potential for ferric maltol to provide effective oral iron treatment with a substantially reduced risk of gastrointestinal side effects compared with ferrous salts.^{31-33,37,38} A 12-week open-label, uncontrolled proof-of-concept study assessed the efficacy and tolerability of ferric maltol in a mixed cohort of patients with and without IBD with IDA and documented intolerance to ferrous sulfate.³⁹ Ferric maltol increased mean Hb from $10.6 \pm 1.5 \text{ g/dL}$ at baseline to $12.6 \pm 1.6 \text{ g/dL}$ after 12 weeks, and safety monitoring indicated a favorable tolerability profile.³⁹

Here, we report data from a phase-3 clinical trial program assessing the efficacy and tolerability of ferric maltol during the treatment of IDA over 12 weeks in patients with IBD who were known to be intolerant of, or unresponsive to, available oral ferrous iron preparations.

METHODS

Study Design

This phase-3 clinical trial program comprised 2 identical clinical trials that evaluated patients with UC and CD according to a 12-week, randomized, double-blind, placebo-controlled, multicenter study design. As UC and CD represent the major subgroups of IBD, data from both trials were prospectively collected and analyzed as a single data set based on a predefined statistical analysis plan, which was devised after consultation with regulatory authorities.

The program was conducted across centers in Austria, Germany, Hungary, and the United Kingdom between August 2011 and December 2013. After a 7- to 14-day screening period, all patients underwent 12 weeks of randomized, double-blind treatment. Randomization to either ferric maltol or placebo was conducted through an interactive voice response system according to a centralized randomization list (SAS v9.2). Patients and all sponsor, clinical research and clinical staff were blinded to the randomization code until all randomized trial processes were complete.

Patients

Patients were males or females aged ≥ 18 years with a confirmed diagnosis of UC or CD. All patients were required to be in remission or to have a mild-to-moderate disease activity of either UC (as defined by a Simple Clinical Colitis Activity Index [SCCAI] score < 4 at screening and randomization) or CD (as defined by a Crohn's Disease Activity Index [CDAI] score of < 220 at randomization). All patients were required to have mild-to-moderate IDA, as defined by an Hb concentration $\geq 9.5 \text{ g/dL}$ and $< 12.0 \text{ g/dL}$ for females and $\geq 9.5 \text{ g/dL}$ and $< 13.0 \text{ g/dL}$ for males⁴⁰ and serum ferritin levels $< 30 \mu\text{g/L}$ at screening. Patients were also required to have previously failed on treatment with oral ferrous products (OFP) for 1 or more of the following reasons: (1) adverse drug effects that led to withdrawal from OFP

(at least one of nausea, diarrhea, constipation, abdominal pain, flatulence); (2) deterioration of the primary disease caused by OFP; (3) lack of efficacy; and (4) other signs of failure of OFP (or documented reasons why OFP could not be used).

Patients receiving protocol-allowed immunosuppressive and immunomodulatory agents (i.e., thiopurines and antitumor necrosis factor) at screening were required to have been on a stable dose for ≥ 4 weeks before randomization. Patients with anemia unrelated to iron deficiency or who had received depot iron preparations, erythropoietin, or blood transfusions within 12 weeks of screening were excluded. Other reasons for exclusion were oral iron treatment within 4 weeks of randomization; treatment with immunosuppressants known to induce anemia (e.g., methotrexate, cyclosporin A, tacrolimus); folate deficiency, uncorrected vitamin B₁₂ deficiency; serum creatinine > 2.0 mg/dL (176 μ mol/L); abnormal liver function tests; and pregnancy.

Treatment

After screening, enrolled patients were randomized in a 1:1 ratio to receive either oral ferric maltol or placebo for 12 weeks. Previously published data suggested that in a compliant study population, 60 mg per day of ferric maltol, administered in 2 divided doses (30 mg twice a day), would result in correction of baseline anemia in the majority of subjects.³⁹ Ferric maltol was therefore supplied in hard orange gelatin capsules, each containing 231.5 mg of ferric maltol (equivalent to 30 mg of elemental iron), to be taken orally on an empty stomach with water first thing in the morning before breakfast and last thing at night (twice a day dosing). Placebo capsules were identical in appearance to ferric maltol and were administered similarly. All study medication was packaged in white polypropylene secure containers and was supplied to patients in study drug kits that were identified by unique numbers from the randomization list. Treatment compliance was evaluated by capsule count at the end of each month (weeks 4, 8, and 12); Patients were considered non-compliant with the study medication if they were $< 80\%$ or $> 100\%$ compliant with the dosage schedule.

Assessments

Both primary and secondary efficacy assessments focused on changes in Hb concentration, as evaluated during routine laboratory measurements at randomization (baseline) and weeks 4, 8, and 12. All laboratory measurements were performed at a central laboratory. The primary efficacy endpoint was change in Hb concentration from baseline to week 12. Secondary efficacy endpoints included changes in Hb concentration from baseline to weeks 4 and 8, serum ferritin concentration, and percentage transferrin saturation (TSAT). A responder analysis was also conducted, where responders to treatment were defined as patients who achieved increases in Hb of ≥ 1 g/dL or ≥ 2 g/dL, or Hb normalization by week 12. Normalization of Hb was defined based on Hb values ≥ 12 g/dL for females or ≥ 13 g/dL for males.⁴⁰

Clinical symptoms were evaluated at randomization and weeks 4, 8, and 12 using the SCCAI⁴¹ in patients with UC and the CDAI⁴² in patients with CD. Disease-specific QoL was assessed

at randomization and week 12 using country-specific, validated versions of the Inflammatory Bowel Disease Questionnaire (IBDQ).^{43,44} General QoL was also assessed based on the 36-item Short-Form (SF-36) questionnaire.⁴⁵

Safety and tolerability were assessed based on adverse events (AEs) (recorded according to MedDRA preferred terms⁴⁶), vital signs measurements, and routine hematological and blood chemistry indices. Patients who developed Hb concentrations ≤ 8.5 g/dL and/or flare-up of UC (as defined by an SCCAI score ≥ 5) or CD (as defined by a CDAI score ≥ 320) were to be withdrawn from the study to receive standard medical treatment. Urine pregnancy tests were conducted in women, and concomitant medications were evaluated in all patients at each clinic visit. Other safety-related stopping rules for premature discontinuation included pregnancy and serious adverse events (SAEs) considered related to the study medication (based on investigator opinion that there was a reasonable possibility that the event may have been caused by the study drug).

Data Analysis

Allowing for dropouts, a sample size of 60 patients per treatment group was calculated as providing sufficient power to detect a minimum of 1.3 g/dL difference (considered the smallest clinically significant benefit) with ferric maltol over placebo based on the Wilcoxon (Mann–Whitney) rank-sum test at the 0.025 one-sided significance level and with an estimated SD of 0.165.

The primary efficacy endpoint was evaluated based on analysis of covariance (ANCOVA), with treatment, gender, and disease as factors and baseline Hb as a covariate. Multiple imputations for missing values were conducted using SAS procedures PROC MI and PROC MIANALYZE. Absolute mean and SD Hb values as well as adjusted mean treatment differences, associated standard errors (SE), and one-sided 97.5% confidence limit (CL) are presented. Changes in Hb concentration from baseline to weeks 4 and 8 were also analyzed using ANCOVA.

For the responder analysis, the proportions of patients who achieved ≥ 1 or ≥ 2 g/dL increases or normalization of Hb from baseline were analyzed by logistic regression with treatment as a fixed effect and baseline Hb as a covariate. Ferric maltol–placebo treatment effects are presented as odds ratios (ORs) with respective 95% confidence intervals (CI). Time to normalization of Hb was assessed using Kaplan–Meier methods, and median time to normalization is presented. The other secondary efficacy endpoints—iron indices, patient symptoms, and QoL—are summarized using descriptive statistics (n, mean, SD, median, and/or range).

A post hoc analysis of Hb response to ferric maltol was conducted based on subgroups of patients categorized according to their baseline disease severity (i.e., quiescent and mild/moderate). Patients were categorized separately based on IBD etiology: SCCAI scores for patients with UC and CDAI scores for patients with CD. Statistical analyses were conducted using methodology identical to that used for the primary efficacy analysis. The second post hoc analysis was also conducted to identify any effect that changes in disease activity on the primary endpoint, where patients were analyzed in categories for time since last disease flare (< 6 or ≥ 6 mo).

Primary and secondary efficacy evaluations were based on an intention-to-treat (ITT) analysis of all randomized patients who received at least 1 dose of study medication (i.e., the ITT full analysis set [FAS]). The prespecified statistical analysis plan also included ITT efficacy analysis of the first 120 subjects randomized, as per the planned study size. A sensitivity analysis was conducted that compared findings in the FAS with the per-protocol (PP) population (i.e., all ITT patients who did not have any major protocol violations); patients who discontinued treatment early due to AEs were still counted as part of the PP population if they attended end-of-study assessments after week 12. Data from the “all-randomized” population (i.e., all patients who were randomized) also underwent statistical analysis identical to those for the FAS and PP population and constituted a further sensitivity analysis. At the time of data cutoff, patient symptom, QoL, and safety data (including AEs) were available from the first 120 randomized subjects (the preplanned population). SAEs were recorded among all randomized patients (i.e., based on the ITT FAS).

ETHICAL CONSIDERATIONS

The trial protocol and all associated materials and amendments were approved by relevant ethics committees. All study procedures were conducted in accordance with Good Clinical Practice Guidelines and the principles and recommendations outlined in the Declaration of Helsinki (1964 and subsequent revisions). Written

informed consent was obtained from all patients before their participation. Trial registration was at ClinicalTrials.gov: identifier no. NCT01340872 or NCT01352221.

RESULTS

Patients

From a total of 329 patients screened, 128 were randomized to treatment (FAS); reasons for screening failure are listed in Figure 1. The PP population comprised 104 patients; reasons for exclusion from the PP population are summarized in Figure 1. A total of 55 ferric maltol-treated patients (86%) and 53 placebo patients (83%) completed 12 weeks of double-blind therapy.

Baseline demographics and disease characteristics were generally comparable between the 2 treatment groups (Table 1). The proportions of patients with UC and CD were identical in the ferric maltol and placebo groups (45% and 55%, respectively). Adverse drug effects and lack of efficacy were the most common reasons for withdrawal from previous OFP therapy. Use of concomitant medications was also comparable between the 2 treatment groups.

Treatment

Overall, patients received study medication for a median of 85 days in both treatment groups, during which time ferric maltol-treated patients received a median (range) total elemental

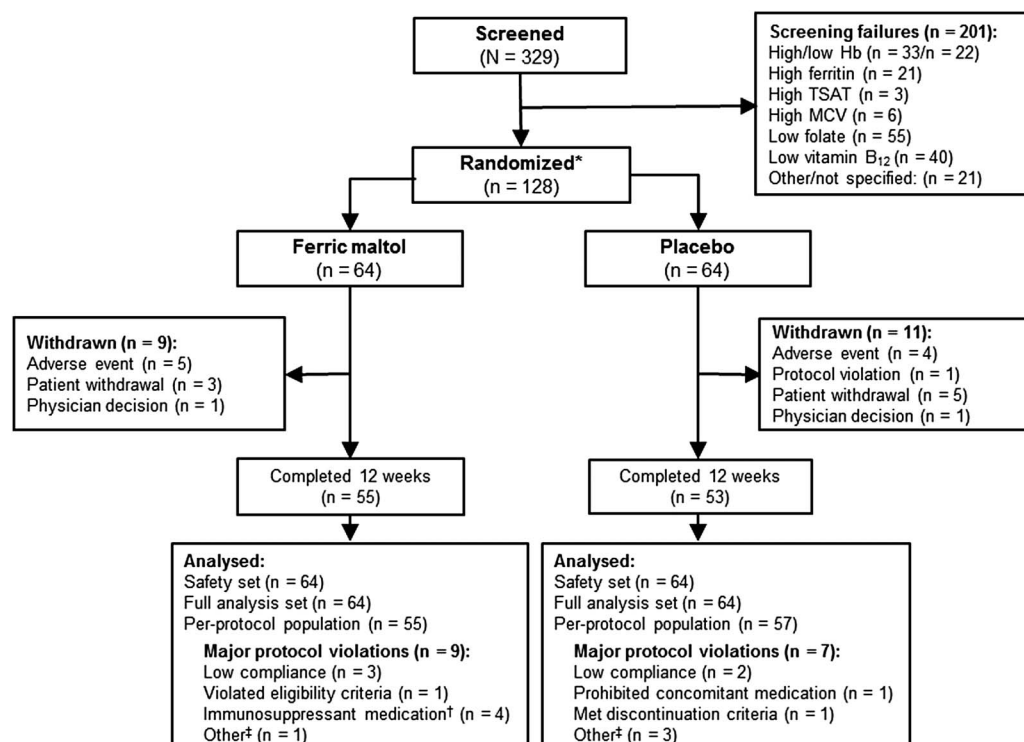


FIGURE 1. Patient disposition. *One hundred twenty-eight randomized patients were included in the main ITT FAS efficacy analysis, and the first 120 patients randomized were included in the safety analysis as predefined by statistical protocol; †Due to dose changes (n = 2) or duration of treatment (n = 1); ‡Due to timings of assessments. MCV, mean corpuscular volume.

TABLE 1. Demographics and Disease Characteristics at Baseline (ITT FAS)

	Ferric Maltol (n = 64)	Placebo (n = 64)
Demographics		
Age, mean (SD), yr	40.1 (13.5)	38.5 (12.3)
Female, n (%)	40 (62.5)	43 (67.2)
Ethnicity, n (%)		
White	62 (96.9)	60 (93.8)
Other	2 (3.1)	4 (6.3)
Disease characteristics, n (%)		
Patients with UC		
Duration of UC, median (range), yr	6.5 (0.3–38.5)	8.4 (1.3–50.6)
Patients with CD, n (%)		
Duration of CD, median (range), yr	10.1 (0.5–40.2)	10.9 (0–30.8)
Time since last IBD flare-up, median (range), mo	8.7 (0–450.4)	6.5 (0–258.8)
Time since last OFP dose, median (range), mo	21.8 (0.2–175.4)	17.4 (0–206.8)
Reasons for OFP failure, n (%)		
Adverse drug effects ^a	44 (68.8)	40 (62.5)
Lack of efficacy	23 (35.9)	24 (37.5)
Deterioration of primary disease	1 (1.6)	2 (3.1)
Other signs of treatment failure	8 (12.5)	10 (15.6)
Laboratory values, mean (SD)		
Hb, g/dL	11.0 (1.03)	11.1 (0.85)
Ferritin, μ g/L	8.6 (6.8)	8.2 (6.5)
TSAT, %	10.6 (11.7)	9.5 (7.5)
Relevant concomitant medications,^b n (%)		
Mesalazine	33 (55.0)	32 (53.3)
Prednisolone (locally acting)	8 (13.3)	6 (10.0)
Azathioprine	17 (28.3)	20 (33.3)
Infliximab	11 (18.3)	13 (21.7)
Adalimumab	10 (16.7)	11 (18.3)
β -Mercaptopurine	6 (10.0)	2 (3.3)

^aAdverse drug effects that led to withdrawal from OFP therapy in ferric maltol-treated and placebo patients included: abdominal pain (in 42.2% and 32.8% of patients, respectively), diarrhea (31% and 30%), nausea (28% and 28%), flatulence (19% and 5%), and constipation (23.4% and 1.6%).

^bBased on available data on medications used by $\geq 10\%$ of patients in preplanned analysis population (N = 120).

iron dose of 4830 (330–5220) mg. The median level of treatment compliance was 98% in both groups.

Efficacy

Hemoglobin

In the primary efficacy analysis, a highly statistically significant increase in Hb concentration was observed in the ferric maltol group compared with placebo at week 12 (Fig. 2). The mean (SE) improvement in Hb in the ferric maltol group versus placebo was 2.25 (0.12) g/dL (one-sided 97.5% CL, 1.81; $P < 0.0001$ based on ANCOVA) (see Fig., Supplemental Digital Content 1, <http://links.lww.com/IBD/A710>). Absolute mean (SD) Hb concentrations improved from 11.00 (1.03) g/dL at baseline to 13.20 (1.04) g/dL at week 12 in the ferric maltol group. In the placebo group, mean (SD) Hb values were similar at

baseline and week 12: 11.10 g/dL (0.85) and 11.20 g/dL (0.98), respectively. The statistical significance of these primary efficacy findings was supported by sensitivity analyses in the PP and all-randomized populations ($P < 0.0001$ in both populations). The preplanned analysis of the first 120 randomized patients produced very similar results to the total randomized population (mean [SE] improvement in Hb in the ferric maltol group versus placebo was 2.25 [0.19] g/dL; one-sided 97.5% CL, 1.88; $P < 0.0001$ based on ANCOVA; see Fig., Supplemental Digital Content 2, <http://links.lww.com/IBD/A711>).

Post hoc analysis of Hb responses according to baseline disease activity scores (i.e., SCCAI scores in patients with UC and CDAI scores in patients with CD), separating patients into quiescent and mild/moderate subgroups, showed significant increases in Hb in each disease severity subgroup (Table 2). Changes were similar in magnitude to those described above for the whole

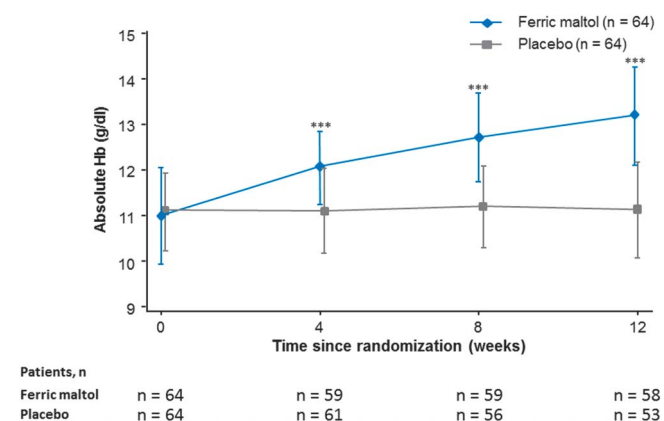


FIGURE 2. Hb concentration from baseline to week 12 (ITT FAS). Data are mean ± SD; ****P* < 0.0001 (ferric maltol versus placebo based on ANCOVA).

patient population with IBD; despite the reduced number of patients per disease severity subgroup compared with the overall population, the lower end of the 97.5% CLs remained well above zero in patients with both UC and CD. In addition, further post hoc analysis of change in Hb according to time since last flare (<6 or ≥6 mo) did not reveal any effect of disease activity on Hb response in either patient subgroups with UC or CD (see Table, Supplemental Digital Content 3, <http://links.lww.com/IBD/A712>).

Secondary efficacy evaluations of changes from baseline to weeks 4 and 8 in the FAS-indicated improved Hb concentrations at both time points with ferric maltol. Absolute mean (SD) Hb concentrations improved from baseline to 12.05 (0.80) g/L at week 4 and 12.8 (0.97) g/L at week 8 in the ferric maltol group. In the placebo group, mean (SD) Hb values at these time points were 11.10 (0.97) g/L and 11.20 (0.98) g/L, respectively. Adjusted mean (SE) treatment differences (ferric maltol versus placebo) were 1.04 (0.11) g/dL at week 4 and 1.73 (0.15) g/dL at week 8 (*P* < 0.0001 in both cases based on ANCOVA). Again, sensitivity analyses in the PP and preplanned analysis patient populations supported these findings.

Findings from the responder analysis are summarized in Figure 3. The majority of ferric maltol-treated patients achieved ≥1 and ≥2 g/dL increases in Hb concentration or normalization of Hb by week 12. Logistic regression analysis showed that IBD etiology (UC or CD) had no effect on the achievement of these predefined treatment goals for Hb. In addition, a higher baseline Hb was associated with reduced likelihood of achieving either a ≥1 g/dL improvement from baseline (OR, 0.487; 95% CI, 0.273–0.870) or a ≥2 g/dL improvement (OR, 0.341; 95% CI, 0.176–0.660). Overall, the median time to normalization of Hb among evaluable ferric maltol-treated patients (n = 64) was 57 days. Time to normalization could not be calculated for the placebo group due to the low number of evaluable patients (n = 13).

Iron Indices

Mean absolute levels of serum ferritin and TSAT are summarized in Table 3 (see Fig., Supplemental Digital Content 2, <http://links.lww.com/IBD/A711>). Iron indices improved between baseline and week 12 in ferric maltol-treated patients but remained largely unchanged in the placebo group. The mean (SD) overall increase in serum ferritin was 17.3 (28.30) μg/L in ferric maltol-treated patients compared with 1.2 (7.85) μg/L in the placebo group: high variability among the placebo patients was indicated by the high SD. A mean (SD) increase of 18.0% (20.2) in TSAT was observed in the ferric maltol group compared with a small reduction (−0.4% [7.8]) in patients who received placebo.

Patient Symptoms and QoL Scores

Among patients with UC, median (range) absolute SCCAI scores were 2.0 (0–3) at baseline and 2.5 (0–6) at week 12 in the ferric maltol group, and 2.0 (0–3) at baseline and 1.5 (0–7) at week 12 in the placebo group.⁴¹ Among patients with CD, median (range) absolute scores on the CDAI decreased from 75.0 (14–199) at baseline to 51.7 (2–231) at week 12 in the ferric maltol group but showed almost no change between baseline and week 12 in the placebo group, 108.0 (10–220) and 109.0 (21–285), respectively.

TABLE 2. Change in Mean (SE) Hb (in grams per deciliters) from Baseline to Week 12 by Severity Subgroup

	Ferric Maltol	Placebo	Treatment Difference	1-Sided Lower 97.5% CL	<i>P</i>
UC					
Overall (n = 58)	2.52 (0.17)	0.21 (0.22)	2.31 (0.27)	1.77	<0.0001
SCCAI subgroups					
Score 0, 1, or 2	2.32 (0.22)	0.28 (0.21)	2.04 (0.29)	1.48	<0.0001
Score 3 or 4	2.72 (0.26)	0.15 (0.39)	2.57 (0.47)	1.66	<0.0001
CD					
Overall (n = 70)	1.93 (0.25)	−0.34 (0.24)	2.27 (0.37)	1.52	<0.0001
CDAI subgroups					
Score <150	2.07 (0.18)	−0.05 (0.18)	2.13 (0.25)	1.63	<0.0001
Score ≥150	1.79 (0.48)	−0.62 (0.43)	2.41 (0.71)	0.96	<0.0001

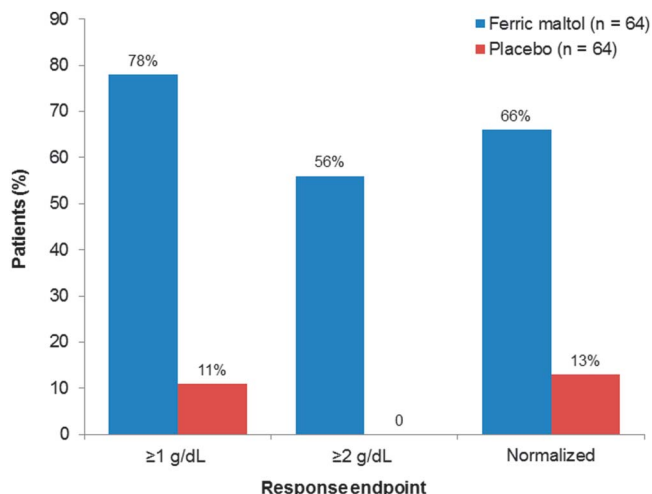


FIGURE 3. Responder analysis: patients achieving 1 and 2 g/dL increases, and normalization of Hb concentration between baseline and week 12 (ITT FAS). Ferric maltol versus placebo ORs were 41.8 (95% CI, 13.5–129.9) for ≥ 1 g/dL increases, not applicable for ≥ 2 g/dL increases, and 15.3 (95% CI, 5.9–39.3) for normalization.

There were no meaningful changes in IBDQ scores in either treatment group between baseline and week 12. In ferric maltol–treated patients, mean (SD) IBDQ scores were 175.6 (31.4) at baseline and 179.7 (32.6) at week 12. Mean (SD) IBDQ scores in placebo patients at these time points were 171.0 (33.8) and 176.0 (32.2), respectively. Scores on all 10 of the SF-36 subscales either improved or remained stable between baseline and week 12 in both the ferric maltol and placebo groups. Percentage improvements in SF-36 subscores ranged from 0.3% to 18% and from –3.4% to 6.8%, respectively. The greatest increase was observed in the vitality domain: 8.2 (18%) in the ferric maltol group and 3.42 (7%) in the placebo group.

TABLE 3. Iron Indices Between Baseline and Week 12 (ITT FAS)

	Ferric Maltol (n = 64),		Placebo (n = 64),	
	n	Mean (SD)	n	Mean (SD)
Ferritin, $\mu\text{g/L}$				
Baseline	64	8.6 (6.8)	64	8.2 (6.5)
Wk 4	59	19.5 (16.4)	61	12.0 (23.2)
Wk 8	59	24.4 (36.2)	56	9.5 (10.7)
Wk 12	59	26.0 (30.6)	53	9.8 (9.6)
TSAT, %				
Baseline	64	10.6 (11.7)	64	9.5 (7.5)
Wk 4	59	29.0 (19.2)	61	9.4 (7.5)
Wk 8	59	24.6 (14.9)	56	12.0 (11.3)
Wk 12	59	28.5 (17.2)	52	9.8 (8.1)

TABLE 4. Incidence of Treatment-Emergent AEs Occurring in $>2\%$ of Patients in Either Treatment Group (Preplanned Safety Set)

	Incidence, n (%)	
	Ferric Maltol (n = 60)	Placebo (n = 60)
Abdominal pain ^a	8 (13.3)	7 (11.7)
Diarrhea	5 (8.3)	6 (10.0)
Constipation	5 (8.3)	1 (1.7)
Nasopharyngitis	4 (6.7)	7 (11.7)
Flatulence	4 (6.7)	0
Abdominal discomfort	3 (5.0)	0
Rectal hemorrhage	3 (5.0)	1 (1.7)
Arthralgia	3 (5.0)	1 (1.7)
Abdominal distension	2 (3.3)	0
Gastroesophageal reflux disease	2 (3.3)	0
Fatigue	2 (3.3)	3 (5.0)
Worsening of CD	1 (1.7)	5 (8.3)
Headache	1 (1.7)	3 (5.0)
Worsening of UC	1 (1.7)	2 (3.3)
Vomiting	1 (1.7)	2 (3.3)
Upper respiratory tract infection	1 (1.7)	2 (3.3)
Oropharyngeal pain	0	3 (5.0)
Hb decreased	0	3 (5.0)
Seasonal allergy	0	2 (3.3)
Pruritis	0	2 (3.3)
Nausea ^b	0	1 (1.7)

^aAmalgamated values for MedDRA terms for “abdominal pain” and “upper abdominal pain.”

^bWhile occurring only in 1.7% of placebo patients, nausea was included in table above as it often occurs in IBD.

Safety and Tolerability

Treatment-emergent AEs were recorded in 35 patients (58%) in the ferric maltol group and in 43 patients (72%) in the placebo group. AEs were mainly gastrointestinal in nature, and most were of mild or moderate severity (Table 4). The overall incidence of gastrointestinal AEs was 23 of ferric maltol–treated patients (38.3%) and 24 placebo patients (40.0%). The most frequent individual gastrointestinal AEs in ferric maltol and placebo groups were abdominal pain (13.3% and 11.7%, respectively), diarrhea (8.3% and 10.0%, respectively), and constipation (8.3% and 1.7%, respectively). Nausea was not recorded in ferric maltol–treated patients but did occur in 1 patient (1.7%) in the placebo group. The only other treatment-emergent AE with an incidence $>10\%$ was nasopharyngitis, which was recorded in 6.7% of ferric maltol–treated patients and 11.7% of placebo patients.

AEs were considered by investigators to be related to study medication in a total of 15 ferric maltol–treated patients (25.0%) and 7 placebo patients (11.7%), respectively. The most common

treatment-related AEs in ferric maltol-treated patients were abdominal pain, constipation, and flatulence, each occurring in 4 patients (6.7%). The respective frequencies of these AEs in the placebo group were abdominal pain (5.0%), constipation (1.7%), and flatulence (0%). All other AEs considered treatment-related, including diarrhea and nausea, were only recorded in one patient in either group.

Study medication was discontinued prematurely due to AEs in a total of 8 patients (13%) in the ferric maltol group and 5 patients (8%) in the placebo group. All treatment-related AEs leading to discontinuation of study medication were gastrointestinal in nature: abdominal pain in 1 ferric maltol-treated patient and 2 placebo patients; diarrhea in 1 patient in each treatment group; and constipation and flatulence in 1 ferric maltol-treated patient each. Discontinuation AEs that were not related to study medication included flare-up of existing IBD in 2 patients in each treatment group (1 case each of CD and UC among ferric maltol-treated patients and 2 cases of CD with placebo), and rectal hemorrhage in 2 ferric maltol-treated patients.

SAEs were recorded in 2 patients in the ferric maltol group and 2 patients in the placebo group; all were gastrointestinal and were considered unrelated to study medication. There were no clinically meaningful safety-relevant trends among changes in routine clinical laboratory parameters, vital signs, or physical examination findings in either the ferric maltol or placebo groups. No deaths occurred during the study.

DISCUSSION

In this randomized phase-3 clinical trial program, we investigated the efficacy and tolerability of ferric maltol (ST-10) in the treatment of IDA in patients with IBD who had previously failed to respond to, or had been intolerant to, previous OFP therapy. A significant improvement in Hb concentration (2.25 g/dL) was observed in ferric maltol-treated patients (versus placebo) over 12 weeks. This is considered a clinically meaningful change based on current guidelines for the management of IDA in IBD.⁶ In addition, a rapid and clinically relevant increase in Hb was observed (1 g/dL by week 4), and this treatment response was not affected by baseline IBD severity (i.e., quiescent versus mild/moderate disease). Hb was normalized in two-third of patients by week 12, with a median time to normalization of less than 2 months. Substantial mean increases in iron indices (ferritin and TSAT) were also observed although data values were highly variable. Overall, oral ferric maltol was equally efficacious in patients with UC and CD, and crucially, ferric maltol demonstrated a safety profile that was comparable with placebo; only constipation occurred more frequently with ferric maltol. No detrimental impact on disease-specific QoL scores, and no adverse effect on disease severity were observed. In particular, these safety- and tolerability-related factors are worth highlighting in view of the fact that this patient cohort had a documented history of intolerance or “lack of efficacy” to OFPs.

These data demonstrate clear advantages for the use of oral ferric maltol in patients with poor tolerability on oral ferrous iron

treatment and suggest that ferric maltol might be a useful alternative to intravenous iron. The favorable gastrointestinal tolerability of ferric maltol is likely due to the novel chemical and pharmacodynamic properties of the ferric iron–maltol complex. After oral ingestion, ferric iron is delivered to the intestinal mucosa in a biologically labile complex form that is believed to allow efficient uptake of elemental ferric iron into enterocytes.^{31–33} As a result, effective gastrointestinal iron uptake is achieved at a relatively low daily dose of elemental iron, which meets current recommendations for the use of oral iron in IBD.^{6,34–36} In addition, unlike unabsorbed ferrous iron, the ferric iron in iron–maltol complexes remains in a chelated form if it is not absorbed.³²

The current efficacy findings seem in line with previous data reported by Harvey et al³⁹ in the earlier proof-of-concept trial with a similar ferric–maltol complex formulation, despite some key methodological differences. Although the previous study was uncontrolled, this trial included a placebo comparator arm. The former study also included patients with and without IBD with IDA (approximately 25% with baseline Hb <9.5 g/dL), whereas only patients with IBD with mild-to-moderate anemia were included here. Nevertheless, the observed improvements in Hb were comparable, albeit slightly larger, in this study, and the proportions of patients with normalized Hb at 12 weeks were similar.

Comparisons of the current trial data with previous studies of oral ferrous salts and intravenous iron therapies are difficult due to differences in patient disease severity at baseline, elemental iron doses, treatment duration, primary study endpoints, and disease assessment scales. In a 4-week open-label study evaluating high-dose oral ferrous sulfate (200 mg thrice a day; i.e., 600 mg/d total dose) in patients with and without IBD, mean Hb increases in mildly anemic patients with UC and CD with inactive disease were 0.4 and 1.7 g/dL, respectively¹⁷; a comparably lower therapeutic response compared with that seen here. In a 12-week randomized controlled trial comparing intravenous ferric carboxymaltose (FeCarb) with oral ferrous sulfate 100 mg twice a day (FeSulf; 200 mg/d total dose) in patients with IBD, mean improvements in Hb were 2.6 and 3.0 g/dL, respectively.⁴⁷ However, this FeCarb–FeSulf trial included patients who were considerably more anemic at baseline: median (range) Hb values were 8.7 (5.0–11.5) g/dL and 9.1 (5.3–11.1) g/dL, respectively. The second large, 12-week, randomized, controlled trial with intravenous FeCarb, this time versus intravenous iron sucrose (FeSuc), included patients with slightly greater anemia at baseline compared with this study (mean baseline Hb values were 10.1 and 10.3 g/dL, respectively).²⁶ Improvements in Hb over 12 weeks with these intravenous iron formulations seemed similar in terms of magnitude and time course.

To date, no clinical study has shown a similar magnitude or time course of improvements in Hb with oral iron therapy in patients with mild-to-moderate anemia. Evaluation of ORs in the responder analysis in this study illustrated that it is more difficult to achieve a clinically significant improvement in Hb in patients with mild-to-moderate anemia than it is in patients with more severe anemia.^{34,35} Although inclusion of only patients with mild-

to-moderate anemia was a prerequisite for the incorporation of a placebo control arm in this trial, it is tempting to speculate whether greater treatment effects could be achieved in patients with more severe anemia at baseline, as have been included in previous published studies assessing ferrous sulfate in IBD.^{17,47}

Ferric maltol demonstrated a good tolerability profile, with a similar overall incidence of AEs compared with placebo. As a result, the proportion of patients who discontinued treatment was similar in ferric maltol-treated and placebo patients; adherence to medication was also very high in both groups. As expected, the majority of AEs in both treatment groups were gastrointestinal in nature, with most being mild or moderate in severity. Notably, only 2 patients in the ferric maltol group and 2 in the placebo groups had a flare-up of their IBD, none of which were considered related to study medication. Few patients discontinued due to study medication-related gastrointestinal AEs. These safety data compare favorably with previous studies assessing OFPs in IBD.^{16,17,22,48}

The interpretation of data from this study is subject to a number of limitations related to the clinical trial design. First, the use of a placebo control arm as opposed to an active control limits the comparability of these findings. The principal objective of this study was to assess the use of ferric maltol in an underserved population: patients with UC and CD who were known to be intolerant of, or unresponsive to, available oral iron preparations. In line with current guidelines for the treatment of IDA in IBD, the only alternative iron replacement treatment for this group of patients is intravenous iron,⁶ but it was not considered appropriate to randomize patients to intravenous placebo injections to establish an active comparator group. Consequently, only patients with mild-to-moderate anemia were included for ethical reasons. Second, the low number of recorded AEs precluded any valid statistical comparison of AEs between the ferric maltol-treated and placebo groups. As a result, we can only assess the safety profile in a descriptive manner. Nevertheless, it is considered unlikely that the difference in incidence of, or instance, constipation, would constitute a statistically significant finding. Finally, it is noteworthy that although the screening failure rate in the current trial was quite high in this study, it was only 10% above those reported in other therapeutic trials in IBD.^{26,47} As summarized in Figure 1, to a degree this reflects the multifactorial nature of IDA in IBD. Aside from Hb outside selected inclusion limits, folate deficiency contributed the largest proportion of failures at screening. However, an amendment to the study protocol regarding folate deficiency criteria midway through this trial resulted in improved patient recruitment: some excluded patients were not “deficient” per se but had values less than or equal to the lower limit of normal.

In conclusion, this randomized controlled study demonstrated that the novel oral iron therapy, ferric maltol, provided rapid and clinically meaningful improvements in Hb concentration, normalized Hb in the majority of patients, and showed a favorable safety and tolerability profile. The favorable gastrointestinal tolerability with ferric maltol compared with currently available oral ferrous iron products, which is at least in part due to the lower doses of elemental iron allowed by this novel

iron–maltol complex formulation, suggests that it may serve as an alternative to intravenous iron therapy in patients with IBD. Patients in this randomized controlled trial have continued ferric maltol treatment in a 12-month open-label extension study, and the long-term effects of ferric maltol on hemoglobin and patient QoL will be reported when data analyses are complete. Data available now from an interim safety analysis with a total treatment duration of 15 months have shown that no patients have had to withdraw due to lack of efficacy or anemia. Considering the possible implications for health care costs, convenience and safety together, these data suggest that ferric maltol could become the first choice treatment in IBD-associated IDA.

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