22 February 2018
EMA/172417/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Feraccru

International non-proprietary name: ferric maltol

Procedure No. EMEA/H/C/002733/II/0010

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE: Adverse Events

BOCF: Baseline observation carried forward

CKD: chronic kidney disease

ECCO: European Crohn's and Colitis organisation

GRAS: Generally Recognised As Safe

Hb: Haemoglobin

CD: Crohn's disease

OFPs: oral iron preparations

IBD: Inflammatory Bowel Disease

ID: Iron Deficiency

IDA: Iron Deficiency Anaemia

GI: Gastrointestinal

GIAE: gastrointestinal adverse event

JECFA: Joint FAO/WHO Expert Committee on Food Additives

LOCF: Last Observation Carried Forward

MA: Marketing Authorisation

MMRM: Mixed Model Repeated Measures

OR: Odds ratio

PPAS: Per Protocol Analysis Set

PPIs: Proton pump inhibitors

ROS: Reactive oxygen Species

TNF: Tumour necrosis factor

TSAT: Serum values of transferrin saturation

UC: Ulcerative Colitis

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Shield TX (UK) Ltd submitted to the European Medicines Agency on 25 August 2017 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to widen the indication for Feraccru from the treatment "in adults with Iron deficiency anaemia in patients with IBD" to the treatment of "adults with Iron deficiency"; As a consequence, sections 4.1, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and RMP (v. 8) have been updated accordingly.
In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0164/2017 on the agreement of a paediatric investigation plan (PIP) and on the granting of a (product-specific) waiver.

At the time of submission of the application, the PIP EMEA-001195-PIP01-11-M03 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Concepcion Prieto Yerro Co-Rapporteur: Harald Enzmann

Timetable	Actual dates
Submission date	25 August 2017
Start of procedure:	16 September 2017
CHMP Co-Rapporteur Assessment Report	7 November 2017
CHMP Rapporteur Assessment Report	14 November 2017
PRAC Rapporteur Assessment Report	13 November 2017
PRAC members comments	22 November 2017
Updated PRAC Rapporteur Assessment Report	23 November 2017
PRAC Outcome	30 November 2017
CHMP members comments	4 December 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	7 December 2017
Request for supplementary information (RSI)	14 December 2017
CHMP Rapporteur Assessment Report	24 January 2018
PRAC Rapporteur Assessment Report	N/A
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	N/A
PRAC Outcome	8 February 2018
CHMP members comments	12 February 2018
Updated CHMP Rapporteur Assessment Report	15 February 2018
Opinion	22 February 2018

2. Scientific discussion

2.1. Introduction

Feraccru is a centrally authorised product.

Iron is an essential micronutrient that is required for adequate erythropoietic function, oxidative metabolism and cellular immune responses. The term "anaemia" is sometimes used synonymously with "iron deficiency anaemia". However, these terms do not cover the same reality. There are about 2-5 times more iron deficient people than individuals with IDA. Iron deficiency is diagnosed when low serum levels of ferritin or transferrin saturation are measured. The most common reasons for ID are insufficient iron intake in the diet, an inability to absorb iron well in the body and/or loss of iron in blood through bleeding. Iron deficiency is the most common cause of anaemia. Iron deficiency anaemia is caused by low levels of iron in the body. Iron deficiency anaemia is the most common cause of anaemia worldwide, affecting over 2 billion people, which equates to approximately 30% of the world's population (Pavord, 2012; NICE CKS, 2013; Zhu, 2010). Epidemiological surveys indicate that in Europe, iron depletion concerns 10-30% of menstruating women with 1.5 to 14% progressing to IDA. In pregnant women the prevalence of IDA, according to different studies and surveys, ranges from 6 to 30% with the highest

levels observed in countries such as Holland (6-28%), Denmark (0-18%) and France (9-30%) where routine iron supplementation is not usually given during pregnancy (Hercberg, 2001).

Typical symptoms of IDA include chronic fatigue, weakness and tiredness as a direct result of altered energy metabolism, thus leading to a subtle impairment of physical capacity, work performance and cognitive functioning. Clinical features also comprise those symptoms associated with central hypoxia such as headaches, dizziness, vertigo, tinnitus or lethargy. Iron deficiency anaemia may also be responsible for dyspnoea, pica, cognitive impairment such as short attention duration, koilonychias, papillary atrophy of the tongue, angular stomatitis and oesophageal webs, among others.

Iron deficiency is a common complication of inflammatory bowel disease (IBD), occurring in about 60-80% of IBD patients. Approximately one-third of patients with IBD are also anaemic. Although anaemia in IBD often involves a combination of IDA and anaemia of chronic disease, IDA remains an important contributor in this condition (Zhu, 2010). Importantly for the therapeutic action of Feraccru, the observed IDA in IBD patients does not appear to be due entirely to an inability to absorb oral iron, even in cases of severe chronic inflammatory disease (Erichsen, 2003; Bartels, 1978).

On 17 December 2015 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Feraccru, intended for the treatment of iron deficiency anaemia in adults with inflammatory bowel disease. The Marketing Authorisation was issued on 18 February 2016 (Feraccru 30 mg hard gelatin capsule; MA number: EU/1/15/1075/001).

This medicinal product is an iron replacement preparation. Its anatomical therapeutic classification (ATC) pharmaco-therapeutic group is iron trivalent, oral preparation; the ATC code is BO3AB10.

It was developed to provide an alternative oral (ferric) iron product for subjects with iron deficiency. Initial clinical development focused on patients with inflammatory bowel disease (IBD) a patient subgroup which is difficult to treat with standard oral (ferrous) iron preparations because of a combination of non-compliance due to side effects and impaired absorption due to the chronic inflammatory state.

The initial marketing authorisation was granted on the basis of sufficient clinical evidence for clinically relevant efficacy in iron deficiency anaemia patients with IBD.

Clinical Development Programme

A clinical development programme was established to provide pivotal registration data to support the marketing authorisation approval (MAA) for Feraccru in the treatment of ID/IDA. The initial development focused on patients with IDA and IBD: this subgroup of IDA patients was perceived as a "worst case" population as they are commonly intolerant to oral ferrous products.

This completed programme included two PK studies (a sub-study) and a pivotal phase III efficacy and safety study (conducted as two separate protocols in ulcerative colitis (UC) and Crohn's disease (CD) patients respectively) that were fully compliant with GCP.

Study ST10-01-101 was an open-label, randomised, multiple dose PK study conducted with 24 subjects with iron deficiency (with or without anaemia). The primary objective of Study ST10-01-101 was to evaluate the kinetics of maltol along with its metabolite, maltol glucuronide, as well as iron uptake in blood and urine after single and repeated bid oral doses of 30 mg, 60 mg or 90 mg Feraccru for 7 days, followed by a final dose on the morning of day 8.

Study ST10-01-102 was a prospective PK sub-study of subjects receiving Feraccru 30 mg bid in the open-label phase of studies ST10-01-301 or ST10-01-302. The objective of ST10-01-102 was to describe the PK profile of Feraccru at steady state after a 30 mg single dose in the target patient population, i.e.,

patients with IDA and IBD.

The pivotal, phase 3, multicentre, randomised, double-blind, placebo-controlled study with Feraccru for the treatment of IDA in subjects with IBD where OFP had failed or could not be used, was conducted via two separate protocols:

• ST10-01-301 (AEGIS 1) in patients with quiescent UC

• ST10-01-302 (AEGIS 2) in patients with quiescent CD.

The study designs for these protocols were essentially identical except for the differing IBD population.

Efficacy was evaluated over the first 12 weeks of randomised treatment. All completed subjects from the randomised phase received open-label Feraccru for up to an additional 52 weeks, with the exception of patients recruited in Austria, where the Ethics Committee would not sanction the 52-week extension of the study unless the sponsor agreed to unblind patients after the initial 12-week placebo period of the protocol. The sponsor was unwilling to agree to this.

In addition, a series of clinical studies (over the last two decades) with Feraccru in healthy subjects and in anaemic patients (with and without IBD), although not conducted to current standards of GCP, has provided a considerable body of knowledge on the absorption, efficacy, safety and tolerability of a range of doses of Feraccru.

Following national scientific advice and agreement that the analysis of a single combined dataset from both studies would be scientifically and statistically valid, the analysis plan was integrated. In addition, the dataset has been reanalysed for the primary efficacy endpoint, within each protocol dataset ([ST10-01-301 and ST10-01-302] according to the IBD diagnosis). An interim safety analysis of the open-label phase (cut-off date 31st March 2014) was performed: this has been superseded by the final study report (ST10-01-31/302 CSR2), which presents data for the double-blind, the full open label and cumulative phases of the study.

The MAH also conducted 2 *in vitro* studies that investigated potential drug-drug interactions: one study (Cyprotex Study No. CYP0747 R3) investigated the effects of Feraccru on the permeability of drugs known to interact with ferrous products, using a Caco-2 cell model to simulate intestinal absorption and the second study (XenoGesis Study no. 2015_06_23, 2015) was conducted to determine the UGT isoenzyme(s) responsible for the glucuronidation of the maltol component of Feraccru.

The MAH obtained advice on design of Phase 3 studies and clinical development from BfArM and MHRA. Specific questions on the acceptability of the endpoints proposed in the Phase 3 studies and the proposed number of patients that would be exposed to Feraccru for 6 and 12 months were proposed. Additional advice was sought from these agencies on the scientific and statistical validity of the analysis of a single combined dataset from both studies and the acceptability of filing on the basis of this single pivotal data set.

Supportive evidence for the efficacy of Feraccru in patients from IDA is provided by further published and unpublished studies. Additional supportive data for Feraccru treatment of ID/IDA is being generated in additional subpopulations, including patients with IDA and chronic kidney disease (CKD).

The MAH applied for the following indication: Feraccru is indicated in adults for the treatment of iron deficiency.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The MAH submitted a justification for not submitting any Environmental Risk Assessment (ERA) studies.

Taking into consideration the nature of the active ingredients of Feraccru complex, electrolytes and carbohydrates, Feraccru is unlikely to result in a significant risk to the environment. Iron is ubiquitously found throughout the environment and maltol a simple sugar and a dehydration product of glucose. Therefore, although the indication is being extended for use in iron deficient anaemia, not related to any disease, this is not expected to pose a risk to the environmental.

Therefore, the MAH justification for absence of Environmental Risk Assessment is accepted.

2.2.2. Discussion on non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

As detailed in the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 1*, 1 June 2006), vitamins and electrolytes are exempted from the need for a complete environmental risk assessment, as they are unlikely to result in a significant risk to the environment. Taking into consideration the nature of the active ingredients of Feraccru complex, electrolytes and carbohydrates, Feraccru is unlikely to result in a significant risk to the environment. Therefore, although the indication is being extended for use in iron deficient anaemia, not related to any disease, this is not expected to pose a risk to the environment. Further studies are not required to support the claimed indication.

2.2.3. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted with this new application which is considered acceptable.

2.3. Clinical aspects

No new clinical study data have been submitted in this application.

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant; the pivotal PK studies (ST10-01-101 and ST10-01-102) were conducted in accordance with GCP, as were the pivotal clinical efficacy and safety studies (ST10-01-301 and ST10-01-302).

Early supportive PK studies (Thompson & Hider, Studies 1, 2, 3 & 4, Maxton et al [1994], Reffitt *et al* [2000], MacPhail [2012], Murray *et al*, Kelsey et al [1991], were not conducted in accordance with GCP. Similarly, the supportive clinical studies Blake & Kelsey, Green & Thompson [1995], Harvey *et al* [1998] and SWIN-189-IM were not conducted in accordance with GCP.

The *in vitro* studies conducted to investigate potential drug-drug interactions were not conducted in accordance with full GLP, as this is not required by current regulations.

- Tabular overview of clinical studies

Table 1: Tabular Summary of the Clinical Pharmacology Studies Conducted with Feraccru

Type of Study	Study ID / Location	Objectives of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects / Patients	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	ST10-01-101 5.3.3.2	To evaluate the PK and iron uptake of ST10 in blood and urine after single and repeated doses	Open-label, randomised, parallel group	Oral ST10 30mg, 60mg & 90mg bd	24	Iron deficient patients (with or without anaemia)	7.5 days	Complete Full
PK	ST10-01-102 5.3.3.2	To describe the PK of ST10 after a 30mg single dose administered at steady state	Open label (within the open-label phase of studies ST10-01-301 and ST10-01-302	Oral ST10 30mg bd	15	Iron deficient patients	7.5 days	Complete Full
PK	Thompson & Hilder,(Study 1) 5.3.3.1	Absorption of iron [^{19}FE(1μCi)]	Open, controlled	Oral ST10 (10mg Fe) capsules Oral $FeSO_4$	9	?	Single dose	Complete Data on File
PK	Maxton *et al*, 1994 5.3.3.2	Comparison of the absorption of iron from iron sulphate and ferric hydroxypyranone complexes in iron deficient patients	Open, controlled	Oral ST10 (10mg Fe) Oral $FeS0_4$ 180mg in capsule or liquid	19	Healthy subjects (7) Iron deficient patients (12)	Single dose	Complete Publication
PK	Thompson & Hilder; (Study 2) 5.3.3.1	To determine the systemic uptake of iron and maltol	Open	ST10 (10mg Fe,10μCi) ^{3}H maltol (10μCi) Oral	2	Healthy Subjects	Single dose	Complete Data on File

Type of Study	Study ID / Location	Objectives of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects / Patients	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	Thompson & Hilder, (Study 3) 5.3.3.1	PK of iron and maltol	Open	5.65g ST10 [706mg Fe, (9mg/kg), 4.9g maltol (63mg/kg)] Oral	1	Healthy Subject	Single dose	Complete Data on File
PK	Thompson & Hilder, (Study 4) 5.3.3.1	PK of maltol component of ST10. Plasma levels of maltol and its glucuronide conjugate measured	Open	800mg ST10 (11mg/kg) 100mg Fe; 700mg maltol Oral	3	Healthy Subjects	Single dose	Complete Data on File
PK	Reffitt *et al*, 2000 5.3.3.1	To compare the kinetics of iron absorption from 4 different formulations of ST10 using colorimetric analysis	Double blind, crossover, randomised, controlled	30mg Fe (as ST10 capsules) Oral	12	Healthy Subjects	Single dose	Complete Publication
PK	MacPhail 5.3.3.2	Absorption of iron after administration of either ferric trimaltol or ferrous sulphate in the presence of an inhibitory meal compared with an empty stomach	Open, randomized, crossover	FeM_3 & $FeS0_4$ 30mg capsules (^{59}Fe: ST10 or ^{55}Fe: $FeSO_4$) Oral	23	Iron deficient patients	Single dose	Complete Data on File
BA / PK	Murray *et al* 5.3.3.2	Bioavailability and PK – the effect of maltol on iron absorption	Open	Aqueous ST10 10mg Aqueous FeSO4 10mg following day (n=1) Oral	6	Healthy subjects (3) Iron deficient patients (3)	Single dose	Complete Data on File

Type of Study	Study ID / Location	Objectives of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects / Patients	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	Kelsey *et al*, 1991 5.3.3.2	Bioavailability	Open, 3-stage sequential, randomised	Aqueous FeM3/FeSO4 (10mg Fe) Tablet FeM3/FeS04 (10mg Fe) Tablet ST10 (60mg FE) Oral	21	Iron deficient patients		Complete Publication
Efficacy	ST10-01-301/302 5.3.5.1	Safety & Efficacy	Multicentre, randomised, double blind, placebo controlled	Oral ST10 30 mg capsule bid vs. placebo	128 (64 ST10; 64 Placebo)	Over 18 years with current IBD or IDA: - Either quiescent UC (SCCAI score of <4) - Or quiescent CD (CDAI score of <220) - Anaemia (Hb ≤9.5g/dL & ≥12.0g/dL for females and ≤9.5g/dL & ≥13.0g/dL for males - Iron deficiency (ferritin <30µg/L) - Past OFP failure or reasons OFP cannot be used	12 weeks plus up to one year open label (Long term safety)	Complete Full
Efficacy	Blake & Kelsey 5.3.5.4	Efficacy	Open, randomised, controlled	ST10 solution (10 mg) FeSO4 tablets (180mg) Oral	31	Iron deficiency anaemia	12 weeks	Complete Data on file

Type of Study	Study ID / Location	Objectives of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects / Patients	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy	Green & Thompson 5.3.5.4	Efficacy	Controlled, randomised	Oral ST10 solution, 30mg Fe/day Oral FeSO4 tablets, 180mg/day	13	Adults with iron deficiency anaemia Hb <13g/dl (M)/<12g/dl (F) with low serum iron (<13µmol/l) and raised TIBC (>70µmol/l) Normal B12 and folate levels	12 weeks	Complete Data on file
Efficacy / safety	Harvey *et al*, 1998 5.3.5.4	Safety and efficacy	Open, uncontrolled	Oral ST10 capsules 30 mg bd (60 mg Fe/day)	24	Documented intolerance to 200mg ferrous sulphate Blood Hb level <130g/dL (<120g/dL in females), serum ferritin levels < 15ug/L and normal serum C reactive protein levels.	12 weeks	Complete Publication
Safety	ST10-01-301/302 5.3.5.4	Long-term safety	Open-label	Oral ST10 30 mg capsule bid	109	Patients with IBD	52 weeks	Complete Interim
Safety	SWIN-189-IM 5.3.5.4	Safety	Double-blind, placebo controlled, crossover	ST10 tablets, 60mg Fe tid FeSO4 tablets, 60mg Fe tid Oral	120	Not known	4 days	Complete Data on file

2.3.2. Pharmacokinetics

No new clinical PK-study data were submitted with this application.

The clinical development program included two prospective PK studies (one of them is a sub-study) that were compliant with GCP.

ST10-01-101 study: open-label, randomised, single and repeat-dose, parallel group study

The first PK study (ST10-01-101) was an open-label, randomised, single and repeat-dose, parallel group study conducted with 24 subjects with iron deficiency (with or without anaemia) but no chronic inflammatory disease at three dosage levels to evaluate the kinetics of maltol, maltol glucuronide and the iron uptake.

The primary objective of Study ST10-01-101 was to evaluate the PK and iron uptake of Feraccru in blood and urine after single and repeated bid oral doses of 30 mg, 60 mg or 90 mg Feraccru for 7 days followed by a final dose on the morning of day 8 through measurement of serum concentrations of total iron, serum values of transferrin saturation (TSAT) and plasma and urine concentrations of maltol and maltol glucuronide.

Maximum serum iron concentrations occurred between 2 and 3 hours post-dose, reaching mean±SD serum concentrations of 32.3±9.04, 49.1±19.3 and 48.7±15.8 µmol/L for the 30, 60 and 90 mg dosing regimens, respectively on Day 1. Mean serum concentrations subsequently declined, and at 6 hours post-dose were 11.8±8.93, 33.0±16.3 and 24.3±19.5 µmol/L above baseline for the 30, 60 and 90 mg dosing regimens, respectively on Day 1. Comparable concentrations were attained on Day 8.

Total serum iron concentration values were generally higher with increasing Ferric maltol dose, with maximum values between 2 and 3 hours post-dose, and then declined gradually after 3 hours on Day 1 and were comparable on Day 8.

Mean TIBC, transferrin and soluble transferrin receptor concentrations remained relatively constant throughout PK sampling, and were comparable between dosing regimens, and between Day 1 and Day 8. Ferritin concentrations remained relatively constant throughout PK sampling, although higher mean values were recorded on Day 8 compared to Day 1 for all dosing regimens.

The secondary objectives of this study were to evaluate the effect of single and repeated bid oral doses of 30 mg, 60 mg or 90 mg Feraccru for 7 days followed by a final dose on the morning of day 8 on serum values of NTBI, serum concentrations of transferrin, total iron binding capacity (TIBC), ferritin and soluble transferrin receptor, routine haematology indices and reticulocyte haemoglobin (CHr) concentrations in whole blood.

ST10-01-102 study: PK sub-study of the pivotal clinical efficacy/safety study

The second study (ST10-01-102) was a PK sub-study of the pivotal clinical efficacy/safety study, where subjects received Ferric maltol 30 mg bid in the open-label phase (of study ST10-01-301 /302) to describe the PK profile at steady state after a 30 mg single dose in patients with iron deficiency anaemia (IDA) and IBD.

The objective of Feraccru-01-102 was to describe the PK profile of Feraccru after a 30 mg single dose administered at steady-state in the morning through measurement of serum iron parameters (transferrin, TSAT, TIBC, ferritin, soluble transferrin receptor, total serum iron), plus plasma and urine concentrations of maltol and maltol glucuronide, following at least 7 days treatment in the open-label phase of studies ST10-01-301 or ST10-01-302.

Secondary objectives were measurement of NTBI as a marker of Feraccru in serum after a 30 mg single dose administered at steady-state, following at least 7 days treatment in the open-label phase of studies ST10-01-301 or ST10-01-302.

Serum total iron concentrations reached a maximum between 1 and 2 hours post-dose. The mean maximum serum iron concentration was 21.9 µmol/L. Serum total iron concentrations gradually declined from Cmax, and appeared to have returned to baseline levels at 8 hours post-dose. From plots comparing total iron and the exposure to maltol or maltol glucuronide, no relationship was observed between them.

Serum values for TIBC and concentrations of transferrin, soluble transferrin receptor and ferritin remained constant throughout the 8-hour sampling period. Total serum iron concentrations, TSAT values and Hb concentrations in this sub-study were consistent with Ferric maltol dosing improving iron deficiency anaemia in these subjects.

Feraccru Dissociation

Feraccru is a chelated form of iron with a very strong bond. Maltol is able to hold the ferric iron in a soluble form at the pH encountered in the intestinal lumen i.e., up to pH 8.0. However, the ferric ion in Feraccru is readily available for ligand exchange with biomolecules, provided those molecules have a similar or greater binding affinity for the ferric ion, thereby avoiding the problems of low bioavailability observed with other ferric products. This process of direct ligand exchange with oxo binding sites on transferrin at the enterocyte wall is the key feature contributing to the safety and efficacy of Feraccru.

Preclinical data in the rat demonstrated that there was no difference in 59Fe absorption from ferric trimaltol given by tube into the stomach compared to 59Fe uptake from ferric maltol injected directly into the duodenum (Barrand 1987), indicating its stability in the stomach. This is supported by the clinical sub-group analysis showing that patients taking proton pump inhibitors (PPIs) had no difference in Hb rise compared to those not taking PPIs in ST10-01-301/2.

The exact location of the dissolution of the ferric iron-maltol-complex contained in Feraccru has not been unequivocally identified. Studies do however indicate that it dissociates either at the epithelial cell membrane or within the endothelial cell itself as intact Feraccru does not enter the systemic circulation.

In the two pivotal PK studies (ST10-01-101 and ST10-01-102), the profiles of total serum iron concentration and TSAT did not match those for maltol or maltol glucuronide. Consequently, no clear relationship could be discerned between either total serum iron concentration or TSAT and exposure to maltol or maltol glucuronide. These observations are consistent with non-clinical studies in which ferric maltol complexes were shown to dissociate at the surface of, or within the enterocyte (Barrand 1991a; Barrand 1991b).

Complete dissociation of iron and maltol is confirmed by the PK studies and is consistent with the absence of Feraccru in blood; Feraccru does not appear in urine. In study ST10-01-102, a single NTBI value $\geqslant$0.2 eLPI units (threshold for a positive result) was determined. However, upon routine retesting, for quality control reasons, this value was 0.0 eLPI units, indicating no 'free' serum iron.

In study ST10-01-101, consistent with the previous PK sub-study, NTBI values $\geqslant$0.2 eLPI units were rare with the 30 mg dosing regimen. Of the four samples for which $\geqslant$0.2 eLPI units were determined, one was taken pre-dose on Day 1 of the study. As all subjects were iron deficient at study entry, and iron preparations were prohibited prior to the study (7 days for oral and 28 days for parenteral iron preparations), the single pre-dose NTBI value $\geqslant$0.2 eLPI units suggests that 'positive' NTBI values may be determined in the absence of any obvious source of excess iron. Mean NTBI values were higher in the 60 and 90 mg dosing regimens. Feraccru increased maltol glucuronide levels dose proportionally. Several studies have shown that significant levels of NTBI are produced when oral ferrous preparations are given with food (Dresow, 2008; Hutchinson, 2004).

Although patient numbers were low and the studies were not conducted in accordance with GCP, clinical investigations performed at St Thomas' Hospital, London, provided some useful preliminary PK data on Feraccru and the results were largely consistent with the pivotal, GCP-compliant PK studies (ST10-01-101 and ST10-01-102).

In the first of these studies the systemic uptake and excretion of iron and maltol was investigated in two healthy male subjects after administration of 10 mg Feraccru radiolabelled with 59Fe and 3H. All 59Fe-associated radioactivity was associated with the high molecular weight protein fractions of the blood. Nearly all 3H radioactivity was associated with the low molecular weight plasma protein fraction. In the two males, 82% and 71%, respectively, of the maltol dose was eliminated in the urine, primarily (95%) as glucuronide conjugate. No Feraccru, maltol or iron was detected in the urine of either subject (Thompson & Hider, Study 2, Data on File).

In a second study, the PK of high-dose ferric 3H-tri-maltol was assessed in one healthy male volunteer. The subject was dosed with 5.65 g of ferric 3H-tri-maltol (approximately 72 mg/kg), which was equivalent to 706 mg of iron and 4.94 g of maltol. Only 0.6% of the iron dose (equivalent to 5 mg iron) was absorbed; in contrast, 55% of the maltol dose was absorbed. Based on the amounts of absorbed iron and maltol, there was no evidence that Feraccru was absorbed as an intact molecule (Thompson & Hider, Study 3).

A further study investigated the PK of maltol following single-dose oral administration of 800 mg Feraccru (equivalent to 100 mg iron and 700 mg maltol) to three healthy male volunteers. Blood samples were obtained pre-dose and at 0, 10, 20, 30, 60, 90, 120, 180, 240, 360 and 480 minutes post-dose. In this study, maltol itself was not detected in the systemic circulation, suggesting that following absorption, maltol undergoes rapid and complete first pass metabolism and is bio-transformed to maltol-glucuronide. No Feraccru, maltol or iron were found in the urine in this study (Thompson & Hider, Study 4).

Absorption

The absorption of iron from Ferric maltol has been evaluated in several clinical pharmacology studies (GCP non-compliant and GCP-compliant studies) in healthy subjects and patients.

The human body carefully regulates absorption of iron from the gut. Because there is no active excretory process for iron once it has entered the bloodstream, the body's control of iron levels is undertaken at the level of the enterocyte (Geisser, 2011). A therapeutic dose of oral iron is taken up by active absorption. The exact mechanism of absorption of ferric iron from the gut however, is still the subject of scientific debate. There are several potential pathways: one involves the reduction of ferric to the ferrous form at the epithelium surface and subsequent uptake by a divalent metal transporter (DMT-1); an alternative mechanism is direct uptake of chelated ferric iron by ligand exchange mediated by the β3 integrin pathway (Conrad & Umbreit 2000). Feraccru does not to inhibit zinc uptake, indicating that iron from Feraccru does not enter the cell via the nonspecific DMT-1 pathway, which would require reduction to Fe2+. Because maltol holds iron firmly in the ferric form and acts as an anti-oxidant then the mechanism for iron uptake from Feraccru is likely to be via non-reductive ligand exchange (Ahmet 1998). Uptake of the iron from ferric trimaltol onto a high affinity binding protein in the duodenal enterocyte was shown in nonclinical study in the small intestine of the rat (Barrand & Callingham 1991) and the uptake was saturable. These findings were consistent with the observations of Teichmann & Stremmel (Teichmann & Stremmel 1990) who observed, using human microvillous membrane vesicles that ferric ions could be taken up by a vesicular pathway as a facilitated but saturable mechanism involving a membrane bound high affinity binding protein.

Under normal circumstances, transferrin in blood is approximately one third saturated. However, when iron is available in excess, transferrin becomes saturated and NTBI circulates in the plasma and is taken up via an unregulated mechanism by endocrine and heart cells, resulting in oxidative stress reactions within these tissues.

The absorption of iron from Feraccru has been evaluated in several clinical pharmacology studies in healthy subjects and patients with ID. Iron absorption from Feraccru was investigated in 21 iron deficient patients in a three-stage sequential study (Kelsey, 1991). In this study, absorption from Feraccru was compared to equivalent doses of ferrous sulphate; two different formulations (aqueous solution and tablets) and two dose levels (10 mg and 60 mg) were also examined. In this study, iron absorption was similar from Feraccru or ferrous sulphate when administered to iron deficient patients in either form.

For the 10 mg dose, the results are presented in the following table:

Dose: 10 mg	Aqueous ferric maltol	Aqueous ferrous sulphate	Ferric maltol tablets	Ferrous sulphate tablets
Serum iron (µmol/L) Mean	5.1 to 19.4 (± 9) 14 (± 6)	8.7 to 19.0 (± 8) 11 (± 7)	5.0 to 15.0 (± 9) 10 (± 9)	3.0 to 17.0 (± 5) 14.3 (± 5.5)

For the 60 mg dose, the results are presented in the following table:

Dose: 60 mg	Ferric maltol tablets	Ferrous sulphate tablets
Serum iron (µmol/L)		
Mean time 0	6.3 ± 0.6	7.0 ± 1.0
Mean 1 h	52.0 ± 29	39.0 ± 13.0
Mean 2 h	62.0 ± 27	47 ± 4.0

Following a 10 mg dose of oral iron, as either ferric maltol or ferrous sulphate in liquid or tablet form, maximal rise in serum iron was seen at 1 hour post-test dose in 50% cases. In the other cases the 2-h level was only marginally higher than that seen at 1 hour indicating considerable plateau of the absorption curve by this time.

A similar plateau after 1 h was seen with the higher dose 60 mg tablets. Proportionate increases in serum iron were also observed in patients receiving the 60 mg doses. For the patients who received Ferric maltol, serum iron increased by approximately 56 µmol/l (equivalent to 14% of the administered dose), to a mean serum iron concentration after dosing of 62 ±27 µmol/l. Patients who took ferrous sulphate experienced a serum iron increase of approximately 41 µmol/l (equivalent to 10% of the administered dose), to a mean serum iron concentration after dosing of 47 ± 4 µmol/l.

There is no statistically significant difference between the results obtained for the two preparations (P > 0·4, unpaired I-test).

A further study compared the absorption of iron from an enteric-coated capsule formulation versus liquid formulations of Feraccru and ferrous sulphate in a total of 41 iron deficient patients, patients with polycythaemia and iron replete controls. Each patient took both Feraccru and ferrous sulphate containing the equivalent of 10 mg iron labelled with 59Fe (2µCi) as acid-resistant capsules, in chicken soup or milk and as an aqueous solution in water adjusted to pH 7. Mean absorption in iron deficient patients was greater than in normal patients for both Feraccru and ferrous sulphate. Rates of iron absorption were comparable from Feraccru or ferrous sulphate in patients regardless of method of delivery. The authors noted that Feraccru is much less likely than ferrous sulphate to cause side effects; indeed, one volunteer took 360 mg and 720 mg doses of iron as ferric maltol without side effects (Maxton, 1994). It could therefore be concluded that iron was absorbed from Feraccru at least as well as iron from ferrous sulphate. The systemic uptake and excretion of iron was investigated in 9 healthy subjects following single dose oral administration of enteric-coated capsules containing ^{59}Fe radiolabelled ST10-021 (Thompson & Hider, Study 1). The percentage absorption of ^{59}Fe 7 days after the oral dose in 9 normal subjects was approximately 15% of the oral dose given. These values are significantly different ($p < 0.05$) but are based on a small number of observations.

A further study reported on the PK of high-dose ferric 3H-tri-maltol in one healthy male volunteer. The subject was dosed with 5.65 g of ferric 3H-tri-maltol (approximately 72 mg/kg), which was equivalent to 706 mg of iron and 4.94 g of maltol (63 times the acceptable daily intake of maltol as a food supplement and 10 times higher than the daily dose of maltol administered in Feraccru capsules). The amount of maltol absorbed from Feraccru at a high dose of 72 mg/kg was <1/10th of the NOEL in completed non-clinical toxicology studies, where maltol was virtually completely absorbed (Thompson & Hider, Study 3).

Distribution

In study ST10-01-101 the PK profiles of both maltol and maltol glucuronide were comparable between Day 1 and Day 8. Although some C0h values for maltol glucuronide were above quantifiable limits on Day 8 in all dosing groups, the Day 8/Day 1 ratios for Cmax and AUC0-t indicated that there was no significant accumulation of maltol or its metabolite, maltol glucuronide, with any of the Feraccru dosing regimens investigated. In addition, exposure to maltol glucuronide was approximately dose proportional on both Day 1 and Day 8 in this study.

The PK of maltol is linear and predictable after Feraccru dosing with 30, 60 or 90 mg bid regimens. In man, iron from Feraccru is utilised and distributed in a physiological manner since the iron rapidly exchanges onto the transport and storage proteins in the body. Since iron is absorbed using the well-defined physiological iron uptake and storage mechanisms, no tissue distribution studies were considered necessary.

Elimination

In study ST10-01-102, exposure to maltol glucuronide was considerably higher than exposure to maltol, and only 0.266% of the maltol dose administered was excreted unchanged in the urine, compared to an equivalent of 41.6% as maltol glucuronide.

Although the liver is the major site of UDP-glucuronosyltransferase expression (Ohno, 2009), a non-clinical study using radiolabelled ferric maltol complex indicated that maltol is also extensively glucuronidated at the site of absorption in the intestinal mucosa (Barrand, 1991b).

In study ST10-01-101, as in the prior PK sub-study (ST10-01-102), the profiles of maltol and maltol glucuronide were similar, although exposure to maltol glucuronide was considerably higher compared to maltol and most of the ingested maltol dose was excreted as maltol glucuronide in the urine. Maltol was rapidly glucuronidated after Feraccru dosing, before being renally excreted.

The same conclusions as above were drawn from the published and unpublished studies in healthy volunteers and subjects with ID conducted by Thompson & Hider Study 2, and Thompson & Hider, Study 4.

Dose proportionality and time dependencies

In study ST-1001-101, dose-normalised parameter for Cmax, AUC0-t, and AUC0-∞ were graphically displayed for maltol and maltol glucuronide as function of the dose, to explore dose-proportionality.

Dose-normalised parameter plots for Cmax, AUC0-t, and AUC0-∞ were consistent with dose-proportional increases in maltol exposure across the 30 mg to 90 mg bid dosing range, although for Subject 101-101-005 in the 60 mg dosing regimen Cmax, AUC0-t, and AUC0-∞ were considerably higher on both days. These values had a considerable impact on the corresponding mean values for this group. Mean values for Cmax, AUC0-t, and AUC0-∞ increased with higher doses. Dose-normalised PK parameter plots for maltol glucuronide indicate that exposure to maltol glucuronide was dose proportional across the 30 to 90 mg bid dose range.

Special populations

<u>Impaired renal function and impaired hepatic function</u>

No specific studies have been performed.

Gender

There were twice as many women as men who participated in studies ST10-01-101 and ST10-01-102, however, subjects were generally well matched across treatment sequences for demographic characteristics including gender. No gender specific PK data on Ferric maltol were noted.

Race

All participants in studies ST10-01-101 and ST10-01-102 were white and mainly Caucasian.

Elderly

There are limited PK data on Ferric maltol in the elderly; the oldest subject in either of the prospective GCP-compliant studies was 57 years old. In a single-dose pilot study, iron absorption from Ferric maltol (administered as a 10 mg iron dose in aqueous solution) was investigated in three elderly patients with anaemia and three elderly healthy subjects (Murray, Blake & Kelsey).

Children

No children specific PK studies on Ferric maltol were performed.

2.3.3. Pharmacodynamics

No new clinical studies were performed.

All available evidence from both nonclinical and clinical data on the absorption from the GI tract, on transport, storage and excretion of iron and maltol after oral administration of Feraccru strongly indicate, that the ST10 complex does not appear in systemic circulation but dissociates completely to ferric iron and maltol. The iron active moiety that is released from Feraccru in the proximal duodenum and delivered to the intestinal enterocytes is a well-established physiological substance and, therefore, no specific studies have been conducted to assess the PD effects of Feraccru or ferric iron. Iron is an essential micronutrient that is required for adequate erythropoietic function, oxidative metabolism and cellular immune responses. Iron deficiency and iron deficiency anaemia are caused by low levels of iron in the body. The most common reasons for ID are insufficient iron intake in the diet, an inability to absorb iron well in the body and/or loss of iron in blood through bleeding. The pharmacodynamic (PD) assessments of iron preparations cannot be based on the standard principles that apply to non-endogenous drugs. The published data discussed above and the pivotal PK studies confirm that iron is absorbed from Feraccru.

Mechanism of action

The iron in Ferric maltol is unable to bind to maltol and transferrin simultaneously. Intracellularly ferric trimaltol can rapidly exchange its iron onto high affinity binding proteins, with the same elution profiles as ferritin and transferrin (Barrand *et al* 1987). The iron from ferric trimaltol would require a specific active mechanism since its molecular size (M Wt 470) would preclude direct absorption through tight channels. Uptake of the iron from ferric trimaltol onto a high affinity binding protein in the duodenal enterocyte was shown in non-clinical study in the small intestine of the rat (Barrand & Callingham 1991) and the uptake was saturable. These findings were consistent with the observations of Teichmann & Stremmel 1990 who observed, using human microvillous membrane vesicles that ferric ions could be taken up by a vesicular pathway as a facilitated but saturable mechanism involving a membrane bound high affinity binding protein.

Primary and secondary pharmacology

Secondary Pharmacological Effects

Administration of Feraccru has not resulted in any secondary pharmacological effects to date.

Pharmacodynamic Interactions

No pharmacokinetic drug interactions studies were submitted either during the initial procedure or in this procedure.

Plasma Concentration-effect Relationship

The absorption of iron from Feraccru or other iron supplements can vary widely depending on the severity of anaemia and/or the level of iron deficiency. Oral iron uptake is regulated to enhance absorption when the body is iron deficient, and to minimise absorption in the iron-replete state. The processes governing iron uptake are highly complex and include controlling uptake from the GI tract, transfer of iron to the systemic circulation and receptor-mediated progenitor cell absorption of iron. An anaemic subject will absorb more iron than a healthy subject and absorption will increase with the level of deficiency. Under normal circumstances there is a maximal level to iron absorption from the gut, and within PK study ST10-01-101 it was demonstrated that a dose of 90 mg bid of Feraccru (i.e., three times the proposed daily dose) did not result in dose-proportional iron absorption and the amount absorbed from such a dose was less than three times what was observed with 30 mg bid.

2.3.4. PK/PD modelling

No formal population pharmacokinetic studies have been conducted with Feraccru however the pharmacokinetic sub-study (ST10-01-102) conducted in a sub-set of patients participating in the open label phase of the pivotal phase 3 studies provides robust data on the PK of Feraccru in the intended patient population.

2.3.5. Discussion on clinical pharmacology

PK data submitted by the applicant are the same information as in the initial procedure (EMEA/H/C/002733/0000). It was based on several studies published since the 90's and two studies conducted in patients with ID of any cause with or without anaemia (ST10-01-101) and in patients with IBD (ST10-01-102).

The ferric trimaltol absorption occurs to a far lesser degree in iron replete subjects, implying that this compound is subject to the normal regulatory mechanisms controlling gastrointestinal iron absorption. Taking into account all the information provided it seems that the absorption of Feraccru could be considered pretty similar in iron deficient and IBD subjects.

Regarding metabolism there are studies in healthy volunteers and subjects with IDA showed that maltol itself was not detected in the systemic circulation, suggesting that following absorption, maltol undergoes rapid and complete first pass metabolism and is bio-transformed to maltol-glucuronide. Lately, both PK studies (ST10-01-101 and ST10-01-102) confirmed these data.

The pharmacokinetic properties of Feraccru was assessed through measurement of plasma and urine concentrations of maltol and maltol glucuronide, together with serum iron parameters after a single dose and at steady state (after 1 week) in 24 subjects with iron deficiency, randomised to receive 30 mg, 60 mg or 90 mg Feraccru twice daily. Blood and urine samples were assayed for maltol and maltol glucuronide. Serum samples were assayed for iron parameters.

Maltol was transiently measured in plasma with a AUC_{0-t} between 0.022 and 0.205 h.µg/mL across all dosing regimens and both study days. Non-clinical studies have shown that maltol is metabolised through UGT1A6 and by sulphation. It is not known if medical products that inhibit UGT enzymes have the potential to increase maltol concentration (see section 4.5). The maltol appeared to be rapidly metabolised to maltol glucuronide (AUC_{0-t} between 9.83 and 30.9 h.µg/mL across all dosage regimens). Maximum maltol and maltol glucuronide concentrations were reached 1 to 1.5 hours after oral administration of Feraccru. Exposure to maltol glucuronide increased dose proportionally over the Feraccru 30 to 90 mg twice daily dosing range and there was no significant accumulation of either after 7 days treatment with Feraccru. Of the total maltol ingested, a mean of between 39.8 % and 60.0 % was excreted as maltol glucuronide. Peak transferrin saturation (TSAT) and total serum iron values were reached 1.5 to 3 hours after oral administration of Feraccru. Total serum iron concentrations and TSAT values were generally higher with increasing Feraccru doses. TSAT and total serum iron profiles were comparable between Day 1 and Day 8.

The pharmacokinetic properties of Feraccru were also investigated at steady state in 15 subjects who were already participating in the AEGIS1/2 study described above and who had been in the open-label treatment phase for at least 7 days (Feraccru 30 mg twice daily). Maltol was again transiently measured in plasma with a half-life of 0.7 hours, with a C_{max} of 67.3 $\pm$ 28.3 ng/mL. The maltol appeared to be rapidly metabolised to maltol glucuronide (C_{max} = 4677 $\pm$ 1613 ng/mL). Maximum maltol and maltol glucuronide concentrations were reached approximately 1 hour after oral administration of Feraccru. Maximum total iron serum concentrations were measured 1-2 hours after administration. The pharmacokinetic profiles of maltol/maltol glucuronide and iron parameters were independent of one another.

Considering that there are several circumstances that affect iron absorption, mainly etiology and severity of iron deficiency, bioavailability has been shown sufficiently even in iron deficiency patients without anemia. With the data provided, although they are scarce, it is considered that absorption and as a result efficacy in patients with ID without anaemia is sufficiently demonstrated.

Feraccru, as a new complex of an existing substance that differs in safety and efficacy to those existing substances, it can be considered to be a new chemical entity, the iron that is released and delivered to the intestinal enterocytes is a known active ingredient with well-established PD drug interactions.

No pharmacokinetic drug interactions studies were submitted during the initial procedure and in this procedure. Conclusions at the end of the initial procedure were that the applicant must perform drug – drug interaction studies and this was included in the RMP as an important potential risk. In December 2016 the Applicant submitted a variation (II/0002/G) of two final study reports for *in vitro* studies conducted as part of post-authorisation measures MEA 001 and MEA 002. This procedure included one DDI study to investigate drug interactions with Feraccru and another DDI study to identify UGT isoenzyme(s) that are responsible for metabolism of ferric maltol. As a consequence, the SmPC was revised accordingly.

2.3.6. Conclusions on clinical pharmacology

Taking into account all the PK/PD data provided it seems that Feraccru could work similarly in IBD patients and in healthy subjects.

There are also some data coming from non-GCP studies which are in line with PK study in relation to serum iron levels increment.

2.4. Clinical efficacy

No new clinical study data were submitted with this variation.

2.4.1. Dose response study

Justification of dose

The dose of Feraccru investigated in the clinical programme was 30 mg bid, i.e., 60 mg/day of iron.

Early clinical studies suggested that 60 mg/day (iron) of Feraccru is sufficient to correct iron deficiency in patients with IDA and ferrous sulphate intolerance (Harvey, 1998). Furthermore, a profile of Feraccru dose versus effective absorption at differing Hb levels has been demonstrated (Powell, 2011). The dose was derived from a model developed to determine the optimal dose.

The model used data from 6 previous studies of Feraccru in subjects with IBD and IDA to estimate absorption rates in the study population. This confirmed that a dose of 60 mg per day was optimal and would normalise Hb levels in nearly 100% of iron deficient males and 80% of iron deficient females after 12 weeks of treatment. This amount was given as two divided doses to minimise any potential GI-related side effects as would be commonly seen with OFPs.

In study ST10-01-101, maximum values of both total serum iron concentration and TSAT occurred between 1.5 and 3 hours post dose. Values for both parameters were consistent between Day 1 and Day 8 and, higher values were recorded for the 60 and 90 mg dosing regimens compared to the 30 mg regimen.

The pivotal phase 3 study demonstrated that 30 mg bid was highly effective in treating IDA in IBD patients (ST10-01-301/302) by normalising both ferritin and Hb levels. There is no scientific rationale for arguing that this dose would not be effective in other diseases associated with IDA, such as women with heavy menstrual bleeding or patients with CKD, given that patients with IBD theoretically might have had impaired uptake of oral iron due to inflammation of the GI tract and can therefore be considered a "worst case" population.

The approved dose is the one valid for IBD patients. During the initial procedure it was observed that 60 mg bid could be more effective than 30 mg bid dose. However, taking into account the tolerability 30 mg bid was selected as the appropriate dose for IDA in patients with IBD. The Applicant stated that there is not argument against that this dose could be effective in other diseases associated with ID.

PK-data show sufficient bioavailability in study- subjects with iron deficiency without anaemia and supportive clinical study data indicate that the recommended dose is sufficient to normalise iron blood indices in patients with ID/IDA or maintain Hb –levels in patients with active blood loss. Data from PK study (ST10-01-101) showed that although doses higher than 30 mg attained better efficacy the safety profile was worse. Moreover, taking into account PK parameters, there were no much differences between 30 mg and the other two doses explored.

The efficacy of the active component iron can be considered 'well established' after resorption has taken place (it was agreed during the MA assessment that the active is not absorbed as a whole but only as two separate components Iron and Trimaltol).

The low dosage of 60 mg of iron per day in Feraccru is also covered by several authorised OFPs and can therefore be considered well established as well.

Therefore, 30 mg bid is considered an acceptable dose for patients with ID.

2.4.2. Main studies

Evidence for the efficacy of Feraccru in increasing both Hb and ferritin levels was generated from one pivotal phase 3 study (ST10-01-301/302) conducted under two separate clinical protocols, one published study (Harvey, 1998) and two unpublished studies (Blake & Kelsey, Data on File; Green & Thompson, Data on File).

The approach of providing data from a single pivotal study is in accordance with the CHMP Guidance: Points to Consider on Application with 1. Meta-analysis; 2. One pivotal study (CHMP/EWP/2330/99), on the basis of:

• Internal validity – there is no indication of bias

• External validity – the study population is suitable for extrapolation to the initial population for the marketed product (patients with IDA and IBD) and for the proposed population (patients with ID)

• The estimated size of treatment effect is considerably greater than the minimally clinically relevant effect (rise in Hb of 2.25 g/dL observed compared to a rise of 1.0 g/Dl which was prospectively identified as being clinically significant)

• The statistical evidence is considerably stronger than the $p<0.05$ usually required, being $p<0.0001$ for the primary endpoint and all key secondary endpoints

• Internal consistency – there is no evidence of pre-specified sub-populations having an effect on response rate (CD and UC sub-populations)

• There are minimal country or centre effects

• The hypothesis tested is plausible.

A post-hoc analysis was provided as part of the procedure. The results of this confirmed that the data from the two separate protocols was independently statistically significant for the primary endpoint. The two studies were comparable in design, execution, key subject characteristics and outcomes. The two sets of subjects from each study were similar enough to enable analysis as a single dataset, and not to miss relevant differences in efficacy or safety measures.

Extrapolation of Efficacy to Patients with ID/IDA not Associated with IBD

Although the Phase 3 studies were conducted in patients with IDA and IBD, efficacy can be extrapolated to IDA associated with other disease states.

The pivotal PK study (ST10-01-101) was conducted in patients with iron deficiency, not restricted to IBD and is relevant for patients with IDA caused by other factors. Iron homeostasis is regulated at the level of iron uptake by body iron stores, although the exact mechanism is not completely understood. There are no available data that indicate that the distribution and utilisation of iron differ substantially between subgroups of patients with IDA. Patients with IBD do not always respond adequately to oral iron therapy, because of a combination of non-compliance due to side effects and impaired absorption due to IBD inflammation. This population can therefore be considered a worst case in terms of both efficacy and safety. The Phase 3 studies show that Feraccru is effective in this population and it is possible to extrapolate the effectiveness to other sub-population of patients with IDA.

Pivotal Phase 3 Study

The primary objective of studies ST10-01-301 and ST10-01-302 was to demonstrate the efficacy effect of oral Feraccru over placebo in the treatment of IDA, as measured by change in Hb concentration from Baseline to Week 12. Following 12 weeks of randomised treatment, all subjects received open-label

treatment with feraccru for up to an additional 52 weeks with the exception of those patients in Austria where the Ethics Committee did not approve the open label phase of the trial. At the request of the MHRA, protocol wording referring to the chapter "Dose Selection and Treatment Duration" of the open label phase of the study was amended and the reference to a possible expansion of treatment duration until an access program to collect long-term safety information on Feraccru has been established was removed. This change was implemented globally in the next version of the Protocol (Version 3.0), at which point the UK protocol was again harmonised with the general protocol.

Placebo was chosen as the comparator as treatment with OFPs would be expected to lead to a high rate of intolerance and discontinuation which would then result in an incomplete and reduced comparator dataset for safety and efficacy. Moreover, use of second line treatments with 'improved preparations', such as lower doses and delayed release or gastroprotective forms of oral iron was considered inappropriate. These treatments have not become widely used as there appears to be little safety or tolerability benefit from these compared to standard ferrous sulphate (Tolkien 2015). The current ECCO guidelines on IDA management in IBD (Dignass 2015) do not recommend use of 'improved preparations', and only recommend ferrous sulphate for mild anaemia in patients with inactive disease. This further supported the use of the placebo control arm in the pivotal studies, instead of a repeat exposure to ferrous products. Patients had to be 18 years of age or above and have a current diagnosis of IBD and IDA [either quiescent UC (SCCAI score of <4) or quiescent CD (CDAI score of <220)], anaemia (Hb ⩾9.5 g/dL and <12.0 g/dL [5.9 to 7.5 mmol/L] for females and ⩾9.5 g/dL and <13.0 g/dL [5.9 to 8.1 mmol/L] for males), iron deficiency (ferritin <30 µg/L) and past failure of OFP and documented reasons why OFP could not be given. This defined patient population was consistent with the target population for the proposed indication. Screening laboratory values were used for inclusion into the study, whereas baseline values were taken at the randomisation visit. Therefore, values could have changed in the 14 days following screening. This is a practical issue for any study relying on the precision and standardisation of a central laboratory. All patients fulfilled the definition of IDA at screening.

The SCCAI and CDAI scoring tools are commonly used to provide a measure of disease activity and were used to identify patients with IDA and UC. As the clinical outcome and efficacy analysis did not use either of these two scales, these measures were not formally validated as the results had no impact on the primary efficacy endpoint or the validity of data supporting the use of Feraccru in the treatment of anaemia.

The definition of intolerance to OFPs used in the conduct of these studies was past failure of OFP (adverse drug effects that led to withdrawal from OFP by at least one of the following conditions: nausea, diarrhoea, constipation, abdominal pain, flatulence, and/or deterioration of the primary disease caused by OFP, and/or lack of efficacy, and/or other signs of failure to OFP, or reasons why OFP cannot be used as documented by the Investigator).

Common prior OFPs used by at least 10% of subjects included ferrous glycine sulphate in 26 (40.6%) Feraccru and 25 (39.1%) placebo subjects, and ferrous sulphate in 20 (31.3%) Feraccru and 13 (20.3%) placebo subjects. There were some differences in the mean and median length of treatment with prior OFPs between the groups. The mean length of time was lower in the Feraccru group (mean 97.29 days) compared to the placebo group (mean 124.69 days), however the median length was longer in the Feraccru group than the placebo group (53.27 versus 45.66 days). Mean and median time since last dose of prior OFP was slightly longer in the Feraccru group (mean 36.17, median 21.82 days) than the placebo group (mean 33.34, median 17.35 days) (Table 2). These differences are not considered to have affected the results of the study.

Table 2: Previous Oral Iron Therapy for Each Subject on Studies ST10-01-301 and 302

OFP Term	ST10-021 (N=64)	Placebo (N=64)
Ferranem	1 (1.6%)	5 (7.8%)
Ferretab	1 (1.6%)	1 (1.6%)
Ferric hydroxide polymaltose	0	1 (1.6%)
Ferric sodium gluconate complex	2 (3.1%)	0
Ferro-folsan	1 (1.6%)	0
Ferrous fumarate	5 (7.8%)	5 (7.8%)
Ferrous gluconate	4 (6.3%)	3 (4.7%)
Ferrous glycine sulphate	26 (40.6%)	25 (39.1%)
Ferrous hydroxide	2 (3.1%)	3 (4.7%)
Ferrous sulphate	20 (31.3%)	13 (20.3%)
Ferrum fol	2 (3.1%)	3 (4.7%)
Floradix	1 (1.6%)	0
Iron preparations	1 (1.6%)	1 (1.6%)
Mineral supplements	0	1 (1.6%)
Multivitamins with iron	0	2 (3.1%)
Pregamal	0	1 (1.6%)
Sodium feredetate	2 (3.1%)	0
Unknown	2 (3.1%)	3 (4.7%)

A post-hoc survey of the clinical trial sites was conducted and responses received from 13 German and Hungarian sites. The percentage of subjects at each site who had received IV iron previously ranged from 100% to 11% with a mean of 55%. The average number of days since last IV iron treatment was 285 (range 84-567).

Across both treatment groups, subjects were well matched for age, race, ethnicity and height.

Almost twice the number of females compared to males participated in the study. The proportion of males was slightly higher in the Feraccru group i.e., 24 (37.5%) compared to 21 (32.8%) in the placebo group, but there is no reason to suppose that this would have any impact on the results of the study.

The only medical history recorded in at least 10% of subjects in either treatment group was intestinal resection in the Feraccru group (7 subjects, 10.9%). Other than presence of CD and UC, the unremarkable medical history profile was consistent with expectations for the study population as a whole. Median duration of IBD disease was similar in both groups.

Fewer than 10% of subjects in both groups were taking oral supplemental vitamin B12 or folic acid. All subjects, with the exception of one were on stable dosing of their supplement from 3 months before randomisation through study Week 12.

The sample size calculation was based on results from previous exploratory studies. A sample size of 49 subjects in each group would have 95% power to detect a probability of 0.711 P (X<Y) that an observation in the control group (placebo) would show a lower increase of Hb concentration than in the test group (Feraccru) using the Wilcoxon (Mann- Whitney) rank-sum test with a 0.025 one-sided significance level. To allow for non-evaluable subjects (e.g., dropouts), a total of 120 subjects were to be recruited, approximately 60 subjects within each study.

The sample size was confirmed in the scientific advice meetings as acceptable provided the drop-out rate was low. A total of 128 subjects were randomised into both studies ST10-01-301 and ST10-01-302. Three hundred and twenty nine subjects were screened in total, 201 of them resulted in screening failures, most of them due to iron levels that were too low. The SAP specified that the first 120 randomised would be included in an initial double-blind analysis, with a sensitivity analysis performed on the final number randomised. Once all subjects had withdrawn or completed the open label phase, the analyses were to be repeated for the complete dataset. Sixty four subjects were treated with Feraccru in the double-blind and open-label phases had a total duration of treatment of median 445.5 days and mean 311.8 days (SD 177.12). Total dose of Feraccru received was median 23340.0 mg and mean 17703.8 mg (SD 10381.38). Forty seven subjects were treated with placebo in the double-blind phase and Feraccru in the open label phase had a duration of Feraccru treatment of median 365.0 days and mean 293.7 days (SD 125.66). Total dose of Feraccru received was median 21240.0 mg and mean 17493.2 mg (SD 7037.00). The blind was broken on 8 December 2013. The Statistical Analysis plan was finalised and signed on the 5 December 2013. No changes were made to the planned analysis after the database was locked. A decision was made on which subjects would be included/excluded from the per protocol analysis based on a review of protocol deviations.

These focused on changes in Hb concentration. For the primary endpoint, missing randomisation Hb values were replaced by screening Hb values if the randomisation was within the protocol-specified window. The robustness of the primary efficacy analysis on the Full Analysis Set (FAS) was confirmed ($p<0.0001$) by a range of sensitivity analyses, including Last Observation Carried Forward (LOCF) analysis, Mixed Model Repeated Measures (MMRM) and analysis of the Per Protocol Analysis Set (PPAS).

A pre-specified analysis was performed with the study data analysed as an integrated data set from the two study protocols. Effectiveness was analysed by determining whether the combined test group showed a statistically significant superiority compared to the combined control group.

In addition, a post-hoc analysis of the primary efficacy endpoint data by IBD diagnosis has been performed. The Applicant re-analysed the combined dataset for the primary efficacy endpoint, according to IBD diagnosis in the study subjects.

Slightly more subjects were randomised into study ST10-01-302 (CD) compared to ST10-01-301 (UC); however, the mean age, race proportions and gender split was very similar across the two groups. In both studies, all randomised subjects were included in the FAS and only a few subjects were excluded from the PP set. A small number of subjects withdrew from the randomised phase of the study due to AEs and this was similar in both groups, suggesting that background disease did not affect AE profile. The proportion of subjects taking proton pump inhibitors (PPIs) was similar between the two study groups, as was the proportion being treated with anti-tumour necrosis factor (TNF) medication. More subjects with UC were treated with acetylsalicylic acid (ASA)-type medications but this was to be expected. Median duration of treatment was lower in the ST10-01-302 (CD) group, although the mean durations of treatment were very similar between the two groups.

Double-blind Phase

In terms of the primary endpoint (first 120 patients randomised), in Feraccru subjects there was a mean overall improvement in Hb levels of 2.25 g/dL (ST10-01-31/302 CSR1). In contrast, mean Hb levels in

placebo subjects were virtually unchanged (11.10 g/dL (SD 0.793) at baseline and 11.13 g/dL (SD 0.970) at Week 12. The mean improvement in Hb levels delivered by Feraccru was statistically significantly different ($p<0.0001$) compared to placebo. Feraccru therefore met the primary efficacy endpoint of change in Hb concentration after 12 weeks of treatment compared to placebo.

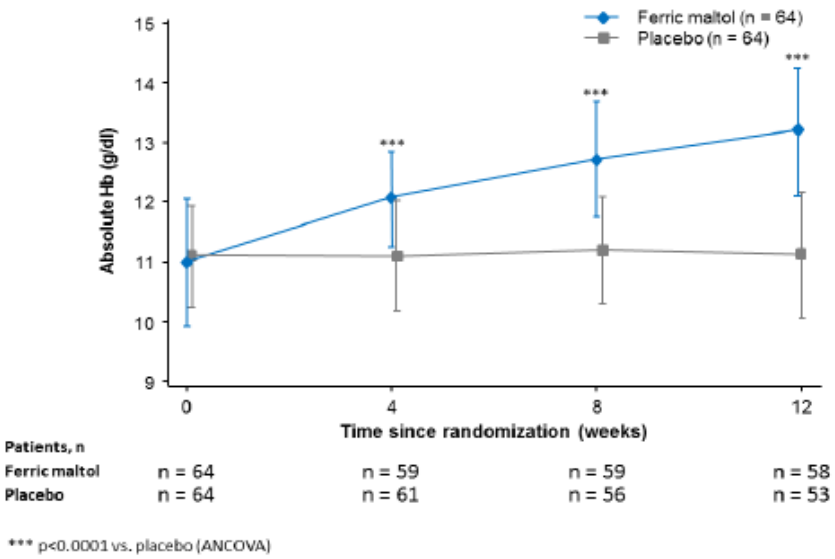
This mean overall improvement in Hb levels of 2.25 g/dL is in excess of the pre-specified change of 1 g/dL and clinically can be considered a highly meaningful change.

The robustness of the primary efficacy analysis on the FAS was confirmed ($p<0.0001$) by all applied sensitivity analyses including analysis of the PPAS; analysis of the FAS using an LOCF approach; analysis of complete cases (subjects with both baseline and Week 12 Hb concentrations) in the FAS; analysis of the FAS using an MMRM approach and analysis of the FAS excluding the non-compliant subjects.

Furthermore, the change from baseline to week 12 in Hb was analysed by pattern mixture model (PMM) using placebo imputation for withdrawn subjects and a baseline observation carried forward (BOCF) analysis in order to assess the effectiveness of treatment taking into account subject discontinuation. Even though this is a conservative approach, the estimated treatment differences are still large and statistically significant for both studies (UC: above 2 g/dl in both cases, CD: 1.87 [0.28] and 1.84 [0.23]), ($p<0.0001$).

The primary endpoint analysis was performed on all 128 subjects randomised and the results from this analysis were entirely consistent with the results from the primary efficacy analysis performed on the first 120 subjects (Figure 1): mean Hb levels improved in Feraccru subjects from baseline (mean Hb 11.00 g/dL [SD 1.027]) to Week 12 (mean Hb 13.20 g/dL [SD 1.044]), i.e., a mean overall improvement of 2.20 g/dL. Mean Hb levels in placebo subjects were similar at 11.10 g/dL (SD 0.851) at baseline and 11.15 g/dL (SD 1.039) at Week 12.

Figure 1. Change in Haemoglobin from Baseline to Week 12 (ST10-01-301/302) (Full Analysis Set; N = 128)



The baseline Hb would be expected to be a predictor of response because there is a physiological upper limit on Hb and patients with a baseline Hb close to normal would not have a large Hb rise, compared to those subjects with a baseline Hb much lower. Patients with a lower baseline Hb value did have a greater response in terms of Hb increase at week 12 compared to subjects with relatively high Hb at baseline. However, the difference compared to placebo in all sub-groups below normal at baseline was still greater

than 2 g/dl and the pvalue <0.0001. Although the Hb difference was less in patients with normal Hb at baseline, there was still a clinically significant rise of 1.11 g/dl recorded and the p-value compared to placebo was <0.0001. Baseline Hb therefore correlates with the magnitude of the response but not with a responder subset. Moreover, responder analysis show a clear relationship between baseline Hb level and the likelihood of achieving a 1 g/dl, a 2g/ dl rise in Hb, or of achieving either Hb within the normal range or a 2 g/dl rise.

In contrast, baseline ferritin, providing it was below normal, does not appear to be a predictor of response. There was no significant difference between means (Feraccru compared to placebo) in patient with ferritin <15 µg/l compared to subjects with baseline ferritin >15 - <30 µg/L.

Patients with normal ferritin (>40 15-<30 µg/l) at baseline do appear to have lower Hb rise in response to treatment with Feraccru. This is most likely because the subgroup of patients with normal ferritin also had a starting Hb closer to normal. The responder analysis however, showed that there was a higher percentage of responders in the <15 µg/L group (83.9% and 60.7% achieving a 1 g/dl and 2 g/dl rise, respectively) compared to the 15-<30 µg/L group (42.9% and 28.6%). However, the percentage of patients that were "responders" as defined by Hb within the normal range or a 2 g/dl increase was similar in both sub-groups (76.8% vs. 71.4%). Responder rates between UC and CD patients were comparable and there was no significant difference in Hb level change from baseline.

Sub-group analysis confirmed that there was no apparent effect of gender or age on the change from Hb at Week 12. Subjects starting with a lower baseline Hb tended towards a greater increase in Hb than subjects starting with a higher baseline Hb, by Week 12.

Feraccru met all key secondary efficacy endpoints that were statistically significantly greater compared to placebo in both the first 120 patients randomised in all 128 patients, including:

• Achieving at least an increase of 1 g/dL from baseline Hb concentration at Week 12 (p<0.0001)

• Achieving at least an increase of 2 g/dL from baseline Hb concentration at Week 12 (p<0.0001)

• Achieving normalised Hb concentration at Week 12 (p<0.0001)

• Achieving improved Hb concentration at Weeks 4 and 8 (p<0.0001).

The logistic regression analyses performed confirmed that the odds of achieving a 1 g/dL increase over baseline and a 2 g/dL increase over baseline with Feraccru were significantly greater than with placebo. Disease type did not significantly affect these odds. Similarly, the logistic regression analysis confirmed that the odds of achieving a normalised Hb concentration with Feraccru were significantly greater than with placebo. Disease type did not significantly affect the odds of achieving a normalised Hb concentration.

Twenty-eight patients in the Feraccru group did not achieve an increase of 2 g/dl over baseline Hb concentration. Amongst these subjects very few appear to have a less than 2 g/dL rise indicating that earlier resistance is not predictive of response to ferric maltol. No patient with a baseline Hb of less than 10 g/dL had less than a 2 g/dL rise.

A rise of less than1 g/dL from baseline in Hb concentration at Week 12 was reported for 14 out of 64 (21.9%) subjects. However, a rise of less than1 g/dL from baseline in Hb concentration at Week 12 was also conservatively applied to subjects not returning to a follow-up visit. As six subjects did not have a Week 12 determination of haemoglobin, only 8 subjects had an actual increase of less than 1 g/dL from baseline to Week 12. These subjects did not have any characteristics in common other than being more likely to have Crohn's disease than ulcerative colitis: they ranged in age and percentage compliance, were males and females, had received different prior iron treatments and as a group experienced both increases and decreases in IBDQ from baseline to Week 12. Therefore there was no pattern in the

demographic characteristics of these subjects linked to a lower Hb response; however as discussed previously a higher starting Hb was associated with a smaller Hb rise by week 12.

The mean improvement in Hb levels to Week 4 and Week 8 delivered by Feraccru was statistically significantly different ($p<0.0001$) compared to placebo. Feraccru therefore met the secondary efficacy endpoints of change in Hb concentration after 4 and 8 weeks of treatment compared to placebo.

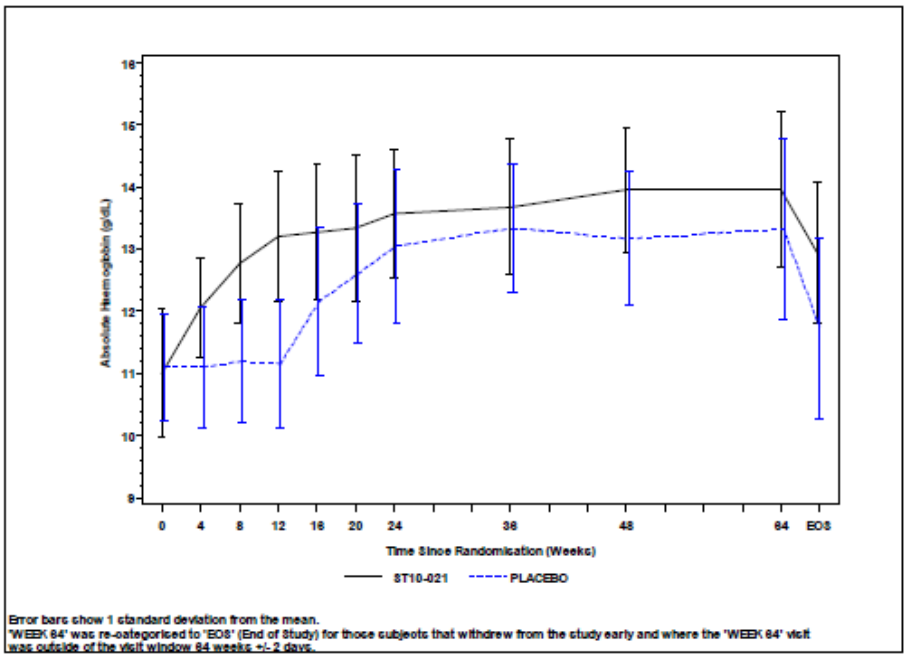
Before the study treatment all patients in the study ST10-01-301 had an SCCAI score of 3 or below. The SCCAI scores gradually increased over the 12 weeks of the study. At week 12, 18.9% of subjects had scores of 4 or above. In study ST10-01-302, all patients had a CDAI score of 220 or below before start of the treatment. There was a slight trend towards increased over the 12 weeks of the study. There was no difference between the SCCAI and CDAI scores recorded at 12 weeks in patients on active compared to placebo treatment (for ST10-01-301/302 CSR2 Section 12.5.3 and 12.5.4).

Patients randomised had active disease. The number of subjects who had baseline scores of 170 or less was around 40% (25 [39.1%] in the Feraccru group and 27 [42.2%] in the placebo group). In other words, 40% of AEGIS patients were not "quiescent" at baseline. This is supported by data that confirm that 38.7% of all patients were receiving TNF inhibitors and 30.6% were on azathioprine. In sub-study ST10-01-301, the majority of patients (51.7%) had experienced a disease flare in the previous 6 months. In study ST10-01-302, the average duration since last flare was longer than in study ST10-01-301: 32.9% of subjects had experienced a disease flare in the previous 6 months and 72.9% in the previous 18 months. The duration since last flare was evenly matched in subjects randomised to Feraccru treatment and to placebo treatment for both study protocols.

Double-blind and Open Label Phase

When the placebo subjects were transferred to Feraccru treatment in the open-label phase, there was a sharp rise in Hb levels that mirrored the response in the Feraccru group in the double-blind phase (Figure 2). There were further increases in Hb up to 48 weeks of treatment and no indication of any reduction in efficacy over the full 64 week treatment period.

Figure 2. Absolute Haemoglobin (g/dL) Over Time: Double-blind and Open-label Phase (Full Analysis Set)



As described above both sub-groups showed a highly significant increase in Hb compared to baseline after 12 weeks treatment with Feraccru, and this appears to be sustained or increased out to week 64 of open label treatment. However, patients treated with placebo in the double blind phase and with Feraccru in the open phase achieved a slight numerical lower Hb increase than those treated with Feraccru over the study period. Subjects were randomised to treatment arm stratified for baseline Hb; there were no obvious imbalances in demographic data or starting Hb. After 12 weeks of Placebo treatment though (and no meaningful Hb rise) the withdrawals in the Placebo group could have led to a slight shift in study subject characteristics during the Open Label phase. However, it should be noted that the study was not powered or designed to compare efficacy of Feraccru between the two treatment arms in the open label phase and there is significant overlap in the errors bars of the mean Hb levels in the 2 groups at week 64. Overall, mean iron indices (ferritin, iron, transferrin, transferrin receptor, total iron binding capacity and transferrin saturation) in Feraccru subjects improved from baseline over 12 weeks. Overall, mean iron indices in placebo subjects remained unchanged over the same period. In the open-label period ferritin continued to rise (but without leading to toxicity or overload) past Week 12. After Week 12 the improvement in iron plateaus and the improvement in transferrin and transferrin receptor increased only minimally. Iron-binding capacity continued to fall gradually with longer-term treatment. Transferrin saturation increased significantly from Baseline with Feraccru treatment; but stabilised at this higher level by Week 12/16.

Post-hoc Analysis of the Primary Efficacy Results

A small set of post-hoc analysis were performed on the primary endpoint and within each study population. This used the same multiple imputation model and analysis model (ANCOVA) as the primary analysis, except for disease state. This analysis was performed on the FAS and Per Protocol (PP) datasets. The estimated mean difference in Hb change at Week 12 was very similar in the two study subgroups when compared to the single IBD dataset.

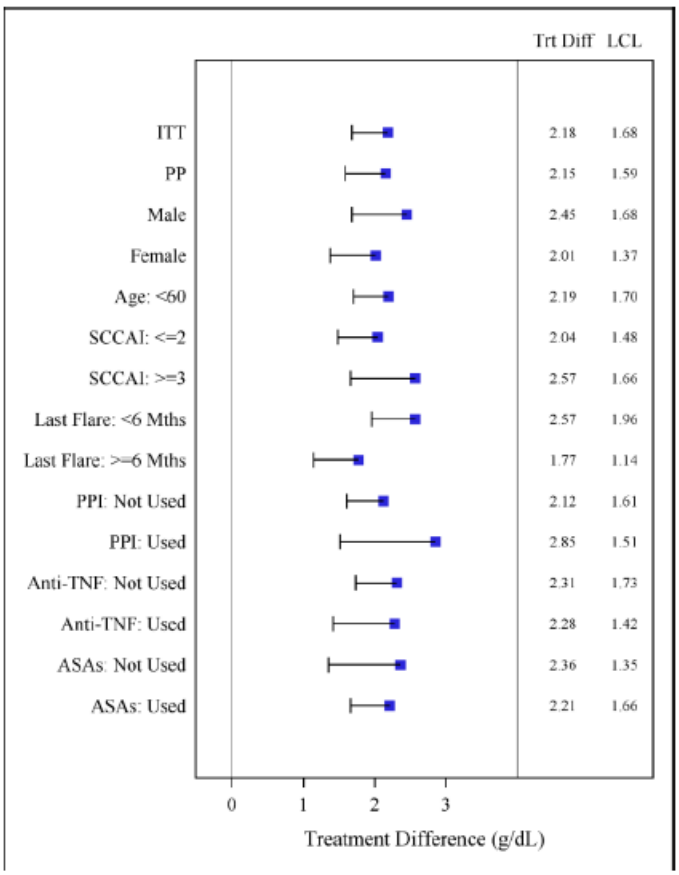
The p-values for the separate studies were both <0.0001, demonstrating independently significant results. These results strongly confirmed that the anaemia-correcting effect of Feraccru is independent of the cause of IBD and that Feraccru works equally well in patients with UC and CD.

The analyses were also repeated on subgroups that reflected disease severity (e.g. baseline disease activity score, use of biological anti-TNF agents, time since last flare), concomitant medications possibly causing drug interactions (e.g., ASAs or PPIs), age and gender.

For each subgroup the ANCOVA analysis was repeated including subgroup and subgroup-by treatment interaction terms. The results were presented as 1-sided 97.5% confidence intervals.

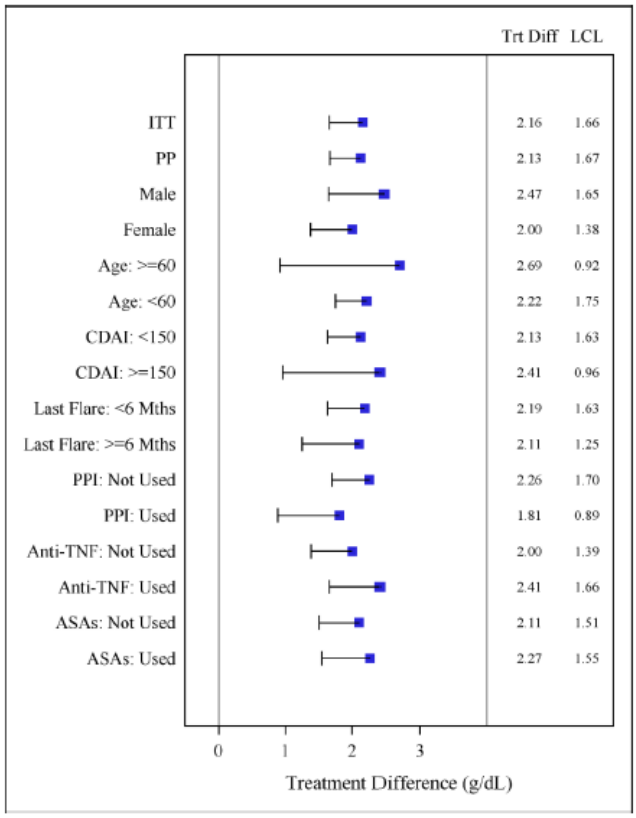
These were plotted as Forest plots (see Figures 3 and 4).

Figure 3. Forest Plot of Haemoglobin (g/dL) Change from Baseline to Week 12 Multiple Imputation Analyses; Full Analysis Set; ST10-021-301



* ITT: Intent To Treat; SCCAI: Simple Crohn's and Colitis Activity Index; CDAI: Crohn's Disease Activity Index; Trt Diff: Treatment Difference; LCL: Lower Confidence Limit

Figure 4. Forest Plot of Haemoglobin (g/dL) Change from Baseline to Week 12 Multiple Imputation Analyses; Full Analysis Set; ST10-021-302



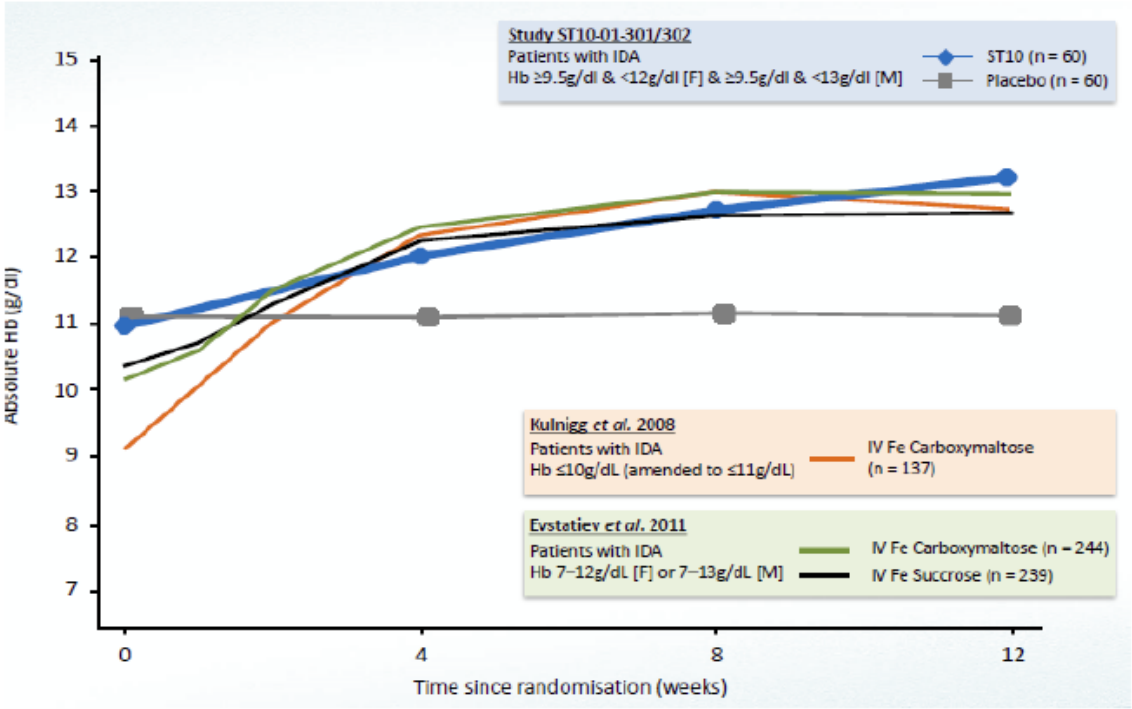
* ITT: Intent To Treat; SCCAI: Simple Crohn's and Colitis Activity Index; CDAI: Crohn's Disease Activity Index; Trt Diff: Treatment Difference; LCL: Lower Confidence Limit

The subgroup analysis conducted within studies ST10-01-301 and ST10-01-302 gave estimated mean differences in Hb at Week 12 between 2 and 3 g/dL improvement; very similar to the overall result. There were no subgroups where the difference trended to a worse or significantly greater result. Although the numbers in the individual groups were sometimes small, the lower 97.5% CI of all subgroups fell well above the 0 g/dL treatment difference.

Comparison of the Rate and Extent of Hb Correction with Feraccru 30 mg bid with Published Results for Existing IV Iron Products

It has been reported that IV iron does not correct IDA any faster or more effectively than oral iron (Bastani, 2000). Figure 5 compares the rate and extent of the increase in Hb observed in study ST10-01-301/302 with those published for the IV iron products ferric carboxymaltose (Kulnigg, 2008; Evstatiev, 2011) and ferric sucrose (Evstatiev, 2011) in subjects with IDA. The data suggest that Feraccru is as fast and as effective in correcting Hb levels as IV iron products and indicates that it is a viable alternative to IV iron therapy in the proposed patient population.

Figure 5. Rise in Hb Levels Observed in Study ST10-01-301/302 for ST10 30 mg bid Compared to Reported Results for IV Iron Products



Comparison of the Efficacy of Feraccru with Other Oral Iron Preparations

A comprehensive comparison of the efficacy of Feraccru with published efficacy data of other oral iron preparations, used both first and second line was conducted by the MAH. The MAH has also reviewed other published data on change in Hb with iron treatment.

A meta-analysis was conducted including data from study ST10-01-301/302 and 21 published studies (Pereira 2015). The median duration of supplementation with ferrous sulphate for these 21 trials was 6 weeks (range 4-20 weeks) and the reported mean Hb increase was 2.2 g/dL (SD 1.2). The mean increase with Feraccru at 4, 8 and 12 weeks was 1.08, 1.79 and 2.26 g/dL, respectively.

The reviewed studies and those included in meta-analyses varied with regards to design, objectives, number of subjects included, tolerance or intolerance to previous oral iron treatment, dose of elemental iron, iron compound and formulation, comparator (active versus placebo), route of administration, duration of treatment, baseline Hb concentration, and patient condition (non-IBD versus IBD); there was none that matched all features of ST10-01-301/302. The mean increase in Hb over 12 weeks (2.26 g/dL) with Feraccru was in line with those observed with other effective oral iron first-line treatments in IBD, including studies with subjects with lower Hb baselines.

The duration of treatment in all of these studies was 6-8 weeks, while generally at least 12-weeks treatment is required with Feraccru in IBD patients.

In the meta-analysis, there was no significant difference for the comparison of change in Hb increase between ferrous sulphate and Feraccru with duration of supplement and baseline Hb as covariates in the ANCOVA model. There was, however, a significant main effect of duration of supplementation ($p = 0.027$) and a pronounced significant main effect of baseline Hb ($p = 0.001$). Hb increase seen in the first 20 weeks of supplementation with Feraccru was in line with that observed with ferrous sulphate in the 21 studies. Furthermore, there was a tendency for a linear association between Hb increase and duration of

treatment in the first 12 weeks (double-bind) phase of supplementation with Feraccru but this did not reach statistical significance (p = 0.074).

Two of the studies in the meta-analysis used modified release formulations (the rest used standard ferrous sulphate). The results from these studies are identified (as MR) below. The study of Guerra Merino *et al* was in post-partum subjects, 7 of whom received oral iron (120 mg per day); the study of Bayoumeu *et al* was in pregnant women, 25 of whom were treated with oral iron (240 mg per day). The studies in IBD are shown adjacent to each other. Only one of the 21 studies (Sutton) had an oral placebo control; the other had an IV ferrous sulphate control.

In most, but not all of the studies listed in the table below, the baseline Hb was appreciably lower than in ST10-01-301/302 (baseline of approximately 11 g/dL) and/or the daily dose of elemental iron was higher.

Study	Duration (weeks)	Daily dose Fe (mg)	Baseline Hb (g/dL)	Hb change (g/dL)
Sutton	6	195	10.4	1.94
Agarwal	6	195	10.7	0.2
Auerbach	6	130	9.7	1.5
Bhandal	6	130	7.5	3.7
Breymann	12	200	9.76	3.13
Charytan	4.1	195	9.7	0.7
Guerra Merino	6	120 [MR]	8.6	4.2
Henry	8	195	10.3	1.6
Seid	6	195	8.88	3.4
Tokars	8	195	≤11	0.8
Van Wyck	8	195	10.1	0.4
Van Wyck	6	195	9	3.3
Van Wyck	6	195	9.4	2.3
Kochar	4	180	7.6	3.1
Vazquez Pacheco	4	195	7.76	0.74
Al-Momen	6.9	180	7.66	3.48
Bayoumeu	4	240 [MR]	9.7	1.3
IBD				
Kulnigg	12	200	9.1	3
Lindgren	20	400	10.38	2.22
Reinisch	8	200	9.61	2.98
Schroder	6	100	9.6	2.1

MR = modified release; Source: Attachment 1: Table 3; Pereira 2015

The meta-analysis showed no significant difference between oral ferrous sulphate and Feraccru in terms of Hb increase (ANCOVA). There were significant effects of duration of treatment and baseline Hb. This result was achieved despite the dose of elemental iron in the oral ferrous sulphate groups (including MR ferrous sulphate) being higher than in ST10-01-301/302 (around 180 mg versus 60 mg per day).

Regarding the studies mentioned in the above table, 5 studies were performed in postpartum patients (Bhandal, Breymann, Guerra Merino, Seid, Van Wyck), 4 in pregnant women (Kochar, Vazquez Pacheco, Al-Momen, Bayoumeu), 4 in non-dyalisis CKD (Agarwal, Charytan, Tokars, Van Wick), 2 with cancer (Auerbach, Henry), 1 in patients with hip and knee replacement (Sutton) and 1 in patients with heavy menorragia (Van Wyck). All of these studies compared ferrous sulphate vs. intravenous treatment.

Hb change observed in almost all studies included in the previous table was similar to the one achieved in clinical trials conducted with Feraccru (pivotal phase 3 study ST10-01-301/302). In CKD patients Hb change was remarkable smaller than in the other groups, perhaps due to a different response to treatment with iron in this specific group of patients.

Supportive Studies

Three supportive studies provided further information on the efficacy of Feraccru in patients with IDA. Doses of Feraccru equivalent to 10/67 mg, 30/202 mg, and 60/403 mg of iron/maltol per day were examined. Treatment duration ranged up to 3 months.

Comparison of Feraccru (ferric maltol) equivalent to 10 mg elemental iron/day versus ferrous sulphate equivalent to 180 mg elemental iron/day (Blake & Kelsey)

The first study was a comparative study in which 31 patients with IDA were randomised (2:1) to receive a 20 ml solution of Feraccru (10 mg iron/day) or ferrous sulphate tablets 200 mg TID (180 mg iron/day). The study duration was 12 weeks, with assessment of haematological response (Hb, MCV, reticulocyte count, serum ferritin) performed every 2 weeks. In this study, Feraccru was administered in the fasted state and ferrous sulphate after a meal.

Response to Administration of Feraccru (10 mg iron/day) or Ferrous Sulphate (180 mg iron/day)

Treatment	Parameter	Time (weeks)						
		0	2	4	6	8	10	12
Ferrous sulphate	Hb g/dl	8.6	11.2	12.4	12.6	13.2	13.6	13.4
(N= 10)	MCV fl	62.0	71.4	77.2	79.8	82.2	84.2	84.4
ST10	Hb g/dl	9.1	9.4	9.7	10.0	10.1	10.4	10.2
(N= 21)	MCV fl	65.0	66.4	66.0	68.1	69.8	71.6	72.0

There was a positive haematological response in both treatment groups; however, 8 of 9 patients in the ferrous sulphate group achieved an Hb level within the normal range compared to 1 of 15 patients treated with Feraccru. The lower response to Feraccru appears to be due to the 18 times lower dose of iron (10 mg daily) administered via Feraccru compared with the group treated with ferrous sulphate (180 mg daily). Serum ferritin did not alter significantly in patients receiving Feraccru.

This was due to the fact that all the available iron was being used for haemopoiesis and was not available for storage whilst anaemia persisted (Blake & Kelsey). In this study only 1 of 15 patients treated with Feraccru achieved an Hb level within the normal range, probably because of lower dose of iron administered in the group of Feraccru vs. ferrous sulphate.

A randomised study of ST10 (ferric maltol) equivalent to 30mg elemental iron/day versus ferrous sulfate equivalent to 18 mg elemental iron/day in anemic patients (Green & Thompson)

In this second study, thirteen patients with IDA were randomised (1:1) to treatment with either ferrous sulphate tablets 200 mg (60 mg iron) tid (n=6) or Feraccru solution, 80 mg (10 mg iron) tid (n=7) for 12 weeks. In the group treated with Feraccru, Hb rose by a mean of 1.4g/dl, serum iron levels by 5.1µmol/l, and ferritin by 3.7µg/l. The values achieved remained below the lower limit of normal in most patients. Five patients withdrew in the ferrous sulphate group as a result of AEs with only one patient in the ferrous sulphate group completing the study through 12 weeks. Therefore, between groups comparisons were not completed. The 5 patients who withdrew from ferrous sulphate treatment were reassigned to Feraccru after an appropriate washout period. Of the 12 patients who were treated with feraccru, only 1 withdrew from the study (as a result of AEs). The group treated with Feraccru achieved an increased in mean Hb level of 1.4 g/dL, while the increase in the group receiving ferrous sulphate is not stated.

In the Phase 2 study by Harvey et al (1998) which was an open-label uncontrolled study in which 23 patients with IDA and documented intolerance to oral ferrous sulphate were treated with Feraccru capsules containing 30 mg iron bid for 3 months. Anaemia was fully corrected in 74% of patients who completed the study (14 out of 19 patients). There was a significant increase in mean Hb and ferritin from pre-treatment levels. After 3 months of treatment, there were 5 patients who still had low Hb concentrations. Two of these patients had substantially improved from baseline (7.6 to 11.8g/dl and 8.4 to 10.6g/dl, respectively) and the remaining three were identified as having active bleeds, but were able to maintain Hb levels with Feraccru treatment. Seventy-three percent of the patients with IBD completed the study. Of these, 82% (n=9) experienced correction of their anaemia following treatment with Feraccru (Harvey, 1998). The results of this study demonstrated that Feraccru 30 mg bid, the proposed clinical dose, improved iron deficiency in patients with IDA who were intolerant to ferrous compounds. In this study (Harvey, 1998) anaemia was fully corrected in 74% of patients.

In each of the three, GCP non-compliant studies described above, administration of Feraccru resulted in improvements in iron deficiency in patients, as evidenced by increases in blood Hb and ferritin concentrations.

The studies conducted with Feraccru have been up to 12 weeks in duration. No evidence of loss of therapeutic effect has been observed in these studies. Furthermore, there is no evidence of persistence of efficacy or loss of therapeutic effect over time with ferrous sulphate in published literature.

Studies and Reviews of Treatment of IDA in Non-IBD Subjects

To provide information on use of other iron compounds, a number of papers describing non-IBD subjects were reviewed.

Liu *et al* (2004) compared a combination ferrous fumarate product (ferrous fumarate, ascorbic acid, folic acid and cyanocobalamin, Ferall) and a polysaccharide iron complex (ferroglycine sulphate, Niferex) in IDA. In Taiwan, the location of the study, Niferex was one of the most common supplements used in IDA although the authors own experience was that patients achieved insufficient response. It was, however, claimed that it had an absorption profile comparable to ferrous fumarate but with fewer GI side effects. In this study, 39 subjects with IDA (Hb <13 g/dL f or men and <12 g/dL for women) were randomised to one capsule of Ferall (equivalent to 151 mg elemental iron per day) and 41 to one capsule of Niferex (equivalent to 150 mg iron) for 12 weeks. The study was completed by 31 randomised to Ferall and 29 to Niferex; the analysis set included all those who received at least one dose and had at least one follow-up: these criteria were met by 36 subjects per group.

A significant difference between products was seen from Week 4 onwards in favour of the combination ferrous fumarate treatment.

Table 3 Haemoglobin Results from Liu et al (2004)

Mean (SE) Hb (g/dL)	Ferall	Niferex	Difference
Baseline	9.38 (0.28)	9.26 (0.28)	0.12
Week 4	11.20 (0.25)	9.44 (0.25)	1.76
Week 8	12.18 (0.24)	9.85 (0.25)	2.33
Week 12	12.30 (0.26)	10.19 (0.27)	2.11
Study end	12.19 (0.27)	9.88 (0.27)	2.31
Change from baseline to study end	2.84 (0.22)	0.60 (0.22)	2.24

Patil *et al* (2013) compared three different iron formulations in anaemic pregnant women. Twenty (20) subjects per group were treated with ferrous fumarate (plus folic acid and vitamin B12), ferrous

bisglycinate and carbonyl iron (each equivalent to 100 mg elemental iron and each with folic acid 1.5 mg and vitamin B12 10 µg) for 90 days. Hb levels increased from mean 8.96 (SD 0.74) g/dL at baseline to 11.48 (0.89) g/dL at day 90 with ferrous fumarate. The Hb levels were mean 9.40 (0.55) and 11.59 (0.46) g/dL at baseline and Day 90 with ferrous bisglycinate and 8.87 (1.17) and 11.10 (1.01) at Day 90 with carbonyl iron. The three treatments were equally effective.

Geisser (2007) reviewed over 25 years of experience with oral iron(III)-hydroxide polymaltose (Maltofer). The review includes several studies in which patients were treated with 100 mg per day or 100 mg BID with pretreatment Hb levels comparable to those in AEGIS (i.e., mean 10.43 to 11.63 g/dL, with some higher, at up to mean 14.61 g/dL) who showed increases from baselines of around 10-11 of 0.96 to 1.35 g/dL over period of approximately 2-3 months. Increases in those with higher baseline of about 14.5 g/dL were lower: 0.3 to 0.7 g/dL over 2-6 months. The ferrous sulphate control showed increases from baselines of around mean 10.6 to 11.4 of 1.3 to 1.8 g/dL over approximately 2 to 3 months.

All of these studies showed a mean increased in Hb levels from 1.3 g/dL to 2.52 g/dL, being greater in those patients with lower baseline Hb level. These increments are in line with the ones observed in pivotal trials conducted with Feraccru. It also confirms that iron preparations are subject to the normal regulatory mechanisms controlling gastrointestinal iron absorption.

2.4.3. Discussion on clinical efficacy

Efficacy data and additional analyses

The applicant has not provided new studies to support this application to extend the indication for Feraccru from the treatment "in adults with Iron deficiency anaemia in patients with IBD" to the treatment of "adults with iron deficiency". This extension is supported by pivotal trial conducted in the initial procedure (ST10-01-301/302) and published supportive studies.

There are scarce data with regards to the use of Feraccru in other pathologies different to IBD. For this reason the applicant did a comparison between other iron preparations and Feraccru in order to demonstrate that changes in media Hb level are similar in all of disease settings.

PK-data showed sufficient bioavailability in study- subjects with iron deficiency without anaemia and supportive clinical study data indicate that the recommended dose is sufficient to normalise iron blood indices in patients with ID/IDA or maintain Hb –levels in patients with active blood loss. Data from PK study (ST10-01-101) showed that although doses higher than 30 mg attained better efficacy the safety profile worsen. Moreover, taking into account PK parameters, there were no much differences between 30 mg and the other two doses explored.

Choice of dose:

The efficacy of the active component iron can be considered 'well established' after resorption has taken place. It was agreed during the MA assessment that the active substance is not absorbed as a whole but only as two separate components Iron and Trimaltol. The low dosage of 60 mg of iron per day in Feraccru is also supported by several authorised OFPs and can therefore be considered well established as well.

Therefore, 30 mg bid is considered an acceptable dose for patients with ID.

There are few data comparing oral iron to intravenous iron preparations. However, with the available data it seems that intravenous iron preparations achieved Hb target levels faster than Feraccru and any oral iron preparation.

The applicant provided a meta-analysis which includes an analysis of efficacy and safety of Feraccru compared to ferrous sulphate. There are 5 studies conducted in postpartum patients (Bhandal, Breymann, Guerra Merino, Seid, Van Wyck), 4 in pregnant women (Kochar, Vazquez Pacheco, Al-Momen, Bayoumeu), 4 in non-dyalisis CKD (Agarwal, Charytan, Tokars, Van Wick), 2 with cancer (Auerbach, Henry), 1 in patients with hip and knee replacement (Sutton) and 1 in patients with heavy menorragia (Van Wyck). Hb change observed in almost all of the studies included was similar to the one achieved in clinical trials conducted with Feraccru (pivotal phase 3 study ST10-01-301/302). In CKD patients Hb change was remarkable smaller than in the other groups, perhaps due to a different response to treatment with iron in this specific group of patients. The data submitted by the MAH indicate that patients with CKD seem to absorb oral iron in the same way as patients with other inflammatory diseases. The MAH is currently conducting a study in this population (ST 10-01-303), results are recommended to be provided when available in order to confirm efficacy in CKD patients.

Duration of treatment

The duration of treatment in all of these studies was 6-8 weeks, while generally at least 12-weeks treatment is required with Feraccru in IBD patients. Bearing in mind that, absorption of iron is under physiological control, and the greater the deficiency the greater the absorption; it is acceptable to have an individualised length of treatment. The duration of treatment is linked not only to replenishment of Hb levels but also to replenishment of iron stores. Therefore, treatment might be longer in severe cases. The treatment duration which was included in section 4.2 of the SmPC as part of the initial MA is also considered justified in non-IBD patients.

Blake and Kelsey was a comparative study where patients received Feraccru or ferrous sulphate tablets. It included 31 patients with IDA. In most of cases cause of anaemia was not identified (51%). Rise in Hb levels in patients treated with ferric maltol 10 mg/day was between 1.1g/dL to 3.2g/dL at 12 weeks (n=5). Data at 8 weeks showed an increase from 0.1g/dL to 1.4g/dL.

Green and Thomson was a comparative study where patients received Feraccru or ferrous sulphate tablets. It included 13 patients with IDA. In the group treated with Feraccru Hb rose by a mean of 1.4g/dL, serum iron levels and ferritin also increased. As expected, it is observed that patients with lower Hb levels had a greater increase than patients with higher Hb levels.

It is difficult to draw firm conclusions from both studies because of the low number of patients included, the dose administered was not the same as the currently proposed and baseline Hb was not homogeneous. However, it seems that patients with a longer treatment and with lower Hb levels had a better response.

All these studies showed a mean increased in Hb levels from 1.3 g/dL to 2.52 g/dL, being greater in those patients with lower baseline Hb level. These increments are in line with the ones observed in pivotal trials conducted with Feraccru. It also confirms that iron preparations are subject to the normal regulatory mechanisms controlling gastrointestinal iron absorption.

All these studies and those included in the meta-analyses did not match with clinical characteristics of patients included in the pivotal trial conducted with Feraccru. The design, number of subjects included, iron preparation, duration of treatment, baseline Hb level and baseline pathology are different making difficult the comparability. Bearing in mind all of these considerations, comparisons between different populations should be made with caution. However, the change in Hb level in these new population seems quite similar to the one obtained by Feraccru during pivotal study over 12 weeks (2.26 g/dL).

There is another piece of information that could be used as a surrogate of efficacy in patients with ID. As it is shown in PK data available ferritin continued to rise over time, in spite of inflammatory status in some patients. It reflects the standard way of replenishment in ID patients, supporting that ferric maltol does work in case of iron deficiency without anaemia.

Although the approach to treatment should be individualised according to aetiology and severity, it is generally accepted that treatment should be initiated in patients with iron deficiency in order to avoid development of anaemia and also to improve some symptoms associated to iron deficiency.

2.4.4. Conclusions on the clinical efficacy

The applicant has not provided new studies to support extension of indication to widen the indication for Feraccru from the treatment "in adults with Iron deficiency anaemia in patients with IBD" to the treatment of "adults with iron deficiency". This extension is supported by pivotal trial conducted in the initial procedure (ST10-01-301/302) and published supportive studies.

PK-data show sufficient bioavailability in study- subjects with iron deficiency without anaemia and supportive clinical study data indicate that the recommended dose is sufficient to normalise iron blood indices in patients with ID/IDA or maintain Hb –levels in patients with active blood loss.

Overall, Feraccru is bioavailable and as a result effective in iron deficiency patients with and without anaemia.

Although the approach to treatment should be individualised according to aetiology and severity, it is generally accepted that treatment should be initiated in patients with iron deficiency in order to avoid development of anaemia and also to improve some symptoms associated to iron deficiency.

According to the data submitted by MAH, patients with CKD seem to absorb oral iron in the same way as patients with other inflammatory diseases.

The CHMP recommends the submission of the results of study ST10-01-303 when available in order to confirm efficacy in CKD patients.

2.5. Clinical safety

Introduction

The total number of patients treated with Feraccru was 128 (age range 18-76 years; 45 males and 83 females). The primary clinical safety data are provided from the pivotal phase III efficacy and safety study, from the protocols ST10-01-301 and ST10-01-302, including data from both the 12-week double-blind phase and the 52-week open-label phase. The safety data from these study protocols were combined in a pre-specified analysis. Additionally, the pivotal study included a PK sub-study (ST10-01-102) in which some safety endpoints were measured.

Safety data was also collected in the prospective PK study (ST10-01-101). In this study, the total number of subjects treated with Feraccru was 24; 9 with 30 mg bid, 8 with 60 mg bid and 7 with 90 mg bid; all cohorts were treated for 8 days.

The safety data from studies ST10-01-301, ST10-01-302, ST10-01-101 and ST10-01-102 are supported by 3 studies from published literature and unpublished data on file. Study SWIN-189-IM was a randomised, double-blind placebo controlled crossover study conducted in 120 volunteers. A further study in 13 patients evaluated the safety of Feraccru solution (30 mg iron/day) and ferrous sulphate tablets 180 mg/day (Green & Thompson).

Harvey, 1998 studied the safety of Feraccru capsules (30 mg bid) in 24 IDA patients. Overall, doses of Feraccru of 10 mg, 30 mg, 60 mg and 90 mg dosed bid have been examined.

Safety Profile of Feraccru

Studies to date in animals and man show that iron released from orally administered Feraccru does not differ in pharmacological activity from iron administered in existing iron-containing preparations. Intact Feraccru has only been found within the GI tract in pharmacological and toxicological studies and the unabsorbed portion is found in the faeces in rat, dog and man (Barrand, 1991). Because Feraccru is not absorbed as a complex molecule, the toxicological profiles of iron and maltol as individual moieties are critical and relevant to evaluating the potential safety profile of Feraccru.

Safety Profile of Iron

Locally, iron has direct corrosive effects on the GI mucosa, resulting in ulceration, oedema, bleeding, venous thrombosis, infarction and perforation (Tenenbein, 1990). The severity of these local corrosive effects depends on the quantity of iron ingested, the concentration of iron in the preparation, the form of iron, the duration of its contact with the mucosa and the amount of mucosal protection provided by food in the stomach at the time of ingestion; greatest mucosal damage with OFPs occurs on an empty stomach. Reactive oxygen species are produced in excess by neutrophils in inflamed intestinal mucosa and are thought to contribute significantly to the tissue injury in IBD. As free ferrous iron is a strong catalyst of ROS production, oral ferrous iron therapy may worsen symptoms in IBD patients and potentially contribute to the disease process and disease exacerbation. This has been shown in multiple pre-clinical studies (de Silva, 2005) and confirmed in clinical practice.

Adverse events associated with OFPs are abdominal pain, nausea and vomiting, constipation, diarrhoea and dark stools. Contact irritation can occur with ferrous sulphate tablets resulting in erosion or ulceration, particularly if they become lodged in the upper GI tract.

Safety Profile of Maltol

Maltol occurs naturally in a variety of foodstuffs and synthetic maltol is widely used as a food additive and has been marketed for many years in pharmaceutical formulations as an excipient and in food products as a flavour enhancer. In addition, maltol is listed as a GRAS substance (Generally Recognised As Safe).

The nonclinical toxicology data support the dose of maltol delivered in Feraccru.

There were weakly positive results reported in some genotoxic studies.

However, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) carried out a comprehensive review of the genotoxicity of maltol and concluded that the inconsistent weakly positive results observed with high concentrations/doses of maltol were not relevant to human oral intake. This conclusion is supported by the results of dietary carcinogenicity studies in rats and mice described previously in which no carcinogenic effects were apparent in either species.

The WHO defines the accepted daily intake of maltol as 1 mg/kg/day. The estimated intake of maltol through Feraccru, given a person weighing 65 kg is 6 mg/kg/day, which would exceed the accepted daily intake. However, the accepted daily intake of maltol as defined by the WHO is applicable for a food supplement and is based on lifetime exposure. Feraccru is designed to treat anaemia and treatment will be stopped when Hb levels and iron stores are returned to the normal range.

Moreover, Maltol has a long history of use as a flavouring agent and dietary toxicity studies ranging in duration from 6 months in both rats (two studies) and mice (one study) to 24 months in rats and 18 months in mice with minor toxic effects observed. Taking the most conservative approach the NOAEL level in animals is more than 20 times the daily dose of maltol given in Feraccru on a mg/kg basis, increasing to 50 to 80 times the daily dose based on the 2nd study in dogs and the 18 and 24 month mice and rat studies.

In man, the maltol component of Feraccru undergoes extensive first-pass metabolism and is rapidly glucuronidated and renally excreted. In the pivotal GCP PK study conducted in patients with IDA, the

plasma and urine concentrations of maltol and maltol glucuronide were measured after single and repeated b.i.d. oral doses of 30 mg, 60 mg and 90 mg for 8 days in subjects with iron deficiency (with or without anaemia (Study ST10-01-101). In the subjects administered up to 90 mg b.i.d. for 8 days, three times higher than the therapeutic dose, there was no indication that the metabolic capacity for glucuronidation and excretion of maltol was approached. Similar results were obtained in study ST10-01-102, a PK sub-study of subjects receiving 30 mg ST10 b.i.d. in the open label phase of the pivotal efficacy studies, ST10-01-301 and ST10-01-302. In these studies, exposure to maltol glucuronide was again considerably higher than exposure to maltol, and only 0.266% of the maltol dose administered was excreted unchanged in the urine, compared to an equivalent of 41.6% as maltol glucuronide.

These findings are consistent with the maltol component of Feraccru undergoing extensive firstpass metabolism and being rapidly glucuronidated and renally excreted at up to 3 times the therapeutic dose at steady state, as observed in early clinical and nonclinical studies. Clinical data on exposure of subjects with IDA for up to 64 weeks also shows that the effect of ferric maltol is positive with regard to Hb and iron stores, and any absorbed maltol does not have the effect of chelating iron stores.

In conclusion, the administration of 6mg/kg/day maltol for the duration of Feraccru therapy is covered by both long-term animal toxicology data, and PK and long-term clinical safety data in man.

Adverse Event Monitoring

Monitoring of AEs was conducted throughout the pivotal Feraccru studies. Subjects were expected to volunteer information about AEs they experienced. In addition, the Investigator or designee questioned the subject at each visit about AEs and recorded these as well as all other AEs apparent at the visit. New AEs, including serious adverse events (SAEs), were captured on the CRFs after informed consent and until 4 weeks after the last dose of study drug.

New-onset AEs and SAEs were monitored until they were resolved or clearly determined to be due to a subject's stable or chronic condition or intercurrent illness.

Laboratory results were compared to up-to-date reference ranges and flagged if outside the normal range or the protocol-specified range for randomisation and/or continued study participation. Investigators reviewed all laboratory test results and if a value was flagged as abnormal, the Investigator documented the abnormality as 'clinically significant' (CS) or 'nonclinically significant' (NCS). Any laboratory abnormality assessed as 'CS' was recorded as an AE if not explained by a coexisting condition as documented in the medical records.

In study ST10-01-301, in subjects with quiescent UC, the SCCAI score was evaluated at every clinic visit and in study ST10-01-302, in subjects with quiescent CD, the CDAI score was evaluated at clinic visits according to the schedule of assessments.

Physical examination was conducted and vital signs (blood pressure and heart rate), body weight and height were measured according to the schedule of assessments. No special approaches were employed to monitor particular AEs. This is considered acceptable since the likely GI AEs would be detected by the AE monitoring described above.

Nature of the Patient Population and Extent of Exposure

The safety and efficacy of Feraccru for the treatment of iron deficiency anaemia was studied in 128 patients (age range 18-76 years; 45 males and 83 females) with inactive to mildly active IBD (58 patients with Ulcerative Colitis [UC] and 70 patients with Crohn's disease [CD]) and baseline Hb concentrations between 9.5 g/dL and 12 / 13 g/dL for females / males.

Nature of the Patient Population

Age

In the PK study (ST10-01-101) and the two pivotal safety and efficacy studies (ST10-01-301 and ST10-01-302) Feraccru was tested in a range of ages, from 18-76 years. In the post-hoc subgroup analysis, there was no difference in results between subjects <60 years of age and those older than 60 years.

The safety of Feraccru in children has not yet been established. Agreement was received from the EMA on 23rd September 2013 on a paediatric investigation plan (PIP), on granting a deferral and on the granting of a waiver for children less than 6 months old for Feraccru. The PIP covers paediatrics aged from 6 months to 18 years of age and requires the development of an age appropriate formulation, together with the conduct of PK and clinical studies.

Gender

In the PK study (ST10-01-101) and the double-blind phase of the two pivotal safety and efficacy studies (ST10-01-301 and ST10-01-302) Feraccru was tested in both genders including women of child-bearing potential. In these studies, Feraccru was evaluated in 128 subjects (83 females [40 and 43 in Feraccru and Placebo double-blind phase groups, respectively] and 45 males [24 and 21 in Feraccru and Placebo double-blind phase groups, respectively]). In the phase 3 studies, the safety of Feraccru for the treatment of IDA in IBD was evaluated in 111 subjects in the open-label phase.

Race and Ethnicity

The majority of patients treated with Feraccru in the two pivotal clinical studies were of non-Hispanic/Latino white origin. A literature search on the impact of racial or ethnic differences on iron treatment outcomes provided limited conclusive data and suggested a current lack of understanding about the factors influencing disparities in prevalence and risk factors relating to IDA and IBD across ethnic and racial groups. There are no known ethnic variations in the normal uptake or metabolism of iron.

Cause of ID/IDA

Phase 3 data has been generated in patient with IBD. Patients with IBD are commonly intolerant to OFPs because GI inflammation occurring in this disease state enhances the GI side effects of OFP treatments. This patient population is therefore considered to be a ”worst case” scenario and the side effect profile in IDA associated with any other disease state is likely to be more favourable or at least no worse than the side effect profile observed in patients with IBD.

Baseline IBD Disease

The two pivotal safety and efficacy studies’ (ST10-01-301 and ST10-01-302) patients had either UC or CD respectively. Of the 128 subjects randomised, 58 (29 in the Feraccru and Placebo groups, respectively) had UC compared to 70 (35 in the Feraccru and Placebo groups, respectively) with CD. The incidence and severity of all treatment-emergent adverse events are very similar for the UC (ST10-01-301) and CD (ST10-01-302) patients. There are no marked differences in the incidence of individual adverse events or in the number or severity of events in any SOC comparing the two populations.

Inclusion and Exclusion Criteria

The majority of the inclusion and exclusion criteria defined a study population consistent with the intended patient population authorised.

Severity of IBD, Baseline Hb and Hypersensitivity

Severity of Disease and Baseline Hb levels had no impact on the safety profile (measured by TEAEs) in cumulative ST10-01-301/302 data.

There were no related hypersensitivity reactions recorded. The only unrelated Immune System AE recorded was seasonal allergy, reported in 4 (3.6%) of subjects (3 mild; 1 moderate). Therefore, no

safety data could be analysed in patients with hypersensitivities.

A number of exclusion criteria excluded patients from the pivotal phase 3 protocols, thereby potentially narrowing the study patient population in comparison to that which would be treated with Feraccru in clinical practice. The safety implications of the differences of these two patient populations are discussed below.

Subjects without IBD were excluded from the studies. The efficacy and safety of Feraccru in patients with IBD can be extrapolated to patients with other disease. The pivotal PK study (ST10-01-101) was conducted in patients with iron deficiency, not restricted to IBD and is therefore relevant for patients with ID caused by other factors. Iron homeostasis is regulated at the level of iron uptake by body iron stores, although the exact mechanism is not completely understood. There are no available data that indicate that the distribution and utilisation of iron differ substantially between subgroups of patients with ID. Patients with IBD do not always respond adequately to oral iron therapy, because of a combination of non-compliance due to side effects and impaired absorption due to IBD inflammation. This population can therefore be considered a worst case in terms of both efficacy and safety. The Phase 3 studies show that Feraccru is effective in this population and it reasonable to extrapolate the effectiveness to other sub-population of patients with ID Subjects who had received within 12 weeks prior to randomisation either a blood transfusion or erythropoietin therapy were excluded from the studies as such recent treatments could be expected to alter a potential subject's iron deficiency status. However in clinical practice, it may be appropriate for a patient who has had a blood transfusion or erythropoietin to be treated with Feraccru for ongoing IDA. However, Feraccru is contraindicated for patients who received repeated blood transfusions.

Subjects who had received within 4 weeks prior to randomisation vitamin B12 injection/infusion, folic acid injection/infusion or an immunosuppressant with known effect of anaemia induction, including, but not limited to methotrexate, cyclosporin A or tacrolimus, were excluded from the studies. This was because the drugs may alter the status of a subject's IDA by inducing or correcting anaemia. In clinical practice, it could be appropriate to treat such patients with Feraccru.

Subjects with vitamin B12 concentration below the LLN or folic acid deficiency were excluded from the studies. This is because a lower amount of these substances could affect responsiveness to iron and the aim of studies ST10-01-301 and ST10-01-302 was to assess the effect of Feraccru on patients with anaemia due to iron deficiency. Both vitamin B12 and folic acid play an important role in iron absorption and are often co-administered with iron replacement therapy.

Subjects with creatinine >2.0 mg/dL (176 μmol/L) or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels ⩾5 times the upper limit of normal (ULN) were excluded from the studies. A raised creatinine level indicates mild renal impairment and elevated liver enzymes can be an indication of impaired hepatic function. Iron is not metabolised and excreted and maltol is rapidly metabolised to maltol glucuronide in the intestinal mucosa prior to being renally excreted. Glucuronides form a routine route of excretion and there are no data to indicate any toxicity of maltol glucuronide in the renally impaired.

Subjects with history of malignancy within the past 5 years with the exception of *in situ* removal of basal cell carcinoma were excluded from the study. This exclusion was in place for completely operational reasons to avoid losing subjects who may have recurrence of their cancer or need for further treatment. In practice, there is no reason why such subjects could not be treated with Feraccru.

Broad exclusion criteria for, firstly, subjects with cardiovascular, liver, renal, haematologic, GI, immunologic, endocrine, metabolic, or central nervous system disease that, in the opinion of the Investigator, may have adversely affected the safety of the subject and/or efficacy of the study drug or severely limit the lifespan of the subject and; secondly, subjects 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, alcohol or drug abuse) were excluded. The rationale for these exclusions was to ensure the safety of the subjects in the study and to deliver good treatment compliance. Therefore, these differences in study and future patient population do not have safety implications.

Patient exposure

Extent of Exposure in Clinical Trial

A total of almost 400 subjects have been exposed to Feraccru in completed studies.

A total of 135 subjects with IDA received Feraccru at a minimum dose of 30 mg bid in the pivotal clinical pharmacology and phase 3 studies. The majority of these subjects received the drug for between 12 and 64 weeks. In ST10-301/302, a total of 111 patients were treated with Feraccru for up to 64 weeks. The 64 subjects treated with feraccru in the double-blind and open label phases of ST10-01-301/302 had a total duration of treatment of median 445.5 days and mean 311.8 days. Total dose of Feraccru received was median 23340.0 mg and mean 17703.8. The 47 subjects treated with placebo in the double-blind phase and Feraccru in the open-label phase had a duration of feraccru treatment of median 293.7 days and mean 219.8 days. Total dose of Feraccru received was median 21240.0 mg and mean 17493.2 mg.

A further 250 subjects have been exposed to Feraccru in the non-GCP compliant studies; 22 subjects received the proposed therapeutic daily dose of 60 mg Feraccru. The majority of these subjects received the drug for between 1 and 3 months. A further 112 subjects received a daily dose of 100 mg or higher. The remaining subjects received 10 or 30 mg daily. In an unpublished study (SWIN-189-IM), 120 patients were exposed to a dose of >100 mg (180 mg) Feraccru daily for 4 days.

In the pivotal phase 3 study, 65 patients were exposed to Feraccru for >1 year at study completion with a further 8 exposed for 363 days. The ICH guideline on the extent of population exposure to assess clinical safety for new active substances intended for long-term treatment of non-life threatening conditions states that 100 patients exposed for a minimum of one-year is considered to be acceptable to include as part of the safety data base. The data should come from prospective studies appropriately designed to provide at least one year exposure at dosage levels intended for clinical use. However, it is considered that the size of the safety database is appropriate, given that Feraccru completely dissociates to iron and maltol.

In ongoing clinical studies in patients with IBD (ST10-01-304) and CKD (ST10-01-303) a further 61 and 96 patients (assuming 2;1 randomisation for the latter), respectively, have been exposed to Feraccru for up to 52 weeks at the therapeutic dose of 30 mg bid (cut-off date: 11 August 2017). No new safety signals have been observed.

Extent of Marketed Exposure

The extent of patient exposure to marketed product is discussed in the latest PSUR. No new safety signals have been observed compared to clinical exposure.

Adverse events

Common Adverse Events

The most frequently reported AEs in Feraccru subjects in the double-blind were GI-related: abdominal pain, flatulence, constipation, abdominal discomfort, diarrhoea, and nausea.

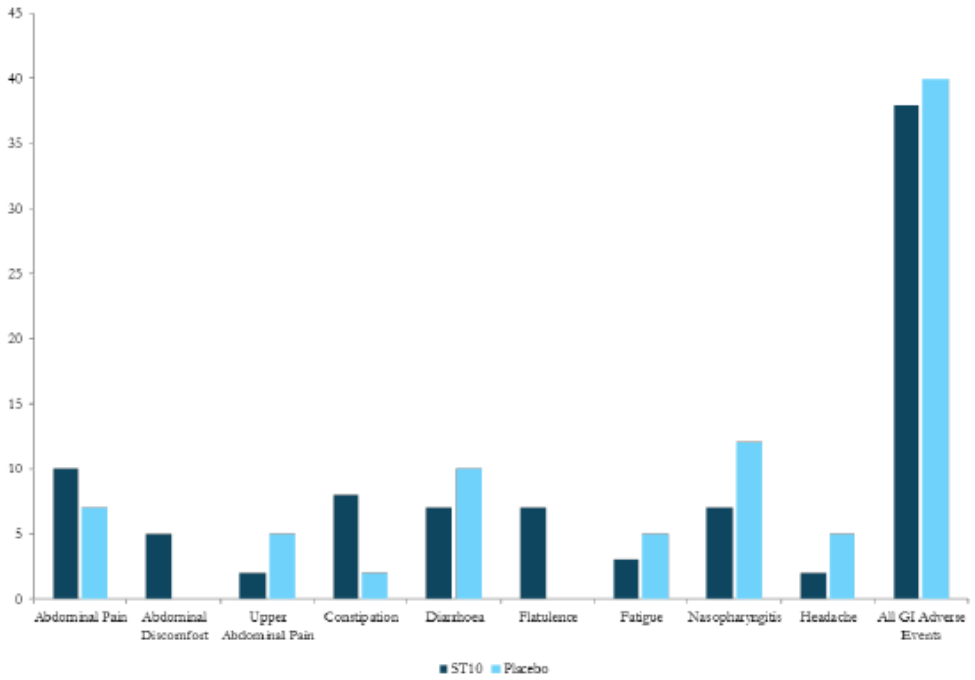
Nasopharyngitis and arthralgia were also frequently reported. The most common AE in Placebo subjects was nasopharyngitis; a number of GI-related events were also common, including abdominal pain, Crohn's disease and diarrhoea; haemoglobin decreased, headache, fatigue, and oropharyngeal pain were also common in Placebo-treated subjects.

The profile of adverse events in the open-label phase to data cut-off was comparable to that of Feraccru-treated subjects in the double-blind phase. The most common TEAEs (>5%) were abdominal pain, ulcerative colitis, Crohn's disease, diarrhoea, flatulence, nausea, arthralgia, back pain and cough. The overall proportion of subjects with TEAEs of the Gastrointestinal Disorders SOC was 23 (46.0%) for those previously treated with Feraccru and 25 (53.2%) for those previously treated with Placebo, but several of the more common gastrointestinal symptoms (abdominal pain, diarrhoea, flatulence and nausea) occurred more frequently in those new to Feraccru treatment (i.e., those previously treated with placebo).

Tolerability to Feraccru was very good: 86% of Feraccru subjects completed double-blind treatment compared to 83% in the placebo group.

Feraccru has a good safety profile as demonstrated by its benign AE profile generally and a similar GI events profile to placebo, as well as its lack of effect on vital signs and physical examination data. The proportion of subjects experiencing AEs in the double-blind phase was generally similar in both groups and slightly lower in the Feraccru group. As expected in an IBD population, GI-related AEs were the most common, with similar proportions of subjects reporting GI events in both treatment groups. Data indicated that Feraccru did not exacerbate IBD symptoms over the 12-week treatment period. The rate of drug-related AEs was low and similar in both treatment groups; flatulence, constipation and abdominal discomfort/distension occurred more frequently following Feraccru administration.

Figure 5. ST10-01-301/302 - All AEs Occurring in at Least 5% Subjects in Either Treatment Group (Double-Blind Phase)



Data from the longer-term open-label phase confirmed the generally benign safety profile of Feraccru

demonstrated in the double-blind phase. In the cumulative data set, the most common TEAEs were gastrointestinal in nature, with the majority becoming apparent within the first 12 weeks of treatment. The most common treatment-related events in the cumulative data set were abdominal pain, constipation, diarrhoea and flatulence, and these tended to be reported within the first 12 weeks of Feraccru treatment. The SCCAI and CDAI demonstrated that Feraccru did not exacerbate IBD symptoms over the 12-week double-blind treatment period or during open label treatment. There was no indication of any increase in frequency or severity of AEs with duration of treatment. Moreover, age, gender, severity of disease, disease sub-group and Baseline Hb had no impact on the safety profile.

There were no meaningful changes in either group's IBDQ scores from randomisation to Week 12. In Feraccru subjects mean total IBDQ score at randomisation was 175.0 (SD 30.92) and 178.3 (SD 32.36) by Week 12. In placebo subjects mean total IBDQ score at randomisation was 171.0 (SD 33.56) and 176.3 (SD 31.50) by Week 12. Over longer-term treatment, the scores for each assessment remained relatively constant. The absence of a change in IBDQ scores indicates that Feraccru did not worsen IBD symptoms over 64 weeks of long-term therapy.

It was noted that 17.1% of Feraccru study patients had TEAEs indicating IBD aggravation, but disease activity scores were not altered.

To exclude an aggravating effect of Feraccru on the IBD-condition the outcome of patients was analysed who either had an aggravation of their IBD severity score and/or for whom one or more IBD associated TEAEs were recorded. Moreover, the score data of the individuals with vs. without IBD-associated AEs was compared.

An improvement of IBD score was recorded for 12 subjects (18.8%) in the Feraccru group and 18 subjects (28.1%) in the placebo group. Worsening was recorded for similar numbers in each group: 9 (14.1%) in the Feraccru group and 10 (15.6%) in the placebo group. These results suggest that IBD deterioration with Feraccru is similar to placebo by the relatively conservative definition of a deterioration of 16 points reduction in IBDQ score.

Overall the number of subjects with IBDQ worsening or an IBD-related AE were identical in the two treatment groups during the double-blind phase. The number of subjects in each group with an IBD associated AE (but no IBDQ worsening) were very similar; (25% and 23.4%, Feraccru and Placebo). The number of subjects in each group with IBDQ worsening but no associated AEs was higher in the Placebo group (3.1% and 12.5%). Therefore, during the double-blind phase, for which there is placebo controlled data, Feraccru did not appear to worsen IBD symptoms as measured by IBDQ, or by IBD-associated AES, when compared to the Placebo group. Not surprisingly, there were more discontinuations owing to adverse events in the categories with IBD-associated TEAEs and the chance of discontinuing was highest in the category with both IBDQ worsening and IBD associated TEAEs.

Although there is no comparator group during the open label phase, and because of the cumulative nature of handling AEs, it is expected that the AE rate is higher compared to the Double-Blind phase. In addition because IBD is a relapsing-remitting disease (and Feraccru is not a disease modifying agent) the proportion of subjects who experience some worsening of disease over the Open-Label phase would also be higher. The actual rate of IBDQ worsening add/or IBD associated AEs was 43% at the end of the open-Label phase; comparing this to the double-blind rates shows no evidence of IBD disease activity worsening with long-term Feraccru exposure.

Therefore, performed analysis did not identify greater risk of IBD deterioration with Feraccru than placebo by the relatively conservative definition of a deterioration of 16 points reduction in IBDQ nor any clear association between the selected IBD-associated TEAEs and deterioration. In older published studies, good tolerance to Feraccru was also demonstrated when it was administered to patients demonstrably intolerant of ferrous sulphate, with no reported AEs (Harvey et al, 1998).

Safety data comes from study ST10-01-101 (PK study) and pivotal phase 3 study (ST10-01-301/302). The most common AEs were gastrointestinal related adverse events. Most of them were mild to moderate more common being in the first 12 weeks of Feraccru treatment. During the initial procedure it was observed that in the double-blind part of the pivotal study some gastrointestinal AEs were more frequent with Feraccru compared to placebo (e.g. abdominal discomfort, abdominal distension). This imbalance could reflect a similar safety profile compared to other iron containing preparations (ferrous).

Long-term safety data comes from ST10-01-301/302 extension published by Schmidt C., *et al* (Aliment Pharmacol Ther 2016;44: 259-270). From a total of 128 patients randomised to study treatment (the FAS), 50/64 (78%) previous ferric maltol patients (the 'continued' group) and 47/64 (73%) previous placebo patients (the 'switch' group) entered the long-term extension.

Among the 97 patients who entered the long-term extension, 37/50 'continued' patients (74%) completed 64 weeks of ferric maltol treatment, and 36/47 'switch' patients (74%) completed 52 weeks on open-label ferric maltol. AEs were the most common reason for patient withdrawal from the long-term extension (12 patients overall: eight in the continued group and four in the switch group; see 'Safety and tolerability' section for details). Most AEs (83%) were mild to moderate in severity and gastrointestinal.

Safety profile of Feraccru in patients with IBD remains favourable after 64 weeks.

Serious adverse event/deaths/other significant events

In the double-blind phase of studies ST10-01-301/301 there were 3 serious adverse events (SAEs) in the Feraccru group and 2 SAEs in the placebo group. None were related to treatment.

In the open-label phase, there were 8 SAEs in the group previously treated with Feraccru and 2 SAEs in one subject previously treated with placebo. Of all of these reports none were reported as probably related to treatment, whilst only one event of severe abdominal pain was reported as possibly related to treatment.

In the PK study (ST10-01-101), one subject who received Feraccru 60 mg experienced an SAE of abscess which led to study withdrawal due to unplanned hospitalisation. The SAE was considered unrelated to the drug; indeed, the patient continued to take Feraccru 60 mg bid after study withdrawal.

After the completion of ST10-01-101, there was a case of pregnancy reported. It was estimated that the patient had become pregnant before receiving Feraccru. Urine pregnancy tests conducted during the study were all negative. The pregnancy was followed up via routine pharmacovigilance activities. There was also a case of pregnancy in study ST10-01-302: pregnancy tests were negative during the double-blind phase and at the first visit during the open-label phase. Four days after this visit, the subject performed a pregnancy test which was positive, confirmed on the following day by a positive urine pregnancy test at the study site.

The subject was withdrawn from the study and subsequently gave birth to a healthy infant. In Study 302, the date of conception was approximately 12 weeks after the start of treatment with ferric maltol. In Study 101, the date of conception was calculated to be prior to the start of treatment with ferric maltol (based on gestational age). It is therefore unlikely that a drug-drug interaction with the contraception played a role in either pregnancy. This is consistent with the lack of a recognised class DDI with the contraceptive pill (FSRH: Drug Interactions with Hormonal Contraception, 2011: http://www.fsrh.org/pdfs/CEUGuidanceDrugInteractionsHormonal.pdf).

There were no deaths reported in any of the studies with Feraccru.

The only significant changes in laboratory values in ST10-01-301/302 following treatment with Feraccru were those measures that demonstrated the efficacy of the drug, i.e., serum iron indices: total iron,

transferrin saturation and ferritin; these parameters all improved. Vital signs and physical examination were unremarkable and similar in both treatment groups.

Relation of Adverse Events to Dose, Dose Regimen and Treatment Duration

The 64 subjects treated with Feraccru in both the double-blind and open-label phases of the pivotal studies had a total duration of treatment of median 445.5 days and mean 311.8 days. The 47 subjects treated with placebo in the double-blind phase and Feraccru in the open-label phase had a duration of Feraccru treatment of median 365.0 days and mean 293.7 days.

The frequency of adverse reactions appeared to lessen with treatment duration in the double blind and open label phases of the pivotal phase 3 study (ST10-01-301/302). In the limited safety data collected in the pivotal PK study (ST10-01-101), probably unsurprisingly there appears to be a trend towards increased frequency of adverse events reported as the dose increased from 30 mg bid to 60 mg bid to 90 mg bid. Size (8 subjects) and design of the study ST10-01-101 however does not allow meaningful conclusions to be made about the relative safety of 30mg, 60mg or 90mg of ferric maltol BID, compared to other published studies or the Phase 3 ST10-01-301/302 studies.

During the PK study (ST10-01-101) it was observed that the percentage of AEs is related to the dose with 57.1% of patients who received 180 mg daily, 50.0% received 120 mg daily and 22.2% received 60 mg daily. As stated before, the selected dose was 30 mg bid considering not only efficacy but also the safety profile.

Overdose

There were no incidences of overdose reported during the double-blind and open-label phases of the two pivotal studies following treatment with Feraccru. Iron is not easily eliminated from the body and acute iron overdose may result in toxicity. Ingestion of 20 mg/kg elemental iron is potentially toxic and ingestion of 200-250 mg/kg, or serum iron levels of greater the 300 ug/dL is potentially fatal. Although Feraccru is not currently proposed for use in children, it is noted that over-dosage of ferrous salts is particularly dangerous to young children.

The lower amount of ferric iron in Feraccru (30 mg) and recommended daily dose of 2 capsules compares favourably to ferrous sulphate tablets 200 mg which contain the equivalent to 65 mg ferrous iron and recommend an adult daily dose is 2-3 tablets daily. Therefore, Feraccru has a greater margin of safety than that of oral ferrous sulphate preparation with respect to potential overdose. In addition, the iron from Feraccru is under physiological control, further protecting against the risk of accidental overdose with Feraccru.

There is no information on the potential for dependence, rebound phenomena or abuse with Feraccru. There is no published information to suggest any of these effects exist for other iron replacement products or maltol; there is therefore no reason to expect these effects to be associated with Feraccru.

Comprehensive Comparison of the Safety of Feraccru with Other Oral Iron Preparations

Comparison of Feraccru Data with Published Data

The meta-analysis performed by Pereira (2015) demonstrated:

• Feraccru has a similar GI AE rate to FeSO4. However, studies ST10-01-301/302 (AEGIS) recruited only FeSO4 intolerant subjects; and the IV comparator studies excluded subjects who could not tolerate oral iron. The AE and GI AE risk to Feraccru-treated subjects is thus no higher than that of first line patients taking FeSO4.

• The GI AE all causality rate is no worse than the overall rate of FeSO4 in IV comparison studies (i.e. in patients with more significant diseases). Furthermore, the OR of GI AEs for Feraccru has an upper 95%

CI below the overall OR, suggesting benefit compared to FeSO4.

• The same finding (a better OR relative to FeSO4) is apparent for the IBD subset of studies (in FeSO4 tolerant subjects)

• OR for modified release iron products appears worse than the overall data. There is no suggestion that modified release products should be used second line or in preference to Feraccru, and these findings do not support using modified release products as a comparator to Feraccru

• The GI AE rate for Feraccru is in line with FeSO4 data in relation to dose.

Safety data of Feraccru PK studies was also compared to published data of standard OFPs. As ST10-01-102 was a sub-study of studies ST10-01-301/302 and no AEs occurred during PK analysis, evaluation was only performed with ST10-01-101 data. The most frequent treatment-related adverse events with Feraccru are gastrointestinal in nature in common with other oral iron treatments. However, the incidence of such events is lower than in many of the published studies with ferrous sulphate and other oral iron treatments.

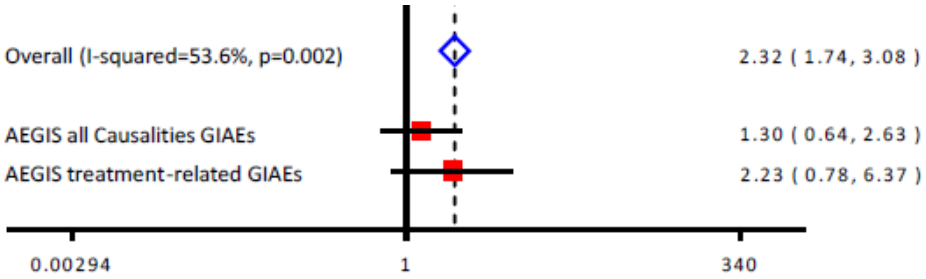
In study ST10-01-101 treatment with Feraccru at 30 mg bid of 9 subjects for 7 days was very well tolerated with no treatment-related AEs, no discontinuations because of adverse events. These results compare favourably with ferrous sulphate clinical studies (as reported in Pereira, 2015 for ferrous sulphate) where a placebo-controlled study was described with a total of 12 (out of 20) subjects reporting symptom(s) during the first week of study treatment, of which 9 (75%) were in the ferrous sulphate group.

As the duration of treatment for ferrous sulphate in Pereira, 2015 was generally longer than in the Feraccru PK study, PK data of ST10-01-101 was compared more accurately with the paper of Gordeuk *et al* (1987), which reported the adverse events after treatment with standard dose ferrous sulphate for one week (high dose Fe 600 mg three given as nontoxic carbonyl Fe compared with standard ferrous sulphate 60 mg Fe++). It was described that GI AEs occurred in 20/24 subjects (83%) with the standard ferrous sulphate arm, which is higher than reported with the highest dose of Feraccru in ST10-01-101. Individual AEs were constipation (4, 17%), diarrhoea (3, 13%), heartburn (2, 8%), nausea (14, 48%), epigastric pain (3, 13%), abdominal cramps (3, 13%), and unpleasant taste (4, 17%) plus headache (2, 8%) and weakness (4, 17%). The great majority of AEs were mild; the remainder were severe in intensity.

The applicant provided two published articles which includes safety data in relation to existing oral iron products (Pereira 2015 and Tolkien 2015). Conclusions from both studies were:

Ferrous sulphate supplementation significantly increased risk of gastrointestinal adverse events (GIAEs) relative to placebo with an odds ratio (OR) of 2.32 [95%CI 1.74–3.08, p<0.0001] and versus IV iron with an OR of 3.05 [95% CI 2.07-4.48, p<0.0001]. Subgroup analysis in IBD patients showed a similar effect versus IV iron (OR = 3.14, 95% CI 1.34-7.36, p= 0.008). A significant increase in the incidence of treatment-related AEs was observed with Feraccru in the AEGIS trial (OR=3.22 [95% CI 1.17-8.88], p=0.02). The odds ratios for all causalities GIAEs with Feraccru were lower than those of ferrous sulphate but this was only statistical significant when compared with ferrous sulphate in the IV iron-controlled trials (p=0.037).

Forest plot for the effect of daily Feraccru on the incidence of gastrointestinal adverse events (GIAEs) against placebo in the AEGIS trial compared with data for ferrous sulphate supplementation from the random-effects meta-analysis of 21 placebo-controlled RCTs (n=3168)



Intensity of Adverse Events and Drug-related Adverse Events

The Pereira (2015) meta-analysis report indicates that the severity of GIAEs with Feraccru falls into range of first line FeSO4 studies.

Pereira (2015) reported 17.2% and 14.1% moderate-severe GI TEAEs. However, 28.1% moderate – severe GI TEAEs were reported for Feraccru (17.2% moderate plus 10.9% severe) vs. 20.3% placebo in studies ST10-01-301/302.

Pereira *et al.* described the following frequencies of gastrointestinal AEs:

Stratification of gastrointestinal AEs (GIAEs) into mild and moderate-severe categories for ferrous sulphate, Feraccru and placebo.

	$FeSO_4$		
	GIAEs (%)	Mild GIAEs (%)	Moderate-Severe GIAEs (%)
Mean	45.9	36.7	9.2
SD	22.2	17.3	9.0
AEGIS trial		ST10	
GIAEs (all causalities)	43.8	26.6	17.2
GIAEs (treatment-related)	18.8	9.4	9.4

Taking into account inherent limitations of indirect comparisons it seems that Feraccru could have a lower frequency of mild GIAEs, while moderate-severe GIAEs seems to be greater in Feraccru group (AEGIS trial).

Post marketing experience

Feraccru is a new complex (chelate) of a chemical substance (iron) previously authorised as a medicinal product in the European Union; iron, complexed with maltol. There is therefore no world-wide marketing experience with Feraccru.

However, various oral and IV iron products for the treatment of IBD have been marketed for many years in doses that, in the case of IV products, far exceed the daily dose recommended for Feraccru. The non-clinical and clinical safety of iron has been thoroughly investigated and can be regarded as well known. In addition, iron is a physiological constituent of the body and dose levels not exceeding physiological mechanisms of absorption, transport, storage, metabolism and excretion can be considered as safe.

Maltol occurs naturally in a variety of foodstuffs and synthetic maltol is widely used as a food additive and has been marketed for many years in pharmaceutical formulations as an excipient and in food products

as a flavour enhancer. In addition, maltol is listed as a GRAS substance (Generally Recognized As Safe). Published non-clinical data support the safety of the maximum daily maltol exposure arising from treatment with Feraccru.

Withdrawals

The discontinuation rate with Feraccru is in line with FeSO4 overall, but the new meta-analysis indicates a more favourable rate for Feraccru in the IBD subgroup. However, it is noted that the ST10-01-301/302 studies recruited only FeSO4 intolerant subjects. The discontinuation rate with Feraccru-treated subjects is thus comparable to that of first line non-IBD patients taking FeSO4 and appears more favourable than first line IBD patients taking FeSO4.

Considering data from the initial procedure 18.0% discontinued because of AEs during Feraccru treatment and 7.2% discontinued because of Feraccru-related adverse events. Pereira *et al.* reported a mean rate of discontinuation due to treatment-related AEs of 7.1±8.1% for ferrous sulphate preparations compared to 7.2% in the ST10-01-301/302 trial.

Including long-term safety data from ST10-01-301/302 extension published by Schmidt C., *et al* (Aliment Pharmacol Ther 2016;44: 259-270), 18/111 (16%) patients who received Feraccru discontinued due to adverse events during 64-weeks of duration of the whole study.

2.5.1. Discussion on clinical safety

Overall safety data comes from study ST10-01-101 (PK study) and pivotal phase 3 study (ST10-01-301/302). In the pivotal trial the safety profile of the ferric maltol group was worse than that of the placebo arm. There were more AEs related to treatment (25.0% vs 11.7%, respectively), moderate to severe related TEAEs were also more frequently with Feraccru (17% vs 7% placebo).

The most common AEs were gastrointestinal related adverse events: abdominal pain (11.7%) (including upper abdomen), flatulence (6.7 %), constipation (8.3%), abdominal discomfort (5.0%), distension (3.3%), diarrhoea and nausea. Most of them were mild to moderate being more common in the first 12 weeks of Feraccru treatment. During the initial procedure it was observed that in the double-blind part of the pivotal study some gastrointestinal AEs were more frequent with Feraccru compared to placebo (e.g. abdominal discomfort, abdominal distension.). The risks of oral iron preparations (OFPs) are well known and mainly consist of common but benign gastro-intestinal ADRs of mild to moderate intensity.

Long-term safety data comes from ST10-01-301/302 extension published by Schmidt C., *et al* (Aliment Pharmacol Ther 2016;44: 259-270). Safety profile of Feraccru in patients with IBD remains favourable after 64 weeks.

During the PK study (ST10-01-101) it was observed that the percentage of AEs is related to the dose with 57.1% of patients who received 180 mg daily, 50.0% received 120 mg daily and 22.2% received 60 mg daily. As stated before in the end the selected dose was 30 mg bid considering not only efficacy but also safety profile.

The MAH provided two published articles which include safety data in relation to existing oral iron products (Pereira 2015 and Tolkien 2015). Taking into account inherent limitations of indirect comparisons it seems that Feraccru could have a lower risk of gastrointestinal AEs compared to ferrous sulphate preparations. However, it has to be considered that comparison was done with IBD patients (ST10-01-301/302 AEGIS trial) not with the general population of subjects with ID/IDA.

Considering data from the initial procedure, 18.0% discontinued because of AEs during Feraccru treatment and 7.2% discontinued because of Feraccru-related adverse events. Pereira *et al.* reported a mean rate of discontinuation due to treatment-related AEs of 7.1±8.1% for ferrous sulphate preparations

compared to 7.2% in the ST10-01-301/302 trial. In Schmidt C., *et al* (Aliment Pharmacol Ther 2016;44: 259-270), 18/111 (16%) patients who received Feraccru discontinued due to adverse events during 64-weeks of duration of the whole study.

According to Pereira meta-analysis it seems that Feraccru could has a lower frequency of mild GIAEs, while moderate-severe GIAEs seems to be greater in Feraccru group (AEGIS trial).

Bearing in mind that no new information with respect to initial procedure has been provided by the applicant, it is considered that treatment with ferric maltol has an acceptable safety profile in patients with IBD, although safety information from a quantitative point of view, remains unknown in ID/IDA caused by other underlying pathologies different to IBD.

In principle, long term treatment with iron preparations should not raise safety concerns considering the mechanism of iron replenishment in patients with iron deficiency, as long as the posology is appropriate. On the other hand, trimaltol is unlikely to raise any important safety concern as it is widely used in the alimentary industry.

In the second PSUR, covering the period from 19 August 2016 and 18 February 2017, the safety of the drug remains in accordance with the expected safety profile of Feraccru.

The last PSUR submitted, covering the period from 19 February 2017 to 18 August 2017, is currently under assessment. In this PSUR 32 SAEs for Feraccru from interventional clinical trials versus 2 SAEs in the placebo groups and 7 SAEs in the IV comparator group were listed.

The comparison of 32 SAEs in the Feraccru treatment groups vs. 9 SAEs in the combined comparator groups (Placebo and IV-iron) is skewed, since most of the SAEs in the Feraccru-groups occurred during the long term open label extension phase where there was no comparator treatment any more. No imbalance in SAEs can therefore be attributed.

There were no serious adverse reactions (SARs) reported during the interval period.

The safety profile is not expected to change with this extension of indication, as the safety of oral iron tablets is well established and there is no signal pointing out to a different risk profile for Feraccru.

Routine Pharmacovigilance monitoring and PSUR assessment are considered sufficient for the risk management of Feraccru.

Additional safety information and data will be provided as part of ongoing study ST10-01-303 performed in CKD patients.

2.5.2. Conclusions on clinical safety

Overall safety data come from study ST10-01-101 (PK study) and pivotal phase 3 study (ST10-01-301/302).

The most common AEs were gastrointestinal related adverse events.

The applicant provided in this procedure mainly two published articles which include safety data in relation to existing oral iron products (Pereira 2015 and Tolkien 2015). Taking into account inherent limitations of indirect comparisons it seems that Feraccru could have a lower risk of gastrointestinal AEs compared to ferrous sulphate preparations.

The long term safety data base is still quite limited (< 100 study subjects with treatment duration over 1 year). However, in principle, long term treatment with iron preparations should not raise additional safety concerns considering the mechanism of iron replenishment in patients with iron deficiency, as long as the posology is followed. In addition, trimaltol is unlikely to raise any important safety concern as it is widely

used in the alimentary industry.

In the second PSUR, covering the period from 19 August 2016 and 18 February 2017, the safety of the drug remains in accordance with that expected. The last PSUR submitted, covering the period from 19 February 2017 to 18 August 2017, is currently under assessment. Taking into account the data provided by the MAH, the risk profile of Feraccru in patients with iron deficiency is therefore considered acceptable and has not changed. Additional safety information and data will be provided as part of ongoing study ST10-01-303 performed in CKD patients.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 8 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed this advice without changes and endorsed the Risk Management Plan version 8 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Gastrointestinal (GI) effects
Important potential risks	Interactions (drugs) Worsening of IBD symptoms (in patients with this disease) Hypersensitivity and allergic reactions
Missing information	Use in pregnancy and lactation Use in children

Pharmacovigilance plan

Not applicable.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Gastrointestinal effects	SmPC Section 4.8; PIL Section 4	none
Interactions (drugs)	SmPC Section 4.5; PIL Section 2	none
Worsening of IBD symptoms (in patients with this disease)	SmPC Section 4.8; PIL Section 4	none
Hypersensitivity and allergic reactions	SmPC Section 4.3; PIL Sections 2 and 4	none
Use during pregnancy and lactation	SmPC Section 4.6; PIL Section 2	none
Use in children	SmPC Sections 4.1, 4.2, 4.4; PIL Sections 1 and 3	none

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The application to extend the indication from:

'Feraccru is indicated in adults for the treatment of iron deficiency anaemia (IDA) in patients with inflammatory bowel disease (IBD) (see section 5.1)'

to 'Feraccru is indicated in adults for the treatment of iron deficiency (ID).'

does not involve a relevant impact on the PIL, Therefore, the company´s justification to not undertake further consultation with target patient groups is considered acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Iron is an essential micronutrient that is required for adequate erythropoietic function, oxidative metabolism and cellular immune responses. The term "anaemia" is sometimes used synonymously with "iron deficiency anaemia". However, these terms do not cover the same reality. There are about 2-5 times more iron deficient people than individuals with IDA. Iron deficiency is diagnosed when low serum levels of ferritin or transferrin saturation are measured. The most common reasons for ID are insufficient iron intake in the diet, an inability to absorb iron well in the body and/or loss of iron in blood through bleeding. Iron deficiency is the most common cause of anaemia. Iron deficiency anaemia is caused by low levels of iron in the body. Iron deficiency anaemia is the most common cause of anaemia worldwide, affecting over 2 billion people, which equates to approximately 30% of the world's population (Pavord, 2012; NICE CKS, 2013; Zhu, 2010). Epidemiological surveys indicate that in Europe, iron depletion concerns 10-30% of menstruating women with 1.5 to 14% progressing to IDA. In pregnant women the prevalence of IDA, according to different studies and surveys, ranges from 6 to 30% with the highest levels observed in countries such as Holland (6-28%), Denmark (0-18%) and France (9-30%) where routine iron supplementation is not usually given during pregnancy (Hercberg, 2001).

Iron deficiency is a common complication of inflammatory bowel disease (IBD), occurring in about 60-80% of IBD patients. Approximately one-third of patients with IBD are also anaemic. Although anaemia in IBD often involves a combination of IDA and anaemia of chronic disease, IDA remains an important contributor in this condition (Zhu, 2010). Importantly for the therapeutic action of Feraccru, the observed IDA in IBD patients does not appear to be due entirely to an inability to absorb oral iron, even in cases of severe chronic inflammatory disease (Erichsen, 2003; Bartels, 1978).

Iron is absorbed at the apical surface of enterocytes to be transported by ferroportin, the only known iron exporter, across the basolateral surface of the enterocyte into circulation. Inflammation from IBD interferes with iron absorption by causing an increase in hepcidin, a peptide hormone synthesised in the liver that inhibits ferroportin activity.

The serum markers of iron deficiency are low ferritin, low iron, raised total iron binding capacity, raised red cell protoporhyrin and increased transferrin binding receptor (sTfR). Serum ferritin is the most powerful test for iron deficiency. The cut-off level of ferritin which is diagnostic varies between 12-15 µg/L. Higher levels of serum ferritin do not exclude the possibility of iron deficiency, and a serum ferritin level of <100 µg/L may still be consistent with iron deficiency in patients with IBD. A transferrin saturation of <16% is indicative of iron deficiency, either absolute or functional. Other findings on a complete blood count panel that are suggestive of iron deficiency anaemia, but are not considered diagnostic, include microcytosis, hypochromia and elevation of red cell distribution width.

3.1.2. Available therapies and unmet medical need

The goals of treatment are to treat the underlying cause, limit further blood loss or malabsorption, avoid blood transfusions in haemodynamically stable patients, relieve symptoms, and improve quality of life. More specifically, therapeutic goals of treatment include normalising haemoglobin levels within 4 weeks (or achieving an increase of >2 g/dL) and replenishing iron stores (transferrin saturation >30%).

Oral iron supplementation has been considered standard treatment because of an established safety profile, lower cost and ease of administration. It has been shown to be effective in correcting anaemia and repleting iron stores. One concern with higher doses of daily oral iron is intolerance due to GI side effects. Symptoms include nausea, vomiting, diarrhoea, abdominal pain, constipation, and melena-like stools.

Table 4: Iron products with similar indications currently available to treat iron deficiency

Generic name	Brand names	Indications
Iron (III) hydroxide dextran complex	Cosmofer solutions for injections/infusion	Treatment of iron deficiency in the following indications: • When oral iron preparations cannot be used, e.g. due to intolerance, or in case of demonstrated lack of effect of oral iron therapy. • Where there is a clinical need to deliver iron rapidly to iron stores.
Iron sucrose	Venofer solution for injection or concentrate for solution for infusions	Where there is a clinical need to deliver iron rapidly. • Oral iron not tolerated; non-compliance. • Active inflammatory bowel disease (IBD) where oral iron Ineffective
Ferric carboxymaltose	Ferinject solution for injection/infusion	Treatment of iron deficiency when oral iron preparations are ineffective or cannot be used.
Iron isomaltoside 1000	Monofer solution for injection/infusion	Treatment of iron deficiency anaemia when oral iron preparations are ineffective or cannot be used or when there is a need to deliver iron rapidly
Ferrous sulphate	Feospan Spansule capsules	Prevention and treatment of iron deficiency
	Fefol Spansule capsules	Fefol is a haematinic preparation for prophylaxis and treatment of iron deficiency and prophylaxis of folic acid deficiency during pregnancy
Ferrous fumarate	Fersaday tablets	Prophylaxis and treatment of iron deficiency
Ferrous gluconate	Ferrous gluconate tablets	The prevention and treatment of iron deficiency

In addition, there are several other products indicated for treatment with iron deficiency anaemia (IDA): IDA is the severest form of iron deficiency - there are mild-to-moderate forms of iron deficiency in which anaemia is absent [WHO 2001; Hercberg 2001]. Oral ferrous iron salts are the most economical and

effective form of treatment for IDA, with ferrous sulphate and ferrous gluconate being the most commonly used salt forms [Harper 2013a].

3.1.3. Main clinical studies

3.2. Favourable effects

In the pivotal trial Feraccru has shown to significantly improve the Hb concentration (change of 2.25 gr/dl from baseline) over 12 weeks of treatment in IBD patients compared to placebo.

The MAH provided published studies in order to compare the increment in Hb levels with ferrous iron preparations vs. increment with Feraccru in the pivotal trial. All these studies showed a mean increased in Hb levels from 1.3 g/dL to 2.52 g/dL, being greater in those patients with lower baseline Hb level. These increments are in line with the ones observed in pivotal trials conducted with Feraccru. It also confirms that iron preparations are subject to the normal regulatory mechanisms controlling gastrointestinal iron absorption.

PK-data show sufficient bioavailability in patients with iron deficiency without anaemia and supportive clinical study data indicate that the recommended dose is sufficient to normalise iron blood indices in patients with ID/IDA or maintain Hb –levels in patients with active blood loss.

Feraccru is bioavailable and as a result effective in iron deficiency patients with and without anaemia.

Although the approach to treatment should be individualised according to aetiology and severity, it is generally accepted that treatment should be initiated in patients with iron deficiency in order to avoid development of anaemia and also to improve some symptoms associated with iron deficiency.

3.3. Uncertainties and limitations about favourable effects

There are limited data with regards to the use of Feraccru in other pathologies different from IBD. The CHMP recommends the submission of an ongoing clinical efficacy study in CKD patients (study ST10-01-303) in order to confirm efficacy in CKD patients.

3.4. Unfavourable effects

No new safety data has been submitted as part of this application. The most common AEs reported in the pivotal trials supporting the initial MA were gastrointestinal related adverse events (3.3% severe), abdominal pain (11.7%), flatulence (6.7%), constipation (8.3%), diarrhoea (2.8%) and nausea (1.8%). Data form latest PSURs confirm that the safety of the drug remains in accordance with what is expected and currently reflected in the SmPC. Overall, the safety profile of Feraccru is considered acceptable.

3.5. Uncertainties and limitations about unfavourable effects

No new data have been submitted by the MAH as part of this extension of indication. Safety information from a quantitative point of view remains unknown in ID/IDA caused by other underlying pathologies different to IBD. However, routine pharmacovigilance is considered sufficient in order to monitor the safety profile of Feraccru in this extended indication.

The long term safety data base is limited. However, the long term treatment with Feraccru should not raise additional safety concerns considering the mechanism of action of iron replenishment in patients

with an iron deficiency, as long as the posology is followed.

3.6. Effects Table

Table 5: Effects Table for Feraccru

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Hb	Changes in Hb concentration from baseline to week 12	gr/dl	2.25	-0.02	Difference between adjusted means (SE) 2.25 (0.19), 97.5%CI 1.88	
Unfavourable Effects						
Gastrointestinal disease	Overall incidence	%	3.3	0		

Abbreviations: Hb: Haemoglobin

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Ferric maltol has shown to increase the Hb concentration correcting the anaemia at week 12 (change of 2.25 gr/dl from baseline) in IBD patients. Indirect comparisons with studies using ferrous iron preparations suggested that increments are in line with the ones observed in pivotal trials conducted with Feraccru.

The safety profile of Feraccru is considered acceptable and in line with other iron preparations.

3.7.2. Balance of benefits and risks

The MAH did not perform new studies to support this extension of indication of Feraccru from the treatment "in adults with Iron deficiency anaemia in patients with IBD" to the treatment of "adults with iron deficiency". This extension is supported by pivotal trial conducted in the initial marketing authorisation procedure (ST10-01-301/302) and published supportive studies. In the pivotal trial Feraccru has shown to significantly improve the Hb concentration (change of 2.25 gr/dl from baseline) over 12 weeks of treatment in IBD patients compared to placebo.

Feraccru is bioavailable and as a result effective in iron deficiency patients with and without anaemia regardless of the underlying pathology. Overall, the safety profile of Feraccru is acceptable. The most common AEs were gastrointestinal related adverse events.

There are limited data with regards to the use of Feraccru in other pathologies different to IBD.

In principle, long term treatment with iron preparations should not raise safety concerns considering the mechanism of iron replenishment in patients with an iron deficiency, as long as the posology is followed.

The safety profile is not expected to change with this extension of indication, as the safety of oral iron

tablets is well established and there is no signal pointing out to a different risk profile for Feraccru.

The Benefit-Risk balance of Feraccru for this extension of indication to widen the indication for Feraccru from the treatment "in adults with Iron deficiency anaemia in patients with IBD" to the treatment of "adults with Iron deficiency" is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Ferracru is positive in the following indication:

"Feraccru is indicated in adults for the treatment of iron deficiency."

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to widen the indication for Feraccru from the treatment "in adults with Iron deficiency anaemia in patients with IBD" to the treatment of "adults with Iron deficiency"; As a consequence, sections 4.1, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and RMP (v.8) have been updated accordingly.
In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.