**EU Risk Management Plan (RMP) for Feraccru® 30 mg capsules (Ferric maltol)**

**RMP version to be assessed as part of this application:**

RMP Version number: 9.1

Data lock point for this RMP: 26-Feb-2025

Date of final sign off: 08-Apr-2025

| | |
|---|---|
| **Rationale for submitting an updated RMP:** | To support the indication for adolescents aged 12 years and older. Results from 2 completed paediatric studies (ST10-01-103, and ST10-01-305) have been incorporated.<br><br>Additionally, results from 1 adult study i.e., ST10-01-104 have also been incorporated into the RMP. |
| **Summary of significant changes in this RMP:** | Part I Product Overview: The indication has been extended to include adolescents aged 12 years and older.<br><br>Part II Module SI Epidemiology of the indication(s) and target population(s): Updated to incorporate details regarding the children and adolescents population.<br><br>Part II Module SIII Clinical trial exposure: Updated to incorporate results from two completed paediatric studies (ST10-01-103 and ST10-01-305) and 1 adult study (ST10-01-104).<br><br>Part II: Module SV Post-authorisation experience: Updated to incorporate cumulative sales of both FERACCRU as well as ACCRUFER till Feb 2025 |

**Other RMP versions under evaluation:** N/A

**Details of the currently approved RMP:**

Version number: 9

Approved with procedure: EMEA/H/C/002733/R/0027

Date of approval (opinion date): 17 Sep 2020

QPPV name: Fabio Miceli

EU QPPV declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The e-signature is available on file.

**Table of content**

**Table of content ..... 2**

**Part I: Product(s) Overview ..... 4**

**Part II: Module SI - Epidemiology of the indication(s) and target population(s) ..... 6**

**Part II: Module SII - Non-clinical part of the safety specification ..... 9**

**Part II: Module SIII - Clinical trial exposure ..... 15**

**Part II: Module SIV - Populations not studied in clinical trials ..... 32**

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme 32

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes 33

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes ..... 33

**Part II: Module SV - Post-authorisation experience ..... 35**

SV.1 Post-authorisation exposure ..... 35

**Part II: Module SVI - Additional EU requirements for the safety specification ..... 36**

**Part II: Module SVII - Identified and potential risks ..... 36**

SVII.1 Identification of safety concerns in the initial RMP submission ..... 36

SVII.2 New safety concerns and reclassification with a submission of an updated RMP 36

SVII.3 Details of important identified risks, important potential risks, and missing information ..... 36

**Part II: Module SVIII - Summary of the safety concerns ..... 41**

**Part III: Pharmacovigilance Plan (including post-authorisation safety studies) ..... 42**

III.1 Routine pharmacovigilance activities ..... 42

III.2 Additional pharmacovigilance activities ..... 42

III.3 Summary Table of additional Pharmacovigilance activities ..... 42

**Part IV: Plans for post-authorisation efficacy studies ..... 43**

**Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities) ..... 44**

V.1. Routine Risk Minimisation Measures ..... 44

V.2. Additional Risk Minimisation Measures ..... 45

V.3 Summary of risk minimisation measures ..... 45

**Part VI: Summary of the risk management plan ..... 47**

II.A List of important risks and missing information ..... 48

II.B Summary of important risks ..... 48

II.C Post-authorisation development plan ..... 52

II.C.1 Studies which are conditions of the marketing authorisation ..... 52

II.C.2 Other studies in post-authorisation development plan ..... 52

**Part VII: Annexes ..... 53**
Annex 1 – EudraVigilance Interface ..... 54
Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme ..... 55
Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan ..... 56
Annex 4 - Specific adverse drug reaction follow-up forms ..... 57
Annex 5 - Protocols for proposed and on-going studies in RMP part IV ..... 58
Annex 6 - Details of proposed additional risk minimisation activities (if applicable) ..... 59
Annex 7 - Other supporting data (including referenced material) ..... 60
Annex 8 – Summary of changes to the risk management plan over time[1] ..... 65

# Part I: Product(s) Overview

Table Part I.1 – Product Overview

| | |
|---|---|
| **Active substance(s)**<br><br>**(INN or common name)** | 3-hydroxy-2-methyl-4H-pyrane-4-one iron (III) complex (3:1) (INN: Ferric maltol)<br><br>Other names are:<br>• Ferric (3-hydroxy-2-methyl-4-pyrone) or<br>• Ferric tri-maltol or<br>• Tris-maltol-iron (III) or<br>• Tri-maltol-iron (III)<br>• Ferric trimaltol<br>• ST10<br>• ST10-021 |
| **Pharmacotherapeutic group(s) (ATC Code)** | ATC Code: BO3AB10 |
| **Marketing Authorisation Holder** | Norgine B.V. |
| **Medicinal products to which this RMP refers** | 1 |
| **Invented name(s) in the European Economic Area (EEA)** | Feraccru® 30 mg capsules |
| **Marketing authorisation procedure** | Centralised |
| **Brief description of the product** | Chemical class:<br><br>Iron trivalent |
| | Summary of mode of action<br><br>Feraccru contains iron in a stable ferric state as a complex with a trimaltol ligand. The complex is designed to provide, in a controlled way, utilisable iron for uptake across the intestinal wall and transfer to the iron transport and storage proteins in the body (transferrin and ferritin, respectively).<br><br>The complex dissociates on uptake from the gastro-intestinal tract and the complex itself does not enter the systemic circulation. |
| | Important information about its composition<br><br>Each capsule contains 91.5 mg of lactose, 0.5 mg of Allura Red AC (E129) and 0.3 mg Sunset Yellow FCF (E110). |
| **Hyperlink to the Product Information** | [Module 1.3.1] |
| **Indication(s) in the EEA** | Current (if applicable):<br><br>Feraccru is indicated in adults for the treatment of iron deficiency |

| | |
|---|---|
| | Proposed (if applicable):<br><br>FERACCRU is indicated for the treatment of iron deficiency in adults and adolescents aged 12 years and older. |
| **Dosage in the EEA** | Current (if applicable):<br><u>Posology</u><br>The recommended dose is one capsule twice daily, morning and evening, on an empty stomach.<br>Treatment duration will depend on the severity of iron deficiency but generally at least 12-weeks treatment is required. The treatment should be continued as long as necessary to replenish the body iron stores according to blood tests.<br>Feraccru capsules should be taken whole on an empty stomach (with half a glass of water), as the absorption of iron is reduced when Feraccru is taken with food. |
| | Proposed (if applicable):<br><br>The recommended dose in adolescents from 12 years of age is the same as in adults.<br><br>No recommendation on the posology of FERACCRU can be made in children less than 12 years of age. |
| **Pharmaceutical form(s) and strengths** | Current (if applicable): 30 mg hard capsules |
| | Proposed (if applicable): N/A |
| **Is/will the product be subject to additional monitoring in the EU?** | No |

# Part II: Safety specification

# Part II: Module SI - Epidemiology of the indication(s) and target population(s)

## Iron Deficiency (ID) and Iron Deficiency Anaemia (IDA)

Iron Deficiency Anaemia (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]. According to the WHO, up to 39% of children who are less than 5 years and 48% of children who are between 5 to 14 years of age are iron deficient in non-industrialised world, as against 20% in less than 5 and 5.9% in 5–14 years from industrialised world [WHO 2001].

**Incidence:** The annual incidence rates of IDA in Europe range between 7.2 and 13.96 per 1000 person-years [Levi 2016].

**Prevalence:** Iron Deficiency Anaemia (IDA) is the most common cause of anaemia worldwide, affecting over two billion people, which equates to approximately 30% of the world's population [Pavord 2012]; [NICE CKS 2013a]; [Zhu 2010]. In Europe, iron deficiency is considered to be one of the main nutritional deficiency disorders affecting large fractions of the population. Prevalence of IDA varies greatly according to age, gender, race, and ethnicity. Most epidemiological data on iron status in Europe was published in the 80s and early 90s and some of these data are invalid because they are only based on haemoglobin determination. Epidemiological surveys indicate that in Europe iron depletion concerns 10- 30% of menstruating women with 1.5 to 14% having 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]. During adulthood, the equilibrium between body loss and gain is maintained, but this is not so well developed in children who are, therefore, more likely to develop IDA [Harper 2013b].

Prevalence rates vary among countries; Iron deficiency (ID) affects 2.4 million children in the USA [Brotanek 2007], 5.4% of children in Spain [Munoz Perez et al; 1995], 14.0% in Estonia [Vendt N et al; 2007], 30.8% in Brazilian children [Vieira AC et al; 2007]. In Europe, the prevalence of depleted iron stores in children varies from 2 to 48% and anaemia from 2 to 4% depending on age group and country, while in adolescents the prevalence varies from 5-43% for iron depletion and 7-8% for anaemia [Hercberg et al., 2001]. In adult men, the prevalence of depleted iron stores varies from 0-3%. Recent epidemiological studies indicate that the prevalence of ID in EU adolescents ranges from 5% to 33%, with higher rates observed in females [Hercberg et al., 2001; Ferrari et al., 2011]. A systematic review by [Iglesia et al, 2019] reported that the prevalence of IDA in European adolescents varies between 1.3% and 5.4%. The incidence of new ID cases in adolescents is estimated at 1.5-2 per 1,000 person-years, with a slightly higher rate for IDA at 2.5-3 per 1,000 person-years [Vos et al., 2012].

**Demographics of the population in the authorised indication and risk factors for the disease:** Females, younger and older patients are at greater risk of IDA, as well as those suffering from gastrointestinal diseases, pregnant women and those with history of menometrorrhagia, and aspirin and/or antacids users [Levi 2016]. Risk factors specific to adolescents include rapid growth, onset of menstruation in females, and dietary habits. A longitudinal study by [Dror et al;2018] found that approximately 20-30% of ID cases in adolescents progress to IDA within two years if left untreated. Female adolescents consuming low-energy diets, vegetarians and vegans are also at high risk of iron deficiency [Hercberg et al., 2001 ].

Heavy menstrual blood losses and pregnancy are the reason for a higher incidence of IDA in premenopausal women [NICE CKS 2013a; WHO 2001] – about 20-30% of cases [NICE CKS 2013a]. In men and post-menopausal women, occult bleeding from the gastrointestinal (GI) tract is the leading cause of IDA [NHS Choices]. A loss of blood of 10 mL per day will typically result in a positive guaiac-based faecal occult blood test (FOBT), although FOBT positivity is highly dependent on the source of the bleed. Bleeding lesions in the GI tract are identified in approximately 50% of patients with IDA.

Race is not considered to have a significant effect upon the occurrence of IDA. However, because diet and socioeconomic factors play a role in the prevalence of iron deficiency, it may be more frequently observed in people of various racial backgrounds living in poorer areas of the world [Harper 2013b]. Additionally, iron deficiency is most common among groups of low socio-economic status [WHO 2001]. If ID is left untreated, susceptibility of that individual to illness and infection increases because a lack of iron in the body affects the immune system [NHS Choices; WHO 2001]. ID may increase the risk of cardiopulmonary complications, such as tachycardia or heart failure, particularly in adults with severe anaemia [NHS choices; NICE CKS 2013b; AHRQ 2006]. Pregnant women with severe or untreated anaemia also have a higher risk of complications before and after birth. Other complications of IDA include reduced work productivity, endurance, and exercise capacity [NICE CKS 2013b; AHRQ 2006].

**The main existing treatment options:** Treatment of iron deficiency should usually begin with dietary replacement (i.e., fortified cereals and breads, red meat, beans, green leafy vegetables). When diet alone is inadequate to restore iron stores and haemoglobin to normal levels, or when anaemia is moderate to severe or has associated clinical symptoms, treatment with exogenous iron supplements is typically implemented. Commonly used oral supplements include ferrous sulphate or ferrous gluconate. However, the bioavailability of iron from diet and oral iron medication is poor, leading to the majority of oral ferrous sulphate or gluconate dose to pass down the GI tract unabsorbed [NICE CKS 2013c].

The indication for Feraccru® is unique for oral iron preparations – there are, however, some intravenous iron preparations that have similar indications (Table 1).

**Table 1 Iron products with similar indications currently available to treat iron deficiency**

| Generic Name | Brand Name | Indication |
|---|---|---|
| Iron (III) hydroxide dextran complex | Cosmofer® solutions for injections/infusion | Treatment of iron deficiency in the following indications:<br>• When oral iron preparations cannot be used, e.g. due to intolerance, or in case of demonstrated lack of effect of oral iron therapy.<br>• 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.<br>• Oral iron not tolerated; non-compliance.<br>• 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. |

| Generic Name | Brand Name | Indication |
|---|---|---|
| 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 states |
| Ferrous gluconate | Ferrous gluconate tablets | The prevention and treatment of iron deficiency states. |

In addition, there are several other products indicated for treatment with IDA:

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].

**Natural history of the indicated condition in the untreated population, including mortality and morbidity:**

The clinical picture varies greatly from one case to another, and it is produced both by the anaemia itself and by the lack of iron, which is essential for cellular energy metabolism. Symptoms can include general weakness, fatigue, irritability, poor concentration, headache, and intolerance to exercise. Patients often show relatively few symptoms spontaneously. Although the impact of ID on the quality of life of the subject is high, they often get used to their symptoms and these are assumed as normal. Some iron-deficient patients might have alopecia, atrophy of lingual papillae, pica, or dry mouth due to loss of salivation [Gisbert 2009].

If iron deficiency anaemia is left untreated, it can make patients more susceptible to illness and infection, as a lack of iron affects the immune system. Severe iron deficiency anaemia may increase the risk of developing complications that affect the heart or lungs, such as tachycardia or heart failure. Pregnant women with severe or untreated anaemia also have a higher risk of complications before and after birth [NHS Choices].

In a comprehensive review of published literature linking IDA to disability and death, conducted by WHO, the available evidence suggested that IDA contributed substantially to death and disability in the world with the majority of this disease burden in Africa and Asia due to anaemia from pregnancy and early childhood [Stoltzfus 2003].

# Part II: Module SII - Non-clinical part of the safety specification

Although the drug substance in Feraccru® 30 mg capsules is ferric maltol, the active moiety is iron. All evidence from both human and non-clinical studies has demonstrated that ferric maltol is not absorbed intact into the systemic circulation. Feraccru® delivers iron via the endogenous iron uptake system in the proximal duodenum. The systemic toxicity and safety of iron and maltol have been assessed separately.

Key safety findings from non-clinical studies and relevance to human usage:

| **Key safety findings (from non- clinical studies)** | **Relevance to human usage** |
|---|---|
| **Single and repeat-dose toxicity**<br><br>***Ferric maltol:*** No acute toxicity data with ferric maltol are available in common laboratory animal species. However, an initial maximum tolerated dose of 500 mg/kg has been determined in a dog sub-acute study [Morgan 1990]. The oral LD50 of elemental iron in the rat is in the range 60 to 100 mg/kg [Food Additive Series 571. Iron, WHO].<br><br>In a 28-day toxicology study in dogs performed under good laboratory practice (GLP), the no observed adverse effect level (NOAEL) for ST10- 021 was determined to be 125 mg/kg bw (65 mg/kg of iron) [Morgan 1990]. The study focused on the GI tract as this is the only organ in the body exposed to ferric maltol itself. The oesophagus, stomach, duodenum, ileum, jejunum, colon and caecum were examined following administration. It was noted that the gastric contents were deep red and the faeces red. This was due to colouration by ferric maltol which is a deep burgundy red compound. There was no suggestion of damage to the GI tract or any blood loss, in contrast to findings with ferrous sulphate and other ferrous compounds in the dog [D´Arcy 1962].<br><br>In the study by D'Arcy, ferrous sulphate was found to be highly toxic in the dog – 600 mg/kg (195 mg/kg as iron) was fatal and a dose of 100 mg/kg (32.5mg/kg as iron) produced extensive damage to the GI tract [D'Arcy 1962].<br><br>***Iron:*** The oral LD50 of elemental iron in the rat is in the range 60 to 100 mg/kg [WHO Food Additive Series 571]. | **Single and repeat-dose toxicity**<br><br>Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.<br><br>***Ferric maltol:*** The dose of iron administered with Feraccru® is 60 mg per day, but the dose of the complex is 463 mg (equivalent to 6.61 mg/kg/day for a 70 kg man), which gives a safety factor of about 19 compared to the dog study NOAEL of 125 mg/kg bw. In mg/m2, this equates to a daily dose of the Feraccru® complex of 245 mg/m$^2$ which, again, is well below the dog study NOAEL of 4500 mg/m2 and gives a safety factor of 18.<br><br>When administered orally, ferric maltol is not absorbed as a complex and as such is not systemically available. Because ferric maltol is not absorbed as a complex molecule, the toxicological profiles of iron and maltol as individual moieties versus the ferric maltol complex as a whole are critical to evaluating the potential safety profile of ferric maltol.<br><br>***Maltol:*** The WHO has evaluated maltol as a food additive [WHO 1980]. The level defined by WHO not to cause toxicological effects in rats was 100 mg/kg (bw) and the estimated acceptable daily intake for man was defined as 1 mg/kg bw. Ferric maltol is administered as an oral dose of 463 mg/day (6.61 mg/kg/day) which equates to 403 mg/day (5.8 mg/kg/day) of maltol which is above the WHO safety human daily intake level but well below the level where toxicological effects were seen. The dose level at which the testicular toxicity finding occurred |

| Key safety findings (from non- clinical studies) | Relevance to human usage |
|---|---|
| ***Maltol:*** Maltol is of low acute toxicity and LD50's range from 550 to 848 mg/kg in female and male mice, respectively to 1,440 mg/kg in male rats and 1,410 mg/kg in male guinea-pigs. Maltol has a long history of use as a flavouring agent and dietary toxicity studies have been performed 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. The only potentially significant toxic effect was reported in mice after 18 months of treatment and was an increased incidence of testicular atrophy at the highest dose level evaluated of 400 mg/kg/day. No toxicity attributable to treatment with maltol was reported in rats and no carcinogenic effects were apparent in either species.<br><br>Two 90-day oral toxicity studies in dogs with maltol have been reported in which maltol was administered by capsule. In one GLP-compliant study dose levels of 0, 100, 200 or 300 mg/kg/day were administered to groups of 8 (4 of each sex) beagle dogs. No treatment-related effects were observed on gross or microscopic pathology, clinical chemistry, haematology or clinical signs. Compared to the controls, the treated females exhibited lower body weights throughout the study. Maltol was administered at dose levels of 0, 125, 250 or 500 mg/kg/day to groups of 4 dogs in a second study. By treatment day 41, three animals receiving 500 mg/kg/day had died exhibiting signs of liver damage, red cell destruction, emesis, ataxia, and prostration and the fourth was killed in extremis. Histopathology revealed pulmonary oedema, pericentral and midzonal hepatic necrosis, fatty degeneration of the myocardium, adrenal cortical and medullary necrosis and testicular degeneration. The author comments, however, that histopathological examination of tissues from these dogs was hampered by post-mortem autolysis. The time interval between death and autopsy was not stated, nor was there any indication of the storage temperature of the carcasses. No similar testicular changes were | in mice represents approximately 70 times the daily clinical exposure to maltol for a patient of 70 kg body weight at the proposed therapeutic dose of 2 x 201.5 = 403 mg / day (5.8 mg/kg/day).<br><br>***Iron:*** It is well documented that iron can produce both local and systemic adverse effects, and it is expected that the nature of the systemic adverse effects will be similar for ferric maltol. Ingestions of less than 40 mg/kg of iron have little risk for toxicity and require no specific treatment, although ingestion of 20 mg/kg in an adult human volunteer study resulted in nausea, malaise, and diarrhoea in all six subjects [Burkhart 1991]. A retrospective review of 199 acute iron exposures revealed that only a small percentage of patients who ingested between 40 and 60 mg/kg of iron developed clinical symptoms (vomiting, diarrhoea, abdominal pain), and no one developed serious toxicity [Klein-Schwartz 1990]. However, acute iron toxicity from overdose, with fatalities, are well described in the paediatric population. In paediatrics, doses >40 mg/kg of Fe2+ are potentially fatal [Madiwale 2005; Manoguerra 2005].<br><br>Locally, iron has direct corrosive effects on the GI mucosa, resulting in ulceration, oedema, bleeding, venous thrombosis, infarction, and perforation [Tenenbein 1990]. These effects can lead to significant fluid loss by direct haemorrhage and as well as the "third spacing" of fluids, both contributing to systemic hypovolemia. The severity of these local corrosive effects depend on the quantity of iron ingested, the form of the iron, the concentration of iron in the preparation, 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 occurs on an empty stomach.<br><br>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 |

| Key safety findings (from non- clinical studies) | Relevance to human usage |
|---|---|
| observed in dogs treated with ST10 or at a dose level of 300 mg/kg/day in the 90-day dog study previously described.<br><br>The repeated dose toxicity data suggest that the finding of testicular atrophy in mice after 18 months of treatment at 400 mg/kg/day was an isolated occurrence since the potentially similar finding observed in dogs receiving 500 mg/kg/day for 41 days is likely due have been a result of autolytic change and no similar findings were apparent in any of the other studies conducted.<br><br>The only potentially significant toxic effect was reported in mice at 18 months treatment and was an increased incidence of testicular atrophy at the highest dose level evaluated of 400 mg/kg/day. No toxicity attributable to treatment with maltol was reported in rats and no carcinogenic effects were apparent in either species. | strong catalyst of reactive oxygen species (ROS) production, oral ferrous iron therapy may worsen symptoms in IBD patients, and potentially contribute to the disease process and disease exacerbation [de Silva 2005]. While ferrous iron from ferrous sulphate administered orally causes severe damage to the GI tract [Nayfield 1976; Tobli 2008], ferric maltol delivers iron in vitro and in vivo by a ligand substitution process which involves dissociation of the complex only immediately before absorption at the intestinal mucosa. Dissociation is associated with donation of the iron to physiological transport proteins such as transferrin and ferritin and is limited to the amount of iron being donated. This minimises damage of the intestinal mucosa by free iron and potentially results in reduced local toxicity with ferric maltol. It should also reduce the risk of systemic intoxication as the rate and amount of absorption appears to be within the physiologically regulated limits. Furthermore, in chronic toxicity studies in dogs and local tolerance studies, there was no damage to the GI tract observed at gross or histopathological level. |
| **Reproductive and developmental toxicity**<br><br>***Maltol:*** Reproductive and developmental toxicity studies were conducted in rats of the F1 generation, the parents of which had been exposed to maltol at 0, 100, 200 and 400 mg/kg/day. The F1 animals were maintained on the same dietary exposure to maltol and mated at days 189 and 245 respectively to produce the F2a and F2b generations of a three generation reproduction study. No effects on fertility were apparent, development of the foetuses and the offspring was unaffected by treatment and there was no evidence of developmental toxicity. | **Reproductive and developmental toxicity**<br><br>There are no data on the effect of ferric maltol on human fertility. Fertility was unaffected following maltol treatment in non-clinical studies. Although there were no findings during non-clinical reproductive toxicity studies with maltol, no nonclinical data for ferric maltol are available and no clinical experience has been acquired with Feraccru® in pregnant or lactating patients. In accordance with other oral iron products, it is not expected that Feraccru® will pose any risk if taken by patients who are pregnant or breast-feeding. However, as a precaution, it is recommended that Feraccru® is not taken during pregnancy or lactation. No additional non-clinical data are required for these populations. |
| **Nephrotoxicity** | **Nephrotoxicity** |

| Key safety findings (from non- clinical studies) | Relevance to human usage |
|---|---|
| No studies to report; the nephrotoxicity profile of iron is well documented. Maltol is rapidly metabolised and excreted with no accumulation seen in PK studies. | N/A |
| **Hepatotoxicity**<br><br>No studies to report; the hepatotoxicity profile of iron is well documented. Maltol is rapidly metabolised and excreted with no accumulation seen in pharmacokinetic (PK) studies. | **Hepatotoxicity**<br><br>N/A |
| **Genotoxicity**<br><br>***Ferric maltol***: The genotoxic effects of ferric maltol have been studied in the Ames test. Mutagenic effects were seen only at high nonphysiological concentrations. Ferrous sulphate tested in parallel was not mutagenic indicating that the mutagenic effect was caused by maltol rather than iron. A range of iron compounds, including ferrous sulphate have been tested in Salmonella typhimurium and L5178Y mouse lymphoma cells under a programme sponsored by the Applied Nutrition Nutrivision with positive outcomes [Halliwell 1990].<br><br>***Maltol:*** A large range of genotoxicity studies have been conducted in vitro and in vivo with maltol. However, maltol produced conflicting results in different test systems with partly clear increases in the frequency of mutations or chromosome aberrations, but also clearly negative results in the same test systems. These conflicting results were not only seen in vitro, but also in vivo in the micronucleus test. Results from three additional recent studies (in vitro micronucleus assay and a micronucleus assay after oral administration of maltol in conjunction with an in vivo Comet assay) were negative. In two long-term carcinogenicity studies in mice and rats, no effect of maltol (doses up to 400 mg/kg) on tumour incidence was seen. | **Genotoxicity**<br><br>***Maltol:*** The Joint FAO/WHO Expert Committee on Food Additives (JECFA) carried out a comprehensive review of the genotoxicity of maltol [WHO 2006]. JECFA concluded that the weakly positive results with high concentrations/doses of maltol both in vitro and in vivo (after intraperitoneal administration) in some genotoxicity studies are not relevant to human oral intake and this conclusion is supported by the results of dietary carcinogenicity studies in rats and mice in which no carcinogenic effects were apparent in either species [WHO Food Additives Series No. 16]. A recent review by EFSA [European Food Safety Authority (EFSA) 2014] presented the results of three studies: an in vitro micronucleus assay and a micronucleus assay after oral administration of maltol in conjunction with an in vivo Comet assay in order to clarify the genotoxic potential of maltol. The results of these studies were negative however the panel concluded that these negative findings could not rule out the concern for genotoxicity for maltol since the data provided to prove systemic availability were inconclusive. The PK data available for ST10 indicate that maltol is immediately glucuronidated and excreted in the urine after oral administration and would therefore not be expected to be present systemically in any significant amount, nor to be distributed to the tissues. The original conclusion by JEFCA that the weakly positive results with high concentrations/doses of maltol both in vitro and in vivo (after intraperitoneal administration) in some genotoxicity studies are |

| Key safety findings (from non- clinical studies) | Relevance to human usage |
|---|---|
| | not relevant to human oral intake are still therefore applicable. |
| **Carcinogenicity**<br><br>***Maltol:*** Although conflicting results were obtained with maltol in genotoxicity studies, no carcinogenic effects was seen in two long-term carcinogenicity studies in mice and rats as reviewed by JECFA [WHO, 1980]. | **Carcinogenicity**<br><br>***Maltol:*** No carcinogenic effects were apparent in dietary carcinogenicity studies in rats and mice [WHO Food Additives Series No. 16]. |
| **General safety pharmacology**<br><br>The absence of data from safety pharmacology studies investigating the cardiovascular or renal safety of ferric maltol is considered to be fully justified since evidence from non-clinical and clinical studies has demonstrated that ferric maltol is not systemically absorbed and is simply a different way of delivering the active moiety, namely iron, to the primary transport and distribution proteins in the blood and tissues, transferrin and ferritin. Maltol is rapidly glucuronidated and is excreted in the urine. | **General safety pharmacology**<br><br>The pharmacological profile of oral iron, in particular ferrous products, is well known. Effects seen in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. The safety data collected to date suggests that Feraccru® would not be a hazard to humans under the recommended conditions of use. |
| **Mechanisms for drug interactions**<br><br>Non-clinical drug-drug interaction studies have not been performed. Ferric maltol is designed to deliver iron to the GI tract when administered orally. The ferric maltol complex is a novel delivery system to provide the existing active substance, ferric iron, in the proximal duodenum for delivery to the intestinal enterocytes; it therefore, does not require evaluation for its potential to induce pharmacodynamic drug interactions. Pharmacokinetic data indicate that the maltol component of ferric maltol, having released the iron with which it is complexed, is rapidly glucuronidated and excreted in the urine.<br><br>Hence, the potential for pharmacodynamic drug interactions or interactions with other metals, e.g. aluminium, with maltol would appear to be very limited. | **Mechanisms for drug interactions**<br><br>Other iron preparations interact with many other drugs with chelating properties, such as the tetracyclines.<br><br>Limited interaction studies have been performed with Feraccru® to date. To minimise the potential for drug interactions, Feraccru® capsules should be taken on an empty stomach. |
| **Other toxicity-related information or data** | **Other toxicity-related information or data**<br><br>The data in normal volunteers, at the high dose of 180 mg (iron), and at the proposed |

| Key safety findings (from non- clinical studies) | Relevance to human usage |
|---|---|
| | therapeutic daily dose of 60 mg in ferrous iron intolerant patients, although limited, suggest that the lack of observed toxicity to the gastro-intestinal tract in the non-clinical toxicity studies may translate to a better tolerated iron product in humans. |

Overall, the non-clinical data indicate that Feraccru® is likely to be safe for use in man at the intended therapeutic dose.

# Part II: Module SIII - Clinical trial exposure

Clinical safety data are provided from the pivotal phase III efficacy and safety study, from the protocols ST10-01-301 (AEGIS 1) and ST10-01-302 (AEGIS 2), 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 one clinical study report (Clinical study report 2, 2015 [CSR2]) and will be presented in this risk management plan. The total number of patients treated with Feraccru® (double-blind plus open-label phases) was 111. Additionally, this pivotal study included a PK sub-study [ST10-01-102] in which some safety endpoints were measured.

Safety data was also collected in a prospective PK study [ST10-01-101], an open-label, randomised, single and repeat dose, parallel group study to evaluate the pharmacokinetics of Feraccru® at three dosage levels (30, 60 and 90 mg for 7 days) in subjects with iron deficiency (with or without anaemia). In this study, the total number of subjects treated with Feraccru® was 24; nine with 30 mg twice daily (bid), eight with 60 mg bid and seven with 90 mg bid.

The safety data from ST10-01-301, ST10-01-302, ST10-01-101, ST10-01-102 are supported by three 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. Subjects were randomised to Feraccru® capsules (60 mg iron three times a day [tid]) or ferrous sulphate tablets (60 mg iron tid). 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, Data on file]. Harvey et al, 1998 studied the safety of Feraccru® capsules (30 mg bid) in 24 IDA patients. These data have shown that Feraccru® can correct iron deficiency with a low incidence of side effects in subjects with ferrous sulphate intolerance. A daily dose of 60 mg iron daily is well tolerated in volunteers and subjects, including those previously intolerant to oral forms of iron, with low incidence of GI side effects compared to oral ferrous products. Overall, doses of Feraccru® of 10 mg, 30 mg, 60 mg and 90 mg dosed twice daily have been examined.

The two pivotal safety and efficacy studies (ST10-01-301 and ST10-01-302) were performed in four EU countries (United Kingdom, Germany, Hungary and Austria). These two placebo-controlled, multicentre, double blind, randomised, Phase 3 studies were designed to determine the safety and efficacy of Feraccru® in patients with IDA and quiescent IBD (ulcerative colitis [UC] and Crohn's disease [CD]), who are unsuitable for treatment with oral ferrous products and were fully compliant with GCP. Subjects were randomised to receive either 30 mg Feraccru® bid or matched placebo control for 12 weeks. Following completion of the 12-week controlled part of the study available subjects were switched to Feraccru® 30 mg bid open–label treatment for a further 52 weeks.

Following regulatory agency agreement that the analysis of a single combined dataset from both studies (ST10-01-301 and ST10-01-302) would be scientifically and statistically valid, the MAH integrated the analysis plan. Safety data presented in this RMP are taken from the completed double-blind phase and from the open-label phase [AEGIS CSR 2, 2015]. In addition, the combined dataset has been reanalysed for the primary efficacy endpoint, according to the IBD diagnosis in the study subjects [Post-hoc Analysis Report]. The MAA consisted of a full set of efficacy and safety data from the 12-week double-blind phase of the studies and the 52-week, open-label extension phase. These two studies will be referred to as the pivotal studies throughout this RMP. Following on from the two pivotal studies, two more clinical trials performed by Shield TX (UK) Limited were completed: ST10-01-303 study titled 'A Phase 3, Randomized, Placebo Controlled, Prospective, Multicentre Study with Oral Ferric Maltol for the Treatment of Iron Deficiency Anaemia in Subjects with Chronic Kidney Disease' was completed on 05 April 2019 and ST10-01-304 study titled 'A phase 3b, randomized, controlled, multicentre study with oral ferric maltol (Feraccru) or intravenous iron (ferric

carboxymaltose; FCM), for the treatment of iron deficiency anaemia in subjects with inflammatory bowel disease' was completed on 25 Jun 2019.

In the pivotal studies, Feraccru® was tested in both genders and in a range of ages, starting from 18 years. Of the 64 subjects randomised to Feraccru® and 64 to placebo in the double-blind phase, 49 and 47 entered the open-label phase. A total of 73 subjects completed the open-label phase. The total number of patients treated with Feraccru® (double-blind plus open-label phases) is 111 [AEGIS CSR 2, 2015].

The efficacy results showed no apparent influence by age or gender of the participants. Feraccru® had a good safety profile as demonstrated by its benign adverse event (AE) profile generally and 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 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 and abdominal pain were considered possibly related to treatment and occurred more frequently following Feraccru® administration. There were no serious adverse events (SAEs) related to Feraccru®. A marked improvement in the overall haematological laboratory profile was evident after 12 weeks of Feraccru® treatment [AEGIS clinical study report, 2014; AEGIS CSR 2, 2015]. The profile of AEs in the open-label phase was comparable to that of Feraccru®-treated subjects in the double-blind phase. The most common Treatment Emergent Adverse Events (TEAEs) (>5%) in the open-label phase were GI-related such as abdominal pain, ulcerative colitis, Crohn's disease, diarrhoea, flatulence, and nausea but also contained 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 ST10 and 25 (53.2%) for those previously treated with Placebo. In the cumulative data set, the most common TEAEs were as well 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 ST10 treatment. The SCCAI and CDAI demonstrated that ST10 did not exacerbate IBD symptoms over the 12-week double-blind treatment period or during open-label treatment.

One long-term follow-up non-interventional study was completed in June 2018 and the final Clinical Study Report was released, following approval of Version 8 of the RMP, on 18 December 2019:

| | |
|---|---|
| Study number | ST10-01-401 |
| Study period | 01 August 2017 to 06 June 2018. |
| Study objectives | Primary: To describe the percentage of patients with normalised haemoglobin (Hb) levels at 12 weeks after initiation of Feraccru®.<br><br>Secondary:<br>• To describe the clinical outcomes associated with the use of Feraccru®in the real world, including:<br>○ Change in Hb levels at 4 and 12 weeks after initiation of Feraccru®;<br>○ Time to normalisation of Hb levels after initiation of Feraccru®;<br>○ Change in serum ferritin levels at 4 and 12 weeks after initiation of Feraccru®; |

| | |
|---|---|
| | ○ Percentage of patients with normalised ferritin levels at 12 weeks after initiation of Feraccru®;<br>○ Time to correction of serum ferritin levels after initiation of Feraccru®;<br>○ Change in transferrin saturation at 4 and 12 weeks after initiation of Feraccru®;<br>○ Percentage of patients with normalised transferrin saturation at 12 weeks after initiation of Feraccru®;<br>○ Time to correction of transferrin saturation after initiation of Feraccru®.<br><br>• To describe the characteristics of patients receiving Feraccru® in the real world, including:<br>○ Age;<br>○ Sex;<br>○ Type of IBD;<br>○ Haematology and biochemistry parameters at baseline (the baseline is defined as the date of Feraccru® initiation);<br>○ Time from diagnosis of IBD to initiation of Feraccru®;<br>○ Time from diagnosis of IDA to initiation of Feraccru®;<br>○ Iron treatment history during the 2 years before initiation of Feraccru®;<br>○ Reason(s) for discontinuing each prior oral ferrous product during the 2 years before initiation of Feraccru®;<br>○ Reason(s) for initiating Feraccru®;<br>○ Percentage of patients discontinuing Feraccru®;<br>○ Reason(s) for discontinuing Feraccru®;<br>Type, severity and time of adverse events related to and caused by (in the clinician's opinion) Feraccru®, from initiation of Feraccru®. |
| Methodology | An observational, multi-centre cohort study was conducted in seven secondary care gastroenterology centres in the UK.<br><br>Patients who were prescribed Feraccru® in routine practice were identified by their care team, approached and asked to provide consent to allow their medical records to be used in the study. There were no changes to the management of patients as a result of taking part in the study. No additional patient investigations or tests were required.<br><br>The observation period was defined as 12 weeks after initiation of Feraccru® (permitting a window from 10 to 16 weeks to allow for variation in timing of routine '12 week' clinic visits). |
| Number of patients | 59 |
| Diagnosis and main criteria for inclusion | Inclusion criteria:<br>• Male and female patients aged ≥18 years at the time of initiation. |

| | |
|---|---|
| | • Patients presenting with mild-to-moderate IDA secondary to either Crohn's disease (CD) or ulcerative colitis (UC), defined as:<br>○ Hb ≥9.5 g/dL and <12.0 g/dL in females;<br>○ Hb ≥9.5 g/dL and <13.0 g/dL in males;<br>○ Serum ferritin concentration <30 µg/L or transferrin saturation of <20%. |
| Summary of conclusions | |
| Key findings | • The mean age of the patients in the study was 42.9 (standard deviation [SD] 17.7) years, with 64% (38/59) of the sample being female and the remaining 36% (21/59) male.<br>• Forty-seven per cent (28/59) of patients were diagnosed with CD, 47% (28/59) with UC and 5% (3/59) with unspecified IBD.<br>• Primary endpoint: of 59 patients, 30 (51%) patients had Hb measurements at baseline and 12 weeks after initiation of Feraccru® (permitted window for '12 weeks': 10–16 weeks); 63% (19/30) of these patients had normalised Hb at 12 weeks.<br>• Median time to normalisation of Hb was 46.0 (IQR: 26.5 to 46.0) days.<br>• The mean change in Hb from baseline to 12 weeks was +1.4 (SD 1.7) g/dL (n=30).<br>• At 12 weeks, 51% (30/59) of patients were ongoing with Feraccru® treatment, 24% (14/59) of patients had discontinued treatment and a further 25% (15/59) had stopped, with the date of discontinuation unknown.<br>• The most common reason for treatment discontinuation was abdominal pain, reported in 12% (7/59) of patients. |
| Conclusion | Since its launch in 2016, Feraccru® has been used in a number of secondary-care gastroenterology centres in the UK for the treatment of IDA in patients with IBD. Clinical studies had previously demonstrated its efficacy, tolerability and pharmacodynamics in clinical trial populations. However, there was a lack of data regarding the real-world treatment of IDA in patients with IBD, and in particular, relating to Feraccru®.<br><br>This study provides valuable data relating to the early use of Feraccru® in UK routine clinical practice. The findings are broadly supportive of the results from clinical trials and contribute to a better understanding about the treatment and outcomes of this patient population in real-world clinical practice. |
| Date of final study report | 18 December 2019 |

Two clinical trials performed by Shield TX (UK) Limited were completed following approval of Version 8 of the RMP:

ST10-01-303 study titled *'A Phase 3, Randomized, Placebo Controlled, Prospective, Multicentre Study with Oral Ferric Maltol for the Treatment of Iron Deficiency Anaemia in Subjects with Chronic Kidney Disease'.*

A summary of this trial is provided in the following table. No new signals or risks arose from this study.

| | |
|---|---|
| Study number | ST10-01-303 |
| Study period | 01 December 2016 to 10 October 2018 |
| Phase of development | 3 |
| Study objectives | Primary: The primary objective of the study was to evaluate the efficacy of oral ferric maltol compared with placebo in the treatment of iron deficiency anaemia (IDA) in subjects with chronic kidney disease (CKD) at 16 weeks.<br><br>Secondary: The secondary objective of the study was to evaluate the efficacy, safety, tolerability, and pharmacokinetics (PK) of ferric maltol in subjects with IDA and CKD over a treatment duration of up to 52 weeks. |
| Methodology | This was a Phase 3, randomized, double-blind, placebo-controlled, prospective, multicentre study. |
| Number of patients | 167 |
| Diagnosis and main criteria for inclusion | Subjects ≥18 years old with chronic kidney disease with an eGFR of ≥15 mL/min/1.73m$^2$ and <60 mL/min/1.73m$^2$, which was calculated using the abbreviated version of the modified diet in renal disease equation and assessed via screening laboratory results. |
| Test product, dose and mode of administration, batch number | Double-blind 16-week treatment period: Ferric maltol (ST10) capsules bid 30 mg: lot number B14423; matching placebo: lot number B14430.<br><br>Open-label 36-week treatment period: Ferric maltol (ST10) capsules bid 30 mg: lot numbers B14543 and B17803. |
| Summary of conclusions | |
| Efficacy results | This study evaluated the effect of oral ferric maltol during both a double-blind 16-week treatment period and an open-label 36-week treatment period in subjects with CKD and IDA. This study showed a statistically significant effect of treatment with ferric maltol on the primary efficacy parameter, change in Hb concentration at Week 16. It is clinically meaningful that the Hb concentration increased during the double-blind 16-week treatment period in the ferric maltol group compared to the placebo group. |
| Safety results | In total, 117 (70.1%) subjects had a TEAE during the double-blind 16-week treatment period: 75 (67.6%) subjects in the ferric maltol |

| | |
|---|---|
| | group and 42 (75.0%) subjects in the placebo group. Thirty-five (21.0%) subjects experienced SAEs: 23 (20.7%) subjects in the ferric maltol group and 12 (21.4%) subjects in the placebo group. In total, 111 (88.8%) subjects experienced a TEAE during the open-label 36-week treatment period: 76 (88.4%) subjects originally from the ferric maltol group and 35 (89.7%) subjects originally from the placebo group. Thirty-six subjects experienced SAEs: 27 (31.4%) subjects originally from the ferric maltol group and 9 (23.1%) subjects originally from the placebo group.<br><br>The most common system organ classes of TEAEs during the double-blind 16-week treatment period were gastrointestinal (GI) disorders (62 [37.1%] subjects): 45 (40.5%) subjects in the ferric maltol group and 17 (30.4%) subjects in the placebo group; and metabolism and nutrition disorders (34 [20.4%] subjects): 21 [18.9%] subjects in the ferric maltol group and 13 [23.2%] subjects in the placebo group. The most common system organ classes of TEAEs during the open-label 36-week treatment period were GI disorders (66 [52.8%] subjects): 48 (55.8%) subjects originally from the ferric maltol group and 18 (46.2%) subjects originally from the placebo group; and infection and infestations (58 [46.4%] subjects): 39 (45.3%) subjects originally from the ferric maltol group and 19 (48.7%) subjects originally from the placebo group.<br><br>The most common system organ class of study drug-related TEAEs during the double-blind 16-week treatment period was gastrointestinal (GI) disorders (24 [14.4%] subjects): 20 (18.0%) subjects in the ferric maltol group and 4 (7.1%) subjects in the placebo group. The most common system organ class of study drug-related TEAEs during the open-label 36-week treatment period was GI disorders (21 [16.8%] subjects): 14 (16.3%) subjects originally from the ferric maltol group and 7 (17.9%) subjects originally from the placebo group.<br><br>Two subjects died during the double-blind 16-week treatment period; both deaths were considered unrelated to study drug by the Investigator. There were no study drug-related deaths during the open-label 36-week treatment period. |
| Conclusion | Ferric maltol resulted in clinically and statistically significant increases in Hb compared to placebo during the double-blind 16-week treatment period. Furthermore, the efficacy parameters in subjects originally in the placebo group moving to the ferric maltol group during the open-label 36-week treatment period mirrored the changes seen in the ferric maltol group patients during the double-blind 16-week treatment period.<br><br>In general, ferric maltol was well tolerated with only minor differences in the safety profile and overall GI side effects compared to placebo. |
| Date of final study report | 05 April 2019 |

ST10-01-304 study titled *'A phase 3b, randomized, controlled, multicentre study with oral ferric maltol (Feraccru) or intravenous iron (ferric carboxymaltose; FCM), for the treatment of iron deficiency anaemia in subjects with inflammatory bowel disease'.*

A summary of this trial is provided in the following table. No new signals or risks arose from this study.

| | |
|---|---|
| Study number | ST10-01-304 |
| Study period | 21 January 2016 to 02 January 2019 |
| Phase of development | 3b |
| Study objectives | Primary Objective: To compare the efficacy of ferric maltol and IV iron (ferric carboxymaltose [FCM]) in the treatment and maintenance of IDA in subjects with IBD.<br><br>Secondary Objectives:<br><br>To evaluate the safety and tolerability of ferric maltol and IV iron in subjects over a treatment duration of up to 52 weeks.<br><br>To evaluate long-term healthcare resources utilised in the management of IDA in IBD. |
| Methodology | This was a randomised, open-label, controlled, multicentre Phase 3b study to assess the efficacy, safety, and pharmacoeconomic (PE) impact of oral ferric maltol compared to IV iron (FCM) for the treatment of IDA in adult subjects with IBD. |
| Number of patients | 250 |
| Diagnosis and main criteria for inclusion | Subjects aged ≥18 years with a confirmed diagnosis of IBD and having an IDA, defined as Hb ≥8.0 g/dL and ≤11.0 g/dL for women or a Hb ≥8.0 g/dL and ≤12.0 g/dL for men and with ferritin <30 ng/mL or ferritin <100 ng/mL with transferrin saturation (TSAT) <20%, were eligible for the trial. |
| Test product, dose and mode of administration, batch number | Ferric maltol 30 mg capsules for oral intake twice daily (bid) Batch numbers (expiry date): B12663 (30 Jun 2017); B16167 (31 Mar 2018); B17462 (31 Mar 2018); B18224 (28 Feb 2019); B18322 (28 Feb 2019); B19740 (31 Jan 2020). |
| Summary of conclusions | |
| Efficacy results | The primary efficacy endpoint was the proportion of subjects achieving either a 2 g/dL increase in Hb or normalisation of Hb (>12 g/dL women, >13 g/dL men) at Week 12. The responder rate at Week 12 was lower in the ferric maltol group than in the IV iron group (67% vs. 84%).The results of the primary hypothesis testing in the PP using an OC approach showed that the risk difference in the responder rates of -0.17 (95% CI: -0.28, -0.06; p-value: 0.298) was outside the pre-defined non-inferiority margin of 20% (i.e. |

| | |
|---|---|
| | difference of <-0.2), thus demonstrating that non-inferiory of ferric maltol to IV iron was not met.<br><br>The key secondary efficacy endpoint was CFB in Hb concentration at Week 12 and resulted in an overall mean of 2.75 g/dL.The LSM CFB in Hb concentration at Week 12 was smaller in the ferric maltol group than in the IV iron group with an LSM difference of -0.61 g/dL (95% CI: -1.00, 0.23; p-value: 0.002) between the ferric maltol group and the IV iron group. The results of the ANCOVA testing showed a larger increase in Hb in the IV iron group than in the ferric maltol group. Similar results were observed for LSM CFB in Hb concentration at Week 4 in the Intention To Treat (ITT [Multiple Imputation]) and re-evaluated per protocol (PP [Observed Case {OC}]). |
| Safety results | Overall, 118 subjects (48%) reported at least 1 TEAE. The proportion of subjects with at least 1 TEAE during the trial was higher in the ferric maltol group than in the IV iron group (59% vs. 36%). The most frequently reported TEAEs in subjects overall by SOC were gastrointestinal disorders (22%) and infections and infestations (21%). The most frequently reported TEAEs in subjects overall by preferred term (PT) were abdominal pain (6%), nasopharyngitis (6%), and abdominal pain upper (4%). Most subjects reported TEAEs of mild or moderate intensity.<br><br>Thirty two subjects (13%) reported at least 1 TEAE assessed as related to investigational medicinal product (IMP) by the investigators. More subjects experienced at least 1 IMP-related TEAE in the ferric maltol group than in the IV iron group (20% vs. 6%). The most frequently reported IMP-related TEAEs in subjects overall by SOC was gastrointestinal disorders (10%). The most frequently reported IMP-related TEAEs in subjects overall by PT were abdominal pain (2%), nausea (2%), and abdominal pain upper (2%). All other SOCs and PTs were reported in ≤1% of subjects.<br><br>For most subjects, no action was required with the study drug. More subjects in the ferric maltol group than in the IV iron group required dose interruptions (9% vs. 2%) or dose discontinuation (10% vs. <1%). One subject receiving ferric maltol died during the course of the study due to natural causes (reported term: natural death); the event was not related to study treatment. |
| Conclusion | This was a Phase 3b study to compare ferric maltol with IV iron in correcting IDA in patients with IBD. In the post hoc analysis for CSR version 2.0, in both study groups, the Hb of subjects increased from baseline to the primary evaluation at Week 12, however ferric maltol did not achieve the primary endpoint of showing non-inferior response compared to IV iron in the re-evaluated PP and ITT populations. This study continued treatment for up to 52 weeks with ferric maltol and IV iron and over the longer treatment duration the response rates of the two treatments were very similar. The safety profile of ferric maltol in this study was consistent with that shown in earlier IBD studies, with no new safety signals. The post hoc |

| | |
|---|---|
| | analysis for CSR version 2.0 and the original analysis for CSR version 1.0 of this study showed that although in the first 12 weeks of treatment IV iron resulted in a quicker response than ferric maltol, ferric maltol was as effective as IV iron in correcting IDA in patients with IBD during longer term treatment whereby ferric maltol maintained Hb in majority of subjects, similar to IV iron when subjects were re-dosed. |
| Date of final study report | 30 Sep 2020 (V2.0) |

Another Phase 1 study was completed on 13 Nov 2020 and the final Clinical Study Report was released in Mar 2021, following approval of Version 9 of the RMP. This study is summarized below:

ST10-01-104 "A Randomized, Open-Label, Single Dose, 4-Way Crossover, Phase 1 Study to Compare the Pharmacokinetics of Ferric Maltol Capsules and Oral Suspension Under Fasted and Fed Conditions in Adult Healthy Volunteers" sponsored by Shield completed on 13-Nov-2020 and results are provided below:

This pharmacokinetic (PK) study compared ferric maltol capsules and suspension formulations under fasted and fed conditions. The study found that both formulations were readily absorbed, with the capsule form showing higher serum iron concentrations in the fasted state. Food intake delayed absorption for both formulations. While some differences in PK parameters were observed between formulations and feeding states, the overall PK profiles were generally similar. There were no study drug-related TEAEs. There were no SAEs, serious TEAEs, or TEAEs leading to discontinuation of study drug, discontinuation from the study, or death. Ferric maltol was safe and well-tolerated after a single dose of 30 mg administered as a capsule or oral suspension in fasted and fed conditions in healthy adult subjects. Overall, no clinically significant safety findings.

**Duration of treatment**

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 at the time of data lock for the described in the interim safety report. 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 of 219.8 days [AEGIS CSR 2, 2015]. The duration of exposure in person time for ST10-01-301/302 double blind phase is 4883 days and 38127 days for the cumulative data including the open label phase.

From study ST10-01-303, overall, 150 subjects received ferric maltol during both treatment periods of the study. Sixty (35.9%) subjects were exposed for a duration of 26 to <52 weeks and 48 (28.7%) subjects were exposed for a duration of >52 weeks.

From study ST10-01-304, most of the randomised subjects (247 of 250 randomised subjects) were treated either with ferric maltol or IV iron. The mean (SD) treatment duration (defined as [day of last dose – day of first dose] +1) was 30.2 (17.94) weeks in the ferric maltol group. IV iron was dosed intermittently and the duration of treatment is therefore not appropriate.

From study ST10-01-401, overall, 59 subjects received Feraccru®. The observation period was defined as 12 weeks after initiation of Feraccru® (permitting a window from 10 to 16 weeks to allow for variation in timing of routine '12 week' clinic visits).

Duration of treatment for IDA is dependent on the individual patient's response to therapy. Since treatment responses are so patient-specific and variable it would be hard to access this trend in the population.

**Table SIII.1: Duration of exposure**

| **Inflammatory Bowel Disease**<br>**Data from ST10-01-301/302 double-blind phase** | | |
|---|---|---|
| **Duration of exposure (weeks)** | **Patients** | **Person time (days)** |
| 0 to <1 | [redacted] | 5 |
| 1 to <4 | 4 | 75 |
| 4 to <12 | 19 | 1421 |
| 12 to <26 | 40 | 3382 |
| **Total person time for indication** | **4883** | |

Source: Manual extraction from Listing 16.2.5.1.

| **Inflammatory Bowel Disease**<br>**Data from ST10-01-301/302 double-blind and open label phase** | | |
|---|---|---|
| **Duration of exposure (weeks)** | **Patients** | **Person time (days)** |
| 0 to <1 | [redacted] | 6 |
| 1 to <4 | 6 | 649 |
| 4 to <12 | 6 | 439 |
| 12 to <26 | 20 | 2718 |
| 26 to <52 | 13 | 5224 |
| >52 | 65 | 29091 |
| **Total person time for indication** | **38127** | |

Source: Post-hoc Analysis June 2015, Table PH14.3 Q15.5

| **Chronic Kidney Disease**<br>**Data from ST10-01-303 double-blind and open label phase** | |
|---|---|
| **Duration of exposure (weeks)** | **Patients** |
| 0 to <1 | [redacted] |
| 1 to <4 | 8 |
| 4 to <12 | 19 |
| 12 to <26 | 14 |
| 26 to <52 | 60 |
| >52 | 48 |
| **Total** | **150** |

Source: Clinical Study Report ST10-01-303, Post-text Table 14.1.9.3

| **Inflammatory Bowel Disease**<br>**Data from ST10-01-304** | | | | |
|---|---|---|---|---|
| **Duration of exposure (weeks)** | **Statistic** | **Ferric Maltol** | **IV Iron** | **Total** |
| | n | 127 | 120 | 247 |
| | Mean | 30.2 | 15.5 | 23.1 |
| | SD | 17.94 | 15.6 | 18.36 |
| | Median | 26.1 | 12.1 | 19.3 |
| | Min, Max | 1, 56 | 0, 55 | 0, 56 |

Source: Clinical Study Report ST10-01-304, Post-text Table 14.3.1.3.1

| **Data from studies by Green & Thompson (Data on file) and Harvey et al, 1998** | |
|---|---|
| **Duration of exposure (weeks)** | **Patients** |
| Single dose | 85 |
| >1 dose and <1 | 108 |
| 1 to <4 | 0 |
| 4 to 12 | 43 |
| **Total** | **236** |

Duration of exposure to ferric maltol was evaluated for the ST10-01-301/302 studies, the ST10-01-303/304 studies and the studies by Green & Thompson (Data on file) and Harvey et al, 1998 as outlined in the tables above. A total of 466 subjects and 236 subjects were exposed to ferric maltol in the studies ST10-01-301/302/303/304 and the studies by Green & Thompson (Data on file) and Harvey et al, 1998, respectively.

**Age and gender**

In the two pivotal studies, men and women, including women of child-bearing potential, 18 years and over were included. In these studies, the efficacy and safety of Feraccru® for the treatment of IDA in IBD has been evaluated in 128 subjects (age range 18-76 years; 45 males and 83 females) with IBD (58 with UC and 70 with CD) [AEGIS CSR 2, 2015]. In the double blind and open label phase of the study ST10-01-301/302 female subjects (70) were more numerous than male subjects (41) with a patient time of 24794 and 13333 days, respectively. In total, 111 received FERACCRU®. In the post-hoc subgroup analysis, there was no difference in results between subjects <60 years of age and those older than 60 years [Post-hoc Analysis Report]. There were four male and one female subject in the age of 65 or older. Planned sub-group analyses indicated that there was no apparent age or gender effect on the extent of Hb response to ST10.

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 patients with anaemia (no IBD) and three healthy subjects [Murray data on file]. The mean age of the anaemic patients was 74 ± 7 years, and the mean age of the healthy subjects was 84 ± 7 years. One of the patients with anaemia was administered the 10 mg ferric maltol and an equivalent dose of ferrous sulphate (10 mg as iron) on consecutive days. Iron formulations were administered after an overnight fast. Serum iron was assayed at baseline and at 1 and 2 hours post-dose. Overall, the results of this study were not substantially different from other studies that examined iron absorption from ferric maltol in younger healthy volunteers or younger patients with IDA. It is considered that the adverse events seen in older patients would typically be the same as those in younger patients.

From study ST10-01-303, the mean age of subjects was 67.4 years and the age category of 65 to 74 years had the most subjects (34.7%). The majority of subjects were female (70.1%). The treatment groups were comparable with respect to demographic characteristics.

From study ST10-01-304, demographic characteristics for the PP were generally comparable between groups, except for the lower proportion of women in the ferric maltol group than in the IV iron group (69% vs. 53%). The overall mean age was 40.2 years and there were more women than men (61% vs. 39%). The difference in gender was more pronounced in the IV iron group (69% vs. 31%) whereas the ferric maltol group had a comparable distribution of women and men (53% vs. 47%). The ITT was comparable with the PP.

**Table SIII.2: Age group and gender**

| By age group and gender (Inflammatory Bowel Disease)<br>Data from ST10-01-301/302 double-blind and open label phase | | | | |
|---|---|---|---|---|
| **Age group** | **Patients** | | **Person time** | |
| | **M** | **F** | **M** | **F** |
| Age group <65 | 37 (90.2%) | 69 (98.6%) | 11797 | 24744 |
| Age group 65-74 | [redacted](4.9%) | 0 | 631 | 0 |
| Age group 74-84 | [redacted](4.9%) | [redacted](1.4%) | 905 | 50 |
| Age group >85 | 0 | 0 | 0 | 0 |
| **Total** | **41(100.0%)** | **70(100.0%)** | **13333** | **24794** |

| By age group<br>Data from ST10-01-303 double-blind and open label phase | |
|---|---|
| **Age group** | **Patients** |
| 18-39 years | 4 (3.6%) |
| 40-64 years | 30 (27%) |
| 65-74 years | 36 (32.4%) |
| 74-84 years | 34 (30.6%) |
| >85 years | 7 (6.3%) |
| **Total** | **111 (100%)** |

Source: Clinical Study Report ST10-01-303, Post-text Table 14.1.4

| By gender<br>Data from ST10-01-303 double-blind and open label phase | |
|---|---|
| **Gender** | **Patients** |
| Female | 78 (70.3%) |
| Male | 33 (29.7%) |
| **Total** | **111 (100%)** |

Source: Clinical Study Report ST10-01-303, Post-text Table 14.1.4

| By age group<br>Data from ST10-01-304 | | | | |
|---|---|---|---|---|
| **Age (years)** | **Statistic** | **Ferric Maltol** | **IV Iron** | **Total** |
| | n | 125 | 125 | 250 |
| | Mean | 40 | 40.4 | 40.2 |
| | SD | 14.58 | 15.54 | 15.04 |
| | Median | 38.0 | 38.0 | 38.0 |
| | Min, Max | 18, 81 | 19, 77 | 18, 81 |

Source: Clinical Study Report ST10-01-303, Post-text Table 14.1.4

| By gender<br>Data from ST10-01-304 double-blind and open label phase | | | |
|---|---|---|---|
| **Gender** | **Ferric Maltol** | **IV Iron** | **Total** |
| Female | 57 (46%) | 48 (38%) | 105 (42%) |
| Male | 68 (54%) | 77 (62%) | 145 (58%) |
| **Total** | **125 (100%)** | **125 (100%)** | **250 (100%)** |

Source: Clinical Study Report ST10-01-303, Post-text Table 14.1.4

**Dose**

Exploratory clinical data suggested that 60 mg/day (iron) of ferric maltol is sufficient to correct iron deficiency in patients with IDA and ferrous sulphate intolerance [Harvey 1998].

The safety and efficacy of this dose (30 mg bid i.e. 60 mg/day iron) was confirmed in the two pivotal studies. In the 64 subjects treated with Feraccru 30 mg BID in both the double-blind and open-label phases of the pivotal studies, the total dose of Feraccru® received was median 23340.0 mg and mean 17703.8 mg with a person time of 4883 days. For the 47 subjects treated with placebo during the double-blind phase and Feraccru® in the open-label phase, the total dose of Feraccru® received was median 21240.0 mg and mean 17493.2 mg with a person time of 38127 days [AEGIS clinical study report 2, 2015].

Studies ST10-01-303 and 304 also followed the 30 mg bid dosing regimen.

It should be noted that daily doses of 60 mg iron are well within the range of current dosing recommendations for marketed iron products [Guidelines IDA 2011].

**Table SIII.3: Dose**

| By dose (Inflammatory Bowel Disease)<br>Data from ST10-01-301/302 double-blind phase | | |
|---|---|---|
| **Dose of exposure** | **Patients** | **Person time** |
| Dose level (30 mg bid) | 64 | 4883 |
| **Total** | 64 | 4883 |

Source: Manual extraction from Listing 16.2.5.1.

| By dose (Inflammatory Bowel Disease)<br>Data from ST10-01-301/302 double-blind and open label phase | | |
|---|---|---|
| **Dose of exposure** | **Patients** | **Person time** |
| Dose level (30 mg bid) | 111 | 38127 |
| **Total** | 111 | 38127 |

Source: Post-hoc Analysis June 2015, Table PH14.3 Q15.5

| By dose (Chronic Kidney Disease)<br>Data from ST10-01-303 double-blind and open label phase | | |
|---|---|---|
| **Dose of exposure** | **Patients** | **Mean Person time (days)** |
| Dose level (30 mg bid) | 150 | 40,560 |
| **Total** | 150 | 40,560 |

Source: Clinical Study Report ST10-01-303, Post Text Table 14.1.9.2

| By dose (Inflammatory Bowel Disease)<br>Data from ST10-01-304 double-blind and open label phase |
|---|

| Dose of exposure | Patients | Mean Person time (days) |
|---|---|---|
| Dose level (30 mg bid) | 127 | 26,847.8 |
| **Total** | 127 | 26,847.8 |

Source: Clinical Study Report ST10-01-304, Post Text Table 14.3.1.3.1

| **By dose (Inflammatory Bowel Disease)**<br>**Data from studies by Green & Thompson (Data on file) and Harvey et al, 1998** | |
|---|---|
| **Dose of exposure** | **Patients** |
| Dose level 10 mg/day | 60 |
| Dose level 30 mg/day | 42 |
| Dose level 60 mg/day | 22 |
| Dose level 100 mg/day | 3 |
| Dose level >100 mg/day | 109 |
| **Total** | 236 |

**Race and ethnicity**

The majority of patients treated with Feraccru® in the two pivotal clinical studies were of non-Hispanic/Latino white origin [AEGIS CSR 2 2015].

From study ST10-01-303, the majority of subjects were not Hispanic or Latino (75.4%), and White (73.7%). The treatment groups were comparable with respect to demographic characteristics.

From study ST10-01-304, demographic characteristics for the PP were generally comparable between groups. Most of the subjects were White (91%) and not Hispanic or Latino (77%).

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.

**Table SIII.4: Ethnic origin**

| **By ethnic or racial origin (Inflammatory Bowel Disease)**<br>**Data from ST10-01-301/302 double-blind and open label phase** | | |
|---|---|---|
| **Ethnic origin** | **Patients** | **Person time** |
| Hispanic or Latino | 0 | 0 |
| Not Hispanic or Latino | 107 (96.4%) | 37331 |
| Unknown | 4 (3.6%) | 796 |
| Total | 111 (100%) | 38127 |

Source: Post-hoc Analysis June 2015, Table PH14.3 Q15.4

| By ethnic or racial origin<br>Data from ST10-01-303/304 double-blind and open label phase | |
|---|---|
| **Ethnicity** | **Patients** |
| Hispanic or Latino | 41 |
| Not Hispanic or Latino | 183 |
| Not reported | 9 |
| Unknown | 3 |
| **Total** | **236** |
| **Race** | |
| Asian | [redacted] |
| American Indian or Alaska Native | [redacted] |
| Black or African American | 29 |
| Native American/ Pacific Islander | [redacted] |
| White | 191 |
| Other | 12 |
| **Total** | **236** |

Source: Clinical Study Report ST10-01-303, Post-text Table 14.1.4 and Clinical Study Report ST10-01-304, Post-text Table 14.1.2.1

**Pregnancy and lactation**

Women of child-bearing potential were included in the two pivotal studies (and studies ST10-01-303 and 304) providing they were using an acceptable and reliable form of contraception throughout the study period and up to four weeks after their final study visit. Pregnant or lactating females were excluded from both studies. No pregnancies were reported during the double-blind or open-label phases of the studies.

One pregnancy was reported during the open-label PK study [Study ST10-01-101]. After study completion, the Sponsor was notified that one subject had apparently been in the early stages of pregnancy during the study, although urine pregnancy tests performed during the study had been negative. The subject received Feraccru® 30 mg bid and was taking the contraceptive Belara® (chlormadinone acetate/ethinylestradiol). The subject had had no previous pregnancies. At the time of the study report, the pregnancy was ongoing, with an estimated expected date of delivery of 27 January 2015. As per the study protocol, subject informed consent and Feraccru® pharmacovigilance plan, a pregnancy monitoring form will be used by the Investigator to provide further follow-up information on the pregnancy/outcome. The subject gave birth on 28 January 2015. Mother and infant status were both normal; no congenital anomalies or birth defects were noted.

There was also a case of pregnancy in a [redacted] female subject with Crohn's disease in study ST10-01-302. Relevant concomitant medications were azathioprine and mesalazine. Study medication (ST10) started on 31 January 2013 and on 25 April 2013 the subject attended the first open-label visit, and the pregnancy test on this date was negative. On 29 April 2013, the subject performed a pregnancy test which was positive. On 30 April 2013, a urine pregnancy test was conducted at the study site which was also positive. The subject was withdrawn from the study. On 06 January 2014, the subject gave birth to a healthy infant; Apgar score was recorded 10/10.

There was also a case of pregnancy from study ST10-01-304. This [redacted] woman was diagnosed with iron deficiency anaemia and Crohn's disease. The subject was randomised to receive IV iron. On Day 84, the subject had a positive pregnancy test. According to the subject, she was

using a double barrier method. At the time of the report, no complications were reported. The expected delivery date was after the end of the trial. The subject did not consent to pregnancy monitoring, however the outcome was a healthy baby delivered at 40 weeks gestation via caesarean section. The subject completed the study according to the protocol. No subjects became pregnant during study ST10-01-303.

To date, there are no data from the intended use of Feraccru in pregnant women or on the effect of Feraccru® on fertility. Feraccru® is not systemically available and dissociates into iron and maltol. Non-clinical studies conducted with maltol did not indicate direct or indirect harmful effects with respect to reproductive toxicity and fertility was unaffected (see Part II: Module SII). As a precautionary measure, the proposed summary of product characteristics (SmPC) advises that it is preferable to avoid the use of Feraccru® during pregnancy.

Non-metabolised ferric maltol is not available systemically and is therefore unlikely to pass into the mother's milk. However, no well-controlled clinical studies are available to date. Patients who are breast feeding are advised to speak to their doctor or pharmacist in the proposed patient information leaflet.

**Table SIII.5: Special populations**

| **Special populations (Inflammatory Bowel Disease)<br>Data from ST10-01-301/302/ 303 and 304 double-blind and open label phase** | | |
|---|---|---|
| **Total population** | | |
| | **Patients** | **Mean Person time (days)** |
| Pregnant women | 0 (2)* | 0 |
| Lactating women | 0 | 0 |
| Renal impairment (eGFR of ≥15 mL/min/1.73 $m^2$ and <60 mL/min/1.73 $m^2$,) | 150** | 40,560 |
| Hepatic impairment (specify or categorise) | 0 | 0 |
| Cardiac impairment (specify or categorise) | 0 | 0 |
| Sub populations with genetic polymorphism (specify) | 0 | 0 |
| Immuno-compromised | 0 | 0 |

* One subject became pregnant during the study conduct and was discontinued when diagnosed. The start of the pregnancy could not be defined clearly therefore person time could not be calculated (see detailed explanation in section "Pregnancy and Lactation" above)

** Includes patients who were originally blinded but all have now been switched to ST10 (all patients are now on ST-10)

### Paediatric population

The safety of ferric maltol in the paediatric population was assessed in a Phase 1 (ST10-01-103) and a Phase 3 (ST10-01-305) open-label, randomized studies sponsored by Shield TX (United Kingdom [UK]) Limited. The results from these 2 studies are summarized below.

**Phase 1 study ST10-01-103 titled**: A Phase 1, Open-Label, Randomised, Repeat Dose, Parallel Group Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Ferric Maltol at Three Dosage Levels in Paediatric Subjects Aged 10-17 Years of Age with Iron Deficiency (with or without Anaemia) was completed on 28 Mar 2018 and is summarized below.

The study assessed three dose levels (7.8 mg, 16.6 mg, and 30 mg BID) over 10 days in 37 subjects. Results demonstrated increased iron uptake across all doses through measurement of serum iron

and transferrin saturation (TSAT), with maltol glucuronide showing dose proportionality and serum iron exhibiting less than dose-proportional increases.

In total, 20 (54.1%) subjects experienced a TEAE. Treatment-emergent adverse events were mostly mild, and no subjects experienced a severe TEAE. One (7.7%) subject in the 16.6 mg dose group experienced a TEAE of tonsillitis that led to withdrawal of study drug and study discontinuation; this event was considered by the Investigator to be moderate in severity and not related to study drug. No subjects died or experienced an SAE during the study.

Overall, the study concludes that all 3 doses of ferric maltol (7.8 mg, 16.6 mg, and 30 mg BID) administered over a 10-day period were well tolerated and had a favourable safety profile in this paediatric population.

**Phase 3 study ST10-01-305 titled**: Randomised, open-label, active-controlled, multicentre, comparative study to evaluate the safety and efficacy of ferric maltol (iron (III) maltol complex) (ST10) oral suspension compared to ferrous sulphate oral liquid in children and adolescents aged 2 to 17 years with iron-deficiency anaemia, incorporating a single arm study in infants aged 1 month to less than 2 years completed on 9 Jun 2024 and is summarized below.

The patients aged 2 to <18 with iron deficiency anaemia received ferric maltol as oral suspension, at doses based on age (in patients aged 2-11 years: 15 mg per dose; in patients aged 12 to <18 years: 30 mg per dose) or ferrous sulphate as oral solution (3 mg/kg/dose), both administered twice daily, for 12 weeks. The efficacy endpoints of the study were represented by changes from baseline to week 4 and week 12 in clinically relevant iron markers, such as haemoglobin (Hb) as the primary efficacy endpoint, and ferritin, serum iron and transferrin saturation (TSAT) as the secondary efficacy endpoints. The mean change from baseline Hb appeared to be greater in the ferrous sulphate group at Week 4, but greater in the ferric maltol group at Week 12, there was a general variability observed in the data of these groups, and overall, Hb values remained similar between groups throughout the Treatment Period.

A higher number of patients randomized to ferrous sulphate reported study drug-related TEAEs compared to patients randomized to ferric maltol. The most commonly reported study drug-related SOC was gastrointestinal disorders (3 [10.0%] patients experienced 5 TEAEs in the ferrous sulphate group and 2 [6.5%] patients experienced 4 TEAEs in the ferric maltol group) and the most common PT was nausea (2 [6.7%] patients experienced 2 TEAEs in the ferrous sulphate group and 1 [3.2%] patient experienced 1 TEAE in the ferric maltol group). Overall, ferric maltol was well tolerated in patients aged 1 month to <2 years and in patients aged 2 to 17 years, with similar instances and types of TEAEs reported between the ferric maltol and ferrous sulphate treatment groups. All TEAEs were considered mild or moderate in severity.

The study confirmed that ferric maltol oral suspension improved iron storage levels and was well tolerated in children/adolescents from 1 month to 17 years using the dosage regimen administered in the study.

# Part II: Module SIV - Populations not studied in clinical trials

## SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

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

**a) untreated or untreatable severe malabsorption syndrome or**

**b) immunosuppressant use**

Reason for exclusion: Potential safety and efficacy implications for the patient

Is it considered to be included as missing information?: No

Rationale: Feraccru® is indicated for the treatment of iron deficiency, not anaemia. The RSI states that iron deficiency or iron deficiency anaemia (IDA) diagnosis should be made based on blood tests; it is important to investigate the cause of the iron deficiency and to exclude underlying causes of anaemia other than iron deficiency.

**Renal, hepatic and cardiac impairment**

Reason for exclusion: Potential safety and efficacy implications for the patient

Is it considered to be included as missing information?: No

Rationale: Renal, hepatic and cardiac impairment is not known to occur with Feraccru®. Feraccru® contains iron in a stable ferric state as a complex with a trimaltol ligand. The complex dissociates on uptake from the gastro-intestinal tract and the complex itself does not enter the systemic circulation. Cardiovascular or renal safety of ferric maltol is considered to be fully justified since evidence from non-clinical and clinical studies has demonstrated that ferric maltol is not systemically absorbed and is simply a different way of delivering the active moiety, namely iron, to the primary transport and distribution proteins in the blood and tissues, transferrin and ferritin. Maltol is rapidly glucuronidated and is excreted in the urine.

**Pregnancy and lactation**

Reason for exclusion: Potential safety implications for the patient due to lack of data in this population clinically and non-clinically with ferric maltol.

Is it considered to be included as missing information?: No

Rationale: The missing data is linked to exclusion criteria from the studies. Post marketing data analysis has revealed no safety concerns in pregnant or breast-feeding women.

**Patients with very low haemoglobin levels**

Reason for exclusion: Potential safety implications to the patient. The rate of haemoglobin correction is not known in this population.

Is it considered to be included as missing information?: No

Rationale: The MAH believes that Feraccru® may be administered to patients with HB <9.5 g/dL if the treating physician believes this is appropriate. Very anaemic patients would be managed with a blood transfusion.

**Patients with B12 or folate deficiency**

Reason for exclusion: Potential safety implications for the patient

Is it considered to be included as missing information?: No

Rationale: Feraccru® may still be administered to these patients providing the treating physician is satisfied that their underlying conditions do not jeopardise the safety of the patient. Levels of B12 or folate should be corrected if present in order to gain maximal benefit from Feraccru®.

## SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure. Additionally, the pivotal studies were not designed to formally investigate apparent relationships between response and concomitant therapy (drug interactions) or the occurrence of adverse drug reactions (ADRs) in relation to age. Furthermore, the number of elderly patients included in the pivotal trials was too small to detect any meaningful trend (6/120 patients were >65 years).

## SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

**Table SIV.2: Exposure of special populations included or not in clinical trial development programmes**

| Type of special population | Exposure |
|---|---|
| **Pregnant women** | Not included in the clinical development program.<br>One subject became pregnant during the study conduct and was discontinued when diagnosed. The start of the pregnancy could not be defined clearly therefore person time could not be calculated. Another patient became pregnant and continued the trial, but did not consent to pregnancy monitoring. (See detailed explanation above). |
| **Breastfeeding women** | |
| **Patients with relevant comorbidities:**<br>• Patients with hepatic impairment<br>• Patients with renal impairment<br>• Patients with cardiovascular impairment<br>• Immunocompromised patients<br>• Patients with a disease severity different from inclusion criteria in clinical trials | Not included in the clinical development program. |
| **Population with relevant different ethnic origin** | Not included in the clinical development program. |

| | |
|---|---|
| **Subpopulations carrying relevant genetic polymorphisms** | Not included in the clinical development program. |

# Part II: Module SV - Post-authorisation experience

## SV.1 Post-authorisation exposure

**FERACCRU**

Feraccru® has been launched in the United Kingdom (Jun 2016), Germany (Oct 2016), Austria (March 2017), Sweden (Aug 2017), Finland (Dec 2017), Norway (Jan 2018), Poland (Feb 2018), Romania (Aug 2018), Denmark (Aug 2019), Belgium (Jan 2021), Luxembourg (Feb 2021)[1].

### SV.1.1 Method used to calculate exposure

An estimate of patient exposure is calculated based on worldwide sales volume in grams of active substance sold during the reporting interval and the WHO Defined Daily Dose (DDD) using the following formula:

Patient exposure [Patient Treatment Years (PTY)] = Total sold x product strength x pack size/ (DDD x 365)

According to the World Health Organisation's ATC Classification System with Defined Daily Dose (DDD), ATC code of B03AB10 was allocated, however the DDD for ferric maltol is not yet assigned for the oral route of administration. Therefore, the currently recommended daily dose (60 mg=0.06 g) will be used in the estimation of patient exposure for ferric maltol.

### SV.1.2 Exposure Table SV.1: Exposure table region

| Time Period | Exposure data in patient-years | | | | | |
|---|---|---|---|---|---|---|
| | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Jan 2019 – Feb 2025** | 8774 | 25229 | 2110 | 1137 | 1991 | 70 |

Overall cumulative exposure

Cumulatively, patient exposure from marketing authorisation (MA) grant to the DLP of this report has been calculated as 38,302 patient years.

**ACCRUFER**

Patient exposure mentioned below is for the US and partner Shield Therapeutics.

**Method used to calculate exposure:** An estimate of patient exposure is calculated using the following formula:

[1] The product has been discontinued from the market in Poland, Romania, Belgium and Luxembourg.

$$\text{Number of patient-years} = \frac{\text{number of packages sold} \times \text{package size (60)} \times \text{product strength (30 mg)}}{\text{recommended daily dose (60 mg)} \times 365 \text{ days}}$$

**Results:**

Cumulatively, the patient exposure for ACCRUFER from MA grant to the DLP of this report has been calculated as 44,229 patient years based on 870,055 packages received in the US.

# Part II: Module SVI - Additional EU requirements for the safety specificatio

**Potential for misuse for illegal purposes**

As an iron-based treatment, Feraccru® does not rank amongst substances known to be addictive. There are no central nervous system effects that make abuse attractive, so it is concluded that there is no potential for abuse or addiction.

# Part II: Module SVII - Identified and potential risks

## SVII.1 Identification of safety concerns in the initial RMP submission

Not applicable as this is an updated RMP submission.

### SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable as the initial RMP was approved in RMP EMA template Rev 1.

### SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable as the initial RMP was approved in RMP EMA template Rev 1.

## SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not Applicable as no new safety concern has been added and/or reclassified with submission of this RMP.

## SVII.3 Details of important identified risks, important potential risks, and missing information

### SVII.3.1. Presentation of important identified risks and important potential risks

**Important Potential Risk: Drug Interaction with chloramphenicol, intravenous iron salts, methyldopa, tetracyclines or dimercaprol**

Potential mechanisms:

Concurrent ingestion of iron causes marked decrease in the bioavailability of a number of drugs due to the formation of iron-drug complexes (chelation or binding of iron by the second drug). The maltol component of Feraccru® may potentially induce UDP-glucuronosyltransferase (UGT).

Evidence source(s) and strength of evidence:

Feraccru® is a chemically very stable form of iron and has been shown not to inhibit zinc uptake [Barker 1989]. A post-hoc subgroup analysis was conducted on the data from the two pivotal studies to investigate the potential for drug interactions from concomitant medications [AEGIS post-hoc efficacy report]. The proportion of subjects taking PPIs was similar between the two study groups, as was the proportion being treated with anti-TNF medication. As expected more subjects with UC were treated with ASA-type medications. 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 [AEGIS post-hoc efficacy report]. These results indicated that there was no apparent effect on efficacy from all common IBD drugs.

However there are currently no formal DDI study data available. Therefore, to minimise the potential for drug interactions, as well as optimising absorption, Feraccru® should be given on an empty stomach.

Oral ferrous iron is known to reduce the absorption of penicillamine, bisphosphonates, ciprofloxacin, entacapone, levodopa, levofloxacin, levothyroxine (thyroxine) (give at least two hours apart), moxifloxacin, mycophenolate, norfloxacin and ofloxacin. Absorption of both iron and antibiotic may be reduced if oral iron is given with tetracycline. Absorption of oral iron may be reduced by calcium and magnesium salts (as magnesium trisilicate). Chloramphenicol delays plasma iron clearance, incorporation of iron into red blood cells and interferes with erythropoiesis. Concomitant use of iron with dimercaprol should be avoided and oral iron can antagonise the hypotensive effect of methyldopa.

This information about potential drug-drug interactions with Feraccru® is stated in the SmPC. UGT is not as highly inducible as enzymes of the P450 group: a maximum of 3-fold induction has been noted in animals or humans with prototypic inducers: furthermore the clinical significance of any induction remains unclear [Soars et al, 2004].

Characterisation of the risk:

As discussed in the previous sections, ID/IDA are often caused by the presence of other conditions, for example, excessive bleeding in the GI tract, pregnancy, or IBD. Therefore, the target population for Feraccru® is likely to be taking concomitant medications to treat these other conditions and these medicines may potentially interact with iron. For example, typical medicines for the treatment of IBD include anti-inflammatories such as aminosalicyclates, antibiotics, corticosteroids, biologic therapies, proton pump inhibitors and other antacids. The efficacy of sulfasalazine, used to treat IBD, may be decreased due to an interaction with iron; ciprofloxacin forms insoluble compounds with divalent cations such as iron so nutritional supplements should be avoided within 2 hours of ciprofloxacin [Irving 2008].

Oral iron is also known to reduce the absorption of penicillamine, bisphosphonates, entacapone, levodopa, levofloxacin, levothyroxine (thyroxine), moxifloxacin, mycophenolate, norfloxacin and ofloxacin. Absorption of both iron and antibiotic may be reduced if oral iron is given with tetracycline. Chloramphenicol delays plasma iron clearance, incorporation of iron into red blood cells and interferes with erythropoiesis. The concomitant use of iron with dimercaprol should be avoided and oral iron can antagonise the hypotensive effect of methyldopa.

Medications that raise gastric pH, such as antacids, H2-blockers, and proton pump inhibitors can limit the intestinal absorption of iron [Goldberg 2013].

A cumulative review of the MAH's safety database revealed a total of 10 cases (5 serious and 5 non serious) reporting potential drug interactions. Among the serious cases, 1 notable interaction

was observed with Duodopa (carbidopa, levodopa), while the remaining four involved interactions with various medications including metronidazole, levothyroxine, simvastatin, verapamil, and dolutegravir. In the non-serious category, two cases specifically highlighted potential interactions with iron, while the other 3 involved interactions with clopidegrol, esomeprazole, cyanocobalamin, and folic acid. The outcome in all reported cases was unknown. No adverse events were reported.

Risk factors and risk groups:

ID/IDA are often caused by the presence of other conditions, for example, excessive bleeding in the GI tract, pregnancy, or IBD. Therefore, the target population for Feraccru® is likely to be taking concomitant medications to treat these other conditions and these medicines may potentially interact with iron. The patients with concurrent conditions are at increased risk of experiencing drug interactions. Similarly, older patients are more likely to have comorbidities which means polypharmacy is more common in elderly patients, thus, are at increased risk of potential drug interactions.

Preventability:

Information about potential drug-drug interactions with Feraccru® are stated in the RSI. To minimise the potential for drug interactions, Feraccru® capsules should be taken on an empty stomach.

Impact on the risk-benefit balance of the product:

This will be dependent on the specific drug ingested, the degree of the interaction, and comorbidities. May cause undesirable effects due to reduced efficacy and tolerability of Feraccru® and/or the concomitant drug.

Public health impact:

Unknown

**Important Potential Risk: Worsening of IBD symptoms (in patients with this disease)**

Potential mechanisms:

Current oral (ferrous) iron therapy may reinforce intestinal tissue injury in IBD patients by catalysing production of ROS [Erichsen 2005]. Feraccru® is a chemically stable ferric iron/maltol complex that makes available biologically labile iron in the gastrointestinal tract. Feraccru® does not appear to catalyse production of ROS. Improved tolerability results from a significantly reduced total dose exposure of unabsorbed iron, which remains chelated and lack of catalysis of ROS. The available data suggests that, unlike OFPs, Feraccru® does not exacerbate underlying disease in IBD patients.

Evidence source(s) and strength of evidence:

There were no flares of underlying disease compared to placebo in IBD patients treated with Feraccru® in the placebo-controlled 12 week phase (one subject treated with ST10 compared to five subjects treated with placebo), and patient-reported disease activity scores showed no worsening, in the two pivotal studies. In the open-label phase, there were two cases of treatment emergent worsening Crohn's disease. However, the SCCAI and CDAI demonstrated that ST10 did not exacerbate IB symptoms over the 12-week double-blind treatment period or during open-label treatment.

Study ST10-01-304, as described above, looked at oral ferric maltol (Feraccru) or intravenous iron (ferric carboxymaltose; FCM), for the treatment of iron deficiency anaemia in subjects with inflammatory bowel disease. One subject was diagnosed with iron deficiency anaemia and Crohn's disease. The subject was randomised to receive ferric maltol. On Day 2, the subject was diagnosed

with non-serious moderate flare of her Crohn's disease. The event was considered related to the study drug and of moderate intensity. The subject received no treatment for the event. The study drug was withdrawn due to the event. The event was assessed as not resolved. No other IBD flare ups were considered related to the study drug.

Furthermore, *Feraccru® Real-World Effectiveness Study in Hospital Practice (FRESH): a real-world study to describe the outcomes associated with the use of ferric maltol (Feraccru®) for the management of iron-deficiency anaemia in patients with inflammatory bowel disease in the UK* aimed to describe the real-world use of Feraccru®, and the characteristics and clinical outcomes of patients with IBD and IDA who receive Feraccru®. This study provided valuable data relating to the early use of Feraccru® in UK routine clinical practice. The findings are broadly supportive of the results from clinical trials and contributed to a better understanding about the treatment and outcomes of this patient population in real-world clinical practice

Oral ferrous iron therapies are known to have the potential to worsen symptoms in IBD patients, and potentially contribute to the disease process. Many oral iron products carry warning or contraindications for use in IBD, as indicated in Table 2.

**Table 2 GI Contraindications/warnings in the summary of product characteristics (SmPCs) for oral ferrous salts**

| Iron Salt | Trade name/MAA Number | Contraindications | Warnings |
|---|---|---|---|
| Ferrous fumarate | Fersamal tablets (210mg)/ PL 12762/0226 (UK) | Active peptic ulcer, regional enteritis and ulcerative colitis. | None |
| Ferrous gluconate | Ferrous gluconate tablets/ PL 30464/0026 | Active peptic ulcer, regional enteritis and ulcerative colitis. | None |
| Ferrous sulphate | Ferrous sulphate 200mg Coated Tablets/ PL 29831/0220 | Active peptic ulcer. | Caution is advised when prescribing iron preparations to individuals with history of peptic ulcer, and inflammatory bowel disease, including regional enteritis and ulcerative colitis. Care should be taken in patients with intestinal strictures or diverticulae. |

In IBD, flares of the underlying disease (CU, CD) have been reported in patients treated with oral ferrous products. Gastrointestinal side effects of oral ferrous iron such as nausea, bloating, diarrhoea, or upper gastrointestinal pain are more pronounced compared with those observed in non-IBD patients taking oral iron therapy [Gasche 2004]. Ferric iron has less pro-oxidant potential,

while non-ionic iron polymaltose has been shown to have no oxidative potency on lipoproteins when tested in healthy subjects [Gasche 2004].

Worsening of IBD symptoms is a recognised potential risk when oral ferrous iron products are administered to IBD patients. Patients will be advised to speak to their doctor or pharmacist if they experience any side effects.

Characterisation of the risk:

About 20% of IBD per annum experience worsening of IBD symptoms; over a lifetime about 90% of all IBD patients will experience at least one flare [personal communication from investigators].

Worsening of IBD symptoms can be caused by a variety of factors and are potentially serious depending on the severity of the flare.

A cumulative review of the MAH's safety database revealed a total of 9 cases (7 serious and 2 non serious) of worsening of IBD symptoms. Among the serious cases, 5 involved ulcerative colitis (3 worsening and 2 flare-ups) and 2 involved Crohn's disease (1 worsening and 1 flare-up). The outcomes for serious cases were predominantly favourable, with 5 cases reported as recovered, while 1 case had an unknown outcome and 1 was not recovered. The 2 non-serious cases both involved ulcerative colitis, with 1 case reporting general symptom worsening (outcome not recovered) and the other specifically noting increased rectal bleeding (outcome recovering).

Risk factors and risk groups:

Most IBD patients experience worsening of IBD symptoms as it is a relapsing remitting condition. Oral ferrous iron therapy have been reported to worsen symptoms in IBD patients, and potentially contribute to the disease process. The number of patients experiencing disease exacerbation, or flare, was similar in the two treatment arms of the pivotal studies, and patient reported disease activity scores showed no worsening, in the two pivotal studies. There are therefore no identified risk groups or risk factors.

Preventability:

Feraccru should not be used in patients with IBD flare or in IBD patients with haemoglobin (Hb) <9.5 g/dl. Although it cannot be ruled out, Feraccru® does not appear to cause worsening of IBD symptoms from the available data. It is therefore not possible to identify patients who might experience worsening of IBD symptoms following treatment with Feraccru®. It should be noted however that dosing can be stopped easily, if necessary, because the product is dosed twice a day as an oral medication.

Impact on the risk-benefit balance of the product:

Given that a worsening of IBD symptoms exacerbates underlying disease and associated symptoms, it would be appropriate to consider that it would be likely to negatively impact on quality of life.

Public health impact:

Unknown

### SVII.3.2. Presentation of the missing information

N/A – there is no missing information in the updated list of safety concerns.

# Part II: Module SVIII - Summary of the safety concerns

**Table SVIII.1: Summary of safety concerns**

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | None |
| Important potential risks | Drug interaction with chloramphenicol, intravenous iron salts, methyldopa, tetracyclines or dimercaprol<br>Worsening of IBD symptoms (in patients with this disease) |
| Missing information | None |

# Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

## III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

**Specific adverse reaction follow-up questionnaires for Feraccru®:**

Norgine is not using any specific adverse reaction follow up questionnaires for Feraccru®.

However, targeted follow up will be completed if any adverse event reports are received that warrant specific questioning to the reporter to clarify details within the report.

**Other forms of routine pharmacovigilance activities for Feraccru®:**

No other forms of routine pharmacovigilance activities are considered necessary.

## III.2 Additional pharmacovigilance activities

Additional pharmacovigilance requirements are no longer considered necessary and routine pharmacovigilance activities are considered sufficient to monitor the benefit-risk profile of the product and detect any safety concerns.

A tabulated summary of completed pharmacovigilance studies is provided in Annex 2.

## III.3 Summary Table of additional Pharmacovigilance activities

There are no ongoing additional pharmacovigilance activities. A tabulated summary of completed pharmacovigilance studies is provided in Annex 2.

# Part IV: Plans for post-authorisation efficacy studies

No PAES studies have been conducted and none are considered required.

# Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

## Risk Minimisation Plan

## V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

| Safety concern | Routine risk minimisation activities |
|---|---|
| **Drug interaction with chloramphenicol, intravenous iron salts, methyldopa, tetracyclines or dimercaprol** | **Routine risk communication:**<br>*SmPC section 4.4 and 4.5.*<br>*PL section 2*<br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br>*Recommendation that special care should be taken if other dietary and/or iron salt supplementation are used concurrently is included in SmPC Section 4.4.*<br>*Recommendation that concomitant administration of intravenous iron, dimercaprol, chloramphenicol and methyldopa should be avoided. Medicinal products that oral iron is known to reduce the absorption of, and iron preparations with calcium and magnesium salts, should be given at least two hours apart from Feraccru®. And administration of iron preparations and tetracyclines should be separated by two to three hours are included in SmPC Section 4.5.*<br>*Instruction that patients should tell their doctor or pharmacist if they are taking any other medicine is included in PL Section 2, along with information to leave at least two hours between taking Feraccru® and certain medicines and to not take Feraccru with certain other medicines.*<br>**Other routine risk minimisation measures beyond the Product Information:**<br>*Medicinal product subject to medical prescription* |
| **Worsening of IBD symptoms (in patients with this disease)** | **Routine risk communication:**<br>*SmPC section 4.4*<br>*PL section 2*<br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:** |

| | |
|---|---|
| | *Recommendation that Feraccru® should not be used in patients with inflammatory bowel disease (IBD) flare or in IBD patients with haemoglobin (Hb) <9.5 g/dl is included in SmPC Section 4.4.*<br><br>*Instruction that patients should avoid taking Feraccru® if they are experiencing a "flare" of their IBD in PL Section 2.*<br><br>**Other routine risk minimisation measures beyond the Product Information:**<br><br>*Medicinal product subject to medical prescription* |

## V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

## V.3 Summary of risk minimisation measures

**Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern**

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| **Important Potential Risk: Drug interaction with chloramphenicol, intravenous iron salts, methyldopa, tetracyclines or dimercaprol** | **Routine risk minimisation measures:**<br><br>SmPC Section 4.4 recommends that special care should be taken if other dietary and/or iron salt supplementation are used concurrently.<br><br>SmPC Section 4.5 and PL Section 2 contain information to leave at least two hours between taking Feraccru and certain medicines and to not take Feraccru with certain other medicines.<br><br>Prescription only medicine.<br><br>**Additional risk minimisation measures:**<br><br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br><br>None<br><br>**Additional pharmacovigilance activities:**<br><br>None |
| **Important Potential Risk: Worsening of IBD symptoms (in patients with this disease)** | **Routine risk minimisation measures:**<br><br>SmPC Section 4.4 and PL Section 2 recommend that patients should | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br><br>None |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| | avoid taking Feraccru if they are experiencing a "flare" of their IBD.<br><br>Prescription only medicine.<br><br>**Additional risk minimisation measures:**<br><br>None | **Additional pharmacovigilance activities:**<br><br>None |

# Part VI: Summary of the risk management plan

## Summary of risk management plan for Feraccru® (ferric maltol)

This is a summary of the risk management plan (RMP) for Feraccru®. The RMP details important risks of Feraccru®, how these risks can be minimised, and how more information will be obtained about Feraccru® risks and uncertainties (missing information).

Feraccru's® summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Feraccru® should be used.

This summary of the RMP for Feraccru® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Feraccru's® RMP.

# I. The medicine and what it is used for

Feraccru® is authorised for the treatment of iron deficiency in adults and adolescents aged 12 years and older (see SmPC for the full indication). It contains ferric maltol as the active substance and it is given by 30mg hard capsules.

Further information about the evaluation of Feraccru's® benefits can be found in Feraccru's® EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/feraccru.

# II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Feraccru®, together with measures to minimise such risks and the proposed studies for learning more about Feraccru's® risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Feraccru® is not yet available, it is listed under 'missing information' below.

## *II.A List of important risks and missing information*

Important risks of Feraccru® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Feraccru®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

| **List of important risks and missing information** | |
|---|---|
| Important identified risks | None |
| Important potential risks | Drug interaction with chloramphenicol, intravenous iron salts, methyldopa, tetracyclines or dimercaprol<br>Worsening of IBD symptoms (in patients with this disease) |
| Missing information | None |

## *II.B Summary of important risks*

| **Important potential risk: Interactions (drugs)** | |
|---|---|
| **Evidence for linking the risk to the medicine** | Feraccru® is a chemically very stable form of iron and has been shown not to inhibit zinc uptake [Barker 1989]. A post-hoc subgroup analysis was conducted on the data from the two pivotal studies to investigate the potential for drug interactions from concomitant medications [AEGIS post-hoc efficacy report]. The proportion of subjects taking PPIs was similar between the two study groups, as was the proportion being treated with anti-TNF medication. As expected more subjects with UC were treated with ASA-type medications. 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 [AEGIS post-hoc efficacy report]. These results indicated that there was no apparent effect on efficacy from all common IBD drugs.<br><br>However there are currently no formal DDI study data available. Therefore, to minimise the potential for drug interactions, as well as optimising absorption, Feraccru® should be given on an empty stomach.<br><br>Oral ferrous iron is known to reduce the absorption of penicillamine, bisphosphonates, ciprofloxacin, entacapone, levodopa, levofloxacin, levothyroxine (thyroxine) (give at least |

| | |
|---|---|
| | two hours apart), moxifloxacin, mycophenolate, norfloxacin and ofloxacin. Absorption of both iron and antibiotic may be reduced if oral iron is given with tetracycline. Absorption of oral iron may be reduced by calcium and magnesium salts (as magnesium trisilicate). Chloramphenicol delays plasma iron clearance, incorporation of iron into red blood cells and interferes with erythropoiesis. Concomitant use of iron with dimercaprol should be avoided and oral iron can antagonise the hypotensive effect of methyldopa.<br><br>This information about potential drug-drug interactions with Feraccru® is stated in the SmPC. UGT is not as highly inducible as enzymes of the P450 group: a maximum of 3-fold induction has been noted in animals or humans with prototypic inducers: furthermore the clinical significance of any induction remains unclear [Soars et al, 2004]. |
| **Risk factors and risk groups** | ID/IDA are often caused by the presence of other conditions, for example, excessive bleeding in the GI tract, pregnancy, or IBD. Therefore, the target population for Feraccru® is likely to be taking concomitant medications to treat these other conditions and these medicines may potentially interact with iron. The patients with concurrent conditions are at increased risk. |
| **Risk minimisation measures** | **Routine risk minimisation measures:**<br><br>SmPC Section 4.5 and PL Section 2 contain information to leave at least two hours between taking Feraccru and certain medicines and to not take Feraccru with certain other medicines.<br><br>Prescription only medicine.<br><br>**Additional risk minimisation measures:**<br><br>None |

| **Important potential risk: Worsening of IBD symptoms (in patients with this disease)** | |
|---|---|
| **Evidence for linking the risk to the medicine** | There were no flares of underlying disease compared to placebo in IBD patients treated with Feraccru®. In the placebo-controlled 12 week phase (one subject treated with ST10 compared to five subjects treated with placebo), and patient-reported disease activity scores showed no worsening, in the two pivotal studies. In the open-label phase, there were two cases of treatment emergent worsening Crohn's disease. However, the SCCAI and CDAI demonstrated that ST10 did not exacerbate IB symptoms over the 12-week double-blind treatment period or during open-label treatment.<br><br>Study ST10-01-304, as described above, looked at oral ferric maltol (Feraccru) or intravenous iron (ferric carboxymaltose; FCM), for the treatment of iron deficiency |

anaemia in subjects with inflammatory bowel disease. One subject was diagnosed with iron deficiency anaemia and Crohn's disease. The subject was randomised to receive ferric maltol. On Day 2, the subject was diagnosed with non-serious moderate flare of her Crohn's disease. The event was considered related to the study drug and of moderate intensity. The subject received no treatment for the event. The study drug was withdrawn due to the event. The event was assessed as not resolved. No other IBD flare ups were considered related to the study drug.

Furthermore, *Feraccru® Real-World Effectiveness Study in Hospital Practice (FRESH): a real-world study to describe the outcomes associated with the use of ferric maltol (Feraccru®) for the management of iron-deficiency anaemia in patients with inflammatory bowel disease in the UK* aimed to describe the real-world use of Feraccru®, and the characteristics and clinical outcomes of patients with IBD and IDA who receive Feraccru®. This study provided valuable data relating to the early use of Feraccru® in UK routine clinical practice. The findings are broadly supportive of the results from clinical trials and contributed to a better understanding about the treatment and outcomes of this patient population in real-world clinical practice.

Oral ferrous iron therapies are known to have the potential to worsen symptoms in IBD patients, and potentially contribute to the disease process. Many oral iron products carry warning or contraindications for use in IBD, as indicated in Table 2.

**Table 2 GI Contraindications/warnings in the summary of product characteristics (SmPCs) for oral ferrous salts**

| Iron Salt | Trade name/MAA Number | Contraindications | Warnings |
|---|---|---|---|
| Ferrous fumarate | Fersamal tablets (210mg)/ PL 12762/0226 (UK) | Active peptic ulcer, regional enteritis and ulcerative colitis. | None |
| Ferrous gluconate | Ferrous gluconate tablets/ PL 30464/0026 | Active peptic ulcer, regional enteritis and ulcerative colitis. | None |
| Ferrous sulphate | Ferrous sulphate 200mg Coated Tablets/ PL 29831/0220 | Active peptic ulcer. | Caution is advised when prescribing iron preparations to individuals with history of peptic ulcer, and |

| | | | | |
|---|---|---|---|---|
| | | | | inflammatory bowel disease, including regional enteritis and ulcerative colitis. Care should be taken in patients with intestinal strictures or diverticulae. |

In IBD, flares of the underlying disease (CU, CD) have been reported in patients treated with oral ferrous products. Gastrointestinal side effects of oral ferrous iron such as nausea, bloating, diarrhoea, or upper gastrointestinal pain are more pronounced compared with those observed in non-IBD patients taking oral iron therapy [Gasche 2004]. Ferric iron has less pro-oxidant potential, while non-ionic iron polymaltose has been shown to have no oxidative potency on lipoproteins when tested in healthy subjects [Gasche 2004].

Worsening of IBD symptoms is a recognised potential risk when oral ferrous iron products are administered to IBD patients. Patients will be advised to speak to their doctor or pharmacist if they experience any side effects.

| | |
|---|---|
| **Risk factors and risk groups** | Most IBD patients experience worsening of IBD symptoms as it is a relapsing remitting condition. Oral ferrous iron therapy have been reported to worsen symptoms in IBD patients, and potentially contribute to the disease process. The number of patients experiencing disease exacerbation, or flare, was similar in the two treatment arms of the pivotal studies, and patient reported disease activity scores showed no worsening, in the two pivotal studies. There are therefore no identified risk groups or risk factors. |
| **Risk minimisation measures** | **Routine risk minimisation measures:**<br><br>SmPC Section 4.4 and PL Section 2 recommend that patients should avoid taking Feraccru if they are experiencing a "flare" of their IBD.<br><br>Prescription only medicine.<br><br>**Additional risk minimisation measures:**<br><br>None |

## *II.C Post-authorisation development plan*

### II.C.1 Studies which are conditions of the marketing authorisation

There are no outstanding studies which are conditions of the MA or specific obligation of Feraccru®.

### II.C.2 Other studies in post-authorisation development plan

There are no ongoing studies required for Feraccru®.

# Part VII: Annexes

# Table of contents

**Part VII: Annexes ..... 53**
Annex 1 – EudraVigilance Interface ..... 54
Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme ..... 55
Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan ..... 56
Annex 4 - Specific adverse drug reaction follow-up forms ..... 57
Annex 5 - Protocols for proposed and on-going studies in RMP part IV ..... 58
Annex 6 - Details of proposed additional risk minimisation activities (if applicable) ..... 59
Annex 7 - Other supporting data (including referenced material) ..... 60
Annex 8 – Summary of changes to the risk management plan over time ..... 65

## *Annex 4 - Specific adverse drug reaction follow-up forms*

N/A

## *Annex 6 - Details of proposed additional risk minimisation activities (if applicable)*

N/A