CLINICAL STUDY PROTOCOL

A phase 3b, randomized, controlled, multicentre study with oral ferric maltol (Feraccru) or intravenous iron (ferric carboxymaltose; FCM), for the treatment of iron deficiency anaemia in subjects with inflammatory bowel disease

Protocol Number: ST10-01-304

EudraCT Number: 2015-002496-26

Test Drug: Ferric maltol

IND Number: 114832

Sponsor: **Shield TX (UK) Limited**

Sponsor Address: **Northern Design Centre**
Baltic Business Quarter
Gateshead Quays
NE8 3DF
United Kingdom

Tel: **+44 (0)191 511 8500**

EU Legal Representative: **Not Applicable**

Version/Date: **Version 7.0 / 30 Apr 2018**

Confidentiality Statement

The information contained in this document is provided in confidence. It is understood that this information will not be disclosed to others without prior agreement of Shield TX (UK) Limited, according to the statement in the clinical study protocol, and in accordance with the confidentiality agreement.

1 PROTOCOL APPROVALS

Name:	**Mark Sampson, MBChB**
Company:	**Shield TX (UK) Ltd**
Position:	**Chief Medical Officer**
Signature:	
Date:	15 MAY 2018

Name:	**Jackie Mitchell, MA DPhil**
Company:	**Shield TX (UK) Ltd**
Position:	**VP Quality and Regulatory Affairs**
Signature:	
Date:	16 MAY 2018

2 SYNOPSIS

Title / Study Number	A phase 3b, randomized, controlled, multicentre study with oral ferric maltol (Feraccru) or intravenous iron (ferric carboxymaltose, FCM), for the treatment of iron deficiency anaemia in subjects with inflammatory bowel disease (IBD) ST10-01 304
Phase	Phase 3b
Objectives	**Primary Objective** To compare the efficacy of ferric maltol and intravenous iron (IVI, FCM) in the treatment and maintenance of iron deficiency anaemia (IDA) in subjects with IBD **Secondary Objective** To evaluate the safety and tolerability of ferric maltol and IVI in subjects over a treatment duration of up to 52 weeks. To evaluate long-term healthcare resources utilized in the management of IDA in IBD.

Study Design	Prospective, multicentre, randomized, controlled Phase 3b study
	• Screening: Up to 14 days
	• Randomized treatment:
	  • 12 weeks treatment period
	  • subjects entered in the 52 weeks treatment period will finish their randomized treatment at week 12, unless they went beyond this visit. If so, the next scheduled visit will be their last treatment visit.
	• End of study: Week 12/premature discontinuation or next scheduled visit if subjects went beyond Week 12.
	• Post-treatment safety follow-up: 14 days (2 weeks) after End of Study visit or premature discontinuation of ferric maltol or FCM

Number of Subjects/Treatments	Approximately 242 subjects with IDA and IBD will be randomized at a ratio of 1:1 into one of the following treatment arms: • Oral ferric maltol, 30 mg capsule twice daily (bid) • Intravenous iron (ferric carboxymaltose), administered as per the local summary of product characteristics (SPC/PI)
Diagnosis/Inclusion Criteria	All of the following criteria must be met to randomize a subject in the study: 1. Subjects must be competent to understand the information given in the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) approved informed consent

form and must sign and date the informed consent prior to any study mandated procedure

2. Subjects must be willing and able to comply with study requirements
3. Age ≥ 18 years
4. Subjects must have a confirmed diagnosis of IBD (endoscopic and/or biopsy)
5. Subjects must be considered suitable for intravenous iron treatment by the Investigator
6. Subjects must have iron deficiency anaemia defined by the following criteria:
    a. Hb ≥8.0 g/dL and ≤11.0 g/dL for women OR a Hb ≥8.0 g/dL and ≤12.0 g/dL for men
    b. AND Ferritin <30ng/ml OR Ferritin <100 ng/ml WITH Transferrin saturation (TSAT) <20%.
7. Female subjects of childbearing potential (including perimenopausal females who have had a menstrual period within 1 year prior to screening) must agree to use a reliable method of contraception until study completion and for at least 4 weeks following their final study visit. Reliable contraception is defined as a method which results in a low failure rate, i.e., less than 1% per year when used consistently and correctly, such as implants, injectables, some intrauterine contraceptive devices (IUDs), complete sexual abstinence, or a vasectomized partner. Oral contraceptive medications are allowed in this study. Female subjects who are surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy) or postmenopausal (defined as no menstrual period within 1 year of screening) are also allowed to participate.

Exclusion Criteria

A subject who meets any of the following criteria is not eligible for participation in the study.

1. Subject with anaemia due to any cause other than iron deficiency, including, but not limited to,
    a. Untreated or untreatable severe malabsorption syndrome
    b. Immunosuppressant use. Immunosuppressants are permitted so long as there is no clinical evidence or suspicion of the immunosuppressant contributing to the subject's anaemia or affecting erythropoiesis.

    Variations to dosing are permitted at the discretion of the investigator so long as there is no clinical evidence or suspicion of the immunosuppressant contributing to the subject's anaemia or affecting erythropoiesis
2. Subject who has received prior to screening

   a. Within 8 weeks intramuscular or intravenous (IV) iron or administration of depot iron preparation
   b. Within 2 weeks a blood transfusion
   c. Oral iron supplementation, taken specifically to treat anaemia, within the previous 4 weeks (Over the Counter (OTC) multivitamins containing iron are permitted)

3. Subjects with active inflammatory bowel disease as defined by a SCCAI (Simple Clinical Colitis Activity Index) score greater than 5 at Screening or a CDAI (Crohn's Disease Activity Index) score greater than 300 in the Screening period (as assessed using the Screening haematocrit (HCT) and CDAI diary card completed by the subject for 7 days prior to planned randomization).
4. Subjects with known hypersensitivity or allergy to either the active substance or excipients of ferric maltol capsules or ferric carboxymaltose solution for IV administration
5. Subjects who have had serious adverse reactions to previous doses of ferric carboxymaltose or any other intravenous iron
6. Subjects with contraindication for treatment with iron preparations, e.g. hemochromatosis, chronic hemolytic disease, sideroblastic anaemia, thalassemia, or lead intoxication induced anaemia.
7. Subjects with vitamin B12 or folic acid deficiency as determined by the central laboratory screening results. **Subjects may start vitamin B12 or folate replacement and rescreen after at least 2 weeks.**
8. Subjects who are pregnant or breast feeding.
9. Concomitant medical conditions with significant active bleeding likely to initiate or prolong anaemia.
10. Participation in any other interventional clinical study within 30 days prior to screening.
11. Subject with cardiovascular, liver, renal, haematologic, gastrointestinal, immunologic, endocrine, metabolic, or central nervous system disease that, in the opinion of the Investigator, may adversely affect the safety of the subject or severely limit the lifespan of the subject (i.e. unlikely to complete the full duration of the study).
12. Subject with significant neurologic or psychiatric symptoms resulting in disorientation, memory impairment, or inability to report accurately that might interfere with treatment compliance, study conduct or interpretation of the results (e.g., Alzheimer's disease, schizophrenia or other psychosis, active or current alcohol or drug abuse).
13. Subject who is an inmate of a psychiatric ward, prison, or other state institution.

14. Subject who is an Investigator or any other team member involved directly or indirectly in the conduct of the clinical study.
15. Subjects with severe renal impairment: creatinine clearance < 30 mL/min. (Applicable to US sites Only)

Concomitant Medication

- Iron preparations other than ferric maltol or ferric carboxy maltose (FCM) are prohibited at baseline and during study, with the exception of:
    - Over the Counter (OTC) oral supplements/multivitamin type preparations which may be taken, however Subjects are encouraged to keep to the same dose during the course of this study
- Blood transfusions or donations are prohibited.
- Erythropoiesis-stimulating agents (ESAs) are permitted during the study, but the subject must have been on a stable dose for the preceeding 3 months before randomization.
- Vitamin B12 and folic acid supplements/replacement are allowed during the study.
- Immunosuppressants are permitted so long as there is no clinical evidence or suspicion of the immunosuppressant contributing to the subject's anaemia or affecting erythropoiesis. Variations to dosing are permitted at the discretion of the investigator so long as there is no clinical evidence or suspicion of the immunosuppressant contributing to the subjects anaemia or affecting erythropoiesis.

Investigational Medicinal Product

Ferric maltol 30 mg capsules bid

Comparator Therapy

Intravenous iron as ferric carboxy maltose (FCM)

Study Endpoints

The primary endpoint of this study is:

- Proportion of subjects achieving either a 2g/dL increase in Hb OR normalization of Hb (>12g/dL women, >13g/dL men) at Week 12

Secondary efficacy endpoints will include the following

- Change in Hb concentration from baseline to Week 12
- Change in Hb concentration from baseline to Week 12 in subjects with a baseline Hb <9.5 g/dL
- Proportion of subjects who experience a change from baseline in Hb concentration ≥1.0 g/dL at Week 12

- Proportion of subjects with baseline Hb <9.5g/dL that achieve an increase in Hb concentration of ≥1 g/dL at Week 12
- Proportion of subjects with Hb concentration within normal limits at Week 12
- Proportion of subjects with baseline Hb concentration <9.5 g/dL that is within normal limits at Week 12
- Change in Hb concentration from baseline to Week 4
- Change in Hb concentration from baseline to Week 4 in subjects with a baseline Hb <9.5 g/dL
- Proportion of subjects who experience a change from baseline in Hb concentration ≥2.0 g/dL at Week 12
- Proportion of subjects with baseline Hb <9.5g/dL that achieve an increase in Hb concentration of ≥2 g/dL at Week 12
- Proportion of subjects who experience a change from baseline in Hb concentration ≥1.0 g/dL at Week 4
- Proportion of subjects with baseline Hb <9.5g/dL that achieve an increase in Hb concentration of ≥1 g/dL at Week 4
- Proportion of subjects with Hb concentration within normal limits at Week 4
- Proportion of subjects with baseline Hb concentration <9.5 g/dL that is within normal limits at Week 4
- Proportion of subjects who experience a change from baseline in Hb concentration ≥2.0 g/dL at Week 4
- Proportion of subjects with baseline Hb <9.5g/dL that achieve an increase in Hb concentration of ≥2 g/dL at Week 4
- Long term efficacy endpoints i.e. proportion of subjects who are non-anaemic at 6 and 12 months; normalization of ferritin levels at 6 and 12 months

Secondary safety endpoints

- Treatment-emergent Adverse Events (AEs)
- Treatment-emergent Serious Adverse Events (SAEs)
- Adverse Events leading to premature discontinuation of study drug
- Adherence to study medication

Pharmacoeconomic endpoints

- Number of hospital or clinic visits for administration of IV iron

- Proportion of subjects who restart FCM during the study
- Other pharmacoeconomic endpoints

3 ABBREVIATION INDEX

AE	adverse event
ALT	Alanine aminotransferase
AMG	Arzneimittelgesetz
ANCOVA	analysis of covariance
AST	Aspartate aminotransferase
AUC	area under the plasma concentration-time curve
bid	twice daily
BOCF	Baseline Observation Carried Forward
BP	blood pressure
BUN	blood urea nitrogen
BW	body weight
C	Celsius
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
Cmax	maximum observed plasma concentration
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive protein
CS	clinically significant
ESA	Erythropoiesis-stimulating agent
FCM	Ferric carboxy maltose
FDA	Food and Drug Administration
GCP	Good Clinical Practice
h	Hour
Hb	Haemoglobin
HCT	Haematocrit
HDPE	High density polyethylene
HR	heart rate
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Conference on Harmonization
IDA	iron deficiency anaemia
IEC	Independent Ethics Committee
IMP	Investigational Medical Product
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	intention-to-treat
IUD	intrauterine contraceptive devices
IV	Intravenous
IVI	Intravenous iron
LCL	lower confidence limit
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
NCS	non-clinically significant
OFP	oral ferrous products

OTC	Over the counter
PE	Pharmacoeconomics
PI	Prescribing Information
PK	Pharmacokinetic
PP	per protocol
QOL	quality of life
RBC	Red blood cell
SAE	Serious Adverse Event
SCCAI	Simple Clinical Colitis Activity Index
SF-36	Medical outcomes study 36-item short form
SIV	Site Initiation Visit
SOC	System Organ Class
SOP	standard operating procedure
SPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reaction
TIBC	total iron binding capacity
TEAE	Treatment-emergent adverse event
$t_{1/2term}$	apparent terminal elimination half-life
Tmax	the actual sampling time to reach the maximum observed plasma concentration
TSAT	transferrin saturation
UC	ulcerative colitis
WBC	White blood cell
WHO	World Health Organization

4 TABLE OF CONTENTS

5 BACKGROUND INFORMATION

5.1 IRON DEFICIENCY ANAEMIA IN INFLAMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) is a chronic relapsing condition of the gut characterised by inflammation of the mucosal and sub-mucosal tissues. The exact aetiology is unknown but there is a significant auto-immune component to disease activity. Disease symptoms depend on whether the IBD is predominantly small intestine (Crohn's Disease; CD) or large bowel (ulcerative colitis; UC), but abdominal pain, diarrhoea and malabsorption occur frequently in both.

Anaemia is a serious systemic complication and a key symptom of IBD. Other recognised co-morbidities of chronic stable IBD include abnormal bone mineral density, sclerosing cholangitis and uveitis. Anaemia is, however, by far the most common clinical presentation, such that specific guidelines were published in December 2007 for the management of iron deficiency and anaemia in inflammatory bowel diseases (IBD) including UC and CD (Gasche, 2007). An update to these guidelines were published in 2015 (Dignass, 2015).

Iron deficiency anaemia (IDA) in IBD is primarily caused by chronic blood loss from inflamed mucosa and/or iron malabsorption during both active and inactive stages of the disease (Bergamaschi, 2010). In addition, chronic abdominal pain and nausea often result in poor dietary intake, whilst mucosal inflammation in the gastro-intestinal tract may lead to inadequate nutrient absorption (Wilson, 2004). While in normal subjects, daily iron loss averages 1-2 mg and is replaced by absorption of the same amount from food sources; in subjects with iron deficiency associated with UC, the iron loss will likely exceed the subject's capacity for iron absorption from a normal diet (Wilson, 2004). Less frequently, anaemia may be drug-induced (sulfasalazine, thiopurines), or arise from haemolysis or myelodysplastic syndrome (Gasche, 2006). Anaemia of these aetiologies, however, is not treatable with iron replacement therapy.

Because it is associated with substantial impairment of quality of life (QOL), anaemia in IBD deserves greater proactive management by gastroenterologists than generally received (Wells, 2006). Characteristic symptoms include chronic fatigue, headache, and subtle impairment of cognitive function. Reasons for not treating anaemia effectively include intolerance to oral iron therapies and difficulty in delivery and/or risks associated with parenteral iron (Biancone, 2008).

Diagnosis of iron deficiency in IBD is based in principle on laboratory blood parameters. Low haemoglobin (Hb) in the setting of a reduced mean corpuscular volume is usually the initial finding on a routine complete blood count. According to World Health Organization (WHO) criteria, anaemia is defined by Hb levels lower than 13.0 g/dl for males and lower than 12.0 g/dl for females (Blanc, 1968). Haemoglobin levels below 10 g/dl are considered indicative of severe anaemia (Gasche, 2007).

The aim of pharmacologic treatment is to correct the IDA, with the ultimate goal of having the serum Hb return to the reference range. Furthermore, it is expected that correcting the anaemia will ameliorate the associated clinical symptoms.

5.2 INVESTIGATIONAL MEDICAL PRODUCT (INVESTIGATIONAL DRUG)

Treatment of iron deficiency should begin with dietary replacement (i.e., fortified cereals and breads, red meat, beans, green leafy vegetables). However, when diet alone is inadequate to restore iron stores and Hb to normal levels, or when anaemia is moderate or severe,

treatment with exogenous iron supplements should be implemented (Blanc, 1968). Ferrous sulphate is available in multiple formulations and dosages, but is typically taken as 300 mg tablets (60 mg elemental iron) and ferrous gluconate as 320 mg tablets (36 mg elemental iron) three to four times daily. However, as the duodenum can maximally absorb only 10-20 mg of iron a day, greater than 90% of ingested iron is not absorbed, leading to symptomatic adverse events including potential erosions and enteric siderosis (Zhu, 2010). Common adverse effects of oral iron supplements include nausea, epigastric discomfort, and constipation, all of which are dose-related. Adverse effects can occur in up to 20% of subjects, impairing compliance (Zhu, 2010).

In an effort to overcome the significant challenges of iron substitution with oral ferrous products (OFP), ferric maltol (also known as ST10-021 or ST10), a chemically stable complex formed between ferric iron (Fe^{3+}) and maltol (3-hydroxy-2-methyl-4-pyrone) was developed. Ferric maltol makes iron available in the gastrointestinal tract, providing the iron in a biologically labile form for uptake onto transferrin and ferritin and ultimate haematopoiesis and storage on ferritin.

Unlike OFPs which are often given with food in order to reduce side effects, ferric maltol can, and should, be given on an empty stomach to maximise bioavailability. Oral ferric iron chelated with maltol can be administered with improved tolerability and the total dose exposure of unabsorbed iron within the gastrointestinal tract is significantly reduced. In addition, the iron is retained in its chelated form if not absorbed and this may reduce the risk of irritation within the gastrointestinal tract that is often seen with OFP.

Pharmacokinetic (PK) data from the pivotal GCP PK studies conducted in both IBD patients and patients with IDA of any cause demonstrated that uptake of maltol and iron into the plasma after administration of ST10 display completely independent absorption profiles (studies ST10-01-101 and ST10-01-102). In study ST10-01-101, the PK and iron uptake of ST10 was investigated in blood and urine after single and repeated bid oral doses of 30 mg, 60 mg and 90 mg for 8 days in subjects with iron deficiency (with or without anaemia) through measurement of total serum iron, transferrin saturation (TSAT), as well as plasma and urine concentrations of maltol and maltol glucuronide. In study ST10-01-102 the PK of ST10 after a 30 mg single dose administered at steady-state were investigated in patients already being treated in the open label phase of studies ST10-01-301 or ST10-01-302 through measurement of serum iron parameters (transferrin, transferrin saturation [TSAT], total iron binding capacity [TIBC], ferritin, soluble transferrin receptor, total serum iron), plus plasma and urine concentrations of maltol and maltol glucuronide.

5.3 RESULTS FROM PREVIOUS CLINICAL STUDIES

Data for ferric maltol in healthy volunteers at a high iron dose of 180 mg and at the expected therapeutic daily dose of 60 mg (as iron) in ferrous intolerant subjects, suggests that the lack of toxicity to the gastrointestinal tract, as demonstrated in these and nonclinical studies, may translate to a better tolerated and efficacious iron product (Shield TX, data on file; Harvey, 1998).

An open label, uncontrolled study of 23 IDA subjects with documented ferrous sulphate intolerance and GI conditions, was conducted with the same ferric maltol dose as intended for this Phase 3 protocol (30 mg bid for 12 weeks) (Harvey, 1998). Anaemia was fully corrected in 74% of subjects who completed the study (14 out of 19 subjects). Mean Hb increased from 10.6 ± 1.5 to 12.6 ± 1.6 g/dl. Similarly, there was a significant increase in ferritin from pre-treatment levels (8.1 ± 3.5 to 17.4 ± 11.4 µg/l ($p < 0.001$).

The majority (74%) of subjects who completed the study reported no significant change in overall mean daily symptom score during the treatment period. Based on these findings, the publication concluded that ferric maltol could correct iron deficiency and resulted in a low incidence of side effects in subjects with a history of ferrous sulphate intolerance.

A recent, randomised Phase III study of ST10 in subjects with IDA and IBD, who were intolerant of oral iron products or unsuitable for treatment with them has been completed (ST10-01-301 and ST10-01-302). One hundred and twenty eight (128) subjects were randomised to 12 weeks of blinded medication (30mg bid ST10 or matched placebo capsule) followed by a 52 week open-label extension period; during which all available subjects received ST10 at the same dose. 87% and 82% of ST10 and Placebo treated subjects, respectively, completed the 12 week double blind period. The difference between the treatment groups in mean Hb from baseline to week 12 was 2.25g/dL (ANCOVA p<0.0001). Hb increased to normal values at week 12 in 65% of ST10 group and 10% of Placebo subjects (see ST10 Investigator's Brochure). When the Placebo subjects were transferred to ST10 treatment in the open-label phase, there was a sharp rise in Hb levels that mirrored the response in the ST10 group in the double-blind phase. There were further increase in Hb up to 48 weeks of treatment and no indication of any reduction in efficacy over the full 64 week treatment period. Patients who were dosed on ST10 for up to 64 weeks demonstrated no evidence of elevated haemoglobin or iron overload.

In the double-blind phase, adverse events (AEs) were recorded in 58% of ST10 and 72% of the Placebo subjects. Gastrointestinal AEs were observed in 38% and 40%, respectively. In the ST10 group the most common AEs were abdominal pain (10%), diarrhoea (7%), constipation (6%) and nasopharyngitis (4%). Study medication was discontinued due to adverse events (AEs) in 8 ST10 and 5 Placebo subjects. There was 1 serious AE in the ST10 and 2 in the Placebo group. AE data and IBD activity scores (SCCAI, CDAI and IBDQ) suggested that ST10 did not increase IBD symptoms over the 12 week period (see ST10 Investigator's Brochure).

The profile of adverse events in the open-label phase was comparable to that of ST10-treated subjects in the double-blind phase. The most common (>5%) events in the cumulative data set were abdominal pain (16.2%)), abdominal pain upper (5.4%), colitis ulcerative (9.9%), constipation (6.3%), Crohn's disease (7.2%), diarrhoea (14.4%) flatulence (8.1%), nasopharyngitis (18.0%) and arthralgia (8.1%). Overall, events of the Gastrointestinal Disorders SOC were recorded for 63 (56.8%) ST10-treated subjects.

During the double-blind phase, the most common study drug-related TEAE, occurring in 7.8% ST10 and 6.3% Placebo subjects, was abdominal pain. Other more common treatment-related events were constipation (6.3% versus 1.6%) and flatulence (6.3% versus 0). All other study drug-related AEs occurred in 1.6% or 3.1% subjects in either treatment group.

The results of this randomized study showed that 30mg bid ST10 effectively increased Hb in IDA with good levels of tolerability and without worsening IBD symptoms (Gasche, 2015).

Pharmacokinetic Studies

The pharmacokinetics and iron uptake of 30mg bid ST10 has also been recently investigated in a cohort of 15 IBD patients participating in the open-label phase of studies ST10-01-301 and ST10-01-302 (Shield TX, data on file). Plasma concentrations of maltol above the limit of assay detection were transiently observed between 15min and 4h after dosing (mean Cmax 67.3ng/mL; median Tmax 1.0h; mean AUC 136h*ng/mL; mean $t_{1/2term}$ 0.8h). However, consistent with earlier studies of ST10, maltol glucuronide predominated in plasma (mean Cmax 4677ng/mL; median Tmax 1.0h; mean AUC 9651h*ng/mL and mean $t_{1/2term}$ 1.1h).

Maximal change in serum iron and TSAT was observed 2h after dosing. The inter-subject variability for AUC of both maltol and maltol-glucuronide in this cohort was low (approximately 27%).

5.4 RATIONALE FOR THE STUDY

Ferric maltol has been shown to be effective and have an acceptable safety profile in a study of IBD/IDA subjects who were not tolerant of traditional oral iron preparations (Gasche, 2015). This study was placebo-controlled because of the ethical issue of re-randomising patients to other oral iron products and the feasibility of using masked placebo IV study medications. Now that the safety and efficacy profile of ferric maltol has been established a direct randomised comparison with IV iron in IBD/IDA is desirable to show what differences in efficacy, safety and burden upon the patient there may be between the two treatments. This will allow better choice of IV versus ferric maltol in treating IDA in subjects both from a patient/physician perspective but also wider healthcare decision making.

5.4.1 Medical and regulatory background

For all patients with IDA, and for IBD patients in particular, there is an ongoing need for well tolerated oral iron therapies that effectively normalize haemoglobin without adversely affecting IBD activity (Weiss, 2005; Zimmerman, 2007). 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 (Gasche, 2007). While intravenous iron is undoubtedly effective in correcting anaemia, it is associated with higher healthcare costs, the inconvenience of intravenous infusion (Stein, 2010; Gasche,2007; Evstatiev, 2011) and a risk of anaphylactic reactions that require immediate emergency intervention (EMA, 2013; Auerbach, 2007; Gomollon, 2014) such that these therapies must be given only when resucitation equipment is at hand.

5.4.2 Population

As no curative treatment is presently available for IBD, treatment options are restricted to controlling symptoms, maintaining remission and preventing relapse. As such, treatment of IDA, a key symptom of the disease, is integral to the medical management of IBD. Iron deficiency anaemia in UC for example is a chronically debilitating disorder which has a significant impact on the QOL of affected subjects. Up to one third of patients with UC suffer from recurrent anaemia, with hospitalisation required in severe cases (Gasche, 2007).

The current protocol will include subjects with IDA in the presence of IBD, diagnosed by either endoscopy or biopsy (see Van Assche, 2010; Dignass, 2012).

5.4.3 Study Design

The study will be performed using a prospective, multicentre, randomised, open-label design. Subjects will be randomised to receive either ferric maltol 30mg bid or Intravenous (IV) iron (ferric carboxymaltose, FCM), dosed according to the local SPC/PI. Efficacy and safety of ferric maltol compared with IV iron (FCM) will be evaluated during the study.

Subjects who entered the study under the previous protocol for the 52 weeks open-label design and completed their study beyond the 12 weeks treatment period, the next scheduled visit will be their End of Study Visit. Otherwise, subjects after the eligibility screening period will enter a 12 weeks treatment period.

The primary endpoint of this study is:

- Proportion of subjects achieving either a 2g/dL increase in Hb OR normalization of Hb (>12g/dL women, >13g/dL men) at Week 12

Secondary efficacy endpoints will include the following

- Change in Hb concentration from baseline to Week 12
- Change in Hb concentration from baseline to Week 12 in subjects with a baseline Hb <9.5 g/dL
- Proportion of subjects who experience a change from baseline in Hb concentration ≥1.0 g/dL at Week 12
- Proportion of subjects with baseline Hb <9.5g/dL that achieve an increase in Hb concentration of ≥1 g/dL at Week 12
- Proportion of subjects with Hb concentration within normal limits at Week 12
- Proportion of subjects with baseline Hb concentration <9.5 g/dL that is within normal limits at Week 12
- Change in Hb concentration from baseline to Week 4
- Change in Hb concentration from baseline to Week 4 in subjects with a baseline Hb <9.5 g/dL
- Proportion of subjects who experience a change from baseline in Hb concentration ≥2.0 g/dL at Week 12
- Proportion of subjects with baseline Hb <9.5g/dL that achieve an increase in Hb concentration of ≥2 g/dL at Week 12
- Proportion of subjects who experience a change from baseline in Hb concentration ≥1.0 g/dL at Week 4
- Proportion of subjects with baseline Hb <9.5g/dL that achieve an increase in Hb concentration of ≥1 g/dL at Week 4
- Proportion of subjects with Hb concentration within normal limits at Week 4
- Proportion of subjects with baseline Hb concentration <9.5 g/dL that is within normal limits at Week 4
- Proportion of subjects who experience a change from baseline in Hb concentration ≥2.0 g/dL at Week 4
- Proportion of subjects with baseline Hb <9.5g/dL that achieve an increase in Hb concentration of ≥2 g/dL at Week 4

- Long term efficacy endpoints i.e. proportion of subjects who are non-anaemic at 6 and 12 months; normalization of ferritin levels at 6 and 12 months

Secondary safety endpoints

- Treatment-emergent Adverse Events (AEs)
- Treatment-emergent Serious Adverse Events (SAEs)
- Adverse Events leading to premature discontinuation of study drug
- Adherence to study medication

Pharmacoeconomic (PE) Endpoints

- Number of hospital or clinic visits for administration of IV iron
- Proportion of subjects who restart FCM during the study
- Other pharmacoeconomic endpoints

5.4.4 Comparator Drugs

Intravenous iron as ferric carboxymaltose (FCM)

5.5 DOSE SELECTION AND TREATMENT DURATION

The dose of ferric maltol will mirror the dose evaluated in the pivotal phase 3 trials (ST10-01-301 and ST10-01-302) of 30mg BID. The comparator product is IV ferric carboxymaltose of which the dose is determined by the local summary of product characteristics (SPC/PI).

Ferric Maltol

Subjects will remain on therapy for the whole duration of the study treatment period (12 weeks). If the subjects went beyond the 12 weeks the next scheduled visit will be their End of Study Visit.

The date of Visit 2 will be the date of initial dosing with ferric maltol.

IV Iron (FCM)

Initial dosing and post randomization dosing will be as per the local SPC/PI with the dose administered being calculated based on a subject's screening visit Hb and weight. Initial dosing should be timed to occur on the same day as randomization wherever possible and within 5 days of randomization if not possible. The date of Visit 2 will be the date of initial dosing of FCM. Hb levels will be used for ongoing treatment decisions at subsequent visits, as required per the local SPC/PI. Subjects who remain anaemic will receive additional FCM IV iron doses according to the local SPC/PI.

This study will continue until the last randomized subject completes the study safety follow up visit or prematurely discontinues from the study.

5.6 RISK-BENEFIT EVALUATION

A positive benefit-risk for treatment with ferric maltol has been established in a randomized clinical study and the data published in a peer-reviewed journal (Gasche, 2015). The safety profile of ferric maltol in IBD is considered to be acceptable, with few discontinuations and no evidence of IBD flare or disease worsening. The Hb rise seen in this group of subjects was also comparable to earlier reports of IDA treatment with intravenous iron. The comparator product, FCM, is approved throughout Europe for the treatment of IDA including in subjects with IBD. There is considered to be a good balance of risks and potential benefits in either treatment arm, justifying randomization of subjects within this open-label clinical study.

The current study design does not pose additional risk for the subjects as no additional interventional procedures are planned during the study period, except for blood sampling similar to clinical routine. Total blood loss as a result of monthly phlebotomy will be approximately 65 millilitres; substantially below the volume of routine blood donation.

Subjects that develop Hb concentrations ≤7.5 g/dL (4.7 mmol/l) will be withdrawn from the study to receive best standard medical care.

The current protocol contains all information to perform the study according to the legal requirements, and to the current revisions of the recommendations of the Declaration of Helsinki, Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) guidelines.

6 STUDY OBJECTIVES

6.1 PRIMARY OBJECTIVE

To compare the efficacy of ferric maltol and intravenous iron (FCM) in the treatment and maintenance of iron deficiency anaemia in subjects with IBD.

6.2 SECONDARY OBJECTIVE

To evaluate the safety and tolerability of ferric maltol and IVI in subjects over a treatment duration of up to 52 weeks.

To evaluate long-term healthcare resources utilized in the management of IDA in IBD.

7 INVESTIGATIONAL PLAN

7.1 STUDY DESCRIPTION

A phase 3b, randomized, controlled, multicentre study with oral ferric maltol or intravenous iron (FCM), for the treatment of iron deficiency anaemia in subjects with inflammatory bowel disease.

Primary efficacy and safety of ferric maltol and intravenous iron (ferric carboxymaltose) will be evaluated after 12 weeks.

In the FCM arm, IV iron treatment will be repeated if the subject is anaemic (see section 5.5) per the local SPC/PI.

The protocol will include subjects with IDA in the presence of IBD, diagnosed by either endoscopy or biopsy (see Van Assche, 2010; Dignass, 2012).

Anaemia entry criteria in this study is defined by an Hb concentration ≥8.0 g/dl and ≤11.0 g/dl (4.96 - 6.83 mmol/l) in females and ≥ 8.0 g/dl and ≤12 g/dl (4.96 - 7.45 mmol/l) in men.

The study will consist of 3 periods:

- Screening: Up to 14 days
- Randomised Treatment:
  - 12 weeks treatment period
  - subjects entered in the 52 weeks treatment period will finish their randomized treatment at week 12, unless they went beyond this visit. If so, the next scheduled visit will be their last treatment visit.

- End of study evaluations will occur Week 12/premature discontinuation or next scheduled visit if subjects went beyond Week 12.
- Post-treatment safety follow-up: 14 days after last treatment visit or premature discontinuation of ferric maltol or FCM

Subjects that develop Hb concentrations ≤7.5 g/dl (4.7 mmol/l) will be withdrawn from the protocol to receive best standard medical care.

Effectiveness will be analysed by determining whether the Test group (ferric maltol) shows a statistically significant non inferiority of responder rate (≥ 2g/dL Hb rise at Week 12 compared to baseline OR normal Hb at Week 12) as compared to IV iron (ferric carboxy maltose).

Approximately 242 subjects in this study will be randomised at a ratio of 1:1, ferric maltol or IV iron (ferric carboxy maltose, FCM).

For the purposes of this protocol, the following conventions are used:

- 1 week equals 7 days
- 4 weeks equal 28 days
- 12 weeks equal 84 days
- 52 weeks equal 364 days

7.2 INVESTIGATIONAL SITES

The study will involve approximately 37 EU sites and 18 US sites.

To ensure the successful completion of the study, the Sponsor may wish to replace sites that have very low subject enrolment. Sites not able to recruit any subjects within 2 months of study initiation or sites with subjects exhibiting major protocol deviations will be considered for closure.

7.3 STUDY VARIABLES

7.3.1 Primary Efficacy variables

- Haemoglobin

7.3.2 Primary Safety variables

General safety and tolerability will be assessed by:

- Adverse events
- Standard laboratory evaluation

Additional exploratory endpoints and variables will also be defined. For details, please refer to the Statistical Analysis Plan.

7.4 SELECTION AND WITHDRAWAL OF SUBJECTS

No deviations to the inclusion or exclusion criteria are allowed.

7.4.1 Inclusion criteria

All of the following criteria must be met to randomize a subject in the study:

1. Subjects must be competent to understand the information given in the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) approved informed consent form and must sign and date the informed consent prior to any study mandated procedure
2. Subjects must be willing and able to comply with study requirements
3. Age ≥ 18 years
4. Subjects must have a confirmed diagnosis of IBD (endoscopic and/or biopsy)
5. Subjects must be considered suitable for intravenous iron treatment by the Investigator
6. Subjects must have iron deficiency anaemia defined by the following criteria:

a. Hb ≥8.0 g/dL and ≤11.0 g/dL for women OR a Hb ≥8.0 g/dL and ≤12.0 g/dL for men

b. AND Ferritin <30ng/ml OR Ferritin <100 ng/ml WITH Transferrin saturation (TSAT) <20%

7. Female subjects of childbearing potential (including perimenopausal females who have had a menstrual period within 1 year prior to screening) must agree to use a reliable method of contraception until they have completed the study and for at least 4 weeks following their final study visit. Reliable contraception is defined as a method which results in a low failure rate, i.e., less than 1% per year when used consistently and correctly, such as implants, injectables, some intrauterine contraceptive devices (IUDs), complete sexual abstinence, or a vasectomized partner. Oral contraceptive medications are allowed in this study. Female subjects who are surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy) or postmenopausal (defined as no menstrual period within 1 year of screening) are also allowed to participate.

7.4.2 Exclusion criteria

A subject who meets any of the following criteria is not eligible for participation in the study.

1. Subject with anaemia due to any cause other than iron deficiency, including, but not limited to:

   a. Untreated or untreatable severe malabsorption syndrome

   b. Immunosuppressant use. Immunosuppressants are permitted so long as there is no clinical evidence or suspicion of the immunosuppressant contributing to the subject's anaemia or affecting erythropoiesis.

   Variations to dosing are permitted at the discretion of the investigator so long as there is no clinical evidence or suspicion of the immunosuppressant contributing to the subject's anaemia or affecting erythropoiesis

2. Subject who has received prior to screening:

   a. Within 8 weeks intramuscular or intravenous (IV) iron or administration of depot iron preparation

   b. Within 2 weeks a blood transfusion

   c. Oral iron supplementation, taken specifically to treat anaemia, within the previous 4 weeks (Over the Counter (OTC) multivitamins containing iron are permitted)

3. Subjects with active inflammatory bowel disease as defined by a SCCAI score greater than 5 at Screening or a CDAI score greater than 300 in the Screening period (as assessed using the Screening haematocrit (HCT) and CDAI diary card completed by the subject for 7 days prior to planned randomization).

4. Subjects with known hypersensitivity or allergy to either the active substance or excipients of ferric maltol capsules or ferric carboxymaltose solution for IV administration

5. Subjects who have had serious adverse reactions to previous doses of ferric carboxymaltose or any other intravenous iron.

6. Subjects with contraindication for treatment with iron preparations, e.g. hemochromatosis, chronic hemolytic disease, sideroblastic anaemia, thalassemia, or lead intoxication induced anaemia.
7. Subjects with vitamin B12 or folic acid deficiency as determined by the central laboratory screening results. Subjects may start vitamin B12 or folate replacement and rescreen after at least 2 weeks.
8. Subjects who are pregnant or breast feeding.
9. Concomitant medical conditions with significant active bleeding likely to initiate or prolong anaemia.
10. Participation in any other interventional clinical study within 30 days prior to screening.
11. Subject with cardiovascular, liver, renal, haematologic, gastrointestinal, immunologic, endocrine, metabolic, or central nervous system disease that, in the opinion of the Investigator, may adversely affect the safety of the subject or severely limit the lifespan of the subject (i.e. unlikely to complete the full duration of the study).
12. Subject with significant neurologic or psychiatric symptoms resulting in disorientation, memory impairment, or inability to report accurately that might interfere with treatment compliance, study conduct or interpretation of the results (e.g., Alzheimer's disease, schizophrenia or other psychosis, active or current alcohol or drug abuse)
13. Subject who is an inmate of a psychiatric ward, prison, or other state institution.
14. Subject who is an Investigator or any other team member involved directly or indirectly in the conduct of the clinical study.
15. Subjects with severe renal impairment: creatinine clearance < 30 mL/min. (Applicable to US sites Only)

7.4.3 Concomitant medication at baseline and during the study

- Iron preparations other than ferric maltol or FCM are prohibited at baseline and during study; with the exception of:
    - Over the Counter (OTC) oral supplements/multivitamin type preparations which may be taken, however Subjects are encouraged to keep to the same dose during the course of this study
- Blood transfusions or donations prohibited
- Erythropoiesis-stimulating agents (ESAs) are permitted during the study, but the subject must have been on a stable dose for the preceeding 3 months before randomization
- Vitamin B12 and folic acid supplements/replacement are allowed during the study
- Immunosuppressants are permitted so long as there is no clinical evidence or suspicion of the immunosuppressant contributing to the subject's anaemia or affecting erythropoiesis. Variations to dosing are permitted at the discretion of the investigator so long as there is no clinical evidence or suspicion of the immunosuppressant contributing to the subjects anaemia or affecting erythropoiesis.

7.4.4 Advice regarding potential ferric maltol drug interactions

Iron-drug interactions of clinical significance have been reported to occur with a large number of concomitant therapies. Concurrent ingestion of oral iron causes marked decrease in the bioavailability of a number of drugs due to the formation of iron-drug complexes (chelation or binding of iron by the second drug). Examples of affected drugs are: quinolone or tetracycline antibiotics, bisphosphonates, angiotensin-converting enzyme inhibitors, folic acid, methyldopa, levodopa, carbidopa, levothyroxine, and mycophenolate.

To minimize the potential for drug interactions, ferric maltol should be taken orally first thing in the morning at least 1 hour before food and concomitant medications and last thing at night before bed at least 2 hours after food and concomitant medications. Capsules must be taken on an empty stomach with water only. There should be at least an 8-hour gap between doses.

7.4.5 Rescreening

A subject who fails initial screening for any reason may be re-screened one additional time; subjects may be screened up to two times total. All screening visits must be adequately documented in the subject's source documents. Subjects who fail screening due to either vitamin B12 or folate deficiency may receive vitamin B12 or folate replacement and then rescreen after a minimum of 2 weeks.

7.4.6 Individual discontinuation criteria

Treatment will be stopped for any of the following reasons:

- Pregnancy or not using a reliable method of birth control (female subjects of childbearing potential)
- Withdrawal of informed consent
- Hb ≤7.5 g/dL
- TSAT above 60% or a ferritin above 800 ng/ml (the subject may remain in the study if the rise is confirmed by a laboratory retest to be transient as a result of recent FCM or ferric maltol administration. Retests must occur 7-10 days after the initial TSAT result becomes available and should be conducted at least 4 hours post dosing with FCM or ferric maltol)
- Serious adverse events that are judged by the Investigator to be related to ferric maltol or FCM treatment
- Use of prohibited co-medications during the study treatment period (see Section 7.4.3)
- Blood transfusions for any cause during the study treatment period
- Any dose changes to dosing of immunosuppressants and/or ESAs that may cause anaemia or affect erythropoiesis

The reason for study drug discontinuation and the date of last dose must be recorded in the CRF. Subjects who prematurely discontinue study drug or withdraw consent must return to clinic for an End of Study Visitat the time of discontinuation. Should the End of Study Visit occur 14 days or more following the last dose of ferric maltol or FCM then a subsequent safety follow-up phone call is not required.

7.4.7 Subject selection

The subject will receive a copy of the written informed consent form containing a complete and comprehensive explanation of the significance, nature, extent and possible risks of the study, duties concerning insurance and the statement that the subject is free to withdraw

from the study at any time without any negative consequences. In addition, a physician will carry out an oral information session during which the subject will be given sufficient time and opportunity to clarify any questions. After this, the written informed consent will be given to the subject for signature. The original must be filed in the Investigator's Study File and a copy will be given to the subject.

The Investigator will confirm that each individual subject has received an explanation in accordance with the study protocol and has signed the appropriate informed consent form.

If an Investigator chooses to advertise for subjects, whether in professional or consumer publications, via public broadcast, or any other means, all advertising must be approved by the Sponsor and the IEC/IRB prior to first use. A copy of the IEC/IRB-approved advertising and approval letter must be provided to the Sponsor.

7.4.8 Replacement policy

While each subject will be expected to complete the full course of the study, a participant may withdraw from the study at any time for any reason. The reason for withdrawal will be documented on the End of Study Case Report Form (CRF).

Discontinuations during the screening phase are considered screening failures and will be replaced. Discontinuations after randomization will not be replaced.

8 STUDY DRUGS

8.1 INVESTIGATIONAL MEDICAL PRODUCT

Eligible subjects will be randomised to receive one of the following treatments for the duration of the study :

- Oral ferric maltol, 30 mg capsule bid.
- Intravenous iron (ferric carboxymaltose, FCM), administered as per the local SPC/PI.

Ferric maltol medication will be capsules to be taken orally first thing in the morning at least 1 hour before food and concomitant medications. and last thing at night before bed at least 2 hours after food and concomitant medications. Capsules must be taken on an empty stomach with water only. There should be at least an 8-hour gap between doses.

For detailed information regarding the components of ferric maltol, please refer to the Investigator’s Brochure.

If a subject forgets to take a morning capsule, this dose may be taken with the evening capsule on an empty stomach with water last thing at night before bed. Missed evening tablets should be documented as ‘missed’ and should not be taken the next day.

Intravenous iron (ferric carboxymaltose) will be administered as per the local SPC/PI.

8.2 PACKAGING

The ferric maltol product will be supplied in a white polypropylene securitainer with a tamper evident standard securitainer cap of white medium density polyethylene. Each bottle will contain 56 capsules.

8.3 LABELLING

All ferric maltol bottles will be identified by lot number and unique bottle number for reconciliation purposes only.

Labels of the ferric maltol Investigational Medicinal Product (IMP) will contain information according to European Directives 2003/94/EC, 2001/20/EC and Annex 13/ 21CFR312.6.

8.4 STORAGE

Ferric maltol IMP must be stored between the range of ≥5°C to <25°C (min/max = 5 - 24.99°C) and must not be refrigerated or frozen. In the event that the drug is exposed to temperatures lower than 5°C or greater than or equal to 25 °C, the Sponsor should be contacted for review and further instruction.

FCM must be stored in accordance with the instructions in the local SPC/PI.

8.5 TREATMENT ASSIGNMENT AND BLINDING

At randomization the eCRF randomization module will assign the subject to either the ferric maltol 30mg bid or IV iron (ferric carboxy maltose, FCM) treatment group. The site will dispense the appropriate number of open-label ferric maltol bottles at each scheduled study visit according to the schedule of assessments (Section 9.1) or administer IV iron (ferric carboxymaltose) as per the local summary of product characteristics/prescribing information. IV iron dosing with FCM should ideally commence on the same day as randomization or no later than 5 days after randomization. The date of Visit 2 is the date of the first dose of IV iron or ferric maltol (see Section 9.2.2).

This is an open label study and treatment assignment is not blinded.

8.5.1 Treatment assignment

Subjects will be randomized 1:1 to either treatment. Randomization will be centrally controlled and stratified by screening Hb (< or ≥ 10g/dL Female; < or ≥ 11g/dL Male) and by IBD (UC or CD).

8.5.2 Subject screening and Randomization number

Subjects who sign the informed consent will be identified at the Screening Visit by a unique number consisting of a 4 digit site number and 3 digit subject number. If a subject is re-screened, they will be identified in the eCRF/database with the same number. The number uniquely identifies every subject eligible for the study.

8.5.3 Maintenance of the randomization code

Not applicable as this study is an open label study.

8.5.4 Emergency unblinding

Not applicable as this study is an open label study.

8.6 TREATMENT COMPLIANCE

Subjects will be instructed to take the ferric maltol study drug as described in detail on the drug labels and by the study site. Subjects will be instructed to return all unused supplies and all clinical study medication packaging at each visit. The delivery of medication to the site, its use and return, as well as subject-specific compliance, will be reconciled and documented using a Drug Accountability Form in order to monitor compliance with the medication schedule. All opened containers, together with remaining contents, and unopened containers will be kept by the Investigator in a secure, locked area until return to the drug supplier by the monitor or the Sponsor approves local destruction at the Investigator site, based on prior documented review that the appropriate SOPs are in place at site and written confirmation of destruction will be provided for the TMF. The Drug Accountability Forms will be maintained

regularly and must be available for inspection at any time. The Investigator will use the IMP only within the framework of this clinical study and in accordance with the existing study protocol. A written explanation must be given for any container/IMP that is missing.

As discussed in Section 8.1, ferric maltol study drug will be capsules taken orally first thing in the morning at least 1 hour before food and concomitant medications and last thing at night before bed at least 2 hours after food and concomitant medications. Capsules must be taken on an empty stomach with water only. There should be at least an 8-hour gap between doses.

If a subject forgets to take a morning capsule, this dose may be taken with the evening capsule on an empty stomach with water, last thing at night before bed. Missed evening tablets should be documented as 'missed' and should not be taken the next day.

If a subject is found to be non-compliant with the study medication (defined as less than 80% or more than 120% compliant with the dosage schedule), the subject will be counselled and trained on the importance of maintaining adherence to study medication. If the subject is repeatedly non-adherent, a decision will be made by the medical monitor and/or Sponsor as to whether the subject should be withdrawn from the study treatment.

Intravenous iron (ferric carboxymaltose) will be administered according to the local summary of product characteristics. Subjects who do not attend for their intravenous iron treatment may be withdrawn from the study. A copy of the relevant local SPC/PI for FCM will be available in the Investigator Site File (ISF). Special safety information and warnings/precautions relating to administration of FCM will be highlighted to the Investigator during the Site Initiation Visit (SIV).

9 STUDY PROCEDURES

9.1 SCHEDULE OF ASSESSMENTS

	Screening Period	Treatment						[8]Follow-up
Duration	**Up to 14 days**	**Week**						**14 days after drug discontinuation**
Week		**0**	**4**	**12**	**(24)[15]**	**(36)[16]**	**(52)[17]**	**(54)**
[9]Visits	**1**	**2**	**3**	**4**	**(5)**	**(6)**	**(7)**	**(8)**
Informed Consent	X							
Eligibility	X	X						
Demographics	X							
Medical history	X							
Physical examination	X							
[1]Vital signs	X							
[2]Height & weight	X	X	X	X	(X)	(X)	(X)	
[3]Basic chemistry	X							
[4]Liver function tests	X							
[5]Haematology; Iron markers	X	X	X	X	(X)	(X)	(X)	
C-reactive protein		X						
[13]Retained plasma and serum samples		X		X				
[6]Randomization		X						
Collect IV Iron History / FCM dosing detail	X	X	X	X	(X)	(X)	(X)	
SCCAI or CDAI[12]	X[12]			X	(X)	(X)	(X)	
[10]Collect pharmacoeconomic (PE) and SF-36 data		X	[11]X	X	(X)	(X)	(X)	
[7]Pregnancy test	X			X			(X)	
Dispense/Administer study medication [14]		X		(X)	(X)	(X)		
Compliance check			X	X	(X)	(X)	(X)	
Adverse events		X	X	X	(X)	(X)	(X)	X
Prior/Concomitant medication	X	X	X	X	(X)	(X)	(X)	X

1 Vital signs (blood pressure & heart rate) are taken after subject has been sitting for 5 minutes
2 Height & weight measured during Screening, weight only at other visits
3 Basic chemistry: bicarbonate, BUN, creatinine, chloride, glucose, potassium, sodium, Vitamin B12 and folate, creatinine clearance (US-only)
4 Liver function tests: ALT, AST and total bilirubin
5 Haematology and Iron markers all visits: haematocrit, haemoglobin, platelets, RBC count, RBC Hb concentration; WBC count and differential; total serum iron; ferritin, transferrin; TSAT.
6 Maximum 14 days between screening and randomization.
7 Urine pregnancy test, kits provided by central laboratory.

8 Follow up is conducted by telephone, unless the Subject has an ongoing AE that requires physical examination or investigations for assessment/management. Visit 8 will take place 14 days after Visit 4 (Week 12/Early Termination) unless subject discontinued treatment early and end of study/ Week 12 assessments occurred 14 days or more after the last dose.

9 Visit Windows: Maximum of 14 days between screening and randomization. Subjects randomised to FCM must complete Visit 2 ideally on the day of randomization or within 5 days. The Subject must visit to complete:
Visits 3 and 4: +/- 1 week relative to date of Visit 2/first dose administered
Visits 4 to 7: +/- 1 week relative to date of Visit 2/first dose administered
Visit 8: 14 days (+5 days) after Visit 4 (unless subject discontinued treatment early and end of study/ Week 12 assessments occurred 14 days or more after the last dose

10 SF36 to be administered at Week 0 (baseline), and Week 12, 24, 36 and 52

11 SF36 is not collected at this visit

12 For CD subjects, a CDAI diary card will be provided at Screening, for completion over the 7 days prior to scheduled Visit 2. The screening haematocrit value will be used for the screening CDAI calculation to assess eligibility prior to randomization and will also count as the baseline CDAI value. For CD subjects, CDAI diary cards will then be provided at Visits 3 and 4. Subjects who went beyond week 12 will receive CDAI diary, at 5 & 6 for completion over the 7 days prior to the scheduled dates of Visit 4, 5, 6 & 7.

13 Retained serum and plasma samples will only be collected from trial subjects at those Investigator sites who have suitable freezer facilities for storage of the samples at -70°C/-80°C, prior to subsequent periodic shipping to the central laboratory on dry-ice. Detailed instructions will be provided in the Laboratory Manual.

14. Dispense/Administer study drug: based on the randomization stratification subjects will receive FCM/Ferric Maltol on Visit 2. If subjects went beyond Visit 4 (Week 12) and their treatment period will be continuing according to previous protocol until the next scheduled visit.

15. Visit 5 (Week 24) will only occur if subjects went beyond Visit 4 according to previous protocol, otherwise this will be the End of Study Visit.

16. Visit 6 (Week 36) will only occur if subjects went beyond Visit 5 (week 24) according to previous protocol, otherwise this will be the End of Study Visit.

17. Visit 7 (Week 52) will only occur if subjects went beyond Visit 6 (Week 36) according to previous protocol, otherwise this will be the End of Study Visit.

9.2 TREATMENT PROCEDURES BY VISIT

9.2.1 Screening visit (Visit 1/between Day -14 and Day -1)

The following screening procedures will be performed at the Screening visit:

1. Fully inform subject regarding study and obtain written informed consent
2. Assign subject number
3. Document demographic information
4. Document medical history including all ongoing conditions and relevant medical history from the past 5 years (including all major hospitalisations and surgeries). Symptoms related to IBD need not be listed on the medical history form; however, worsening of any symptoms and flares during the course of this study must be captured as AEs.
5. Conduct a brief physical exam including vital signs (BP and HR), body weight, height, and review of the following systems: General appearance; skin; head, eyes, ears, nose and throat; cardiovascular; respiratory; abdominal and gastrointestinal; and musculoskeletal.
6. Collect basic chemistry, liver function, iron markers and haematology samples
7. Document concomitant medications including all ongoing medications and those taken within the last 12 weeks, plus
    a. Document all prescription iron replacement therapies taken in the last 12 months, all prior oral ferrous treatment history (with associated IBD disease severity score, see Section 10.4.1) and all prior IV iron treatment history where applicable.
    b. Verify that subject has not received any prohibited concomitant medications as described in the inclusion/exclusion criteria and Section 7.4.3
8. For UC subjects, record the SCCAI score. For CD subjects dispense CDAI diary and instruct the subject to complete for 7 days prior to randomization. Use the central laboratory screening haematocrit value to calculate the CDAI score for eligibility assessment, which will also count as the baseline value.
9. For female subjects of childbearing potential, perform urine pregnancy test and document method of contraception
10. Complete the Visit Specific eCRFs

Subjects who appear to meet all inclusion and exclusion criteria will be scheduled for randomization within 14 days of Screening. CD subjects will be reminded to complete their CDAI diary for the 7 days prior to scheduled randomization date.

9.2.2 Randomization visit (Visit 2/ Day 0)

Subjects who meet all Inclusion/Exclusion criteria are eligible to be randomised during this visit. Subjects will be randomized into one of two dose groups; 30 mg ferric maltol bid or Intravenous iron (ferric carboxymaltose, FCM). Randomization must occur no more than 14 days after the Screening Visit (Visit 1).

Initial dosing with ferric maltol must occur on the same day of randomization at Visit 2. Dosing with IV iron (FCM) should occur on the same day of randomization wherever possible and within 5 days from randomization if not. The date of Visit 2 is the date of first dose with ferric maltol or FCM.

The following procedures will be completed. Procedures 1-8 must be completed prior to randomising the subject and first dosing with ferric maltol or FCM.

1. Collect haematology, iron markers, C-reactive protein and retained samples (see Section 10.2.12 for additional information regarding retained samples collection)
2. Review and record all concomitant medications. Subjects who have received an excluded medication since Screening (Visit 1) will be ineligible for randomization
3. Collect IV Iron History
4. Measure subject's body weight
5. For CD subjects, use the screening period CDAI diary data and screening haematocrit (HCT) value from the central laboratory to calculate the CDAI score for eligibility assessment, which will also count as the baseline value
6. Collect pharmacoeconomic (PE) and SF-36 data
7. Review all Inclusion/Exclusion criteria
8. Record all AEs since last visit
9. If subject qualifies, complete the eCRF Randomization module to treatment assignment
10. If the subject has been assigned to receive ferric maltol, dispense 3 bottles from study drug kit which will be sufficient for 12 weeks of treatment. Remind the subject to take the study medication first thing in the morning at least 1 hour before food and concomitant medications. and last thing at night before bed at least 2 hours after food and concomitant medications. Capsules must be taken on an empty stomach with water only. There should be at least an 8-hour gap between doses.
11. If the subject has been assigned to receive IV ferric carboxymaltose follow the dosing instructions as per the local summary of product characteristics/prescribing information and record the FCM dosing information in the eCRF.
12. Instruct the subject to call the clinic or return promptly should an AE occur
13. Schedule the Week 4 visit
14. Complete the Visit Specific eCRFs

9.2.3 Visit 3 (Week 4)

The following procedures will be completed during the visit:

1. Collect haematology and iron markers samples
2. Collect FCM dosing history information
3. Collect PE data
4. Measure subject's body weight
5. Check Hb, TSAT and ferritin levels (when central laboratory results available).
6. FCM subjects may be administered IV iron as per the local summary of product characteristics/Prescribing Information, if clinically required.
7. Review and record all concomitant medications
8. Record all AEs since last visit
9. For subjects assigned to ferric maltol, remind the subject to take the study medication first

thing in the morning at least 1 hour before food and concomitant medications, and last thing at night before bed at least 2 hours after food and concomitant medications. Capsules must be taken on an empty stomach with water only. There should be at least an 8-hour gap between doses.

10. For subjects assigned to ferric maltol, check bottles dispensed at prior visit, perform drug accountability and a compliance check and return bottles to subject.
11. Schedule Visit 4 at Week 12
12. For CD subjects, dispense CDAI diary and instruct subject on completion for 7 days prior to planned Visit 4
13. Complete the Visit Specific eCRFs

9.2.4 Visit 4 (Week 12) or End of Study

The following procedures will be completed at Visit 4 (Week 12):

1. Collect haematology, iron markers and retained samples (see Section 10.2.12 for additional information regarding retained samples collection)
2. Collect FCM dosing history information
3. Measure subject's body weight
4. For UC subjects, record the SCCAI score; for CD subjects, collect CDAI diary dispensed at Visit 3 and calculate the current CDAI score using the Visit 4 HCT result from the central laboratory (when available)
5. Collect PE and SF-36 data
6. For female subjects of childbearing potential, perform urine pregnancy test
7. Check Hb, TSAT and ferritin levels (when central laboratory results available)
8. For ferric maltol study drug continuation, dispense 3 bottles from study drug kit which will be sufficient for 12 weeks of treatment. Check compliance and remind the subject to take the study medication first thing in the morning at least 1 hour before food and concomitant medications. and last thing at night before bed at least 2 hours after food and concomitant medications. Capsules must be taken on an empty stomach with water only. There should be at least an 8-hour gap between doses.
9. FCM subjects who have low Hb (see section 5.5) should be administered IV iron as per the local summary of product characteristics/ prescribing information.
10. Review and record all concomitant medications
11. Record all AEs since last visit
12. Collect bottles dispensed at prior visit and perform drug accountability and a compliance check
13. Instruct the subject to call the clinic or return promptly should an AE occur
14. For CD subjects, dispense CDAI diary and instruct subject on completion for 7 days prior to planned Visit 5, if subjects went beyond Visit 4.
15. Schedule a telephone follow up visit at least 14 days after Visit 4.
16. Complete the Visit Specific eCRFs

9.2.5 Visit 5 (Week 24) or End of Study

The following procedures will ONLY BE COMPLETED if subjects went beyond week 12 according to previous protocol. In that case this visit will be the End of Study Visit.

1. Collect haematology and iron markers samples
2. Collect FCM dosing history information
3. Measure subject's body weight
4. For UC subjects, record the SCCAI score; for CD subjects, collect CDAI diary dispensed at Visit 4 and calculate current CDAI score using the Visit 5 HCT result from the central laboratory (when available)
5. Collect PE and SF-36 data
6. Check Hb, TSAT and ferritin levels (when central laboratory results available)
7. Review and record all concomitant medications
8. Record all AEs since last visit
9. Collect bottles dispensed at prior visit and perform drug accountability and a compliance check
10. Instruct the subject to call the clinic or return promptly should an AE occur
17. Schedule a telephone follow up visit at least 14 days after Visit 5.
11. Complete the Visit Specific eCRFs

9.2.6 Visit 6 (Week 36) or End of Study

The following procedures will ONLY BE COMPLETED if subjects went beyond week 12 according to previous protocol. In that case this visit will be the End of Study Visit

1. Collect haematology and iron markers samples
2. Collect FCM dosing history information
3. Measure subject's body weight
4. For UC subjects, record the SCCAI score; for CD subjects, collect CDAI diary dispensed at Visit 5 and calculate current CDAI score using the Visit 6 HCT result from the central laboratory (when available)
5. Collect PE and SF-36 data
6. Check Hb, TSAT and ferritin levels (when central laboratory results available)
7. Review and record all concomitant medications
8. Record all AEs since last visit
9. Collect bottles dispensed at prior visit and perform drug accountability and a compliance check
10. Instruct the subject to call the clinic or return promptly should an AE occur
11. Schedule a telephone follow-up visit at least 14 days after Visit 6. Complete the Visit Specific eCRFs

9.2.7 Visit 7 (Week 52) or End of study visit

ONLY BE COMPLETED if subjects went beyond Visit 6 according to previous protocol. The following procedures will be completed during the visit:

1. Collect haematology and iron markers samples
2. Collect FCM dosing history information
3. Measure subject's body weight
4. For UC subjects, record the SCCAI score; for CD subjects, collect CDAI diary dispensed at Visit 6 and calculate current CDAI score using the Visit 7 HCT result from the central laboratory (when available)
5. Collect PE and SF-36 data
6. For female subjects of childbearing potential, perform urine pregnancy test
7. Review and record all concomitant medications
8. Record all AEs since last visit
9. For ferric maltol subjects, collect bottles dispensed at prior visit, perform drug accountability and calculate compliance.
10. Instruct the subject to call the clinic or return promptly should an AE occur
11. Schedule Visit 8 at Week 54 telephone follow up
12. Complete the Visit Specific eCRFs

9.2.8 Telephone follow up

1. Review and record all concomitant medications
2. Record all AEs since last visit
3. Complete the Visit Specific eCRFs

Note: this follow-up call does not need to occur if End of Study Assessments have occurred 14 days or more from the date of last dose of ferric maltol or FCM.

If an AE is reported or is ongoing at the time of this visit, or if a significant lab abnormality is identified at the last visit prior to this visit, the Investigator must follow the event until resolution or until there is a satisfactory explanation of the changes observed.

9.2.9 Premature Discontinuation

All subjects have the right to withdraw formal consent without prejudice at any time during the study. If a subject withdraws formal consent, the Investigator should make a reasonable effort to determine the cause for withdrawal of consent and completed and end of study visit.

Subjects who prematurely discontinue the study, but do not withdraw consent, must return to clinic for visit end of study visit, according to the schedule of assessments (Section 9.1).

10 ASSESSMENTS

10.1 EFFICACY

10.1.1 Haemoglobin

Haemoglobin concentration measurement is among the most commonly performed blood tests, usually as part of a complete blood count. Results are reported in g/L, g/dL or mmol/L.

One g/dL equals approximately 0.6206 mmol/L. In this study, Hb will be evaluated using a central laboratory at every clinic visit, according to the schedule of assessments (Section 9.1).

10.2 SAFETY

10.2.1 Definitions

10.2.2 Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable or unintended sign or symptom, intercurrent illness, injury, or any concomitant impairment of the subject's health, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

A treatment-emergent AE is any AE temporally associated with the use of a study drug, whether or not considered related to the study drug.

Adverse events include:

- Exacerbation of a chronic or intermittent pre-existing condition/disease including either an increase in frequency and/or intensity of the condition/disease.
- Disease or medical condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at baseline that worsen within the study.
- Events considered by the Investigator to be related to study-mandated procedures.
- Abnormal safety assessments, e.g. laboratory test abnormalities, physical exam findings or vital sign measurements must be reported as AEs if they represent a clinically significant finding in the medical and scientific judgment of the Investigator, symptomatic or not, which was not present at baseline or if present at baseline, worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study drug. However, if an abnormal laboratory or other safety-related test result is associated with clinical signs or symptoms, the signs or symptoms should be recorded as an AE. If signs and symptoms are part of a diagnosis, then the diagnosis should be recorded as AE.
- Signs, symptoms of a suspected drug interaction.
- Signs, symptoms of a suspected overdose of either the study drug or a concomitant medication (overdose per se will not be reported as AE/SAE).

Adverse events **do not** include:

- Medical or surgical procedure, e.g., surgery, appendectomy, endoscopy, tooth extraction, transfusion (as these are treatments for an AE). However, the event resulting in the procedure is an AE (e.g. appendicitis, abdominal pain).
- Pre-existing disease or medical condition that does not worsen.
- Situations in which an adverse change did not occur, e.g., hospitalisations for cosmetic elective surgery or for social and/or convenience reasons.

- Anticipated day-to-day fluctuations or seasonal fluctuations (e.g. allergic rhinitis) of pre-existing disease(s) or condition(s) present or detected at the start of the study and recorded on the Medical History CRF.
- The disease/disorder being studied, or the expected progression, signs or symptoms (including laboratory values) of the disease/disorder being studied, unless it is more severe than expected for the subject's condition.
- Overdose of either study drug or concomitant medication without any signs or symptoms.

10.2.3 Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose

- is fatal,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity,
- results in a congenital anomaly/birth defect or
- is otherwise judged as medically significant (may jeopardise the subject).

Besides the explanations already included in the definition, the following guidelines should be used:

Life-threatening: Refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Inpatient hospitalisation: Subject has to stay in hospital at least overnight

The following reasons for hospitalisations are not considered AEs, and therefore not SAEs:

- Hospitalisations for cosmetic elective surgery, social and/or convenience reasons.
- Standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalisation for coronary angiography in a subject with stable angina pectoris.
- Elective treatment of a pre-existing disease or medical condition that did not worsen, e.g., hospitalisation for chemotherapy for cancer, elective hip replacement for arthritis, vein stripping for preventive and/or cosmetic purpose.

Prolongation of hospitalisation: Complications that occur during hospitalisation are AEs. However, if a complication prolongs hospitalisation or would have required hospitalisation or fulfils any other serious criteria, that complication is considered an SAE. In any case, admission to an intensive care unit is considered a prolongation of hospitalisation. When in doubt as to whether "prolongation of hospitalisation" was necessary, the AE should be considered serious.

Significant disability: The term significant disability means that there is a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, accidental trauma (e.g. sprained ankle) or uncomplicated chronic diseases which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

Medically significant: Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might/may jeopardize the subject or might/may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Serious adverse event related to study-mandated procedures: Such SAEs are defined as SAEs that appear to have a reasonable possibility of causal relationship (i.e., a relationship cannot be ruled out) to study-mandated procedures (excluding administration of study drug) such as discontinuation of subject's previous treatment during a washout period, or complication of a mandated invasive procedure (e.g., blood sampling, heart catheterization), or car accident on the way to the hospital for a study visit, etc.

All other AEs not fulfilling any of the criteria above are considered as “non-serious.”

10.2.4 Reporting and Documentation

Adverse events should be documented in terms of a medical diagnosis. When this is not possible, the AE should be documented in terms of signs and/or symptoms observed by the Investigator or reported by the subject at each study visit.

Any pre-existing conditions or signs and/or symptoms not related to IDA or IBD present in a subject prior to the start of the study should be recorded on the Medical History CRF.

All AEs that occur after informed consent is obtained through study completion or premature discontinuation must be reported on the AE form in the eCRF. All AEs must be reported REGARDLESS OF WHETHER OR NOT THEY ARE CONSIDERED DRUG RELATED.

Any SAE that occurs during the clinical study or within four weeks of receiving the last dose of study drug, whether or not related to the study drug, must be reported by the Investigator to the Study Safety officer at Clinipace Worldwide via the eCRF or by FAX or telephone within 24 hours of awareness.

Deaths or congenital abnormalities if brought to the attention of the Investigator AT ANY TIME after cessation of study drug AND considered by the Investigator to be possibly related to study drug, should be reported to the Sponsor.

At each visit AEs will be solicited. Adverse events not previously documented in the study will be recorded on the AE CRF. The nature of each event, date and time (where appropriate) of onset, outcome, course (i.e., intermittent or constant), maximum intensity, actions taken with respect to dosage, and relationship to study treatment should be established. Details of changes to study drug dosing or any subsequent treatment should be recorded on the appropriate pages of the CRF.

Adverse events already documented in the CRF (i.e., at a previous assessment) and designated as 'ongoing' should be reviewed at subsequent visits as necessary. Upon resolution, the date of resolution should be recorded in the CRF. If an AE increases in frequency or severity during a study period, a new record of the event should be started. If the AE lessens in intensity, no change in the intensity is required as only the worst intensity must be reported

All AEs and SAEs, including those that are ongoing at the end of the study or at premature discontinuation, will be followed up until resolution or stabilization or until the event is otherwise explained.

10.2.5 Immediate reporting

The following AEs must be reported within 24 hours:

- Serious Adverse Events
- Pregnancies

Pregnancy is not considered as an AE, but must be reported immediately

For immediate reporting, the Investigator must notify the Study Safety Officer at Clinipace Worldwide **within 24 hours** after awareness via the eCRF or FAX (also for pregnancies).

If the site obtains relevant follow-up information, this information needs to be forwarded to the Study Safety Officer within 24 h of awareness.

Other documents must be submitted upon request. All documents must be blinded with respect to the subject's personal identification to meet data protection requirements, e.g., on the discharge summary this data must be blinded and the subject number added.

As soon as the Study Safety Officer is informed about an SAE, they will organise evaluation and potential reporting to the IRB/IEC, Regulatory (Competent) authorities and other concerned parties.

10.2.6 Non-immediate reporting

Adverse events that do not qualify for immediate reporting will be documented in the CRF and reported with the Integrated Study Report.

10.2.7 Evaluation

Adverse events and the corresponding entries in the CRF will be reviewed by the Investigator or qualified member of the study staff.

10.2.8 Intensity

The intensity will be rated by the Investigator as "mild", "moderate" or "severe":

Mild: transient or mild discomfort (< 48 hours); medical intervention/therapy may not be required.

Moderate: discomfort enough to cause interference with usual activity and may warrant intervention.

Severe: incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention.

A mild, moderate or severe AE may or may not be serious. These terms are used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction). However, a severe event may be of relatively minor medical significance (such as severe headache) and is not necessarily serious. For example, nausea lasting several hours may be rated as severe, but may not meet the definition of seriousness. Fever of 39 °C that is not considered severe may become serious if it prolongs hospitalisation.

10.2.9 Causality

In addition, the Investigator is expected to discern the relationship of the AE to the IMP by answering the following question with **"yes"** or **"no":**

"According to your clinical experience is there a reasonable possibility that the event may have been caused by the study drug?"

If there is any valid reason (e.g., temporal relationship, de-challenge (diminishing) or re-challenge behaviour) even if undetermined or untested, for suspecting a possible cause-and effect relationship between the study drug and the occurrence of the AE, the answer should be “yes”.

If no valid reasons exist for suggesting a possible relationship, then the answer should be “no”.

10.2.10 Outcome

The outcome of each AE has to be assessed as follows:

Fatal: The AE resulted in death (“Death” is recorded as an outcome, not as the AE)

Ongoing/Not resolved: The AE has not resolved

Recovered with sequelae: Resolution of the AE has occurred, but the subject retains some sequelae

Recovered: The AE fully resolved with no observable residual effects

Unknown: The outcome of the AE is not known as the subject did not return for follow-up and attempts to locate the subject and/or to obtain follow-up information were unsuccessful (lost to follow-up).

10.2.11 Re-exposure

If an AE requires discontinuation of IMP and is judged to be treatment-related by the Investigator or by the Sponsor, re-exposure is not allowed. If an AE requires discontinuation of IMP and is judged by the Investigator to be unrelated to investigational products, the IMP may be restarted at the discretion of the Investigator. Discontinuation of the IMP (unless protocol specified) on more than one occasion, or for longer than 4 weeks continuously (unless protocol specified) will require the subject to withdraw from the study. The decision to re-introduce the medication requires prior approval of the Sponsor or designee.

10.2.12 Clinical laboratory

Haematology and iron markers samples will be collected at screening and Visits 2-4, as well as at premature discontinuation and unscheduled visits for FCM administration, if applicable. Basic safety chemistry, liver function and Vitamin B12/folate samples will be collected at screening only. Serum CRP will be measured at Visit 2 only. A central laboratory will analyse all protocol-specified clinical laboratory tests. In addition, a urine pregnancy test will be performed at screening and Visit 4/early discontinuation for female subjects of childbearing potential.

Processing, labelling, and shipping of the samples will be completed following central laboratory guidelines as provided in a Laboratory Manual. Additional laboratory tests may be performed if clinically relevant abnormal values are obtained at any time during the course of the study.

Haematology (all visits): haematocrit, haemoglobin, platelets, RBC count, RBC Hb concentration; WBC count and differential.

Iron markers (all visits): total serum iron, ferritin and transferrin. TSAT will be calculated and reported from the values obtain in these analysis at each visit.

Basic safety chemistry, liver function and vitamins (Visit 1 only): Serum ALT, Serum AST, total bilirubin, creatinine, blood urea nitrogen (BUN), sodium, potassium, chloride, bicarbonate, glucose, vitamin B12, folate.

C-reactive protein will be measured at Visit 2 only.

Retained Samples: Additional serum and plasma samples will be collected at Visit 2 and Week 12 (Visit 4) for possible future analysis related to IBD, anaemia and/or iron deficiency. No genetic testing will be completed on any samples obtained during this study without the further consent of the subject. Only Investigator sites with access to secure -70°C/-80°C freezer storage facilities will be required to collect and process blood for retained serum and plasma samples at Visit 2 and Visit 4.

Retained samples will stored at site (-70°C/-80°C) for subsequent periodic dry-ice shipping to the Central Laboratory. Full details will be provided in the Laboratory Manual.

Urine Pregnancy Test: For female subjects of childbearing potential, a urine pregnancy test will be performed as per visit schedule at the investigative site. Sites will be provided with urine pregnancy test kits by the Central Laboratory.

Up-to-date reference ranges will be provided during the study in the Laboratory Manual. Laboratory results will be compared to these reference ranges and flagged if they are outside the normal range or the protocol-specified range for randomization and/or continued study participation.

Investigators will review, sign and date all lab results upon receipt from the Central Laboratory. If a value is flagged as abnormal, the Investigator must document the abnormality as 'clinically significant' (CS) or 'non-clinically significant' (NCS). Any lab abnormality assessed as 'CS' must be recorded as an AE if not explained by a coexisting condition (documented in the medical history).

The signed paper copy of the laboratory result is retained at the investigational site. The electronic file transferred from the Central Laboratory to the Sponsor will be considered source data for laboratory analysis.

10.3 PHARMACOECONOMICS COLLECTION

10.3.1 Medical outcomes study 36-item short form

A 36-item short-form (SF-36) QOL questionnaire will be administered at Randomization and other study visits as indicated in the schedule of assessments (Section 9.1). The SF-36 was constructed to survey health status in the Medical Outcomes Study and was designed for use in clinical practice and research, health policy evaluations, and general population surveys (www.SF-36.org). The SF-36 includes one multi-item scale that assesses eight health concepts:

- limitations in physical activities because of health problems;
- limitations in social activities because of physical or emotional problems;
- limitations in usual role activities because of physical health problems;
- bodily pain;
- general mental health (psychological distress and well-being);
- limitations in usual role activities because of emotional problems;
- vitality (energy and fatigue); and
- General health perceptions.

The survey was constructed for self-administration by persons 14 years of age and older, and for administration by a trained interviewer in person or by telephone. The survey will be completed by the subjects in their native language.

10.3.2 Pharmacoeconomics

The pharmacoeconomic data collected will contain but not be limited to the number of hospital or clinical visits for administration of IV iron, or unscheduled visits for repeat testing of Hb/Iron. Also the nature of the subjects' transport (own or hospital/clinic) will be recorded. These two items will be included in a pharmacoeconomic analysis of the two treatment arms.

10.4 BASELINE PARAMETERS AND CONCOMITANT MEDICATIONS

10.4.1 Baseline demographics and disease characteristics

The following baseline demographics and disease characteristics are to be recorded in the CRF:

- Year of birth, age
- Race and ethnicity
- Weight
- Height
- Gender
- Relevant and significant medical history of the last 5 years preceding randomization
- Month and Year of diagnosis of IBD
- Month and Year of the last 3 flares of IBD preceding randomization
- IBD sub group
- Whether the subject has received IV iron previously or not
- Prior oral ferrous product(s) and IV iron use history. Severity of IBD at the time of prior OFP failure will also be recorded in the CRF if applicable (from documented historical SCCAI/CDAI, Mayo and/or Montreal classification score (see Van Assche, 2010; Dignass, 2012), or any other guideline used to confirm disease severity at the time of OFP failure)
- The most recently prescribed oral iron medication including dose and time of last administration
- Method of contraception for female subjects of childbearing potential

10.4.2 Concomitant medications

All concomitant medications are to be reported on the CRF

- Iron preparations other than study medications are prohibited at baseline and during study; with the exception of:
    - Over the Counter (OTC) oral supplements/multivitamin type preparations which may be taken, however Subjects are encouraged to keep to the same dose during the course of this study
- Blood transfusions or donations are prohibited from screening and throughout the study period.
- Erythropoiesis-stimulating agents (ESAs) are permitted during the study, but the subject must have been on a stable dose for the preceeding 3 months before

randomization

- Vitamin B12 and folic acid supplements are allowed during the study.
- Immunosuppressants are permitted so long as there is no clinical evidence or suspicion of the immunosuppressant contributing to the subject's anaemia or affecting erythropoiesis.

  Variations to dosing are permitted at the discretion of the investigator so long as there is no clinical evidence or suspicion of the immunosuppressant contributing to the subject's anaemia or affecting erythropoiesis.

All non-iron concomitant medications ongoing at time of screening or stopped within 1 month of screening have to be recorded in the CRF. Prescription iron replacement therapies stopped within 12 months of screening have to be recorded in the CRF, along with prior oral ferrous product(s) and IV iron use history.

Concomitant medications initiated, stopped, up-titrated or down-titrated after randomization will also be recorded.

11 ENDPOINTS

11.1 PRIMARY EFFICACY ENDPOINT

Proportion of subjects achieving either a 2g/dL increase in Hb OR normalization of Hb (>12g/dL women, >13g/dL men) at Week 12

11.2 SECONDARY EFFICACY ENDPOINTS

- Change in Hb concentration from baseline to Week 12
- Change in Hb concentration from baseline to Week 12 in subjects with a baseline Hb <9.5 g/dL
- Proportion of subjects who experience a change from baseline in Hb concentration ≥1.0 g/dL at Week 12
- Proportion of subjects with baseline Hb <9.5g/dL that achieve an increase in Hb concentration of ≥1 g/dL at Week 12
- Proportion of subjects with Hb concentration within normal limits at Week 12
- Proportion of subjects with baseline Hb concentration <9.5 g/dL that is within normal limits at Week 12
- Change in Hb concentration from baseline to Week 4
- Change in Hb concentration from baseline to Week 4 in subjects with a baseline Hb <9.5 g/dL
- Proportion of subjects who experience a change from baseline in Hb concentration ≥2.0 g/dL at Week 12
- Proportion of subjects with baseline Hb <9.5g/dL that achieve an increase in Hb concentration of ≥2 g/dL at Week 12

- Proportion of subjects who experience a change from baseline in Hb concentration ≥1.0 g/dL at Week 4
- Proportion of subjects with baseline Hb <9.5g/dL that achieve an increase in Hb concentration of ≥1 g/dL at Week 4
- Proportion of subjects with Hb concentration within normal limits at Week 4
- Proportion of subjects with baseline Hb concentration <9.5 g/dL that is within normal limits at Week 4
- Proportion of subjects who experience a change from baseline in Hb concentration ≥2.0 g/dL at Week 4
- Proportion of subjects with baseline Hb <9.5g/dL that achieve an increase in Hb concentration of ≥2 g/dL at Week 4
- Long term efficacy endpoints i.e. proportion of subjects who are non-anaemic at 6 and 12 months; normalization of ferritin levels at 6 and 12 months

Pharmacoeconomic endpoints:

- Number of hospital or clinic visits for administration of IV iron
- Proportion of subjects who restart FCM during the study

11.3 SECONDARY SAFETY ENDPOINTS

During the randomised phase of the study, safety endpoints will include:

- Treatment-emergent Adverse Events (AEs)
- Treatment-emergent Serious Adverse Events (SAEs)
- Adverse Events leading to premature discontinuation of study drug
- Adherence to study medication

12 STATISTICAL CONSIDERATIONS

12.1 GENERAL CONSIDERATIONS

The analysis of the study data is the responsibility of the Sponsor or its designee.
The primary analysis will be a non-inferiority comparison of ferric maltol to FCM, comparing Response Rate from baseline to Week 12 where response is ≥ 2g/dL rise in Hb OR moved from anaemic to non-anaemic at Week 12.

Randomization will be centrally controlled and stratified by screening Hb (< or ≥ 10g/dL Female; < or ≥ 11g/dL Male) and by IBD (UC or CD).

12.2 SAMPLE SIZE AND POWER CALCULATIONS

This study is designed with a 'responder %' primary endpoint, where response is ≥ 2g/dL rise in Hb OR moved from anaemic to non-anaemic at Week 12. The comparator group responder rate (FCM) is assumed to be 75% and the absolute non-inferiority margin is 20%. The non-inferiority margin is based on clinical opinion, coupled with the fact that in a previous study, the response rate in the placebo arm was less than 5% at 12 weeks.

The study is powered at 90% when the true response rate in the ferric maltol arm is 75%, i.e. the true difference to FCM is 0%. The primary statistical test is based on the 2-sided, 95% confidence interval for the difference in response rate between the two groups. This requires 108 subjects per arm. In order to allow for protocol deviations, this number has been increased by 12% to 121 per arm.

12.3 STATISTICAL METHODS

12.3.1 Primary endpoint analysis

The null hypothesis for the study is that the proportion of responders in the ferric maltol arm is lower that the proportion of responders in the FCM arm. The alternative hypothesis is that the proportion of responders in the ferric maltol arm is not lower than the proportion of responders in the FCM arm (i.e. ferric maltol non-inferior to FCM for response rate).

The primary analysis will be conducted using both the ITT and the PP population (See Section 12.4). Subjects whose responder status is unknown will be assumed not to have responded (a Baseline Observation Carried Forward (BOCF) approach).

The analysis will be based on the lower confidence limit (LCL) of a 2-sided, 95% confidence interval for the difference between the proportion of responders in the ferric maltol arm and the FCM arm. The confidence interval will be calculated based on a logistic regression, adjusting for study treatment, baseline haemoglobin, and UC or CD IBD disease.

The null hypothesis will be rejected, i.e. ferric maltol will be deemed non-inferior to FCM, if the LCL for the difference in proportions of responders (ferric maltol – FCM) is at least -20% for both the PP and the ITT analyses.

12.3.2 Secondary and Exploratory Analyses

Details regarding methods for analysis of secondary endpoints will be provided in the Statistical Analysis Plan. In addition, pre-defined exploratory endpoints, as well as long-term endpoints and analyses, will be provided in detail in the Statistical Analysis Plan.

No formal multiple comparisons procedure will be used to control the type I error rate for the analysis of secondary or other exploratory endpoints, including those defined for the long-term open-label phase of the study. For these analyses, confidence intervals and/or p-values will be displayed for descriptive purposes only.

12.3.3 Sensitivity analyses

Analysis of primary and key secondary parameters will be performed also with the per protocol (PP) population in the sense of sensitivity analyses. Both data-sets, ITT and PP populations, will be defined prior to the analysis (see Section 12.4).

Sensitivity analyses will also be performed for the primary endpoint, including an analysis using last observation carried forward (LOCF) and complete case analysis using ANCOVA and a mixed model repeated measures (MMRM) analysis.

12.3.4 Imputation of Missing Data

The handling of missing data for the primary endpoint is described in Section 12.3.1. Missing values for efficacy variables will be replaced for the secondary endpoint analyses as follows:

- For the endpoint 'Hb concentration within normal range' subjects not returning to a follow-up visit will be assumed to have Hb concentration not within normal range.
- For the endpoint 'Increases in Hb concentration of ≥1g/dL' subjects not returning to a follow-up visit will be assumed to have not reached the desired concentration.
- For the endpoint 'Increases in Hb concentration of ≥2g/dL' subjects not returning to a follow-up visit will be assumed to have not reached the desired concentration.

Additionally, the key secondary endpoints will also be evaluated using the multiply imputed data.

Safety data will be used according to availability, with no imputation for missing data.

Imputation of missing values for long-term and exploratory efficacy analyses will be defined in the Statistical Analysis Plan.

12.3.5 Safety analyses

Adverse Events

Adverse events will be categorized by primary system organ class and MedDRA preferred term as coded using the MedDRA dictionary. The number, intensity, relation to study medication and action taken will be described by incidence tables. Serious adverse events will be discussed separately.

Laboratory variables

Laboratory measurements will be summarized with descriptive statistics including changes from baseline and shift tables.

12.3.6 Pharmacoeconomic Analysis

The Hb response data, plus the QOL and other resource use information collected as part of this study, will be used in a pharmacoeconomic analysis. This will compare the two treatment arms for correction and maintenance treatment of IDA over a minimum of 12 weeks period.

12.3.7 Statisical Analysis

A two stage analysis of the safety and efficacy data will be performed: the primary and secondary analyses will be conducted when all subjects have completed 12 weeks of treatment. The results will be provided in an interim study report. The final study report will be finalised on completion of the remaining visits. The analysis would include the longer term endpoints as well for those with longer treatment period.

12.4 DEFINITION OF POPULATIONS

12.4.1 Randomised Population

All subjects who are randomised.

12.4.2 Safety population

All subjects who have had at least one dose of study drug and one subsequent contact with the Investigator will be analysed for safety.

12.4.3 Intention-to-treat population (Full analysis set)

For efficacy, all randomised subjects will be included in the ITT analysis. The ITT analysis will be used in the primary efficacy analysis.

12.4.4 Per protocol population

The PP population includes all subjects eligible for ITT evaluation and, in addition, who do not have major protocol deviations. Protocol deviations occurring during the study will be classified as major or minor prior to study database lock.

12.5 SOFTWARE APPLIED

The data analysis will be performed in a validated working environment according to the requirements of the ICH-Guidelines E3 [1995].

The software to be used for data evaluation will be described in the statistical analysis plan.

12.6 QUALITY CONTROL

The statistical analysis will be performed according to the statistician's standard operating procedures (SOPs), the statistical analysis plan, the clinical study protocol, and all its amendments. All evaluation steps will be completely documented, and the software to be used is validated. In-process controls will be performed and documented.

13 DATA MANAGEMENT

Data management, including data quality assurance, will be performed according to international guidelines (GCP, ICH), Clinipace Worldwide SOPs and Working Instructions. Data Management procedures for this protocol will be fully documented in the Data Management Plan by Clinipace Worldwide.

14 ETHICAL CONSIDERATIONS

14.1 SUBJECT INFORMATION AND INFORMED CONSENT

IRB/IEC approval of the written Informed Consent Form must be obtained prior to use. The consent form will contain a phrase by which consent is given for the access to the non-personalised data by the Sponsor / applicant, national and regulatory authorities. In addition, it states that the subject is free to withdraw from the study at any time without any negative consequences. The consent form gives a complete and comprehensive explanation of the significance, nature, extent and possible risks of the study. For details of the informed consent procedure please refer to Section 7.4.7 of this protocol. The procedure complies with all applicable regulations governing the protection of human subjects, such as national drug laws (German Drug Law: AMG, US-FDA regulations), ICH-GCP guidelines, and the Declaration of Helsinki.

14.2 INSTITUTIONAL REVIEW BOARD / INDEPENDENT ETHICS COMMITTEE

The Clinical Study Protocol and Amendments, the Informed Consent, advertisements, and any other written information to be provided to the subjects have to be approved by the local IRB/IEC.

The Sponsor or designee is responsible for submitting the documents to the IRB/IEC.

During the study the following documents will be sent to the IRB/IEC for their review:

- Investigator Brochure updates, both periodic and annual

- Reports of AEs that are serious, unlisted and associated with the IMP (SUSARS),

- Protocol amendments and revised informed consent forms (if any).

The Sponsor or designee will provide a safety update of the specific study site to the local IEC/IRB, including line listings, individual reports of SUSARs, if applicable, and a discussion of AEs annually, or more frequently if requested.

At the end of the study, the Sponsor or designee will notify the IEC/IRB of the study completion. Furthermore, the Sponsor or designee will provide the synopsis of the final report to the IEC/IRB within one year after end of the clinical study.

14.3 SUBJECT INSURANCE

Every subject participating in the study is insured in accordance with local law against injuries to health which may occur during the study.

Excluded from this, however, are injuries to health and deterioration of illnesses already in existence which would have continued to exist even if the subject had not taken part in the study.

Insurance coverage will be jeopardised if the subject fails to immediately report to the Investigator or responsible physician any injury to health which might have resulted from the participation in the study, or if he/she undergoes any other medical treatment (except for emergency treatment) without the Investigator's knowledge before his/her participation in the study has officially ended. In case of emergency treatment, the subject is obliged to inform the Investigator as soon as possible after the treatment.

Any injury to health which might have occurred as a result of participating in the study must be reported by the subject to the insurer without delay. The subject may also inform the Investigator, who is obliged to make a report to the insurer.

Subject insurance will be arranged by the Sponsor.

15 STUDY MANAGEMENT

15.1 LEGAL REQUIREMENTS

The planning and execution of the clinical study are subject to the local legal regulations (e.g. § 40, § 41, § 42 and § 67 of the German Drug Law), and the recommendations of the Declaration of Helsinki (current revision). Furthermore, the current ICH-GCP guidelines will be observed.

15.2 DATA COLLECTION

The Investigator must ensure that all source documents (i.e., study and/or medical records) are completed and maintained according to the study protocol, and are available at the site.

15.2.1 Case Report Forms

It is the responsibility of the Investigator to maintain and submit accurate eCRFs to the Sponsor as soon as possible.

If a subject does not complete the study, all data collected on the subject prior to the discontinuation will be made available to the Sponsor. The End of Study CRF should be filled out accordingly.

Instructions for completing the CRFs and any corrections necessary will be provided in the Case Report Form Completion Guidelines Manual and in the CRF.

15.2.2 Source documents

The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to Sponsor in the CRFs and in all required reports, and as such will be asked to sign and date the appropriate CRFs, as verifying and taking responsibility for the data collected. This also applies to records for those subjects who fail to complete the study (including screen failures). If a subject withdraws from the study, the reason must be noted on the CRF.

All data reported on CRFs will be verified against source documents. The CRF will not act as source except in the instance of a subject self-completion of a questionnaire.

15.2.3 Confidential subject identification list and screening log

In order to permit easy identification of the individual subject during and after the clinical study, the Investigator is responsible for keeping an up-dated Confidential Subject Identification List. This document will be reviewed by the monitor for completeness. However, in order to ensure subject confidentiality, no copy will be made.

A Screening Log documenting all subjects who sign Informed Consent and who are evaluated for inclusion in the clinical study must be completed by the Investigator. The Screening Log will include the following data: subject number, date of screening, date of informed consent and randomization or reason for screen failure, as applicable.

15.3 ACCESS TO DATA

Upon request by the clinical monitor, auditor, IRB/IEC, or any regulatory authority, the Investigator/study site must provide access to all requested study-related records. The anonymity of participating subjects must be maintained. All subject data will be identified only by a subject identification number. Documents that identify the subject (e.g., the signed Subject Information Sheet and ICF) must be maintained in confidence by the Investigator. However, in compliance with federal guidelines regarding the monitoring of clinical studies and in fulfilment of his/her obligations to the Sponsor, the investigator must permit the study monitor, Sponsor representative or auditor, and/or FDA representative or other regulatory authority to review the portion of the subject's medical record that is directly related to the study. This shall include all study-relevant documentation including medical history to verify eligibility, admission/discharge summaries for hospital stays occurring while the subject is enrolled in the study and autopsy reports if a death occurs during the study.

15.4 MONITORING

To ensure accurate, complete, consistent, and reliable data, the Investigative sites and study procedures will be monitored by a representative of the Sponsor. The Sponsor representative will visit the site to review the source documents and CRFs for protocol compliance and accuracy, and to assess facilities and equipment, recruiting, protocol adherence, AE reporting,

and other factors. Frequency and scope of the monitoring visits will be defined in the Clinical Monitoring Plan which will also define the extent of source data verification required.

15.5 AMENDMENTS

Any change to a protocol must be considered an amendment. A proposed amendment should be reviewed by the Principal Investigator(s) or Steering Committee, as appropriate.

Revisions to the Informed Consent requested by IRB/IEC are not considered amendments, so long as they do not affect the protocol.

Non-substantial amendment

Minor administrative or logistical changes require a non-substantial amendment. Such changes include, but are not limited to changes, in study staff or contact details (e.g., Sponsor instead of CRO monitors) or minor changes in the packaging or labelling of study drug.

The implementation of a non-substantial amendment could be done with or without (according to national regulations) notification to the appropriate IRB/IEC and Regulatory (Competent) Authorities. A non-substantial amendment does not require the approval or acceptance by the Investigators.

Substantial amendment

Significant changes to the protocol require a substantial amendment. Significant changes include, but are not limited to: new data affecting the safety of subjects, change of the objectives/endpoints of the study, eligibility criteria, dose regimen, study assessments/procedures, treatment or study duration, with or without the need to modify the Informed Consent.

Substantial amendments are to be approved by the appropriate IRB/IEC and in some countries by the Regulatory (Competent) Authorities. The implementation of a substantial amendment can only occur after formal approval by the appropriate IRB/IEC and/or Regulatory (Competent) Authorities and must be accepted by the Investigators.

15.6 AUDITS

An independent quality control unit may audit the study protocol, the documentation and, if applicable, the performance of the study and the clinical study report to ensure that the study is performed in accordance with ICH-GCP guidelines and regulatory requirements.

Correspondingly, the agreements to this section are also valid for possible visitors from members of the quality control unit (GCP auditing or governmental control unit) in the event of a check of the performance of this clinical study according to ICH-GCP guidelines and regulatory requirements.

15.7 CONFIDENTIALITY AGREEMENT

Any information concerning data or procedures of this clinical study must be handled confidentially by all persons involved.

15.8 NOTICE TO THE LOCAL AND NATIONAL AUTHORITIES

The local and national Regulatory (Competent) Authorities will be notified about the conduct of this clinical study according to local law.

15.9 RETENTION OF RECORDS

The Investigator must retain the informed consent documentation, disposition of the IMP, CRFs, medical records, and other source data for at least 2 years after the last approval of a

marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

If the Investigator retires, or for any other reason withdraws from the responsibility for maintaining records for the period of time required, custody of the records may be transferred to another person who will accept responsibility for the records. Notice of such a transfer must be given in writing to the Sponsor.

In addition, the Sponsor will retain copies / originals (as appropriate) of any study-related documents in the Trial Master File until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

15.10 INVESTIGATOR MEETING

An Investigator Meeting may be organised to give study specific information and to support a homogenous execution of the study procedures at all participating study sites. The same information will be provided during the Site Initiation Visit prior to study start at each site.

15.11 SECURITY AND PUBLICATIONS

This study protocol remains the Sponsor property until the final fulfilment of the contract and may only be passed on to registration authorities and license partners with the Sponsor / Applicant's approval. The study site will treat all knowledge about the study product and/or its manufacturer with strictest confidentiality.

The Sponsor/Applicant ensures that substances used in the manufacture of the IMP are generally known in pharmaceutical science and have been released by the appropriate national authorities for use in medications, cosmetics or food. Furthermore, the Sponsor ensures that the manufacture of the IMP was carried out in accordance with the guidelines of European Directives 2003/94/EC, 2001/20/EC and Annex 13/ 21CFR 312.23.

The study results, including the report and documentation, become the property of the Sponsor as soon as the final report has been signed and the final payment to the study site has been made. Publication rights will be described in the Investigator contract. The study site's agreement is not required for using the study results at registration authorities or for negotiations with companies interested in purchasing the product. Information for specialist circles can likewise be compiled without the study site's specific written consent.

If information about this study is published, the subject's personal information will not be identified.

16 REFERENCES

Auerbach M, Rodgers GM. Intravenous iron. N Engl J Med. 2007;357:93-94.

Bergamaschi G, Di Sabatino A, Albertini R, Ardizzone S, Biancheri P, Bonetti E, Cassinotti A, Cazzola P, Markopoulos K, Massari A, Rosti V, Bianchi Porro G, Corazza GR. Prevalence and pathogenesis of anaemia in inflammatory bowel disease. Haematologica 2010; 95: 199-205.

Biancone L, Michetti P, Travis S, Escher JC, Moser G, Forbes A, Hoffmann JC, Dignass A, Gionchetti P, Jantschek G, Kiesslich R, Kolacek S, Mitchell R, Panes J, Soderholm J, Vucelic B, Stange E for the European Crohn's and Colitis Organisation (ECCO). European evidence-based Consensus on the management of ulcerative colitis: Special situations. J Crohn's and Colitis 2008; 2: 63-92.

Blanc B, Finch CA, Hallberg Let al. Nutritional anaemias. Report of a WHO Scientific Group. WHO Tech Rep Ser 1968; 405: 1-40.

Dignass A, Eliakim R, Magro F, Maaser C, Chowers Y, Geboes K, Mantzaris G, Reinisch W, Colombel JF, Vermeire S, Travis S, Lindsay JO, Van Assche G. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. J Crohns Colitis. 2012, 6(10):965-990.

Dignass AU, Gasche C, Bettenworth D, Birgegård G, Danese S, Gisbert JP, Gomollon F, Iqbal T, Katsanos K, Koutroubakis I, Magro F, Savoye G, Stein J, Vavricka S; European Crohn's and Colitis Organisation [ECCO]. European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. J Crohns Colitis 2015; 9(3): 211-222.

EMA (European Medicines Agency). New recommendations to manage risk of allergic reactions with intravenous iron-containing medicines. 13 September 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/IV_iron_31/WC500151308.pdf.

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;141:846-853 e841-842.

Gasche C (2008). Anaemia in Inflammatory Bowel Diseases. Bremen; UNI-Med.

Gasche C, Kulnigg S. Intravenous iron in inflammatory bowel disease. Semin Hematol 2006; 43 (suppl 6): S18-S22.

Gasche C, Berstad A, Befrits R, Beglinger C, Dignass A, Erichsen K, Gomollón F Hjortswang H, Koutroubakis I, Kulnigg S, Oldenburg B, Rampton D, Schroeder O, Stein J, Travis S, Van Assche G. Guidelines on the Diagnosis and Management of Iron Deficiency and Anaemia in Inflammatory Bowel Diseases. Inflamm Bowel Dis 2007;13: 1545–1553.

Gasche C, Ahmad T, Tulassay Z, Baumgart DC, Bokemeyer B, Büning C, Howaldt S, Stallmach A; AEGIS Study Group. 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(3): 579-88

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;39:743-744.

Harvey RSJ, Reffitt DM, Doig LA, Meenan J, Ellis RD, Thompson RPH, Powell JJ. Ferric trimaltol corrects iron deficiency anaemia in patients intolerant of iron. Aliment Pharmacol Ther 1998; 12: 845-848.

Latest version of the Investigator's Brochure for Ferric Maltol (ST10-021, ST10).

Stein J, Hartmann F, Dignass AU. Diagnosis and management of iron deficiency anemia in patients with IBD. Nature Rev Gastroenterol Hepatol. 2010;7:599-610.

Study SWIN 189/ IM, Shield, fragments of statistical analysis on file

Van Assche G, Dignass A, Panes J, Beaugerie L, Karagiannis J, Allez M, Ochsenkühn T, Orchard T, Rogler G, Louis E, Kupcinskas L, Mantzaris G, Travis S, Stange E; European Crohn's and Colitis Organisation (ECCO). The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Definitions and diagnosis. J Crohns Colitis 2010; 4(1): 7-27

Wilson A, Reyes E, Ofman J. Prevalence and outcomes of anaemia in inflammatory bowel disease: A systematic review of the literature. Am J Med 2004; 116(7A): 44S-49S.

Wells CW, Lewis S, Barton JR, Corbett S. Effects of changes in haemoglobin level on quality of life and cognitive function in inflammatory bowel disease patients. Inflamm Bowel Dis 2006; 12: 123-130.

Weiss G, Goodnough LT. Anemia of chronic disease. New England J Med. 2005;352:1011-1023.

WGO. World Gastroenterology Organisation Global Guideline. Inflammatory bowel disease: a global perspective. 2009. Available at: http://www.guideline.gov/content.aspx?id=15231&search=iron+deficiency+anemia.

www.SF-36.org.

Zhu A, Kaneshiro M, Kaunitz JD. Evaluation and treatment of iron deficiency anaemia: a gastroenterological perspective. Dig Dis Sci. 2010;55(3):548-59.

Zimmermann MB, Hurrell RF. Nutritional iron deficiency. Lancet. 2007;370:511-520.

17 APPENDICES

17.1 SCORING SYSTEM FOR THE SIMPLE CLINICAL COLITIS ACTIVITY INDEX

Symptom	Description	Score
Bowel frequency (day)	1-3	0
	4-6	1
	7-9	2
	>9	3
Bowel frequency (night)	0	0
	1-3	1
	4-6	2
Urgency of defecation	None	0
	Hurry	1
	Immediately	2
	Incontinence	3
Blood in stool	None	0
	Trace	1
	Occasionally frank	2
	Usually frank	3
General well-being	Very well	0
	Slightly below par	1
	Poor	2
	Very poor	3
	Terrible	4
Extracolonic features	Per manifestation	1

17.2 SCORING SYSTEM FOR THE CROHN'S DISEASE ACTIVITY INDEX

Crohn's Disease Activity Index				
Symptom/characteristic		**Count**	**multiplier**	**total**
Number of liquid and very soft stools (Sum of last 7 days)			x 2 =	
Abdominal Pain (Sum of last 7 days)			x 5 =	
General well-being (Sum of last 7 days)			x 7 =	
Other symptoms or findings of Crohn's Disease __ Arthritis or arthralgia __ Iritis or uveitis __ Skin or mouth lesions e.g. erythema nodosum, pyoderma gangrenosum, aphthous stomatis __ Anal fissure, fistula or perirectal abscess __ Other bowel related fistula __Fever above 37.5˚C during past week		Number of ticked items:	x 20 =	
Symptomatic treatment of diarrhea (e.g. loperamide, opiates) during past week		__ No = 0 __ Yes = 1	x 30 =	_____
Abdominal mass		__ None = 0 __ Questionable = 2 __ Definite = 5	x 10 =	_____
*Hematocrit _____%	f: 42 – HCT m: 47 – HCT	= +/- ____	x 6 =	+/- ____
**Body Weight __ __ . __kg Standard Weight __ __ . __kg (1 – body weight/standard weight)		= +/ - _____	x 100 =	+/- ____
			**CDAI Sum:	_____

*HCT value from Visit, use central lab results. For Screening period CDAI to determine eligibility for study, use HCT value from Screening laboratory results.
**If using a CDAI calculator online tool, please document detail. For manual calculation, please use Standard Weight/Height tables for males and females.

17.3 SF-36 QUALITY OF LIFE QUESTIONNAIRE

Questionnaire not attached. SF-36 v2 will be used for this study and provided to trial subjects in validated local language, IEC-approved versions for completion at the required study visits (see www.SF-36.org).

17.4 WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Patients

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)

55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)

59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human patients, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human patients to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

5. Medical progress is based on research that ultimately must include studies involving human patients. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human patients, the well-being of the individual research patient must take precedence over all other interests.

7. The primary purpose of medical research involving human patients is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is patient to ethical standards that promote respect for all human patients and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human patients in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research patients set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research patients.

12. Medical research involving human patients must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human patients must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for patients and provisions for treating and/or compensating patients who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post study access by study patients to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research patients set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human patients must be conducted only by individuals with the appropriate scientific training and qualifications. Research

on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research patients must always rest with the physician or other health care professional and never the research patients, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human patients must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first patient.
20. Physicians may not participate in a research study involving human patients unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human patients may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research patients.
22. Participation by competent individuals as patients in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research patients and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human patients, each potential patient must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential patient must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential patients as well as to the methods used to deliver the information. After ensuring that the potential patient has understood the information, the physician or another appropriately qualified individual must then seek the potential patient's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential patient is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research patient who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential patient, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research patient who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential patient's dissent should be respected.

29. Research involving patients who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving patients with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the patient or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human patients and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or

therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research patients.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

    • The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or

    • Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be patient to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.