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Ferric maltol therapy for iron deficiency anaemia in patients with inflammatory bowel disease: long-term extension data from a Phase 3 study

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[a]See Appendix.

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SUMMARY

Background
Ferric maltol was effective and well-tolerated in iron deficiency anaemia patients with inflammatory bowel disease during a 12-week placebo-controlled trial.

Aim
To perform a Phase 3 extension study evaluating long-term efficacy and safety with ferric maltol in inflammatory bowel disease patients in whom oral ferrous therapies had failed to correct iron deficiency anaemia.

Methods
After 12 weeks of randomised, double-blind treatment, patients with iron deficiency anaemia and mild-to-moderate ulcerative colitis or Crohn's disease received open-label ferric maltol 30 mg b.d. for 52 weeks.

Results
111 patients completed randomised treatment and 97 entered the open-label ferric maltol extension. In patients randomised to ferric maltol ('continued'; $n = 50$), mean ± s.d. haemoglobin increased by 3.07 ± 1.46 g/dL between baseline and Week 64. In patients randomised to placebo ('switch'; $n = 47$), haemoglobin increased by 2.19 ± 1.61 g/dL. Normal haemoglobin was achieved in high proportions of both continued and switch patients (89% and 83% at Week 64, respectively). Serum ferritin increased from 8.9 μg/L (baseline) to 26.0 μg/L (Week 12) in ferric maltol-treated patients, and to 57.4 μg/L amongst all patients at Week 64. In total, 80% of patients reported ≥1 adverse event by Week 64. Adverse events considered related to ferric maltol were recorded in 27/111 (24%) patients: 8/18 discontinuations due to adverse events were treatment-related. One patient was withdrawn due to increased ulcerative colitis activity.

Conclusions
Normal haemoglobin was observed in ≥80% of patients from weeks 20–64 of long-term ferric maltol treatment, with concomitant increases in iron storage parameters. Ferric maltol was well-tolerated throughout this 64-week study.

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INTRODUCTION

Anaemia is a common complication in patients with inflammatory bowel disease,[1–4] and is often caused by iron deficiency.[3, 5] Iron deficiency anaemia in inflammatory bowel disease results from impaired iron uptake through the duodeno-jejunal mucosa and chronic blood loss from the inflamed mucosa of the gut.[6, 7] Clinical symptoms include fatigue, headache, dizziness, tachycardia, reduced cognitive function and decreased ability to work.[3, 4, 8] Iron deficiency anaemia therefore has a significant impact on patient day-to-day functioning and quality of life.[8–11]

Iron replacement therapy is recommended in all inflammatory bowel disease patients when iron deficiency anaemia is present, with the treatment goal of achieving normal haemoglobin concentrations and iron stores.[3, 11] Most commonly, patients with iron deficiency anaemia are treated with oral iron preparations.[12] However, widely used oral ferrous (Fe^{2+}) agents such as ferrous sulphate, ferrous gluconate and ferrous fumarate are associated with low intestinal absorption leading to minor efficacy and gastrointestinal side effects.[3, 11, 13–16] The gastrointestinal tolerance of currently available oral iron preparations in often poor, irrespective of pre-existing or iron-induced tissue damage.[4, 13–15] Oral ferrous iron has been shown to aggravate chemically induced inflammation in animal models.[16]

Poor tolerability to oral ferrous iron frequently leads to low patient compliance with therapy, which prevents effective correction of iron deficiency anaemia. Indeed, in some countries label contraindications or special warnings exist regarding the use of these agents in patients with iron deficiency anaemia associated with inflammatory bowel disease. Slow response to oral iron therapy can be a further limitation, with correction of iron deficiency anaemia using oral ferrous iron preparations ranging from 1 to 6 months.[13]

Intravenous iron replacement therapy generally provides more rapid treatment effects and is currently recommended in Europe for patients who have clinically active inflammatory bowel disease, previous intolerance to oral iron, severe anaemia (haemoglobin <10 g/dL), and/or a need for erythropoiesis-stimulating agents.[3] However, intravenous administration of iron is associated with a small but significant risk of anaphylactic reactions, such that specific safety measures are required by healthcare regulators with regard to the administration of intravenous formulations. These measures are associated with substantial healthcare costs and increase the inconvenience of intravenous iron infusion.[3, 17–20]

Ferric maltol is a novel oral iron therapy comprising a stable complex of ferric iron (Fe^{3+}) with maltol [3-hydroxy-2-methyl-4-pyrone]. This formulation allows ferric iron to reach the intestinal mucosa in complex form, with more efficient uptake of elemental iron into enterocytes at relatively low iron dose levels, which helps to meet current recommendations for the use of oral iron in inflammatory bowel disease.[21–25] A recent pivotal Phase 3 clinical trial program comprising two 12-week prospective, randomised, double-blind, placebo-controlled trials with ferric maltol in patients with ulcerative colitis and Crohn's disease demonstrated rapid, clinically meaningful improvements in haemoglobin over 4–12 weeks of treatment, with a high proportion of patients achieving clinically meaningful increases (+2 g/dL) and/or achievement of normal haemoglobin by study end.[26] Crucially, ferric maltol was associated with a low incidence of treatment-related gastrointestinal adverse events that was similar to placebo, irrespective of disease aetiology. Furthermore, ferric maltol had no impact on inflammatory bowel disease severity as assessed by the number of observed flares and Crohn's Disease Activity Index (CDAI), Simple Clinical Colitis Activity Index (SCCAI) and Inflammatory Bowel Disease Questionnaire (IBDQ) scores.[26] It is considered likely that the observed good tolerability and lack of disease impact was at least in part due to the lower elemental iron doses required with ferric maltol.

Risk factors for iron deficiency anaemia such as intestinal blood loss and poor dietary iron intake can be persistent. Iron deficiency anaemia has been shown to recur frequently and often soon after iron replacement therapy.[3] Some patients will therefore require iron maintenance treatment, but this cannot be achieved in any patients with intermittent intravenous iron infusion, nor is it achievable with oral ferrous iron preparations in patients with demonstrable intolerance to such therapies.[3, 11]

We report data from a long-term, open-label extension of the original 12-week Phase 3 trial program with ferric maltol, summarising findings up to 64 weeks of treatment.

MATERIALS AND METHODS

Study design

Both of the original prospective, randomised, double-blind, placebo-controlled trials in the ferric maltol Phase 3 program included 7–14 day screening periods and 12-week 1:1 randomised, double-blind treatment

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periods. A detailed description of the methodology of the randomised controlled trials has been published previously.[26] All patients completing 12 weeks of randomised therapy in either trial were able to continue into a 52-week open-label extension, which was followed by a 14-day safety follow up period. The overall study period (randomised + extension) was between October 2011 and October 2014.

Ethical approval, written informed consent and study conduct in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines in the long-term extension were identical to those reported previously for the randomised trials.[26] Both studies were registered on ClinicalTrials.gov: identifiers NCT01340872/NCT01352221.

Patients

Male and female adult patients with a confirmed diagnosis of ulcerative colitis or Crohn's disease and iron deficiency anaemia were included in the initial randomised trial, amongst all of whom therapy with oral (mainly ferrous) iron agents had previously failed due to one or more of: adverse drug effects (e.g., nausea, diarrhoea, constipation, abdominal pain, flatulence) that led to treatment discontinuation; deterioration of the primary disease; lack of efficacy; or other signs or documented reasons why oral ferrous products could not be used. Patients were enrolled from a total of 54 centres in Austria (randomised phase only), Germany, Hungary and the UK.

In all enrolled patients, inflammatory bowel disease was in remission or of mild-to-moderate severity (SCCAI score <4 or CDAI score <220). Iron deficiency anaemia was of mild-to-moderate severity (haemoglobin ≥9.5 g/dL and <12.0 g/dL for females and ≥9.5 g/dL and <13.0 g/dL for males). Iron deficiency was judged based on serum ferritin concentration <30 μg/L. Full information regarding patient inclusion/exclusion criteria can be found elsewhere.[26]

Treatment

During randomised treatment, patients received either ferric maltol 30 mg b.d. or matching placebo.[26] After Week 12, all participating patients on ferric maltol continued with their ongoing treatment for a further 52 weeks (total ferric maltol treatment period 64 weeks). Patients who received placebo from Weeks 1–12 were switched to receive treatment with ferric maltol 30 mg b.d. between Week 13 and Week 64 (total ferric maltol treatment period 52 weeks). Treatment compliance was evaluated by capsule count at the end of each month of treatment up to Week 64.

Efficacy assessments

The main efficacy endpoint throughout the study was absolute change in haemoglobin from baseline, where baseline was Day 0 of treatment at the beginning of randomised therapy.[26] The proportion of patients achieving normal haemoglobin levels (i.e., ≥12 g/dL for females or ≥13 g/dL for males)[27] was also assessed. In addition, absolute serum ferritin concentration and transferrin saturation were measured at 4- to 12- weekly intervals. All clinical laboratory measurements were conducted at a central laboratory that operated in accordance with guidelines for Good Laboratory Practice.

Disease-specific quality of life and general quality of life were assessed at randomisation, Week 12, and at 12-weekly intervals thereafter during the long-term extension using the IBDQ[22, 23] and the 36-item Short-Form (SF-36) questionnaire,[28] respectively.

Safety and tolerability

Safety and tolerability were assessed based on adverse events (recorded according to MedDRA preferred terms), vital signs measurements and routine haematological and blood chemistry indices. Inflammatory bowel disease symptoms were evaluated at each visit using the SCCAI for ulcerative colitis patients[29] and the CDAI for Crohn's disease patients.[30] If patients developed haemoglobin concentrations ≤8.5 g/dL and/or flare-up of ulcerative colitis (SCCAI score ≥5) or Crohn's disease (CDAI score ≥320) they were required to be withdrawn from the study and received standard medical treatment.

Data analysis

Long-term assessments of both efficacy and safety were based on an integrated data set including patients with ulcerative colitis and Crohn's disease. All data analyses based on the long-term extension period were descriptive in nature: no statistical testing was conducted.

Efficacy endpoints were assessed for the intent-to-treat (ITT) full analysis set (FAS), which included all randomised patients who received at least one dose of study medication. Safety and tolerability were assessed using a cumulative ferric maltol safety set, which comprised all patients with at least one dose of study drug and subsequent double-blind or open-label contact with an investigator. Data from this cumulative safety set are presented to assess findings across the entire study (randomised and long-term extension; Weeks 0–64) relative to data

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obtained during randomised therapy (up to Week 12), including the incidence of all treatment-emergent adverse events, and all adverse events and serious adverse events considered by treating physicians as possibly related to study medication. Discontinuations related to the respective adverse event types are also presented.

All parametric data are presented using continuous descriptive statistics (mean, s.d., median and range). Non-parametric data are described using categorical data analyses based on patient numbers (%).

RESULTS

Patients

From a total of 128 patients randomised to study treatment (the FAS), 50/64 (78%) previous ferric maltol patients (the 'continued' group) and 47/64 (73%) previous placebo patients (the 'switch' group) entered the long-term extension. Ten Austrian patients (four ferric maltol and six placebo) who completed the 12-week randomised phase did not have the option to enter the extension phase due to lack of independent ethics committee approval of the extension protocol. Among all other patients, who were allowed to enter open-label treatment, none declined to continue treatment after completing randomised therapy.

Among the 97 patients who entered the long-term extension, 37/50 'continued' patients (74%) completed 64 weeks of ferric maltol treatment, and 36/47 'switch' patients (74%) completed 52 weeks on open-label ferric maltol (Figure 1). Adverse events were the most common reason for patient withdrawal from the long-term extension (12 patients overall: eight in the continued group and four in the switch group; see 'Safety and tolerability' section for details). There were no withdrawals due to lack of efficacy (i.e., decreased haemoglobin).

Patient demographics and disease characteristics were generally comparable between the two treatment groups at baseline,[26] with mean (±s.d.) ages and gender (% female) evenly distributed between the ferric maltol [40.1 (13.5) years; 63%] and placebo groups [38.5 (12.3); 68%]. Mean (±s.d.) haemoglobin in the two groups [11.0 (1.03) and 11.1 (0.85) g/dL, respectively], as well as ferritin [8.6 (6.8) and 8.2 (6.5) μg/L, respectively] and transferrin saturation values [11% (12%) and 10% (8%), respectively] were comparable at baseline.

Concomitant medications were within normal expectations for the study population, and the proportions of patients taking them were similar between the double-blind and extension phases, overall. The most common inflammatory bowel disease-specific concomitant medications taken among all patients during the randomised and long-term extension periods (i.e., between baseline and Week 64) were: mesalazine (in 58% of patients), azathioprine (31%), adalimumab (20%), infliximab (20%) and prednisolone (17%).

Treatment

The median total duration of ferric maltol treatment was 446 days among continued patients and 365 days among switch patients. A total of 65/111 (59%) patients who received ferric maltol during the randomised and/or extension periods were treated for ≥52 weeks. Median treatment compliance was very high (97%) during the long-term extension (in both continued and switch patients), similar to that seen during the randomised period (97%).

Efficacy

Haemoglobin concentration. Absolute haemoglobin concentrations in continued patients and switch patients throughout the whole study period are shown in Figure 2. As anticipated, haemoglobin increased most during the initial 12 weeks of ferric maltol treatment in both patient groups (i.e., Weeks 0–12 in continued patients and Weeks 12–24 in switch patients). Increases during the first 12 weeks of treatment were similar in the continued and switch groups. Beyond Week 24, mean absolute haemoglobin concentrations were maintained up to the end of the study (Week 64): it was not possible to assess the statistical significance of the increases between Week 12 of active treatment and Week 64 due to the study design. Mean (±s.d.) haemoglobin concentrations increased from 11.00 (1.03) g/dL at baseline to 13.95 (1.26) at Week 64 in the continued group, and from 11.10 (0.85) at baseline to 13.33 (1.46) g/dL at Week 64 in the switch group. Absolute mean (±s.d.) and mean change data values are listed in Table S1.

Among all ferric maltol-treated patients (including both continued and switch patients; $N = 111$), 71% had normal haemoglobin after 12 weeks on ferric maltol, and 78% achieved normal haemoglobin by Week 16 (Figure 3). The overall proportion of patients achieving normal haemoglobin was approximately stable during the remainder of the extension period, up to Week 64 (86% of patients).

Key iron indices. Serum ferritin and transferrin saturation measurements showed a high degree of variability

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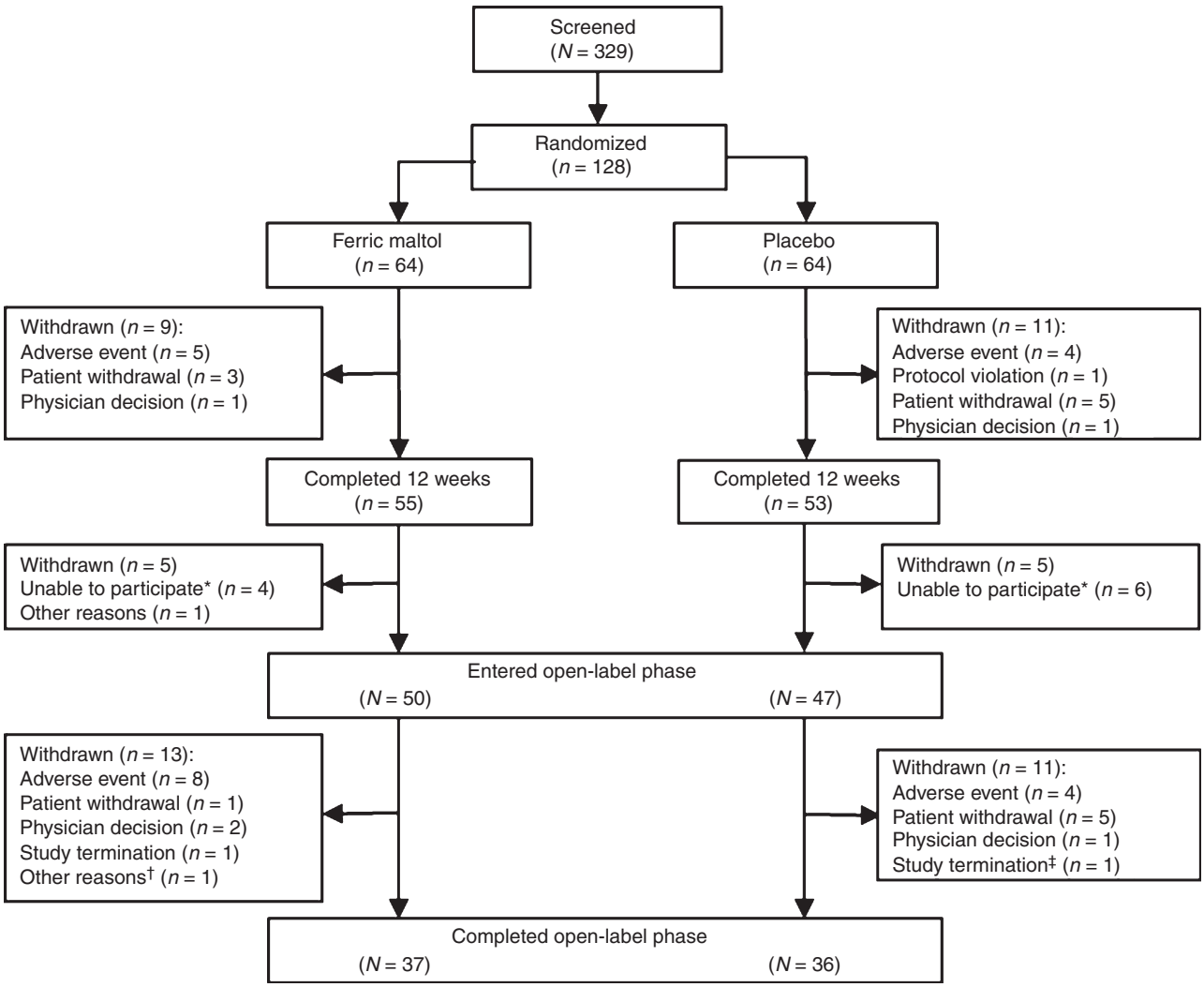

Figure 1 | Patient disposition. *Ten Austrian patients (four initially randomised to ferric maltol and six to placebo) who completed double-blind treatment did not have the option of entering the extended phase of the study due to lack of Austrian IEC approval of the study protocol; †one patient randomised to ferric maltol discontinued during open-label treatment but had no recorded reason for withdrawal at the end of study; ‡one patient was recorded as withdrawn from extension treatment due to study termination by the sponsor.

among the overall study population. Improvements in these two parameters were observed during both randomised and long-term extension treatment with ferric maltol (Figure 4). Mean (±s.d.) absolute serum ferritin increased from 8.4 (6.6) at baseline (N = 128) to 25.5 (42.9) μg/L by Week 16 (N = 91), and 57.4 (77.4) μg/L at Week 64 (N = 72) (Table S2). Mean (±s.d.) absolute transferrin saturation increased from 10% (10%) at baseline (N = 128) to 26% (17%) by Week 16, beyond which it generally remained at the same level up to Week 64 [29% (13%); N = 72] (Table S3). Due to high variability of these parameters, differences were not statistically significant.

Disease activity and quality of life

Among all ferric maltol-treated ulcerative colitis patients (N = 58), mean (s.d.) total SCCAI scores decreased slightly from 1.6 (1.140) at baseline to 1.3 (1.40) at Week 24 and 1.1 (1.29) at Week 64. (N = 70) (Table S4). Mean (s.d.) total CDAI scores among all Crohn's disease patients who received ferric maltol decreased slightly from 95.9 (51.76) at baseline to 82.0 (61.10) at Week 24 and 64.4 (40.52) at Week 64 (Table S5).

No deterioration of patient quality of life was observed based on the quality-of-life indices in this study. There were no notable changes from baseline in disease-specific QoL, as assessed by the IBDQ (Table S6). The mean

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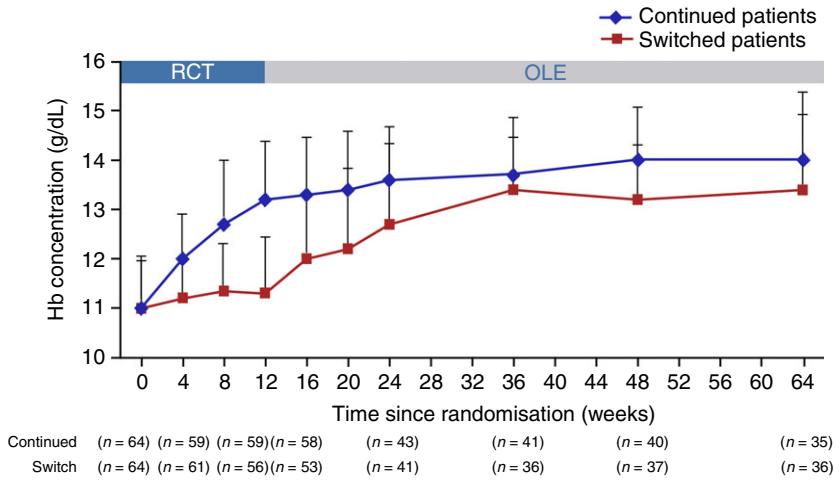

Figure 2 | Absolute haemoglobin concentrations in continued patients and switch patients over time (N = 128). Data points are means + s.d. RCT, randomised controlled trial; OLE, open-label extension.

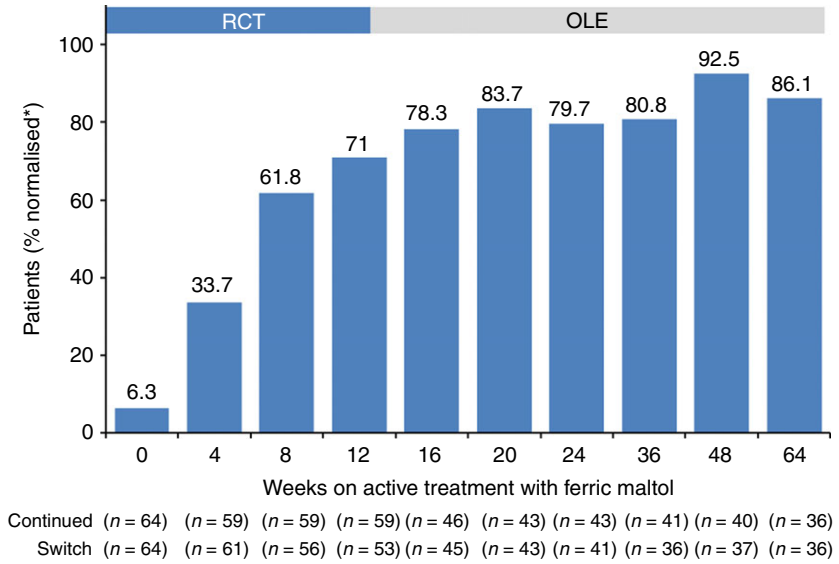

Figure 3 | Cumulative proportions of patients with normal haemoglobin by number of weeks on active treatment with ferric maltol (full analysis set; N = 128). *Cumulative proportion includes all patients from both continued switch group who had normal haemoglobin levels at each time point according to number of weeks on active treatment (i.e., ferric maltol therapy). 6.3% of patients who had haemoglobin values ≥9.5 g/dL and <12.0 g/dL for females and ≥9.5 g/dL and <13.0 g/dL for males at screening had normal values at initiation of randomised treatment.

(±s.d.) total IBDQ score at baseline among all evaluable patients (N = 127) was 173.0 (32.2), and remained stable up to Week 64 [179.0 (33.5); N = 72]. The mean bowel system score of the IBDQ was similarly unchanged between baseline (quiescent disease) and Week 64. None of the general patient quality of life (SF-36) domain scores showed notable changes between baseline and Week 64 (data not shown).

Safety and tolerability

Table 1 summarises the occurrence of treatment-emergent adverse events and serious adverse events (SAEs) seen in ≥2% of patients in the cumulative safety population up to Week 12 and during the entire study (N = 111). Adverse events were recorded in a total of 63 (57%) patients treated with ferric maltol up to Week 12 (and subsequently included in the cumulative safety set),

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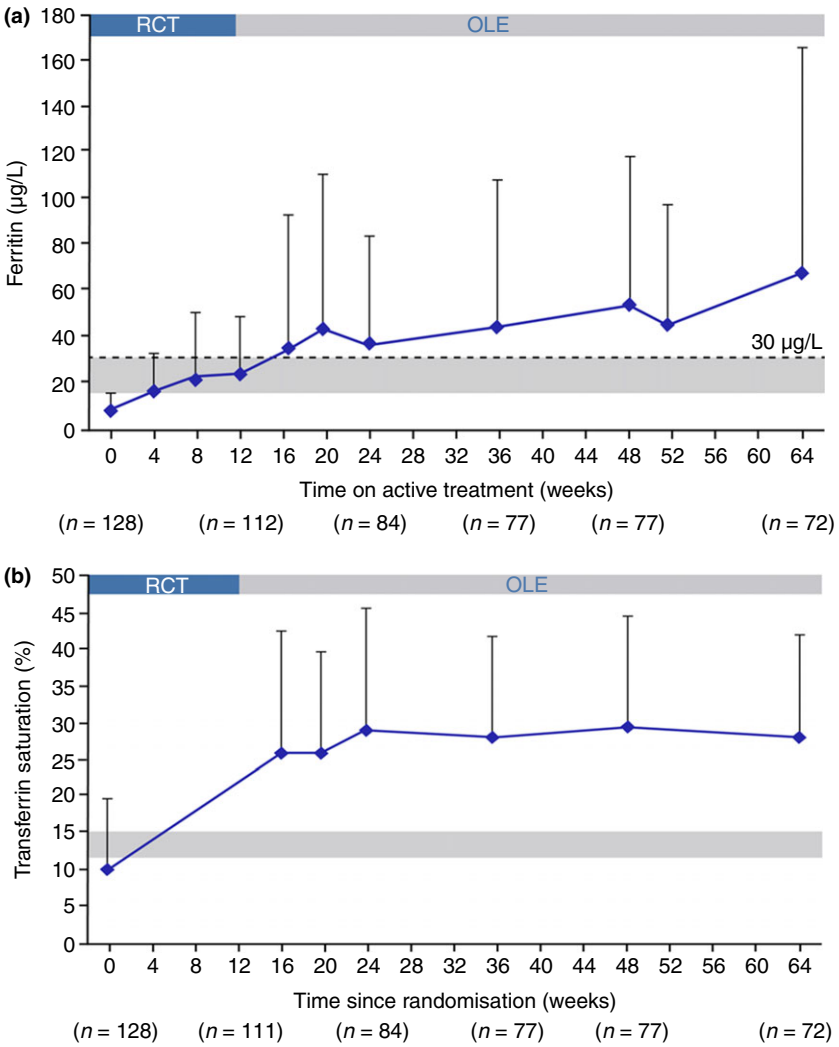

Figure 4 | Absolute serum ferritin concentration (a) and transferrin saturation (b) in all ferric maltol-treated patients during randomised and extension treatment (full analysis set; *N* = 128), including both continued and switch patients; data points are means + s.d. Note: grey box in panel (a) represents lower limits of normal in women and men: 15 µg/L and 30 µg/L, respectively; horizontal dashed line at 30 µg/L in denotes the study inclusion criterion for 'iron deficiency'; grey box in panel (b) represents lower limits of normal in women and men: 12% and 15%, respectively.

and 89 (80%) treated patients over the entire course of the study, Most adverse events (83%) were mild or moderate in severity. Overall, adverse events were mainly gastrointestinal in nature, including abdominal pain, diarrhoea, worsening of existing ulcerative colitis, flatulence, constipation, worsening of existing Crohn's disease.

Adverse events considered related to ferric maltol treatment were recorded in 20 (18%) patients during randomised therapy up to Week 12, and in a total of 27 (24%) patients during the entire study. Overall, the most frequent treatment-related adverse events recorded up to Week 64 were abdominal pain [in 8/111 (7%) patients], constipation [5/111 (5%)], flatulence [5/111 (5%)] and diarrhoea [3/111 (3%)].

During randomised therapy up to Week 12, three SAEs were recorded in one patient in the ferric maltol group. During the long-term extension, eight SAEs were recorded in eight continued patients (two cases of severe abdominal pain and one case each of worsened ulcerative colitis, herpes zoster, peritonitis, hernia, cholesteatoma removal and rectal haemorrhage). Three SAEs were recorded in two switch patients (mild angina pectoris in one patient and pneumonia and pulmonary embolism in another patient). Only one serious adverse event (severe abdominal pain in a switch patient) was

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Table 1 | Incidence of treatment-emergent adverse events in ≥2% of patients in the cumulative safety population (N = 111)

	Incidence, *n* (%)	
	Up to Week 12	Up to Week 64
Summary statistics		
Total patients with ≥1 adverse event	63 (57)	89 (80)
Total patients with ≥1 treatment-related adverse event	20 (18)	27 (24)
Total patients with ≥1 serious adverse event	1 (<1)	11 (10)
Total patients with ≥1 treatment-related serious adverse event	0	1 (<1)
Individual adverse events in ≥2% of patients*		
Nasopharyngitis	8 (7)	20 (18)
Abdominal pain	15 (14)	18 (16)
Diarrhoea	12 (11)	16 (14)
Ulcerative colitis†	2 (2)	11 (10)
Flatulence	6 (5)	9 (8)
Arthralgia	4 (4)	9 (8)
Crohn's disease†	3 (3)	8 (7)
Constipation	6 (5)	7 (6)
Abdominal pain, upper	4 (4)	6 (5)
Nausea	2 (2)	5 (5)
Rectal haemorrhage	4 (4)	5 (5)
Headache	3 (3)	5 (5)
Abdominal discomfort	3 (3)	4 (4)
Abdominal distension	3 (3)	4 (4)
Vomiting	3 (3)	4 (4)
Back pain	2 (2)	4 (4)
Haematochezia	2 (2)	4 (4)
Seasonal allergy	0	4 (4)
Gastro-oesophageal reflux disease	2 (2)	3 (3)
Influenza	2 (2)	3 (3)
Rash	1 (1)	3 (3)
Sinusitis	1 (1)	3 (3)
Cough	0	3 (3)

* ≥5% of patients either during the first 12 weeks or over the entire 64-week study duration.

† Refers to an exacerbation of the existing condition. Note that 'abdominal pain' and 'abdominal pain, upper' are reported as per official MedDRA preferred terms.

considered possibly related to ferric maltol treatment. There were no deaths.

Overall, 22/111 patients (20%) discontinued due to adverse events during the 64-week course of the study. Six patients (5%) from the ferric maltol group and four (4%) from the placebo group discontinued during the 12-week randomised period, and 12 patients (11%) discontinued during the extension period. The total number of patients who discontinued ferric maltol treatment during the entire study was therefore 18 (16%). Overall, most adverse events associated with discontinuations (n = 10) were due to the natural course of the patients' disease and were judged by the treating physician as unrelated to study medication. Eight patients (7%) discontinued due to adverse events that were considered by the physicians to be possibly treatment-related: three cases of abdominal pain, three of diarrhoea, one of flatulence and one of constipation. Among these adverse events, three occurred before Week 12 and five occurred during the extension period. One ulcerative colitis patient from the continued group was withdrawn by the treating physician due to increased disease activity (SCCAI score ≥5).

There were no notable safety-relevant changes in routine clinical laboratory parameters. In particular, there were no notable or consistent changes or differences in C-reactive protein (CRP) levels between ferric maltol-treated and placebo patients during either randomised or extension therapy. Safety monitoring noted only one instance of increased CRP (mild) during the first 12 weeks of randomised ferric maltol therapy, but no such increases were observed between Weeks 13 and 64 of active treatment. Vital signs and physical examination findings were unremarkable during both randomised and extension treatment (data not shown).

DISCUSSION

This long-term study demonstrated that, after significant improvements in haemoglobin during the initial 12 weeks of randomised ferric maltol treatment, continued treatment with this novel oral iron therapy maintained or further improved haemoglobin up to 64 weeks without substantial numbers of adverse events. It was not possible to demonstrate a significant increase in haemoglobin between Weeks 12 and 52 as the study was not powered to show a further increase during open-label treatment. Nevertheless, it is important to note that increases in haemoglobin during the initial 12 weeks of active treatment in patients switched from 12-week placebo to ferric maltol treatment paralleled those seen over Weeks 1–12 in patients who received ferric maltol from baseline to Week 64. In addition, it is notable that no patients in this long-term study discontinued treatment due to lack of efficacy.

Overall, approximately one-third of patients achieved normal haemoglobin by Week 4, and this proportion increased to three-quarters by Week 12. Improvements in key iron storage indices (ferritin and transferrin

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saturation) were slower over the course of the study, indicating that premature discontinuation of ferric maltol treatment should be considered carefully in order to avoid recurrence of iron deficiency. It is also important to highlight that replenishment of iron stores can vary considerably from patient to patient,[13] as exemplified in this study.

Patients with inflammatory bowel disease have several risk factors for iron deficiency anaemia, including gastrointestinal bleeding and inadequate dietary iron intake and/or absorption, which can result in recurrence of iron deficiency anaemia even when the disease appears to be under control.[3] For this reason it has been noted that in inflammatory bowel disease patients with iron deficiency anaemia treated with oral iron preparations, oral iron therapy should be continued for ≥3 months after iron deficiency has been corrected so that stores are adequately replenished.[31] Among inflammatory bowel disease patients treated with intravenous therapy, iron deficiency and anaemia can also recur frequently and rapidly after treatment, and has been reported in up to 50% of patients within 10 months of infusion.[3, 32] The speed of iron deficiency anaemia recurrence in such cases has been shown to relate to the magnitude of post-treatment iron stores, with iron deficiency being less likely in patients with higher post-treatment ferritin levels.[3, 27] Patients treated with intravenous iron preparations therefore require regular monitoring (e.g., every 3 months), and may require repeated intravenous infusions over a prolonged period.[3, 17, 33]

Many inflammatory bowel disease patients demonstrate poor gastrointestinal tolerability to oral ferrous compounds (e.g., ferrous sulphate).[3, 11] The most important finding in the current study was that the safety and tolerability profile of ferric maltol during extension treatment (Weeks 12–64) was similar to that seen during initial randomised treatment (Weeks 0–12).[26] The incidence and type of gastrointestinal adverse events among ferric maltol-treated patients in the cumulative long-term safety set in this study (57%) were similar to those observed in the placebo group (40%) during the 12-week randomised trial.[26] No treatment-related serious adverse events were recorded during 12-week randomised ferric maltol treatment, and only one serious adverse event (abdominal pain) was considered possibly related to study treatment throughout 52 weeks of extension treatment. It is also notable that while several patients had mild-to-moderate inflammatory bowel disease at baseline, worsening of ulcerative colitis and Crohn's disease was recorded as an adverse event in <10% of patients overall, and only one patient was withdrawn due to exacerbation of existing ulcerative colitis (SCCAI score ≥5) based on physician judgement.

The absence of an intravenous comparator arm in the current study makes it difficult to compare the current findings with data from trials assessing intravenous iron due mainly to the fact that the vast majority of efficacy data with intravenous formulations come from short-term studies conducted over 5–12 weeks.[3, 11, 34–37] Similarly, there are few previous studies that allow comparison of the current long-term ferric maltol data with other oral iron compounds.

A recent systematic review and meta-analysis of randomised controlled trials reported increased gastrointestinal side-effects with ferrous sulphate in adults, regardless of either patient population or specific formulation.[38] The duration of all except two of the identified trials in inflammatory bowel disease was 6–12 weeks. In a 20-week randomised trial comparing oral ferrous sulphate with intravenous iron sucrose in 91 patients with anaemia (haemoglobin <11.5 g/dL),[39] only 22 patients (48%) tolerated the prescribed oral ferrous sulphate dose, and 52% reduced the dose or discontinued ferrous sulphate because of poor tolerability. Consequently, haemoglobin increased by ≥2 g/dL in only 47% of patients on oral iron, compared with 66% of patients given intravenous iron sucrose.[39] In a 6-month open-label trial that also compared oral ferrous sulphate with intravenous iron sucrose, this time in 100 patients with iron deficiency anaemia (haemoglobin >10 g/dL),[40] only 4/78 (5%) patients who received ferrous sulphate discontinued treatment due to 'medication intolerance'.[40] Extrapolation of findings from this latter study to match the duration of the current study gives an estimated 1-year discontinuation rate of approximately 10%, which is surprisingly low given the well-known poor tolerability of oral ferrous iron.[38] Nevertheless, the current data still compare favourably with this previous report, with only 7.2% of patients discontinuing due to treatment-related adverse events up to Week 64.

In considering the safety and tolerability data from the current study, it is important to bear in mind that the current study population was sensitive to the adverse effects of oral iron therapy as it only included patients with a documented history of treatment failure with oral ferrous products. Reasons for previous failure of oral ferrous iron treatment (recorded at screening) included poor gastrointestinal tolerability in approximately two-thirds of patients and lack of efficacy in approximately one-third. The data on discontinuations due to

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treatment-related gastrointestinal adverse events are therefore open to a degree of positive historical bias, with patients more likely to discontinue than would otherwise be observed with ferric maltol in a standard inflammatory bowel disease population including treatment-naïve patients and those who are able to tolerate oral ferrous iron.

It is likely that, overall, the patient population of this study was too mildly affected by iron deficiency anaemia to show discernible improvements in disease-specific or general patient QoL, even over the long-term, based on the quality-of-life parameters employed (IBDQ and SF-36, respectively). Nevertheless, the quality-of-life data indicate that long-term treatment with ferric maltol did not have any detrimental impact on QoL. This finding is considered at least in part attributable to the favourable safety and tolerability profile of ferric maltol. In addition, the fact that no patients in this study discontinued treatment due to lack of efficacy indicates potential benefits for prolonged ferric maltol maintenance treatment. However, it should be borne in mind that other relevant factors, such as iron storage indices, vary a great deal from patient to patient. Follow-up assessments with appropriate testing should therefore be scheduled during long-term therapy in order to ensure maintained iron balance.

The limitations of our study are as follows. The lack of an active oral comparator arm, which is due to (i) the placebo-controlled design of the initial randomised trial and (ii) the fact that the initial randomised trial was the first trial reported to date that included only patients in whom oral ferrous products had previously failed,[26] precludes direct comparison of ferric maltol with other iron formulations. Furthermore, the open-label nature of this extension study confers a number of inherent difficulties in terms of avoiding patient selection bias and limiting analyses to purely descriptive data assessments. In addition, the study design did not allow an assessment of the possibility of whether the absence of a sustained deficit of iron balance might have influenced the haemoglobin results: future subgroup analyses may help to address this. While the initial randomised trial was adequately powered to discern statistically significant differences between ferric maltol and placebo, this long-term open-label analysis was not powered to demonstrate additional statistically significant improvement of iron deficiency anaemia parameters, and no comparable untreated cohort data are available. Based on the absence of an untreated cohort, maintained levels of haemoglobin could be associated either with sustained efficacy of ferric maltol or to the absence of sustained deficit of iron balance. Finally, while no evidence of significant worsening of (subclinical) mucosal inflammation was observed, the size of this study population did not enable us to rule out the possibility of such effects. Similarly, the study was not powered to exclude the possibility that long-term ferric maltol treatment for >12 months could increase the risk of IBD reactivation.

In conclusion, the current findings substantially extend knowledge gained from the initial randomised trial with ferric maltol[21] and the early proof-of-concept study with a ferric iron compound.[41] Long-term ferric maltol treatment beyond 12 weeks increased or maintaining haemoglobin concentration, allowing sustained normal haemoglobin in a high proportion of patients throughout 64 weeks of treatment. Ferric maltol also increased the proportion of patients with corrected ferritin and transferrin saturation. Future analyses will be required to define which patients benefitted most from long-term ferric maltol treatment and which patients did not need long-term treatment. Such analysis will need to discern long-term improvements in haemoglobin and iron parameters that related to treatment from those related to reductions in underlying inflammatory bowel disease severity. The tolerability of this novel ferric iron formulation remained favourable throughout this long-term (64-week) study, with few patients withdrawing due to medication-related effects. Overall, ferric maltol shows promise as a new option for the long-term treatment of iron deficiency anaemia in patients with inflammatory bowel disease.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Absolute levels and changes from baseline in haemoglobin concentration from baseline to end of study in continued and switch patient groups (full analysis set; $N = 128$).

Table S2. Absolute levels and changes from baseline in serum ferritin in all patients from baseline to end of study (full analysis set; $N = 128$).

Table S3. Absolute levels and changes from baseline in transferrin saturation in all patients from baseline to end of study (full analysis set; $N = 128$).

Table S4. Total SCCAI scores by number of weeks on ferric maltol (full analysis set; $N = 58$).

Table S5. Total CDAI scores by number of weeks on ferric maltol (full analysis set; $N = 70$).

Table S6. Summary of IBDQ response over time during open-label phase (full analysis set; $N = 128$).

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AUTHORSHIP

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Author contributions: CS, CB, TA, ZT, DCB, BB, SH and AS participated in the conduct of the study, provided clinical data, had access to study data analyses and provided critical review of the content of the manuscript throughout its preparation. CS co-wrote the first draft of the manuscript based on editorial support from MR.

All authors approved the final version of the manuscript.

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Declaration of personal interests: AS has served as a board member for Abbvie, Hospira, Jansen, MSD and Takeda, and has received consultancy fees from Abbvie, Hospira and Takeda, speaker honoraria from Abbvie, MSD, Ferring, Falk HLR and Takeda, and travel expenses from Shield Therapeutics (UK) Ltd. BB has received travel expenses from Shield Therapeutics (UK) Ltd, consultancy fees from Abbvie, MSD, Shire, Ferring, UCB, Hospira, Taekda and Movetis, speaker honoraria from Abbvie, MSD, Ferring, Merck, FALK HLR, UCB and Vifor, and research funding from Abbvie, Ferring and UCB. CB has served as a board member for MSD and Takeda, and has received speaker honoraria from Abbvie, Ferring, MSD, and Shield Therapeutics (UK) Ltd and travel expenses from Abbvie, Ferring, MSD, Takeda, and Shield Therapeutics (UK) Ltd. CS has received consultancy fees from Abbvie, MSD and Takeda, speaker honoraria from Abbvie, Falk, Merckle, MSD, Norgine, Novartis, Shire, Takeda and UCB, and research funding from Abbvie. DCB has received research grant support from Abbott Laboratories/AbbVie, Hitachi, and Shire, has consulted for Abbott Laboratories/AbbVie, Celgene, Genentech, MSD, Pfizer, Takeda and Vifor, and has received speaker fees from Abbott Laboratories/AbbVie, the Falk Foundation, Ferring Pharmaceuticals, MSD, Shire, and TiGenix/Cellerix: all of his activities and contracts are in conformity with the "FSA-Kodex Fachkreise" (voluntary self-monitoring code for expert consultants to the pharmaceutical industry), have been checked by the Medicolegal Department of Charité – Universitätsmedizin Berlin, and have been approved by the directorate of the Faculty of Medicine. SH has received consulting fees and travel expenses from Shield Therapeutics (UK) Ltd. TA has received research funding from Shield Therapeutics (UK) Ltd, consultancy fees and research funding from Abbvie and Merck, and speaker honoraria from Merck. ZT has no competing interests to declare.

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REFERENCES

1. Goldberg ND. Iron deficiency anemia in patients with inflammatory bowel disease. *Clin Exp Gastroenterol* 2013; **6**: 61–70.
2. Breuer W, Hershko C, Cabantchik ZI. The importance of non-transferrin bound iron in disorders of iron metabolism. *Transfus Sci* 2000; **23**: 185–92.
3. Dignass AU, Gasche C, Bettenworth D, *et al.* European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. *J Crohns Colitis* 2015; **9**: 211–22.
4. Stein J, Hartmann F, Dignass AU. Diagnosis and management of iron deficiency anemia in patients with IBD. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 599–610.
5. Gomollon F, Gisbert JP. Anemia and inflammatory bowel diseases. *World J Gastroenterol* 2009; **15**: 4659–65.
6. Gasche C, Beguin Y, de Silva AD, *et al.* IBD and anemia. In: Gasche C, ed. *Anemia in Inflammatory Bowel Diseases*. Bremen, London, Boston: UNI-MED Verlag AG, 2008; 15–53.
7. Van Assche G, Dignass A, Reinisch W, *et al.* The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Special situations. *J Crohns Colitis* 2010; **4**: 63–101.
8. Wells CW, Lewis S, Barton JR, Corbett S. Effects of changes in hemoglobin level on quality of life and cognitive function in inflammatory bowel disease patients. *Inflamm Bowel Dis* 2006; **12**: 123–30.
9. Ershler WB, Chen K, Reyes EB, Dubois R. Economic burden of patients with anemia in selected diseases. *Value Health* 2005; **8**: 629–38.
10. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med* 2005; **352**: 1011–23.
11. Gasche C, Berstad A, Befrits R, *et al.* Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases. *Inflamm Bowel Dis* 2007; **13**: 1545–53.
12. Blumenstein I, Dignass A, Vollmer S, Klemm W, Weber-Mangal S, Stein J. Current practice in the diagnosis and management of IBD-associated anaemia and iron deficiency in Germany: the German AnaemIBD Study. *J Crohns Colitis* 2014; **8**: 1308–14.
13. Gasche C, Beguin Y, de Silva AD. *Anemia in Inflammatory Bowel Diseases*. Bremen, London, Boston: UNI-MED Verlag AG, 2008.
14. Tolkien Z, Stecher L, Mander AP, Pereira DI, Powell JJ. Ferrous sulphate supplementation causes significant gastrointestinal side effects in adults: a systematic review and meta-analysis. *PLoS ONE* 2015; **10**: e0117383.
15. Dignass A, Lindsay JO, Sturm A, *et al.* Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. *J Crohns Colitis* 2012; **6**: 991–1030.
16. D'Arcy PF, Howard EM. The acute toxicity of ferrous salts administered to dogs by mouth. *J Pathol Bacteriol* 1962; **83**: 65–72.
17. Evstatiev R, Marteau P, Iqbal T, *et al.* FERGIcor, a randomized controlled trial on ferric carboxymaltose for iron deficiency anemia in inflammatory bowel disease. *Gastroenterology* 2011; **141**: 846–53 e1–2.
18. European Medicines Agency (EMA). New recommendations to manage risk of allergic reactions with intravenous iron-containing medicines. 13 September 2013. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000435/human_med_001171.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125 (accessed 22 April 2016).
19. Gomollon F, Chowers Y, Danese S, *et al.* Letter: European Medicines Agency recommendations for allergic reactions to intravenous iron-containing medicines. *Aliment Pharmacol Ther* 2014; **39**: 743–4.
20. Auerbach M, Rodgers GM. Intravenous iron. *N Engl J Med* 2007; **357**: 93–4.
21. Barrand MA, Callingham BA, Dobbin P, Hider RC. Dissociation of a ferric maltol complex and its subsequent metabolism during absorption across

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the small intestine of the rat. *Br J Pharmacol* 1991; **102**: 723–9.
22. Kelsey SM, Hider RC, Bloor JR, Blake DR, Gutteridge CN, Newland AC. Absorption of low and therapeutic doses of ferric maltol, a novel ferric iron compound, in iron deficient subjects using a single dose iron absorption test. *J Clin Pharm Ther* 1991; **16**: 117–22.
23. Kelsey SM, Blake DR, Hider RC, Gutteridge CN, Newland AC. Absorption of ferric maltol, a novel ferric iron compound, in iron-deficient subjects. *Clin Lab Haematol* 1989; **11**: 287–8.
24. Barrand MA, Callingham BA. Evidence for regulatory control of iron uptake from ferric maltol across the small intestine of the rat. *Br J Pharmacol* 1991; **102**: 408–14.
25. Levey JA, Barrand MA, Callingham BA, Hider RC. Characteristics of iron(III) uptake by isolated fragments of rat small intestine in the presence of the hydroxypyrones, maltol and ethyl maltol. *Biochem Pharmacol* 1988; **37**: 2051–7.
26. Gasche C, Ahmad T, Tulassay Z, *et al.* Ferric maltol is effective in correcting iron deficiency anemia in patients with inflammatory bowel disease: results from a phase-3 clinical trial program. *Inflamm Bowel Dis* 2015; **21**: 579–88.
27. World Health Organisation (WHO). Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. In: Maria de Regil, L, ed. *Vitamin and Mineral Nutrition Information System* (WHO/NMH/NHD/MNM/11.1). Geneva: World Health Organization, 2011; 1–4.
28. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; **30**: 473–83.
29. Walmsley RS, Ayres RC, Pounder RE, Allan RN. A simple clinical colitis activity index. *Gut* 1998; **43**: 29–32.
30. Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology* 1976; **70**: 439–44.
31. Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. *Lancet* 2015; **387**: 907–16.
32. Kulnigg S, Teischinger L, Dejaco C, Waldhor T, Gasche C. Rapid recurrence of IBD-associated anemia and iron deficiency after intravenous iron sucrose and erythropoietin treatment. *Am J Gastroenterol* 2009; **104**: 1460–7.
33. Qunibi WY. The efficacy and safety of current intravenous iron preparations for the management of iron-deficiency anaemia: a review. *Arzneimittelforschung* 2010; **60**: 399–412.
34. Kulnigg S, Stoinov S, Simanenkov V, *et al.* A novel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: the ferric carboxymaltose (FERINJECT) randomized controlled trial. *Am J Gastroenterol* 2008; **103**: 1182–92.
35. Schroder O, Mickisch O, Seidler U, *et al.* Intravenous iron sucrose versus oral iron supplementation for the treatment of iron deficiency anemia in patients with inflammatory bowel disease–a randomized, controlled, open-label, multicenter study. *Am J Gastroenterol* 2005; **100**: 2503–9.
36. Bodemar G, Kechagias S, Almer S, Danielson BG. Treatment of anaemia in inflammatory bowel disease with iron sucrose. *Scand J Gastroenterol* 2004; **39**: 454–8.
37. Erichsen K, Ulvik RJ, Nysaeter G, *et al.* Oral ferrous fumarate or intravenous iron sucrose for patients with inflammatory bowel disease. *Scand J Gastroenterol* 2005; **40**: 1058–65.
38. Stein J, Dignass AU. Management of iron deficiency anemia in inflammatory bowel disease - a practical approach. *Ann Gastroenterol* 2013; **26**: 104–13.
39. Lindgren S, Wikman O, Befrits R, *et al.* Intravenous iron sucrose is superior to oral iron sulphate for correcting anaemia and restoring iron stores in IBD patients: a randomized, controlled, evaluator-blind, multicentre study. *Scand J Gastroenterol* 2009; **44**: 838–45.
40. Gisbert JP, Bermejo F, Pajares R, *et al.* Oral and intravenous iron treatment in inflammatory bowel disease: hematological response and quality of life improvement. *Inflamm Bowel Dis* 2009; **15**: 1485–91.
41. Harvey RS, Reffitt DM, Doig LA, *et al.* Ferric trimaltol corrects iron deficiency anaemia in patients intolerant of iron. *Aliment Pharmacol Ther* 1998; **12**: 845–8.

APPENDIX

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